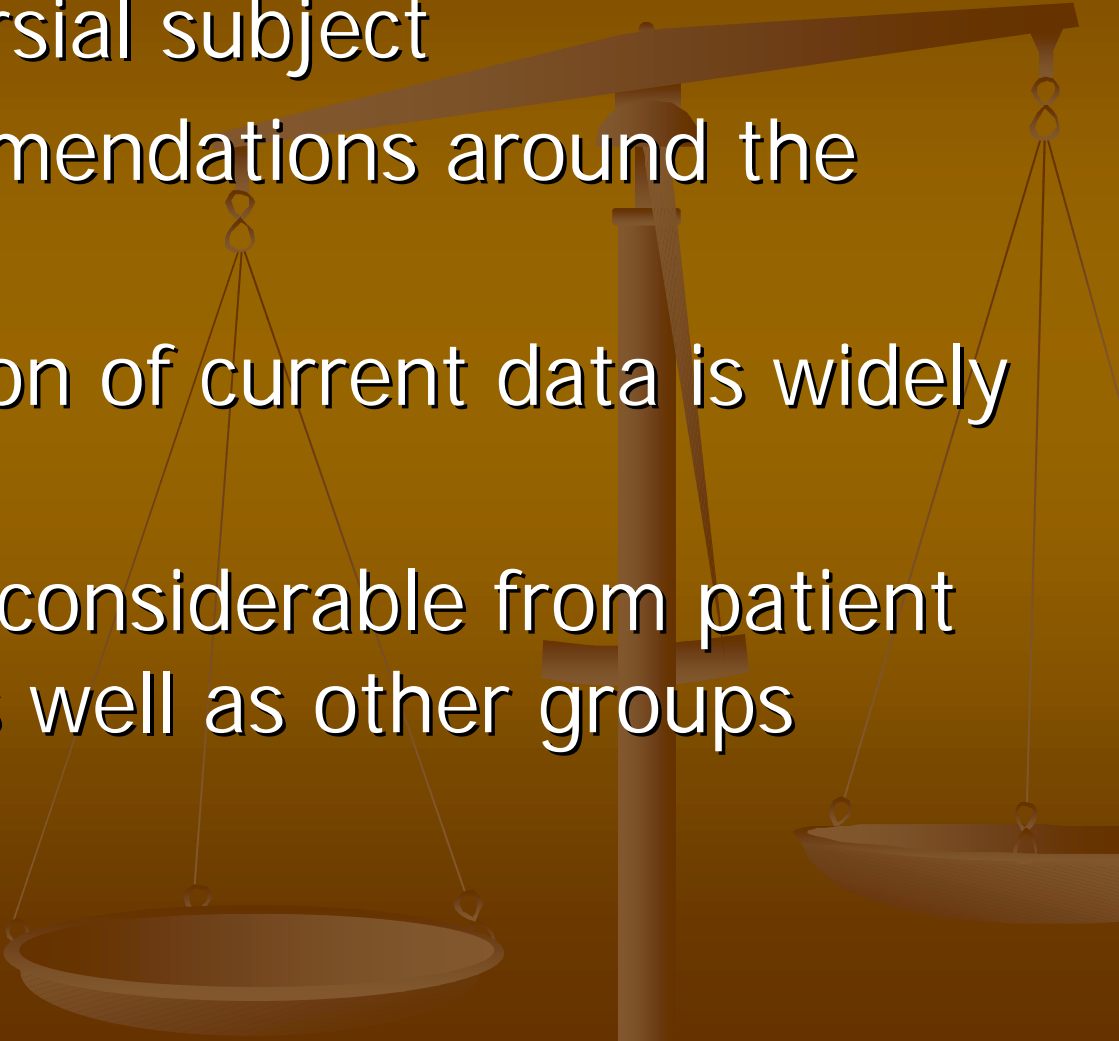




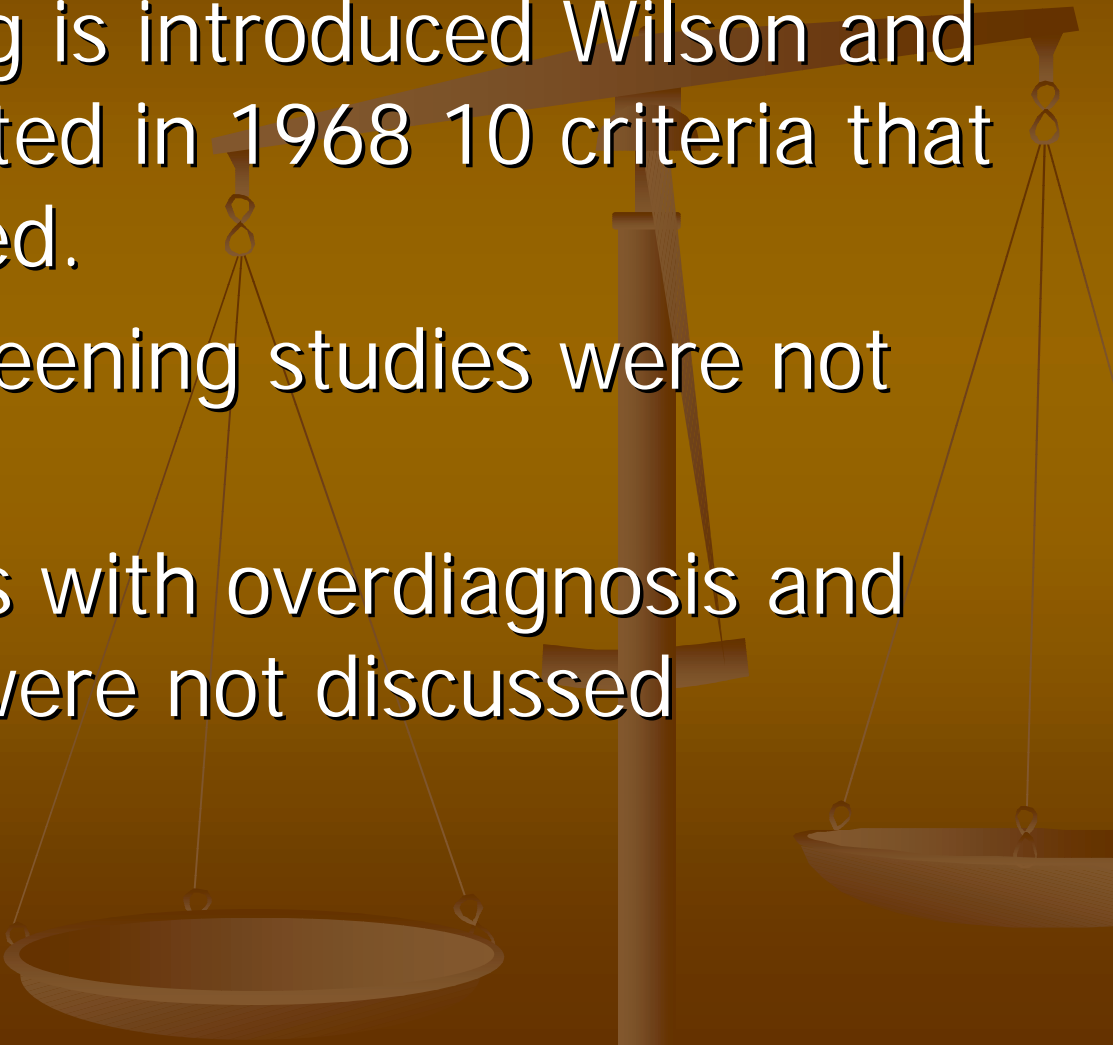
# Screening for prostate cancer

Jonas Hugosson  
Department of Urology  
Sahlgrenska Academy, Göteborg University  
Göteborg, Sweden

