

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: 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. DOI: 10.1056/NEJMoa0810084.

Appendix 1: Acknowledgements.

The following people are being acknowledged for their contribution to the ERSPC study.

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Drs. A. Boeken-Kruger, urologist
Drs. C. Wijburg, urologist
Drs. M. Forouzanfor, urologist
Drs. M. De Boer, urologist
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COD committee = Causes of Death committee.

The United Kingdom.

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Appendix 2: Grants received per centre.

The Netherlands:

The Dutch Cancer Society (KWF 94-869, 98-1657, 2002-277, 2006-3518); The Netherlands Organisation for Health Research and Development (ZonMW-002822820, 22000106, 50-50110-98-311).

Belgium:

Europe against Cancer, Flemish Ministry of Welfare, Public Health and Family, Province and City of Antwerp, Public Centre for Social Welfare Antwerp

Sweden:

Abbott Pharmaceuticals, Sweden, Af Jochnick's foundation, Catarina and Sven Hagstroms family foundation, Gunvor and Ivan Svensson's foundation, Johanniterorden, King Gustav V Jubilee Clinic Cancer Research Foundation, Sahlgrenska University Hospital, Schering Plough, Sweden, Swedish Cancer Society, Wallac Oy, Turku, Finland.

Finland:

The Academy of Finland, The Cancer Society of Finland, The Finnish Cancer Institute, The Medical Research Fund of Tampere University Hospital, The Competitive Research Funding of the Pirkanmaa Hospital District, The Sigrid Juselius Foundation, The Pirkanmaa Cancer Society, The Finnish Cultural Foundation, The Helsinki University Central Hospital Research Funds, The Foundation of K. Albin Johansson, The Finska Läkaresällskapet, The Medical Research Fund of Seinäjoki Central Hospital, The Stockman Foundation, The Helsingin Sanomat Centenarian Foundation, The Europe Against Cancer Program, Perkin Elmer-Wallac, Doctoral Programme in Public Health, AstraZeneca Group and Pharmacia Corporation in support of a PhD thesis

Italy:

Italian League for the Fight against Cancer - LILT Lega Italiana per la Lotta contro i Tumori

Italian Association for Cancer Research - AIRC Associazione Italiana Ricerca sul Cancro

National Research Council - CNR Consiglio Nazionale delle Ricerche

Tuscany Region - Regione Toscana

Spain:

The Spanish "Fondo de Investigación Sanitaria": 96/0248, 99/0245, 02/0732, 06/0831.

Switzerland:

The Horten Foundation, Aargau Cancer League, Swiss Cancer League (Grant Nr KFS 787-2-1999 and 01112-02-2001), Health Department of Canton Aargau, Prostate Cancer Research Foundation and Baugarten Foundation.

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;

Unconditional grants:

Beckman-Coulter-Hybritech Inc.

Appendix 3: Pathology review

The Pathology Committee of ERSPC.

Composition and mandate:

The Pathology Committee of the ERSPC is composed of the reference pathologists representing one of each ERSPC screening center (see below for list of members). Their mandate is to enhance the application of the guidelines on reporting of prostate biopsies of participants of the screening arm of the ERSPC trial (see documentation 1, below).

Objectives of the Pathology Committee:

- 1) To guard the uniformity in tissue processing and nomenclature of diagnosis and staging terms in the histopathological reporting of sextant needle biopsies taken from participants of the screening arm of the ERSPC trial.
- 2) To enhance the quality of histopathological diagnosis of prostate biopsies.
- 3) To reduce the inter-observer variation among screening centers particularly with regard to Gleason score of prostatic adenocarcinomas .

Duties of the members of the Pathology Committee

- 1) Supervision of the pathology reporting of the prostate biopsies obtained from participants in the ERSPC screening centers.

In most centers the reference pathologists reviewed all needle biopsies of patients with a diagnosis of adenocarcinoma or a lesion suspicious for carcinoma. They further provide low threshold (intradepartmental) inter-collegial consultations for prostate biopsy diagnostics. In a few centers the reference pathologists examines and reports all prostate biopsies of the participants of the screening arm of the ERSPC trial.

