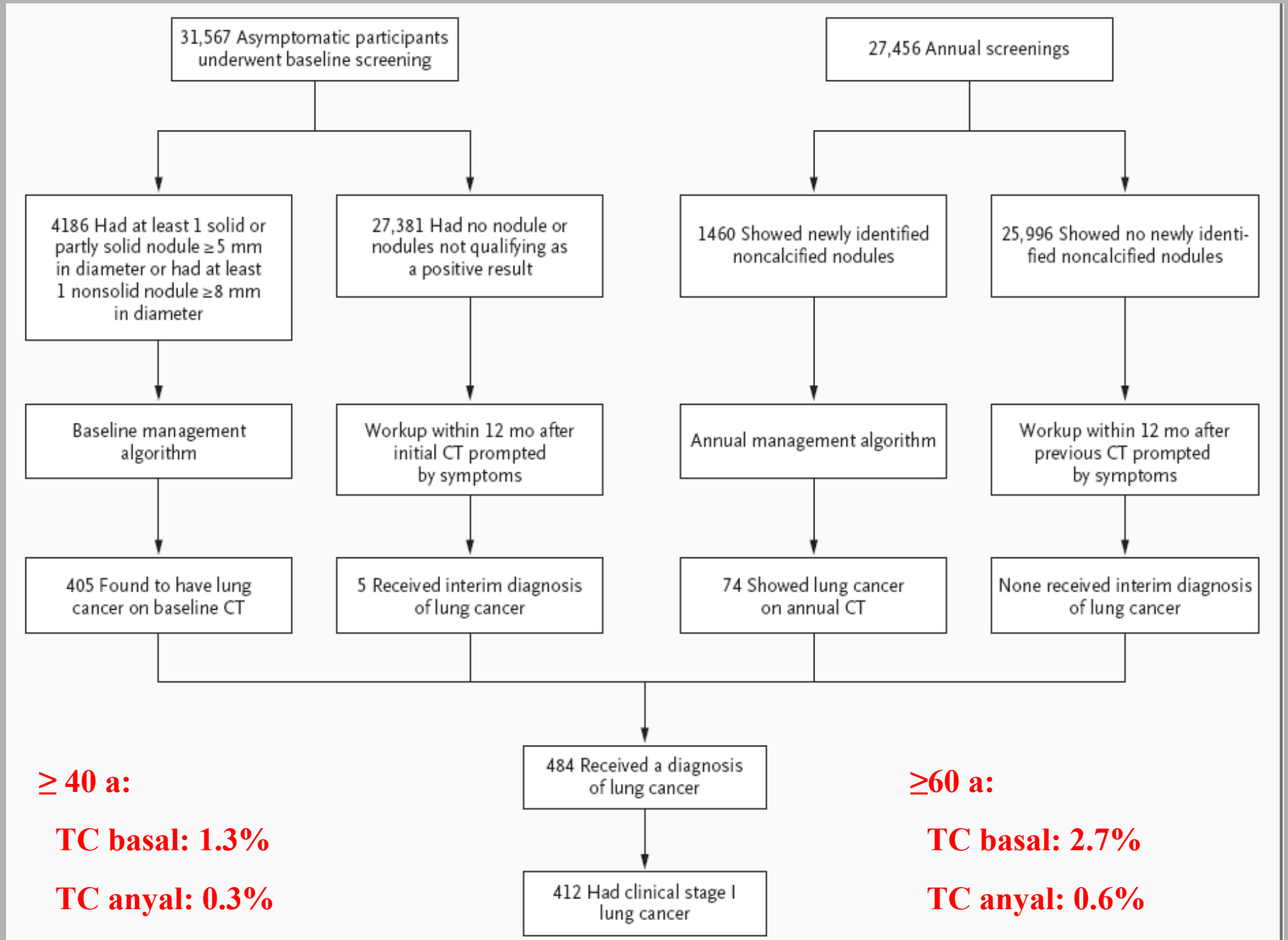
Cribatge del Càncer de Pròstata

Càncer de Pulmó. Cribatge amb TC anyal. Estudi ELCAP



≥ 40 a:

TC basal: 1.3%

TC anyal: 0.3%

≥60 a:

TC basal: 2.7%

TC anyal: 0.6%

Cribatge. Mamografies. Experiència a Osona

- **1ª Ronda (2000-02)**
  - **Població convocada: 8767**
  - **Participació: 78.8%**
  - **Neoplasies detectades en estadis 0 i I: 87%**

- **2ª Ronda (2003-04)**
  - **Població convocada: 11804**
  - **Participació: 89.2%**
  - **Neoplasies detectades: 34 (3.2‰)**
  - **Neoplasies detectades en estadis 0 i I: 75.8%**
  - **Tractament conservador: 82%**

Cribatge. Mamografies.