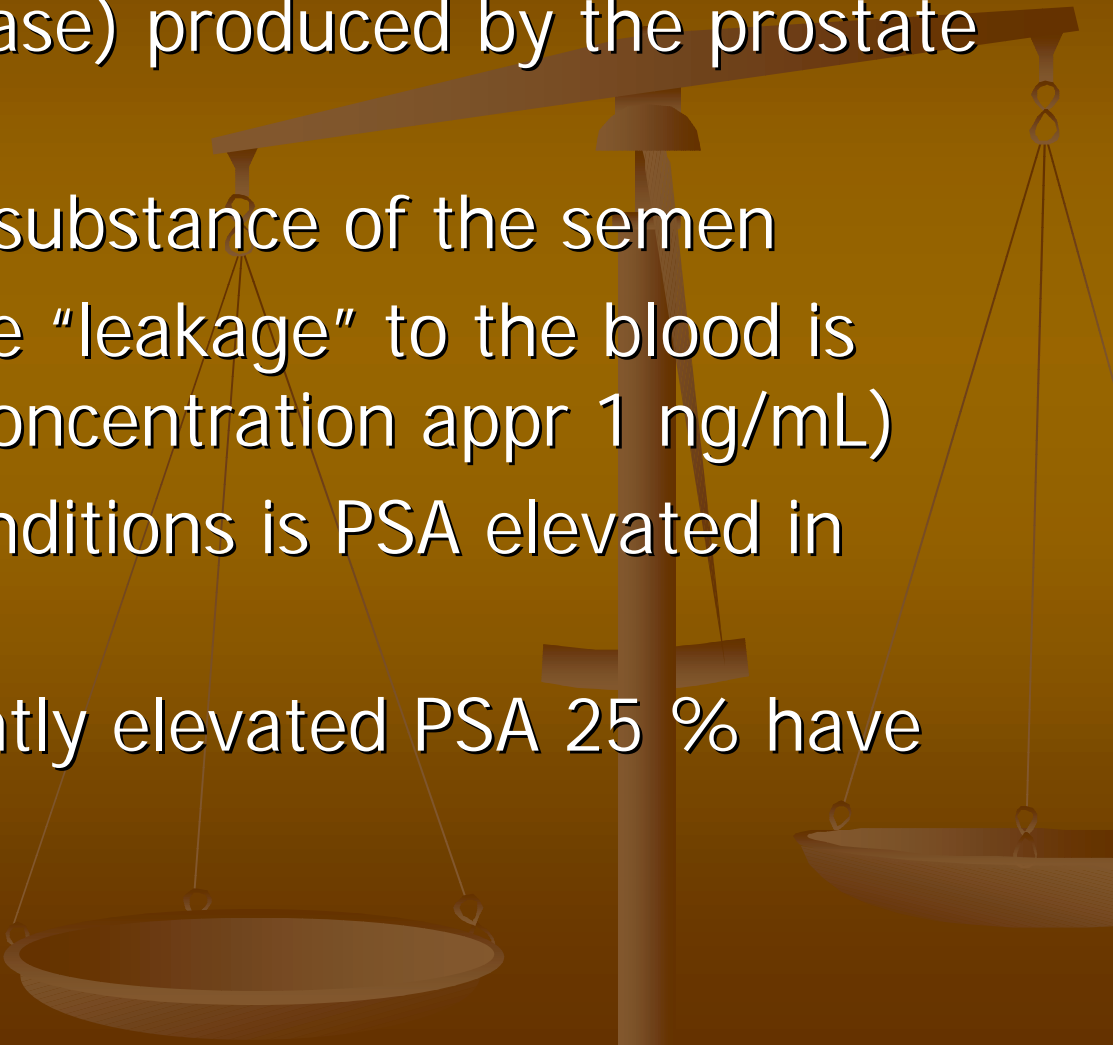
# Background

- Highly controversial subject
  - Different recommendations around the world
  - The interpretation of current data is widely disparate
  - The pressure is considerable from patient organizations as well as other groups
- 

# Current knowledge and how looks future

- Before screening is introduced Wilson and Jungner suggested in 1968 10 criteria that should be fulfilled.
  - Randomized screening studies were not one criteria
  - Ethical problems with overdiagnosis and overtreatment were not discussed
- 