- 2) Attendance of the annual Pathology Committee used for discussion of issues regarding quality assurance, uniform reporting and Gleason scoring.
- 3) Participation in slide reviews and educational sessions, designed for reduction of inter-observer variation of Gleason score and diagnosis.

Actions to reduce inter-observer variation for Gleason score on prostate biopsies:

- 1) Educational sessions using multihedder microscope.
- 2) Inter-observer studies using virtual microscopy (see Helin H, Lundin M, Lundin J, Martikainen P, Tammela T, Helin H, Van der Kwast TH. Web-based virtual microscopy in teaching and standardizing Gleason grading. Hum Pathol. 2005; 36: 381-386).
- 3) On site review of prostate biopsies of the Finnish ERSPC trial by two members of the pathology committee (Van der Kwast, Hoedemaeker) in order to improve grading consistency (see document 2 for details).

Documents / publications produced by the Pathology Committee of the ERSPC:

1. Guidelines document accepted at the Consensus Workshop on Prostatic Screening held in Antwerp (see Denis L, Murphy GP, Schröder FH. Cancer 1995; 75: 1178-1207): van der Kwast TH, Lopes C, Santonja C, Pihl C-G, Martikainen P, Di Lollo S, Bubendorf L, Hoedemaeker RF, and members of the pathology committee of the ERSPC. Guidelines for processing and reporting of prostatic needle biopsies. J. Clin Path 2003; 56:336-40.
2. Van der Kwast TH, Roobol MJ, Wildhagen MF, Martikainen PM, Määttä L, Pihl C-G, Santonja C, Bubendorf L, Neetens I, Di Lollo S and Hoedemaeker RF. Consistency of prostate cancer grading results in screened populations across Europe. BJUI 2003; 92 (S2): 88-91.
3. Van der Kwast TH, Lopes C, Martikainen PM, Pihl CG, Santonja C, Neetens I, Di Lollo S, Hoedemaeker RF. Report of the Pathology Committee: false-positive and false-negative diagnoses of prostate cancer. BJU Int. 2003 Dec;92 Suppl 2:62-5.

4. Van der Kwast TH, Ciatto S, Martikainen PM, Hoedemaeker R, Laurila M, Pihl C-G, Hugosson J, Neetens I, Nelen V, Di Lollo S, Roobol MJ, Maattanen L, Santonja C, Moss S and Schröder FH. Detection rates of high-grade prostate cancer during subsequent screening visits. Results of the European Randomized Screening Study for Prostate Cancer. Int J Cancer 2006; 118: 2538-2542

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C-G. Pihl	ERSPC section Goteborg
P.M. Martikainen	ERSPC section Tampere/Helsinki
M. Laurila	ERSPC section Tampere/Helsinki
L. Bubendorf	ERSPC section Aarau
C. Santonja	ERSPC section Getafe (-2007)
I. Neetens	ERSPC section Antwerp
S. DiLollo	ERSPC section Florence
C. Mazerolles	ERSPC section Toulouse
C. Lopes	ERSPC section Oporto

Appendix 4: Medical ethical approvals per centre.

The Netherlands:

Institution	Date of issue	Record number
Health Council of The Netherlands	March 29, 1996	1996/02
Health Council of The Netherlands	December 15, 2000	2000/05
Health Council of The Netherlands	July 24, 2007	2007/03

Belgium:

Institution	Date of issue	Record number
Ministry of the Flemish Community, the minister of welfare, national health and family	1999	ZG/PET/ERSPC 06031
Ministry of the Flemish Community, the minister of welfare, national health and family	2002	ZG/PET/ERSPC 06031
Ministry of the Flemish Community, the minister of welfare, national health and family	2004	ZG/PET/ERSPC 06031

Sweden:

Institution	Date of issue	Record number
University of Göteborg	02-02-1994	463-93
University of Göteborg	31-05-1995	180-95

Finland:

Institution	Date of issue	Record number
Helsinki University Central Hospital (HUCH)	21-2-1994	
City of Espoo, Jorvi Hospital	22-9-1995	4/1995
Tampere University Hospital/Pirkanmaa Hospital District	30-4-1995	95077
Population Register Centre	15-12-1995	1058/40/95
National Research and Development Centre for Welfare and Health	15-11-1995	2054/54/95
University of Helsinki, Faculty of Medicine	12-3-1996	
City of Helsinki, Office for Health Care	4-6-1996	6/96
City of Vantaa	2-2-1996	6/96
Ministry of Social Affairs and Health in Finland	1-10-1999	51/07/1999
City of Tampere	13-12-2000	7649/403/2000
Hospital District of Helsinki and Uusimaa	29-1-2001	55/2000

The National Authority for Medico legal Affairs
Statistcs Finland

27-2-2002 601/32/300/02
19-12-2003 tk-53-1610-03

Italy:

Institution	Date of issue	Record number
The Centro per lo Studio e la Prevenzione Oncologica , Firenze	03-06-1996	1996/06/03

Spain:

Institution	Date of issue	Record number
Hospital Universitario de Getafe	22-03-2006	Acta -3/06

Switzerland:

Institution	Date of issue	Record number
Kantonsspital Aarau	09-09-1998	1998-09-09/rk

Appendix 5:Table 1A: Randomization, participants and results of screening per center (all ages)

	Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total
Period of randomization	Nov 1993 – March 2000	June 1991- Dec 2003	31 Dec 1994	Jan 1996- Jan 1999	Oct 1996 – Oct 2000	Feb 1996 – June 1999	Sep 1998 - Aug 2003	
Randomized – N	43,368	10,359	19,911	80,379	14,972	3702	10,309	182,000
- screening	21,206 (50.1%)	5,188 (50.1%)	9,957 (50.0%)	31,970 (39.8%)	7,497 (50.1%)	1840 (49.7%)	5,158 (50.0%)	82,816 (45.5%)
- control	21,162 (49.9%)	5,171 (49.9%)	9,954 (50.0%)	48,409 (60.2%)	7,475 (49.9%)	1,862 (50.3%)	5,151 (50.0%)	99,184 (54.5%)
Age at randomization (aver. / median)	63,6 / 63,2	64,3 / 64,1	56,8 / 56,4	59,6 / 58,7	62,4 / 62,0	57,5 / 56,6	61,6 / 61,0	61,4 / 61,2
- age screen population	63.6 / 63.2	64.3 / 64.0	56.8 / 56.3	59.6 / 58.7	62.4 / 61.9	57.1 / 56.1	61.5 / 60.9	61.5 / 61.3
- age control population	63.7 / 63.2	64.4 / 64.2	56.8 / 56.4	59.6 / 58.7	62.4 / 62.1	57.9 / 57.1	61.7 / 61.2	61.3 / 61.1
Screened, 1st screen N (% of randomized to screening)	19,970 (94.2)	4567 (88.0)	5,855 (58.8)	20,796 (65.1)	5,106 (68.1)	1840 (100)	4,923 (95.4)	63,057 (76.1)
Screen interval (years)	4	4-7	2	4	4	4	4	---
Screened at least once - N	19,970	4,649	7,510	23,608	5,841	1840	4,942	68,360
Screen tests done – N	38,586	6,847	26,709	48,900	11,646	3317	9319	145,324
Positive tests – N (%)	9,064 (23.4)	1,136 (16.6)	4,154 (15.6)	5,528 (11.3)	1,308 (11.4)	543 (16.4)	1,915 (20.5)	23,648(16.3)
Biopsies – N (%)	8,085 (89.2)	825 (72.6)	3,626 (87.4)	4,991 (90.3)	849 (64.9)	394 (72.7)	1,467 (76.6)	20,237 (85.6)
Prostate cancers								
Screening arm total – N	2,153	437	997	2,493	296	87	367	6,830
Screen detected N	26.6	208	805	1,477	185	78	277	4,860
Interval and Non attender N	323	229	192	1,016	111	9	90	1,970
PPV (S det cancers/biopsy, %)	22.6	25.2	22.2	29.6	20.1	19.8	18.9	23.9
Det. rate (total cancers / all rand. To S arm, %)	10.2	8.4	10.0	7.8	3.9	4.7	7.3	8.3
Prostate cancers								
Control arm – N	901	332	577	2,632	138	33	168	4,781 (4.8)