Als 40 anys:

10.000 dones s'han de fer una Mx anyal, durant 10 anys, per salvar 4 vidas.

Als 50 anys:

10.000 dones s'han de fer una Mx anyal, durant 10 anys, per salvar 37 vidas.

466-479 falsos +

500 anormals

10.000 Mx 21-34 verdaders +

9500 normals

Prevalença de cribatge. adults americans segons cobertura sanitaria any '04

	Nonelderly (<65 Years)						Elderly (Age ≥65 Years)	
	US Adults		Health Insurance		No Health Insurance		With Health Insurance	
	Prevalence (%)	95% CI	Prevalence (%)	95% CI	Prevalence (%)	95% CI	Prevalence (%)	95% CI
Colorectal cancer (adults ≥50 years)								
Either a flexible sigmoidoscopy or colonoscopy*	45.6	(45.1–46.1)	42.2	(41.5–43.0)	18.8	(17.4–20.4)	53.1	(52.4–54.0)
FOBT home kit†	19.0	(18.4–19.1)	16.5	(16.0–17.0)	9.3	(8.2–10.5)	22.6	(22.0–23.2)
FOBT or endoscopy‡	52.1	(51.6–52.6)	49.1	(48.4–49.8)	24.4	(22.8–26.2)	59.6	(58.9–60.3)
Breast cancer (women ≥40 years)								
Mammogram§	58.0	(57.5–58.5)	60.0	(59.4–60.7)	33.2	(31.3–35.1)	62.5	(61.6–63.4)
Mammogram and CBE¶	51.0	(50.4–51.4)	54.7	(54.0–55.4)	28.2	(26.4–30.1)	51.1	(50.1–52.0)
Cervical cancer (women ≥18 years)								
Pap test**	85.0	(84.4–85.1)	90.0	(89.2–90.1)	75.7	(74.3–77.0)	72.1	(71.0–73.2)
Prostate cancer (men ≥50 years)								
PSA††	54.0	(52.9–54.6)	50.0	(48.6–51.0)	25.7	(22.8–28.7)	62.4	(61.1–63.7)
DRE‡‡	50.5	(49.6–51.3)	49.0	(47.7–50.0)	23.0	(20.5–25.5)	57.0	(55.4–58.1)

Alteracions del PSA. Causas

- Malalties prostàtiques: Prostatitis, Hipertrofia Benigna i Càncer
- Activitat física
- Infeccions
- Fàrmacs: Finasteride (reducció dels nivells 50%)
- Manipulacions via urinària:
  - Cistoscòpia i biopsia prostàtica (3-4 st)
  - Ejaculació i TR no l'alteran significativament

probabilitat de càncer segons PSA i tacte rectal

Tacte rectal	PSA 0-2	PSA 2-4	PSA 4-10	PSA >10
normal	1%	15%	25%	>50%
anormal	5%	20%	45%	>75%

Catalona WJ, JAMA 1998, 279:1542-7

Screening

Quina es la probabilitat de que, si hi ha un càncer de pròstata, el test ho detecti ?

Sensibilitat: capacitat en detecció de malignitat.

Amb un PSA normal (≤ 4 ng/mL)

Sensibilitat 67.5-80%

20-30% de tumors no seràn diagnosticats

Quina es la probabilitat de que, si no hi ha un càncer de pròstata, el test ho descarti?

Especificitat: capacitat per a excloure benignitat.

Especificitat: 60-70% amb PSA > 4 ng/mL

Biologia del PSA. Mecanismes de millora

25% de pacients amb càncer de pròstata tenen un PSA normal (≤4ng/ml).

Un nivell de PSA anormal (>4ng/ml) correspon en un 66% de pacients a una patologia benigna.

- Punts de tall específics per edat.
- Densitat de PSA: Ajust a volum prostàtic
- Velocitat d'increment de PSA
- Isoformas de PSA (lliure/total)

Original Article

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., Anssi Auvinen, M.D., for the ERSPC Investigators

N Engl J Med
Volume 360(13):1320-1328
March 26, 2009

The NEW ENGLAND JOURNAL of MEDICINE

Mètodes

Objectiu primari: taxa de mort per càncer de pròstata

Randomitzacio variable:

Finlàndia, Suècia i Itàlia: abans del consentiment

Holanda,Bèlgica, Suissa i Espanya: després del consentiment

Població diana: homes 55-69 a. (inclusió variable segons pais)

Tall de PSA per indicació de biopsia: 3

Finlàndia: 4. Si 3-3.9: TR i ratio ≤ 0.16.