# Prostate-specific Antigen (PSA)

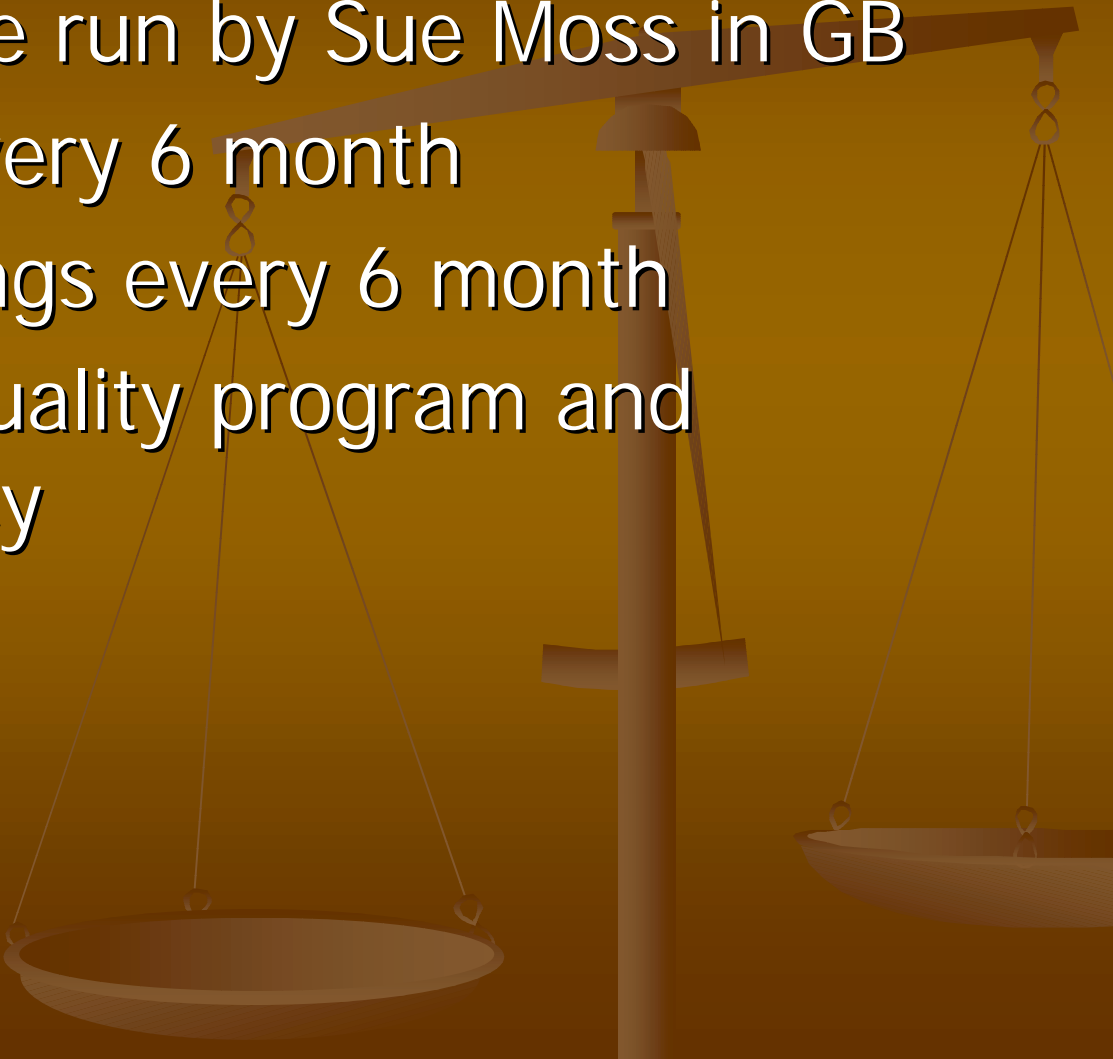
- An enzyme (protease) produced by the prostate gland
  - It is an important substance of the semen
  - In healthy men the “leakage” to the blood is very low (serum concentration appr 1 ng/mL)
  - In pathological conditions is PSA elevated in blood
  - Of those with slightly elevated PSA 25 % have prostate cancer
- 

**Table 7. Key characteristics of the study protocols in the ERSPC and PLCO trials.**

	ERSPC								PLCO
	Finland	Netherlands	Sweden	Belgium	Italy	Spain	Switzerland	France	
Age at entry	55/59/63/67	55-74	51-66	55-74	55-70	45-70	55-70	55-69	55-74
Screening interval	4	4	2	7	4	4	4	2	1
Recruitment	Population-based	Volunteers	Population-based	Volunteers	Population-based	Volunteers	Population-based	Population-based	Volunteers
Randomization	Before consent	After consent	Before consent	After consent	Before consent	After consent	After consent	Before consent	After consent
Target sample size*	80,000	42,000	20,000	10,000	15,000	4,300	10,000	101,000	74,000
PSA threshold ( $\mu\text{g/l}$ ) <sup>†</sup>	4.0	3.0	2.54	3.0	4.0	3.0	3.0	3.0	4.0
Supplemental screening criteria <sup>‡</sup>	%FPSA	-	-	DRE	DRE/ TRUS	%FPSA	%FPSA	-	DRE