* Interval PC are cases that were clinically detected during the screening interval, Non attender PC are clinically detected cases in men who refused screening

Appendix 6: Distribution of Clinical T-stages and biopsy Gleason scores at diagnosis per study arm.

() = M1 or PSA > 100 where no bone scan was performed

Core age group, all centers combined.

Table A: Presentation of the raw data, unadjusted for missing information. M1 = positive bonescan or PSA > 100 where no bone scan was performed

T-Stage	Screening arm N=5.990		Control arm N=4.307	
		M1		M1
<u>T1/T1A/T1B</u>	190	(1)	207	(4)
<u>T1c</u>	3.086	(25)	1.346	(19)
<u>T2</u>	1.571	(32)	984	(55)
<u>T3</u>	456	(59)	559	(138)
<u>T4</u>	60	(32)	117	(79)
<u>missing</u>	627	(5)	1.094	(9)
<u>Total</u>	5.990	(149)	4.307	(304)

M1 disease 0.39 per 1000 person years in C-arm versus 0.23 per 1000 person years in I arm, a 41% reduction (P < 0.0001)

Gleason score	Screening arm N=5.990	Not yet in the data base	Control arm N=4.307	Not yet in the data base
2-6	3.520		1.518	
7	990		799	
> 7	363		455	
Total	4.873	1.126	2.772	1.538

Table B: Adjusted for missing information by extrapolation from data given in table A, assuming similar stage distribution in missing cases

T-Stage	Screening arm N=5.990	Control arm N=4.307
<u>T1/T1A/T1B</u>	212	277
<u>T1c</u>	3.447	1.805
<u>T2</u>	1.755	1.320
<u>T3</u>	509	749
<u>T4</u>	67	156
<u>Total</u>	5.990	4.307

T3+T4 cases: 1.15 per 1000 person years in C-arm versus 0.90 per 1000 person years in I arm, a 22% reduction (P < 0.0001)

Appendix 7: Distribution of primary treatments per study arm.

Treatment	Total group N=10.309 N/ (%)	Screening arm N=5.990 N/(%)	Control arm N=4.307 N/(%)
Surgery alone	2.911 (28.3)	2.020 (33.7)	891 (20.7)
Radiotherapy alone	1.727 (16.8)	1.198 (20.0)	529 (12.3)
Surgery & Radiotherapy	28 (0.3)	13 (0.2)	15 (0.3)
Hormone therapy alone	1.061 (10.3)	409 (6.8)	652 (15.1)
Surgery & hormone therapy	109 (1.1)	69 (1.2)	40 (0.9)
Hormone & Radiotherapy	976 (9.5)	405 (6.8)	571 (13.2)
Surgery, Hormone & Radiotherapy	4 (0.04)	3 (0.05)	1 (0.02)
Surgery & Gene therapy	2 (0.02)	1 (0.02)	1 (0.02)
Watchful Waiting	1.553 (15.1)	1.116 (18.6)	437 (10.1)
W Waiting/Surgery	13 (0.1)	7 (0.1)	6 (0.14)
W Waiting/Radiotherapy	1 (0.01)	1 (0.02)	-
W Waiting/Hormone Therapy	4 (0.04)	2 (0.03)	2 (0.05)
Not Known	1.908 (18.5)	746 (12.5)	1.162 (26.9)
Total	10.297 (100.0)	5.990 (100.0)	4.307 (100.0)

Appendix 8: Deaths within 30 days after prostate cancer diagnosis per study arm.

Arm	PC Cases (N)	Deaths (N,%)
Screening	5.990	13 (0.22)
Control	4.307	23 (0.53)