Itàlia: 4. Si 3-3.9:TR i Eco

Holanda i Bèlgica: TR+Eco+PSA 4 fins ’97. Després sols PSA

Mètodes

Biopsia:

Fins Juny'06: biopsies per sexants guiades per Eco. Després biopsies per sextants pero lateralitzades.

Finlàndia: 10-12 biopsies.

Itàlia: biopsies transperineals >'02

Intervals: 4 anys (a 6/7): 87% dels subjectes (Suècia: 2 a, Bèlgica: 7 a)

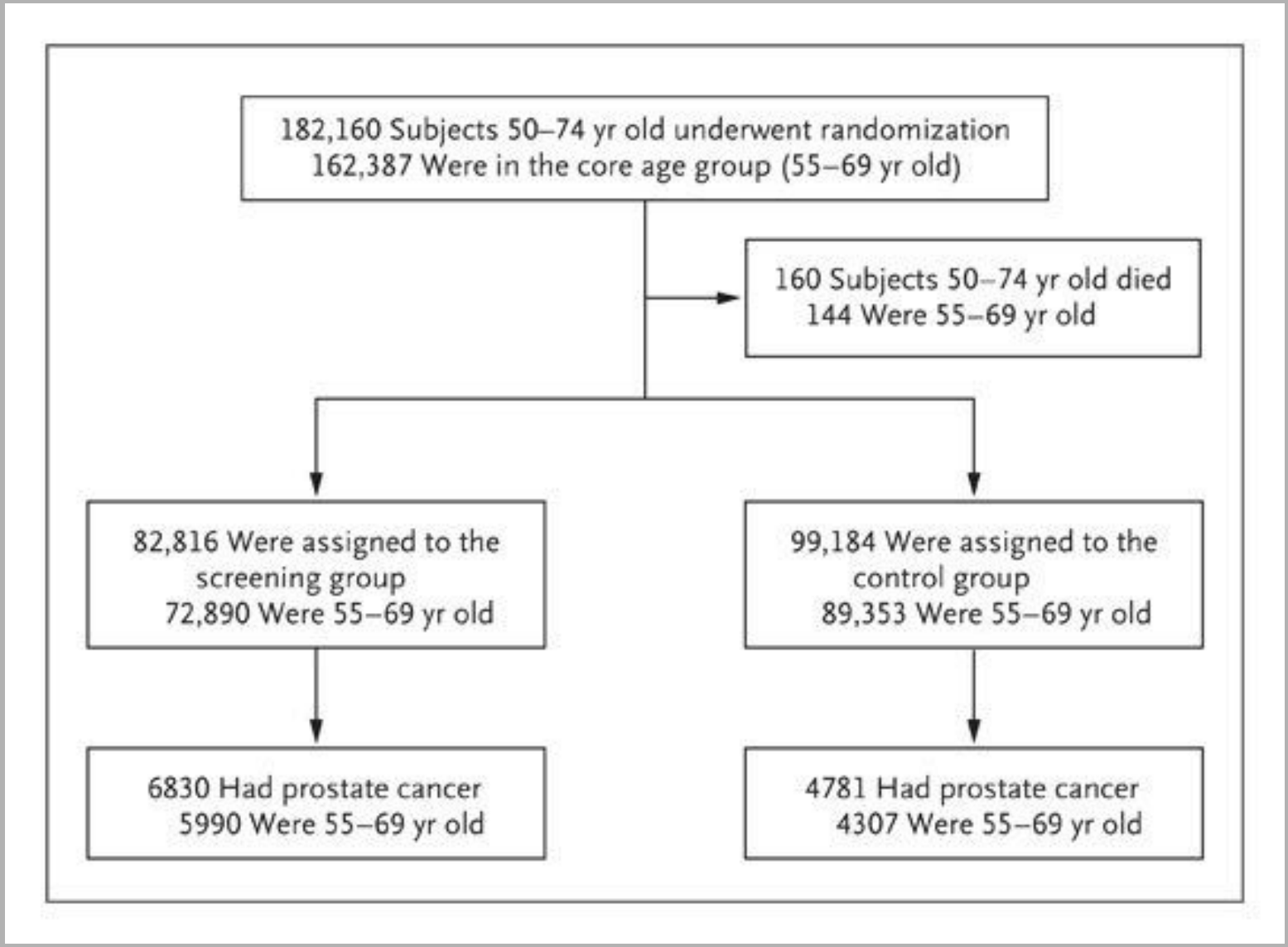
F-up: causa de mort avaluada a cec i classificades en un comité independent

