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Interval cancers in the Antwerp European randomised study of screening for prostate cancer study, using a 6 year screening interval

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ABSTRACT

Background: The European randomised study of screening for prostate cancer (ERSPC) was initiated to evaluate the effect of Prostate Specific Antigen (PSA) screening on prostate cancer mortality. Variations in screening modalities between participating centres, such as the interval between screening rounds are likely to affect the outcome of screening.

Methods: The study describes the number and characteristics of interval cancers in men in the screening arm of the Antwerp ERSPC aged 55–65 years at the time of randomisation and participating in the screening rounds they were invited for. The interval between the first screening rounds was 6 years on average. Interval cancers were defined as cancers diagnosed during the screening interval but not detected by screening. Cases with a positive screening test were considered as interval cancers if diagnosis through biopsy occurred more than 1 year after screening. Interval cancer cases were identified through linkage with cancer registries. Aggressive interval cancer was defined as cancer with at least one of the following characteristics: stage M1 or N1, Gleason score higher than 7 or World Health Organisation (WHO) score of 3.

Results: The 10 year cumulative incidence of interval cancers was 3.0% ($n = 50$) and the cumulative incidence of aggressive interval cancers was 0.5% ($n = 8$). During the first screening interval 36 interval cancers were detected. Of these 20 (55.6%) were detected more than 4 years after the initial screening and 5 (13.9%) were considered aggressive. All aggressive interval cancers emerged more than 4 years after initial screening.

Conclusion: The occurrence of interval cancers in this study was higher than in the ERSPC centres that used a shorter screening interval. Aggressive interval cancers only started to emerge 4 years after initial screening.

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1. Introduction

Prostate cancer is one of the most common cancers in men, accounting for 22.2% of newly diagnosed cancers in men in Europe in 2008. Prostate cancer was responsible for 9.3% of cancer deaths in men in Europe in 2008.[1] The incidence has increased markedly over the last decades, most likely due to the use of the Prostate Specific Antigen (PSA) blood test.[1–3] In the Flanders region of Belgium prostate cancer was the most incident cancer in men in 2006 with a crude rate of 197.9 prostate cancers per 100,000 inhabitants.[4] Prostate cancer was the 3rd cause of cancer death in men with a rate of 49.0 per 100,000.[5] The European randomised study of screening for prostate cancer (ERSPC), is initiated to prove or disprove the effect of PSA based screening for prostate cancer on prostate cancer mortality.[6,7] First results, after a median follow-up of 9 years, show a 20% reduction of mortality from prostate cancer in the screened group versus the control group. For the men that were actually screened the reduction was 27%. At the same time the study pointed at the disadvantages coinciding with the mortality reduction, being overdiagnosis, especially if it leads to overtreatment.[8]

Next to the main goal to prove an effect on mortality the study aimed to look at the impact of screening modalities on the outcome. The ERSPC study was performed through cooperation of different centres. Variations in screening protocol, e.g. the interval between screening rounds are likely to influence the outcome of screening because the length of the screening interval has implications on the detection rate, efficacy and costs. The rate of interval cancers gives an indication of the sensitivity of the screening programme and on the appropriateness of the length of the screening interval.[9]

The aim of this study is to describe interval cancers that were diagnosed in the Antwerp centre of the ERSPC, where the screening interval between the first two rounds was on average 6 years.

2. Methods

2.1. Characteristics of the study population

The study population consists of the participants of the Antwerp ERSPC centre. After several pilot studies, recruitment started in 1992 and ended in 2004. Men aged 55–74 years, living in the city of Antwerp, were identified from the population data base of the city of Antwerp and were invited to participate in the trial. After receiving a written informed consent, men were randomly assigned either the screening or the control arm of the trial. Details of the study protocol and procedures have been described previously.[10]

A total of 26.5% of the men invited participated in the study. In total 10,359 men were recruited and randomised, 5188 into the screening arm and 5171 into the control arm. The percentage of men in the screening arm actually screened for prostate cancer was 90.2. In the earlier protocols the men screened received a PSA blood test and a digital rectal examination (DRE) and transrectal ultrasound (TRUS) examination; in the later protocol from 1996 on only PSA blood test and DRE were performed.

In general, according to the ERSPC protocol, a prostate biopsy was indicated for men with a PSA level of 3 ng/mL or higher. In the earlier protocols of the Antwerp ERSPC a PSA level of 4 ng/mL or higher or positive digital rectal examination (DRE) or transrectal ultrasound (TRUS) examination were biopsy indications. Men were invited for subsequent screening rounds until the age of 74. Biopsy technique were lateralized sextant biopsies.