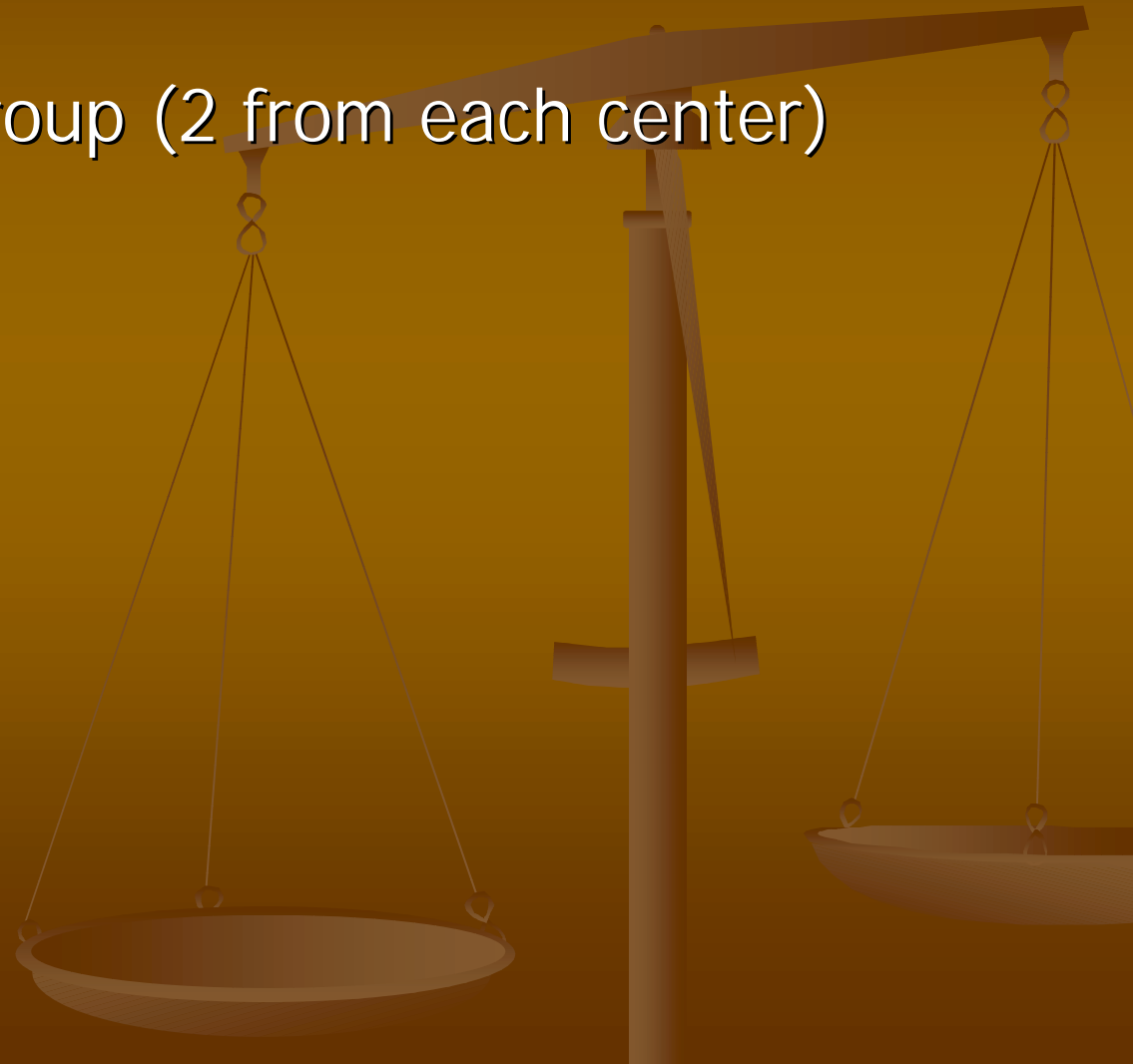
\* Crude. <sup>†</sup>, <sup>‡</sup> Current protocol.

