A comparison of the overdiagnosis estimates in prostate and cancer screening

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PERGAMON

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Prostate cancer screening: the problem of overdiagnosis and lessons to be learned from breast cancer screening

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Similarities

1. They are both frequent, lethal, socially relevant diseases.
2. They have a similar growth pattern, slow, usually progressing from local disease to distant metastases.
3. They are both curable with locoregional treatment, particularly in the initial stages.
4. They are often hormone-dependent and hormonal treatment may control progression for a long time

Differences

1. Their incidence is age-dependent but prostate cancer tends to affect **older subjects**, with a lower life expectancy and a lower potential benefit of screening (life years to be gained).
2. Compared with breast cancer, subjects with prostate cancer, even advanced, have a higher **probability of dying 'with' rather than 'of' cancer, from other concurrent causes of death in elderly males,** and the potential benefit of palliative treatment is higher compared with breast cancer. This may reduce the importance of early detection.
3. Clinical diagnosis of prostate cancer in the presence of symptoms occurs often at a very advanced stage. **Detection in the absence of symptoms implies a potential great diagnostic anticipation. This may allow more effective treatment, but also has negative effects (much earlier awareness of disease and exposure to treatment side-effects), which might possibly outweigh survival benefits**

Esserman L : Rethinking screening for breast cancer and prostate cancer *JAMA. 2009*

- Screening's Limited Effect on Mortality and Significant Effect on Incidence.

- Develop and Validate Biomarkers to Differentiate Significant- and Minimal-Risk Cancers.
- Reduce Treatment Burden for Minimal-Risk Disease

Effect on PC mortality of PSA Screening

The NEW ENGLAND JOURNAL of MEDICINE

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., and Anssi Auvinen, M.D., for the ERSPC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

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., and Christine D. Berg, M.D., for the PLCO Project Team*

Prostate cancer screening in the randomized PLCO Cancer Screening Trial: mortality results after 13 years of follow-up

Andriole et al JNCI 2012

- *76,693 randomized men*
- Annual PSA for 6 years
- Annual DRE for 4 years
- Cut off 4 ng/ml
- Assessment phase after a positive PSA committed to GP

Prostate cancer mortality after 13 yrs of follow up

- Study group =3.7*10000 py
- Control group =3.4*10000 py
- RR=1.09 (95%CI .9-1.4)

Andriole et al JNCI 2011

PLCO's limits

- 44% of enrolled subject have had a PSA before the start of the study

  ➔**low statistical power**

- More than 75% of the control group referred to have performed at least one PSA in the last 3 years (90% in the study group)

  (Pinsky et al Clinical Trials 2010)

  ➔ **high contamination**

- Less of 40% of PSA positive men performed a prostatic biopsy
- ➔ **low appropriatness**

Conclusion of PLCO

- “….After 13 years of follow-up, there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with opportunistic screening, which forms part of usual care …”

Andriole et al JNCI 2011

Screening for Prostate Cancer: A critical update from ERSPC at 11 years of follow-up

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., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Paula M. Kujala, M.D., Bert G. Blijenberg, Ph.D., Ulf-Hakan Stenman, M.D., Andreas Huber, M.D., Kimmo Taari, M.D.,Matti Hakama, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

Prostate cancer mortality Intention to screen analysis, FU ≥12 years

- Relative risk of PC death 0.79 (95%CI 0.68-0.91) p=0.001, a 21% reduction
- NNI (NNS): 936 NND (NNT): 33 (in excess of the control group)

Prostate cancer mortality
Adjustment for non compliance

- Results adjusted for non compliance relate to men who are actually screened
- RR of PC death is 0.71 (95% CI 0.58-0.86), a 29% relative mortality reduction (whole study period)
- Adjustment for contamination will be carried out

Excess Incidence /overdiagnosis

PLCO after 13 years of follow up
Incidence

- Cumulative incidence study group =108*10000 py
- Cuulative incidence control group =97*10000 py
- RR=1,12 (95%CI 0.97-1.17)

Observed and estimated Excess of incidence /Overdiagnosis .