For this study men aged 55–65 at the time of first screening were used to be comparable with the other ERSPC centres. Only data from men who participated in the screening rounds they were invited for were analysed. Men in the study group had at least two screening rounds. Prostate cancer was diagnosed until December 2007 but no more than 10 years after randomisation. Prostate cancer diagnosis was retrieved through linkage with the national or regional cancer registry.

2.2. Definition of interval cancers

Prostate cancer, detected within the screening protocol after a positive screening test, was confirmed pathologically through sextant biopsies within 1 year after screening. If a lesion was present an additional core biopsy was taken from the lesion. Repeat biopsies were not provided in the protocol, cases with a negative biopsy were invited in the next screening round.

An interval cancer is defined as any prostate cancer occurring outside the screening protocol within the screening interval. Interval cancers were identified through linkage with the national and regional cancer registry. Prostate cancers that were diagnosed outside the study protocol due to patient non-compliance, e.g. not responding to biopsy invitation ($N = 9$), were not classified as interval cancers. Prostate cancers that were diagnosed outside the study after a longer period than the screening interval due to patient non-participation ($N = 18$) or old age were also excluded as interval cancers. The characteristics of the cancers at time of diagnosis are cancer registry data. An aggressive interval cancer was defined as an interval cancer with at least one of the following characteristics: stage M1 or N1, Gleason score higher than 7 or World Health Organisation (WHO) score of 3. Because these cancers are potentially incurable and might have been detected with a shorter screening interval they are studied separately.

2.3. Statistical analysis

The rates of all prostate cancers, of interval cancers and of aggressive interval cancers are calculated and compared to the rates of cancers in the control arm.

3. Results

3.1. Cancer detection rates

After applying the inclusion criteria for age and participation to screening, 1660 men from the screening arm of the Antwerp ERSPC were eligible for analysis and formed the study cohort (Table 1). During the study period (up to December 2007) all men had at least two screening visits. The interval between the first two rounds was 6.1 years on average. In total 125 cancers were detected by screening, a

Table 1 – Numbers in the consecutive phases of the European randomised study of screening for prostate cancer (ERSPC) study population in Antwerp. Aggressive disease was defined as stage M1 or N1 or a Gleason score of more than 7 or a World Health Organisation (WHO) grade of 3.

Men randomly assigned to the screening arm after consent, age 55–65		3251
Selection of men who attended initial screening		2809
Men eligible for analysis: screened two times or more, max 10 years after initial screening, follow-up to 31st December 2007		1660
Total PCA		175
	Screen detected PCA	125
	Interval PCA	50
	Aggressive interval PCA	8

cancer detection rate of 7.5%. The mean follow-up time was 8.39 years. During the same follow-up period 150 cancers were detected in the control group, a cancer detection rate of 4.7% (Table 2).

3.2. *Identification of interval cancers*

During the follow-up period 50 interval cancers were diagnosed (10 year cumulative incidence of 3.0%). Eight of them (16%) had characteristics of aggressive cancer (10 year cumulative incidence of 0.5%). In nine cases a previous positive screening resulted in a negative biopsy, in 41 cases previous screening was negative. All aggressive cancers had a previous negative screening result.

The detection rate of interval cancers in the screening arm (50/1660) was 64% of the detection rate of prostate cancer in the control group (150/3212) in the same follow-up period.

3.3. *Interval cancers per screening interval*

The interval cancers were classified per year after the initial screening (Table 3). During the first screening interval of 6 years, a total of 36 interval cancers were detected. Of these 20 (55.6%) were detected more than 4 years after the initial screening and 5 (13.9%) were considered aggressive. All aggressive interval cancers emerged more than 4 years after the initial screening.

Data on the clinical stage and grade of the interval cancers were retrieved from the cancer registry data. Two interval

Table 3 – Number of interval prostate cancers and aggressive interval cancers per year after initial screening (up to 10 years after initial screening visit) in the Antwerp ERSPC.[a]

Years after initial screening	Interval cancers, all	Interval cancers, aggressive
0–1	3	0
1–2	2	0
2–3	5	0
3–4	6	0
4–5	8	3
5–6	12	2
6–7	6	1
7–8	0	0
8–9	2	0
9–10	6	2
Total	50	8
% of total screened	3.01	0.48
% of total interval cancers	NA	16.00

[a] Interval cancer = clinically diagnosed prostate cancer in the interval between 2 screening visits; aggressive interval cancer = interval cancer with at least one of the following criteria: stage M1 or N1, a Gleason score of 7 or higher or a WHO grade of 3; NA = not applicable.