Estadistica

- Potència d'un 86% per a demostrar una diferència de mortalitat del $\geq$ 25%

- Te en compte la no adherencia en el grup cribatge i la contaminació al grup control: presunció en el grup control d'una compliance del 82% i una contaminació del 20% i una reducció del 25% dels asignats a cribatge

Enrollment and Outcomes, According to Age Group at Randomization



Schroder FH et al. N Engl J Med 2009;360:1320-1328

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Numbers of Subjects and Results of Screening, According to Study Center

Table 1. Numbers of Subjects and Results of Screening, According to Study Center.*

Variable	The Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total
	November 1993–March 2000	June 1991–December 2003	June 1991–December 2003	January 1996–January 1999	October 1996–October 2000	February 1996–June 1999	September 1998–August 2003	June 1991–December 2003
Total no. of subjects	34,833	8562	11,852	80,379	14,517	2197	9903	162,243
Screening group — no. (%)	17,443 (50.1)	4307 (50.3)	5,901 (49.9)	31,970 (39.8)	7,265 (50.0)	1056 (48.1)	4948 (50.0)	72,890 (44.9)
Control group — no. (%)	17,390 (49.9)	4255 (49.7)	5,951 (50.1)	48,409 (60.2)	7,252 (50.0)	1141 (51.9)	4955 (50.0)	89,353 (55.1)
Age at randomization — yr								
All subjects								
Mean	61.9	63.0	59.8	59.6	62.2	61.0	61.6	60.8
Median	61.7	63.0	59.7	58.7	61.8	60.4	61.1	60.1
Screening group								
Mean	61.9	63.0	59.8	59.6	62.2	60.5	61.6	60.9
Median	61.7	63.0	59.7	58.7	61.7	59.7	61.0	60.3
Control group								
Mean	62.0	63.0	59.8	59.6	62.2	61.4	61.7	60.7
Median	61.7	63.1	59.7	58.7	61.9	61.1	61.2	59.9
First round of screening — no. (%)	16,502 (94.6)	3795 (88.1)	3,649 (61.8)	20,796 (65.0)	4,961 (68.3)	1056 (100)	4721 (95.4)	55,480 (76.1)
Screening interval — yr	4	4–7	2	4	4	4	4	NA
Screened at least once — no. (%)	16,502 (94.6)	3876 (90.0)	4,466 (75.7)	23,608 (73.8)	5,675 (78.1)	1056 (100)	4740 (95.8)	59,923 (82.2)
No. of screening tests performed	34,526	6042	14,848	48,900	11,377	1846	8923	126,462
Positive PSA tests — no. (%)	7,707 (22.3)	984 (16.3)	2,751 (18.5)	5,528 (11.3)	1,267 (11.1)	354 (19.2)	1846 (20.7)	20,437 (16.2)
Biopsies — no. (%)	6,929 (89.9)	728 (74.0)	2,382 (86.6)	4,991 (90.3)	828 (65.4)	263 (74.3)	1422 (77.0)	17,543 (85.8)
Prostate cancers								
Total detected in screening group — no. (%)	1,736 (10.0)	363 (8.4)	697 (11.8)	2,493 (7.8)	280 (3.9)	68 (6.4)	353 (7.1)	5,990 (8.2)
Detected during screening — no.	1,521	182	550	1,477	180	60	265	4,235
Detected outside of screening protocol — no.	215	181	147	1,016	100	8	88	1,755
Positive predictive value of screening — %†	22.0	25.0	23.1	29.6	21.7	22.8	18.6	24.1
Total detected in control group — no. (%)	685 (3.9)	252 (5.9)	421 (7.1)	2,632 (5.4)	133 (1.8)	24 (2.1)	160 (3.2)	4,307 (4.8)

* The results are for the predefined core age group for this study, which included men between the ages of 55 and 69 years. The dates that are listed for each country are the periods in which subjects underwent randomization. NA denotes not applicable, and PSA prostate-specific antigen.

† The positive predictive value of biopsy was calculated as the number of screen-detected cancers divided by the number of biopsies.