Source **ERSPC** data *(scrhoder et al, 2009, 2012 , Heinsdijck, 2012)*

	9° year Observed	11° year Observed	**Model estimate**
Study Arm	8.2% (5990)	9.6% (6963)	**14.1%**
Control Arm	4.8% (4307)	6.0% (5396)	**11.2%**
Excess Incidence	**1.71%**	**1.59%**	**1.26%**
Overdiagnosis	?	?	**1.26%**

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Quality-of-Life Effects of Prostate-Specific Antigen Screening

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Overdiagnosed Cancers /lives gained .

Source ERSPC data (scrhoder et al,2009 2012 , Heinsdijck, 2012

	9° year Observed	11° year Observed	Model (End of life estimate)
ERSPC	48	33	7-5

Table 4. Predicted Effects of Prostate-Cancer Screening, as Compared with No Screening, at Various Ages over the Lifetime of 1000 Men.*

Variable	Age at Screening					
	55–69 Yr (Base Model)	55–74 Yr	55–69 Yr	55 Yr Only	60 Yr Only	65 Yr Only
Screening data						
Interval (yr)	1	1	4	NA	NA	NA
Screening tests (no.)	8242	10,577	2250	548	584	588
Men invited for screening (no.)	853	891	833	685	730	735
Men who underwent screening (no.)	845	883	777	548	584	588
Effects						
Cancers diagnosed (no.)	45	73	29	3	9	19
Cancers detected on screening (no.)	104	150	70	8	23	42
Overdiagnosed cancers (no.)	45	72	29	2	8	19
Rate of overdiagnosis in cancers detected on screening (%)	43	48	41	30	35	45
Negative biopsies (no.)	247	372	166	18	52	102
Prostate-cancer deaths (no.)	−9	−11	−6	−1	−2	−3
Relative reduction in prostate-cancer mortality (%)†	37	41	32	27	29	31
Lead-time (yr)	1134	1508	750	106	262	419
Life-yr gained (no.)	73	82	52	12	22	25
QALYs gained (no.)	56	56	41	12	19	17
Relative reduction in life-yr gained after adjustment for quality of life (%)	23	32	21	6	15	33
Men who would need to be screened to prevent one prostate-cancer death (no.)	98	84	129	490	249	186
Cancers that would need to be detected to prevent one prostate-cancer death (no.)	5	7	5	2	4	6

Comparison between breast and prostate screening

* The value of overdiagnosis of uk Indipendent Review is reported in a comparable way with other figures

	EUROSCREEN Working Group (2012)	**UK Independent Review, 2012**	Prostate (NEJM 2012)
Reduction in specific mortality	-25% -31%	- 20%	- 21%
Overdiagnosis	+ 6%	+11% *	+26% (+59%)
Overdiagnosed cancer * 1 life saved	0.6	3	5-7 (33)

Side effects of PC treatment

Complication of Radical Prostatectomy

Table 16: Complications of RP

Complication	Incidence (%)
Perioperative death	0.0-2.1
Major bleeding	1.0-11.5
Rectal injury	0.0-5.4
Deep venous thrombosis	0.0-8.3
Pulmonary embolism	0.8-7.7
Lymphocoele	1.0-3.0
Urine leak, fistula	0.3-15.4
Slight stress incontinence	4.0-50.0
Severe stress incontinence	0.0-15.4
Impotence	29.0-100.0
Bladder neck obstruction	0.5-14.6
Ureteral obstruction	0.0-0.7
Urethral stricture	2.0-9.0

Guidelines on Prostate Cancer- European Association Urology

In comparison with Breast cancer Screening Prostate screening has:

- The same reduction in mortality
- A higher overdiagnosis
- Higher side effects of over treatment

Challenges for the future

- To reduce overdiagnosis
- To disentangle overdiagnosis from over treatment (➔ Active Surveillance)