Table 2 – Numbers and rates of interval cancers versus prostate cancer detected in the screening and the control group during follow-up of the Antwerp centre of the ERSPC trial.[a]

Number/rate	Antwerp data	
Number of men eligible for analysis	1660	
Number of interval cancers	50	
Number of aggressive interval cancers	8	
Number of screen detected cancers	125	
Number of cancers in the control arm	150	
		95% CI
Detection rate of screen detected cancers, %	7.53	6.35–8.90
Detection rate of interval cancers, %	3.01	2.23–3.96
Detection rate of all PCA detected, %	10.54	9.15–12.11
Detection rate of PCA in control group, %	4.67	3.94–5.40
Detection rate of aggressive interval cancers, %	0.48	0.23–0.97
Rate of interval cancer/rate of screen detected PCA	0.40	0.29–0.55
Rate of interval cancer/rate of PCA in control group	0.64	0.47–0.88
Rate of aggressive interval cancer/rate of screen detected PCA	0.06	0.03–0.13
Rate of aggressive interval cancer/rate of PCA in control group	0.10	0.05–0.21

[a] Interval cancer = clinically diagnosed prostate cancer in the interval between two screening visits; aggressive interval cancer = interval cancer with at least one of the following criteria: stage M1 or N1, a Gleason score of 7 or higher or a WHO grade of 3.

cancers had stages T3-4, 2 had metastasis and 6 had WHO grade 3. The completeness of data from the cancer registry on stage and grade was 74% for T stage, 82% for grade.

The 10 year cumulative incidence of all prostate cancers was 10.5%. The cumulative incidence of interval cancers was 3.0% and the cumulative incidence of aggressive interval cancers was 0.5%.

4. Discussion

This study showed results for all cancers, screen detected and interval cancers found in the Antwerp ERSPC in men aged 55–65 years at entry, that were screened with a screening interval between round 1 and 2 of 6 years on average. The 10 year cumulative incidence for all prostate cancers in the Antwerp ERSPC study was 10.5%, 7.5% for screen detected cancers and 3.0% for interval cancers.

These rates can be compared to the rates, described by Roobol et al., of the Rotterdam and Gothenburg centres that used a screening interval of, respectively, 4 and 2 years.

The rate for all prostate cancers detected was 8.4% in Rotterdam and 13.1% in Gothenburg with a detection rate of screen-detected cancers of 8.0% in Rotterdam and 12.4% in Gothenburg. From these data it is clear that more frequent screening results in the detection of more cancers; mainly for a 2 year compared to a 4 or 6 year interval.

The cumulative incidence of interval cancers in Antwerp was 50 (3.0%) versus 0.43% in Rotterdam and 0.7% in Gothenburg. The rate of aggressive interval cancers was 8 (0.5%) in Antwerp versus 0.1% in Rotterdam and 0.1% in Gothenburg.[9]

All three cohorts were part of the randomised populations of the ERSPC screening study. Screened men, non-participants and control men were closely followed through linkage with the national or regional cancer registries. All centres of the ERSPC were reviewed by the ERSPC quality control committee.[11]

The 10 year cumulative incidence of interval cancer, total and aggressive, in the Antwerp study was much higher than in the two other centres that applied a shorter screening interval. The mean follow-up time that was higher in Antwerp than in the two other centres may partly explain the higher incidence (8.39 years in Antwerp versus 7.16 in Rotterdam and Gothenburg). Both studies used men aged 55–65 years, with a mean age in Antwerp of 61.0 years but despite this there may have been differences in age distribution. To account for differences in age distribution the risk ratio for interval cancers in the screening arm compared to cancers in the control arm was calculated. Follow-up time and age in the control arm were comparable to the screening arm with 8.22 years of follow-up and a mean age of 61.1 years. The detection rate of interval cancers amounted to 64% of the detection rate in the control group. In Rotterdam and Gothenburg this was only 18% and 11%, respectively. The detection rate of interval cancers was even higher than the 50% ratio of detection rates of interval cancers and expected cancers observed in breast cancer screening using a 2-year interval.[12]

The aggressiveness of the interval cancers was low, 36% was detected with clinical stage T1, 34% with clinical stage T2. A total of 36% were WHO grade 1, 34% grade 2. The completeness of data from the cancer registry on stage and grade was 74% for T stage, 82% for grade. For the interval cancers, PSA level at diagnosis could not be evaluated because it was not available in the registry data. Many detected interval cancers were locally confined and well to moderately differentiated and had, therefore, a favourable outcome. The low aggressiveness and the relatively high detection rate of interval cancers can point towards an effect of opportunistic screening between screening rounds. Data on this so-called contamination are scarce in Belgium. Results from the Swedish study showed that opportunistic screening in both the screening and the control arm was low in the mid nineties (3% in 1995) and increased to 25% in 2005.[9] Results from the Dutch centre showed an opportunistic screening rate of 14.4% in 2001 and 19.4% in 2005.[9] Effective contamination, where elevated PSA levels lead to biopsy, was limited to 10% in the Rotterdam study in the period 1997–2000.[13]