Resultats (1)

- Nombre total de homes de poblacio diana randomitzats: 162.387
- Anys inclusió: juny'91-set'98 fins des'03-des'03
- Edat mitjana: 60.8 a
- 82.2% cribats com a minim un cop
- Compliance millor si consentiment abans de random (88-100 vs 62-68%)
- Mitja de 2.1 PSA per home
- PSA positius: 16.2%
- Compliance amb recomanacions de biopsia: 85.8%
- Falsos "positius" de la biopsia: 75.9%

Resultats (2)

- 5990 càncers al grup de cribatge i 4307 al grup control: 8.2 vs 4.8%
- Valor predictiu positiu de la biopsia: 24% (nombre de cancers al cribatge dividit per nombre de biopsies)
- Malaltia localitzada: 0.23‰ vs 0.39‰ ($p<.001$)
- Gleason ≥ 7: 27.8 vs 45.2%

Resultats (3)

- Ratio de mort per cancer de prostata:

  0.80 (0.67-0.95): p 0.01

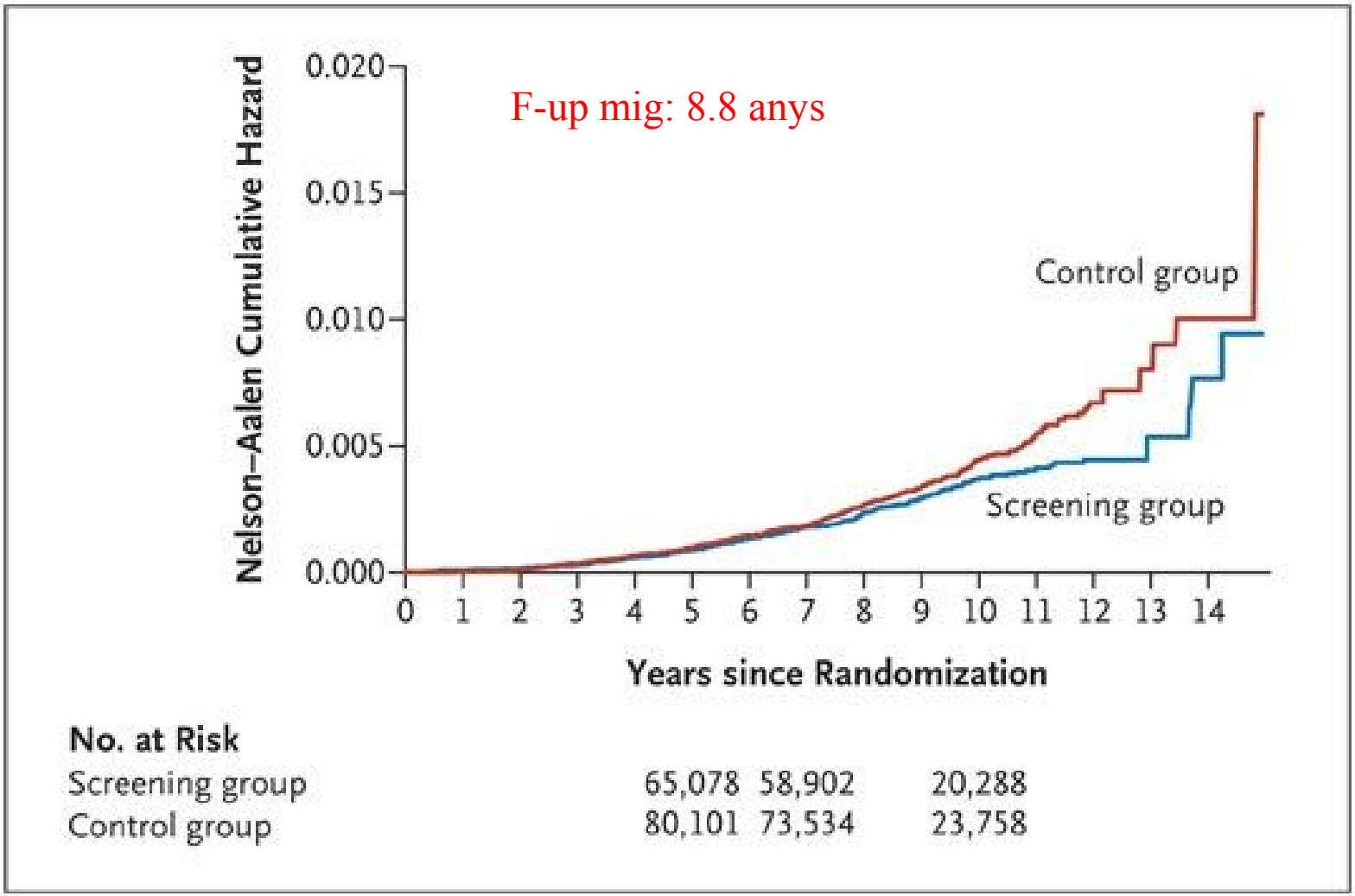
- Anàlisi per intenció de cribatge. Diferència absoluta cribat vs control:

  0.71‰ morts per CP

  total d'homes cribats per a prevenir una mort per CP: 1410, amb un global de 1.7 visites per home durant 9 anys

  augment de incidencia de CP del 34 ‰ al grup cribat. Per cada CP diagnosticat n'hem de tractar 48 per prevenir-ne una mort