# Organization of ERSPC

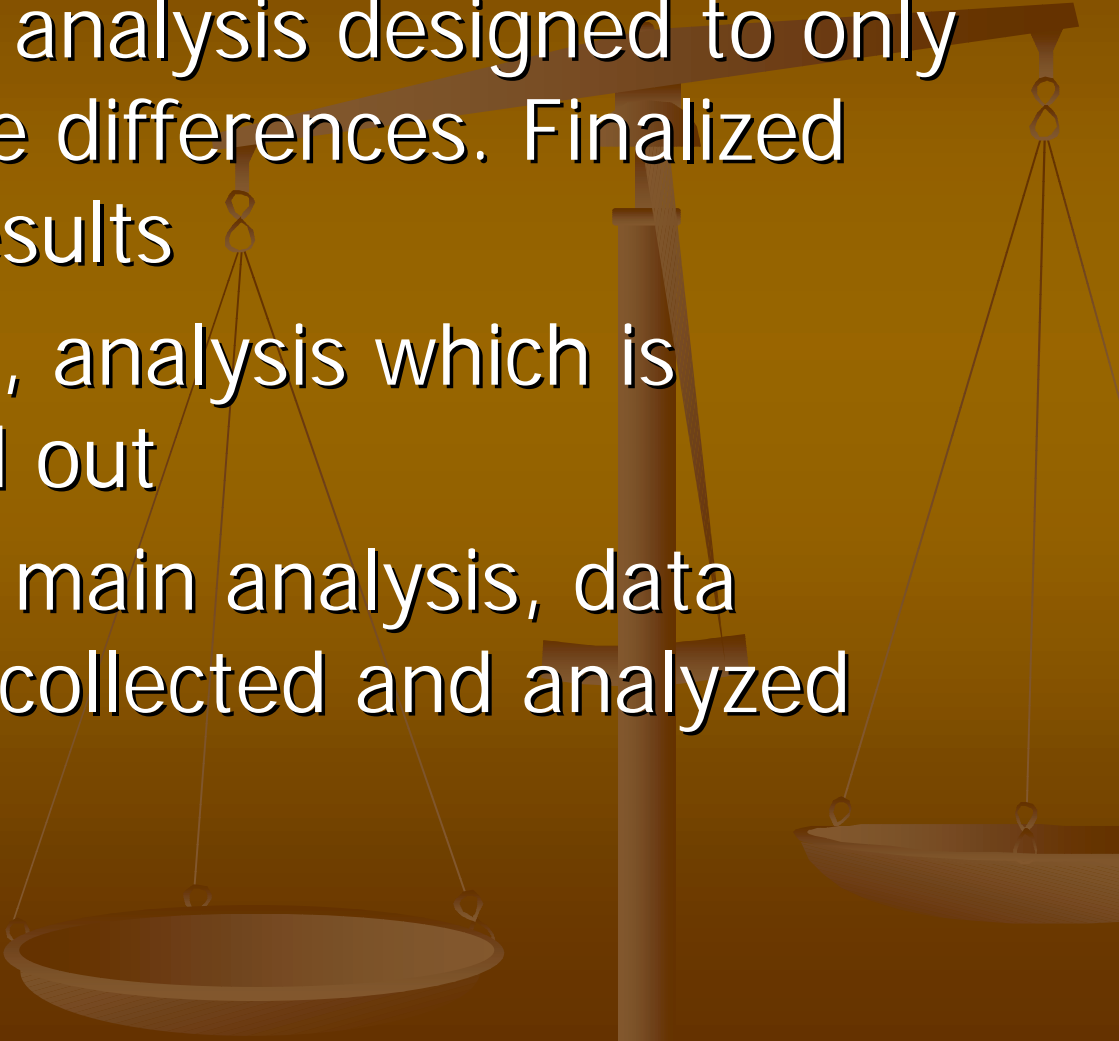
- Central database run by Sue Moss in GB
  - Data delivery every 6 month
  - Scientific meetings every 6 month
  - Agreement of quality program and publication policy
- 