Some recent studies suggest that the screening interval should be related to the initial PSA level. Aus et al from the Swedish ERSPC centre found only 0.9% cancer detection rate in men aged 50–66 years, with an initial PSA concentration of less than 1.0 ng/mL and a median follow-up of 7.6 years after biennial screening.[14] Roobol et al., from the Dutch ERSPC centre, concluded that the screening interval of men aged 55–65 years with a PSA concentration of 1.0 ng/mL or less could be as long as 8 years with a minimal risk of missing an aggressive cancer at a curable stage.[15] In our study six men with an interval cancer within 10 years after initial screening had a PSA level at initial screening of 1.0 ng/mL or lower. All except one of these emerged after 4 years of follow-up. One interval cancer emerged within the first year after initial screening with low PSA and positive TRUS, followed by a negative biopsy.

The rate of interval cancers in Antwerp was 7 and 4 times higher than in the Rotterdam and Gothenburg centres that used a shorter screening interval of 4 and 2 years. Correcting for the number of cancers in the control group the rate in Antwerp was 4 and 6 times higher than in Rotterdam and Gothenburg. More than half (55.6%) of the detected interval cancers in the first interval of 6 years were detected in the years 5 and 6. The rate of detecting aggressive interval cancer was 10% of the detection rate in the control arm. This was higher than the detection rate in Rotterdam (5%) and especially in Gothenburg (2%).

The first aggressive interval cancers emerged 4 years after initial screening. These data suggest that a 6 year screening interval is too long and 4 year interval may be more effective when the early detection of aggressive prostate cancers is considered.

5. Conclusions

The 10 year cumulative incidence of interval cancers in this study was higher than in the Rotterdam and Gothenburg centres that used a shorter screening interval. The occurrence[2] of aggressive interval cancers applying a 6 year screening interval was low but higher than in the centres applying a 4 or 2 year screening interval. Aggressive interval cancers only started to emerge 4 years after the initial screening.

Conflict of interest statement

None declared.

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REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2008;**46**(4):765–81 [March].
2. Nelen V. Epidemiology of prostate cancer. Recent results in cancer research, vol. 175. Berlin, Heidelberg: Springer-Verlag; 2007. p. 1–8. ISBN 978-3-540-408970.
3. Bray FP, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer, accepted for publication.
4. Belgian cancer registry. Available at: <www.kankerregister.org> (last accessed 02.07.10).
5. Vlaams agentschap zorg en gezondheid. Available at: <www.zorg-en-gezondheid.be/statistiek-doodsoorzaken.aspx> (last accessed 02.07.10).
6. Schröder FH, Denis LJ, Roobol M, et al. The story of the European Randomized Study of Screening for Prostate cancer. *BJU Int* 2003;**92**(Suppl. 2):1–13 [December].
7. Roobol MJ, Schröder FH. European randomized study of screening for prostate cancer: achievements and presentation. *BJU Int* 2003;**92**(Suppl. 2):117–22.
8. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;**360**(13):1320–8 [Epub 2009 March 18, March 26].
9. Roobol MJ, Grenabo A, Schröder FH, Hugosson J. Interval cancers in prostate cancer screening: comparing 2- and 4-year screening intervals in the European Randomized Study of Screening for Prostate Cancer, Gothenburg and Rotterdam. *J Natl Cancer Inst* 2007;**99**:1296–303.
10. Nelen V, Thys G, Neels H, et al. ERSPC: features and preliminary results from the Antwerp study centre. *BJU Int* 2003;**92**(Suppl. 2):17–21 [December].
11. Ciatto S, The ERSPC. The ERSPC quality control committee. *BJU Int* 2003;**92**(Suppl. 2):57–61.
12. Wang H, Bjurstam N, Bjorndal H, et al. Interval cancers in the Norwegian breast cancer screening program: frequency, characteristics and use of HRT. *Int J Cancer* 2001;**94**:594–8.
13. Otto SJ, van der Cruijsen-Koeter IW, Liem MK, et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. *Int J Cancer* 2003;**105**:394–9.
14. Aus G, Damber J-E, Khatami A, et al. Individualized screening interval for prostate cancer based on prostate-specific antigen level. *Arch Int Med* 2005;**165**:1857–61.
15. Roobol MJ, Roobol DW, Schröder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population based screening setting? (ERSPC section Rotterdam). *Urology* 2005;**65**:343–6.