Cumulative Risk of Death from Prostate Cancer



Schroder FH et al. N Engl J Med 2009;360:1320-1328

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Death from Prostate Cancer, According to the Age at Randomization

Table 2. Death from Prostate Cancer, According to the Age at Randomization.*

Age at Randomization	Screening Group		Control Group		Rate Ratio (95% CI)†
	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	
All subjects	261	737,397 (0.35)	363	878,547 (0.41)	0.85 (0.73–1.00)
Age group					
50–54 yr	6	55,241 (0.11)	4	53,734 (0.07)	1.47 (0.41–5.19)
55–59 yr	60	316,389 (0.19)	102	402,062 (0.25)	0.73 (0.53–1.00)
60–64 yr	76	191,542 (0.40)	95	221,113 (0.43)	0.94 (0.69–1.27)
65–69 yr	78	135,470 (0.58)	129	162,410 (0.79)	0.74 (0.56–0.99)
70–74 yr	41	38,755 (1.06)	33	39,228 (0.84)	1.26 (0.80–1.99)

* The result of the chi-square test for heterogeneity among subjects in the core age group (55 to 69 years) was 2.44 (P=0.49).
† Rate ratios were calculated with the use of Poisson regression and compare the rate of death from prostate cancer in the screening group with the rate in the control group.

Schroder FH et al. N Engl J Med 2009;360:1320-1328

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Study Overview

- In this trial, investigators tested the effect of prostate-specific-antigen testing on the death rate from prostate cancer in more than 162,000 men between the ages of 55 and 69 years in seven European countries
- A significant reduction in prostate-cancer mortality was found after a median follow-up of 9 years
- Overdiagnosis and overtreatment were important limitations of the screening program
- PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis (que s'estima es del 50% al grup cribat)

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Original Article

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb, III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., Christine D. Berg, M.D., for the PLCO Project Team

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The NEW ENGLAND JOURNAL of MEDICINE

Mètodes

- Homes 55-74 anys
- Periode d'inclusió: '93-'01
- 10 centres als US
- Criteris exclusió: cancer previ i > 1 PSA als 3 anys previs

- Grup de cribatge: PSA anyal x 6 i TR anyal x 4
- Tall de PSA: > 4

- 44% ambdos grups tenien ≥1 PSA

Mètodes

- End point primari: Mortalitat per CP (dins del PLCO)
- Previsio de contaminacio del 20%
- Aval.luació semestral de dades:
  - Nov'08: decisio de aturar l'estudi per manca persistent de diferencies de mortalitat junt a informacio de prejudici al grup cribat

Characteristics of the Subjects at Baseline

Table 1. Characteristics of the Subjects at Baseline.*

Variable	Screening Group (N=38,343)	Control Group (N=38,350)
	percent	
Age		
55–59 yr	32.3	32.3
60–64 yr	31.3	31.3
65–69 yr	23.2	23.2
70–74 yr	13.2	13.2
Race or ethnic group†		
Non-Hispanic white	86.2	83.8
Non-Hispanic black	4.5	4.3
Hispanic	2.1	2.1
Asian	4.0	3.9
Other	0.8	0.9
Missing data	2.4	5.0
Enlarged prostate or benign prostatic hyperplasia	21.4	20.5
Previous prostate biopsy	4.3	4.3
Family history of prostate cancer	7.1	6.7
PSA test within past 3 yr		
Once	34.6	34.3
Two or more times	9.4	9.8
Digital rectal examination within past 3 yr		
Once	32.8	31.9
Two or more times	22.2	22.0

* PSA denotes prostate-specific antigen.
† Race or ethnic group was self-reported.

Resultats (1)

- Mitjana de f-up: 11.5 anys
- Cumpliment grup cribatge: 85% PSA i 86% TR
- Contaminació grup control: desde 40% PSA 1er any fins 52% al sisé

- Als 7 anys: ratio càncer cribatge/control: 1.22 (1.16-1.29)
- Als 10 anys: 1.17 (1.1-1.22)

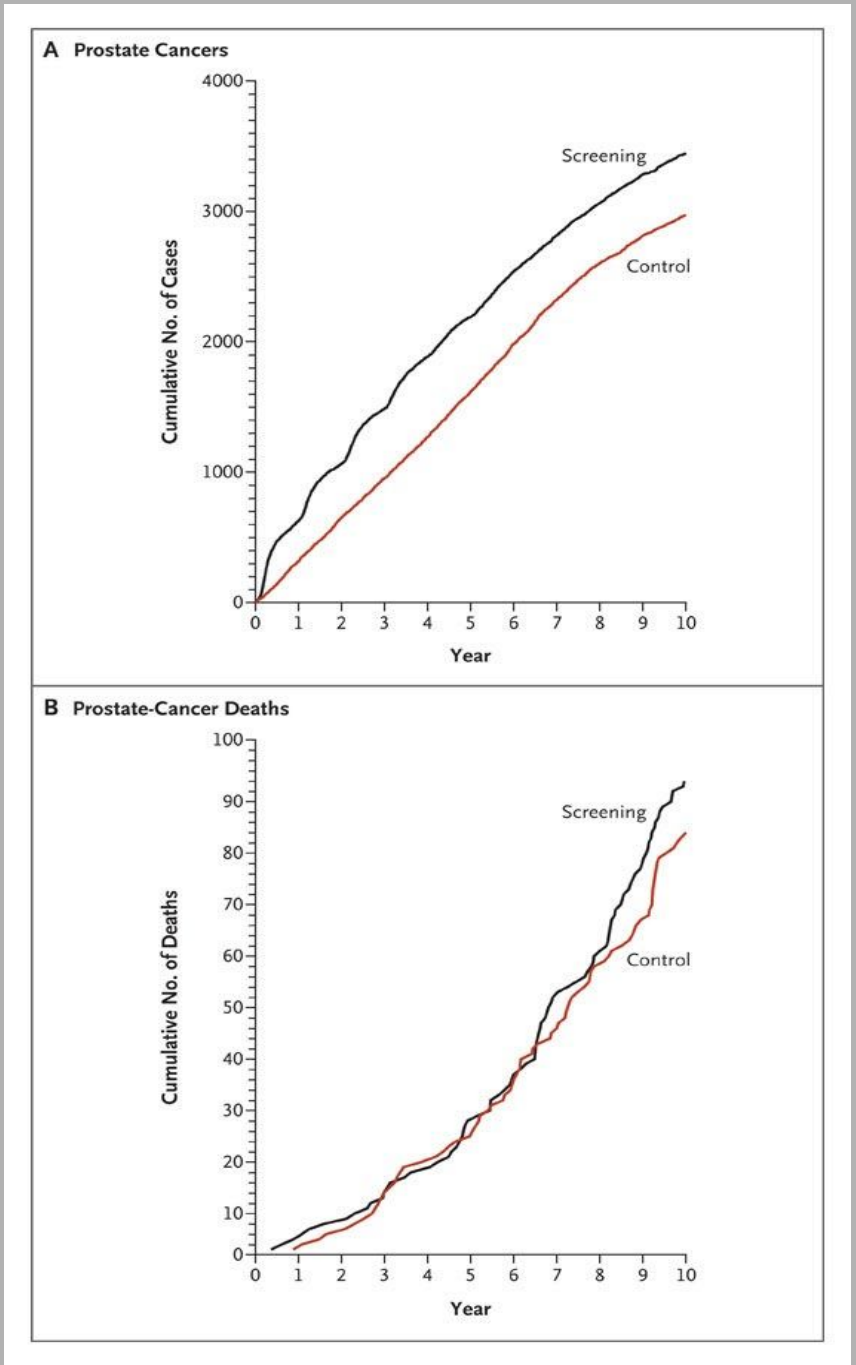
Resultats (2)

- Estadis avançats (III i IV): similar ambdos grups
- Gleason >7: 289 vs 341

- Riscs al grup cribat: sobretot en relacio amb procediments terapeutics

- Ratio mortalitat per CP:
  - Als 7 a 1.13 (0.75-1.7)
  - Als 10 a: 1.11 (0.8-1.5)

Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B)



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Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis

Table 2. Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis.*

Variable	Screening Group						Control Group
	According to Method of Detection					All Subjects (N=3452)	All Subjects (N=2974)
	Never Screened (N=154)	*After Screening (N=875)*	*Outside of Screening Protocol (N=374)*	*Screen Detected at Baseline (N=549)*	*Screen Detected at Yr 1–Yr 5 (N=1500)*		
	number (percent)						
Clinical stage							
I	1 (0.6)	5 (0.6)	8 (2.1)	2 (0.4)	2 (0.1)	18 (0.5)	15 (0.5)
II	138 (89.6)	838 (95.8)	347 (92.8)	516 (94.0)	1458 (97.2)	3297 (95.5)	2790 (93.8)
III	5 (3.2)	7 (0.8)	3 (0.8)	12 (2.2)	22 (1.5)	49 (1.4)	56 (1.9)
IV	10 (6.5)	20 (2.3)	9 (2.4)	19 (3.5)	15 (1.0)	73 (2.1)	79 (2.7)
Unknown	0	5 (0.6)	7 (1.9)	0	3 (0.2)	15 (0.4)	34 (1.1)
Histopathological type							
Adenocarcinoma							
Any	144 (93.5)	824 (94.2)	346 (92.5)	511 (93.1)	1375 (91.7)	3200 (92.7)	2802 (94.2)
Acinar	9 (5.8)	48 (5.5)	25 (6.7)	36 (6.6)	124 (8.3)	242 (7.0)	158 (5.3)
Other	1 (0.6)	3 (0.3)	3 (0.8)	2 (0.4)	1 (0.1)	10 (0.3)	14 (0.5)
Gleason score on biopsy†							
2–4	11 (7.1)	1.7 (1.9)	36 (9.6)	64 (11.7)	94 (6.3)	222 (6.4)	137 (4.6)
5–6	78 (50.6)	500 (57.1)	228 (61.0)	278 (50.6)	963 (64.2)	2047 (59.3)	1656 (55.7)
7	39 (25.3)	252 (28.8)	74 (19.8)	132 (24.0)	318 (21.2)	815 (23.6)	779 (26.2)
8–10	16 (10.4)	95 (10.9)	25 (6.7)	55 (10.0)	98 (6.5)	289 (8.4)	341 (11.5)
Unknown	10 (6.5)	11 (1.3)	11 (2.9)	20 (3.6)	27 (1.8)	79 (2.3)	61 (2.1)

* Subjects with available data for tumor staging but not for nodal status or the presence or absence of metastasis were classified as having stage II disease. Percentages may not total 100 because of rounding.

† The Gleason score ranges from 2 to 10, with higher scores indicating more aggressive disease.

Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years

Table 3. Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years. *

Variable	Years after Randomization									
	1	2	3	4	5	6	7	8	9	10
Screening group										
Cumulative deaths — no.	3	6	12	16	26	35	50	59	76	92
Cumulative person-yr — no.	37,864	75,292	112,234	148,635	184,490	219,752	254,295	287,196	316,244	340,230
Death rate	0.8	0.8	1.1	1.1	1.4	1.6	2.0	2.1	2.4	2.7
Control group										
Cumulative deaths — no.	1	4	12	18	23	34	44	56	65	82
Cumulative person-yr — no.	37,838	75,231	112,123	148,444	184,154	219,135	253,317	285,777	314,463	338,083
Death rate	0.3	0.5	1.1	1.2	1.2	1.6	1.7	2.0	2.1	2.4
Rate ratio (95% CI)	3.00 (0.31–28.82)	1.50 (0.42–5.31)	1.00 (0.45–2.22)	0.89 (0.45–1.74)	1.13 (0.64–1.98)	1.03 (0.64–1.65)	1.13 (0.75–1.70)	1.05 (0.73–1.51)	1.16 (0.83–1.62)	1.11 (0.83–1.50)

* Rate ratios are the rates of death in the screening group divided by those in the control group.

Andriole GL et al. N Engl J Med 2009;360:1310-1319

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Study Overview

- In this study involving nearly 77,000 men, investigators analyzed the effect of screening with prostate-specific-antigen testing and digital rectal examination on the rate of death from prostate cancer, as compared with usual care
- After a follow-up of 7 years, the death rates from prostate cancer did not differ significantly between the two study groups
- Data from the 10-year follow-up (which were 67% complete) also showed no significant difference in prostate-cancer mortality

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Reflexions (1)

Punt de tall de PSA < 4 (ex: ajustat a edat, ratio…)

Criteris heterogenis ERSPC

Contaminació estudi PLCO: PSA grup control 52% vs 85% al cribat

Curt periode de f-up (9-11 a)

Morbilitat: sobretractaments al 50% pacients ¡¡

Individualitzar tractaments: no tots s'han de tractar

No s'ha de fer mai si expectativa de vida < 10 a.

Consells diveregents

- En contra: US preventive task force,
- A favor: AUA PSA+TR >40 a, ACS >50 a (abans i afroam/antecfam), NCCN >40 a

Reflexions (2)

Trial	Incidence count (% of patients diagnosed with prostate cancer)		Mortality count (prostate cancer deaths per 10 000 person-years)	
	Screening group	Control group	Screening group	Control group
PLCO [19]	2820 (7.4)	2322 (6.1)	50 (2.0)	44 (1.7)
ERSPC [20••]	5990 (8.2)	4307 (4.8)	261 (3.5)	363 (4.1)

Per cada 1.000 homes cribats

Evitem la mort de 0.6/any