# Organization of ERSPC, committees

- Scientific
- Voting member group (2 from each center)
- DMC
- Epidemiology
- Quality control
- PSA
- Pathological
- Causes of death
- PR

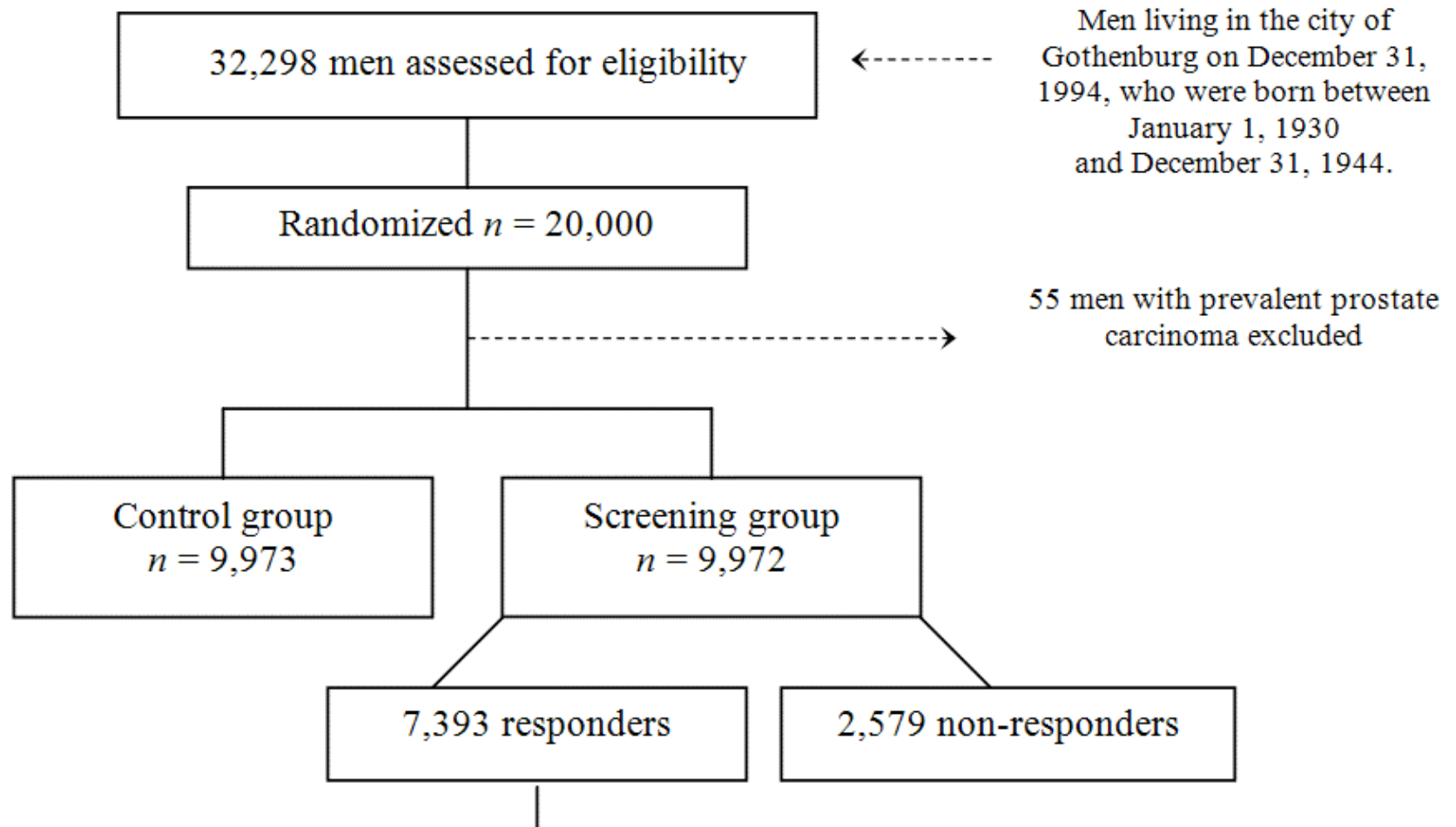


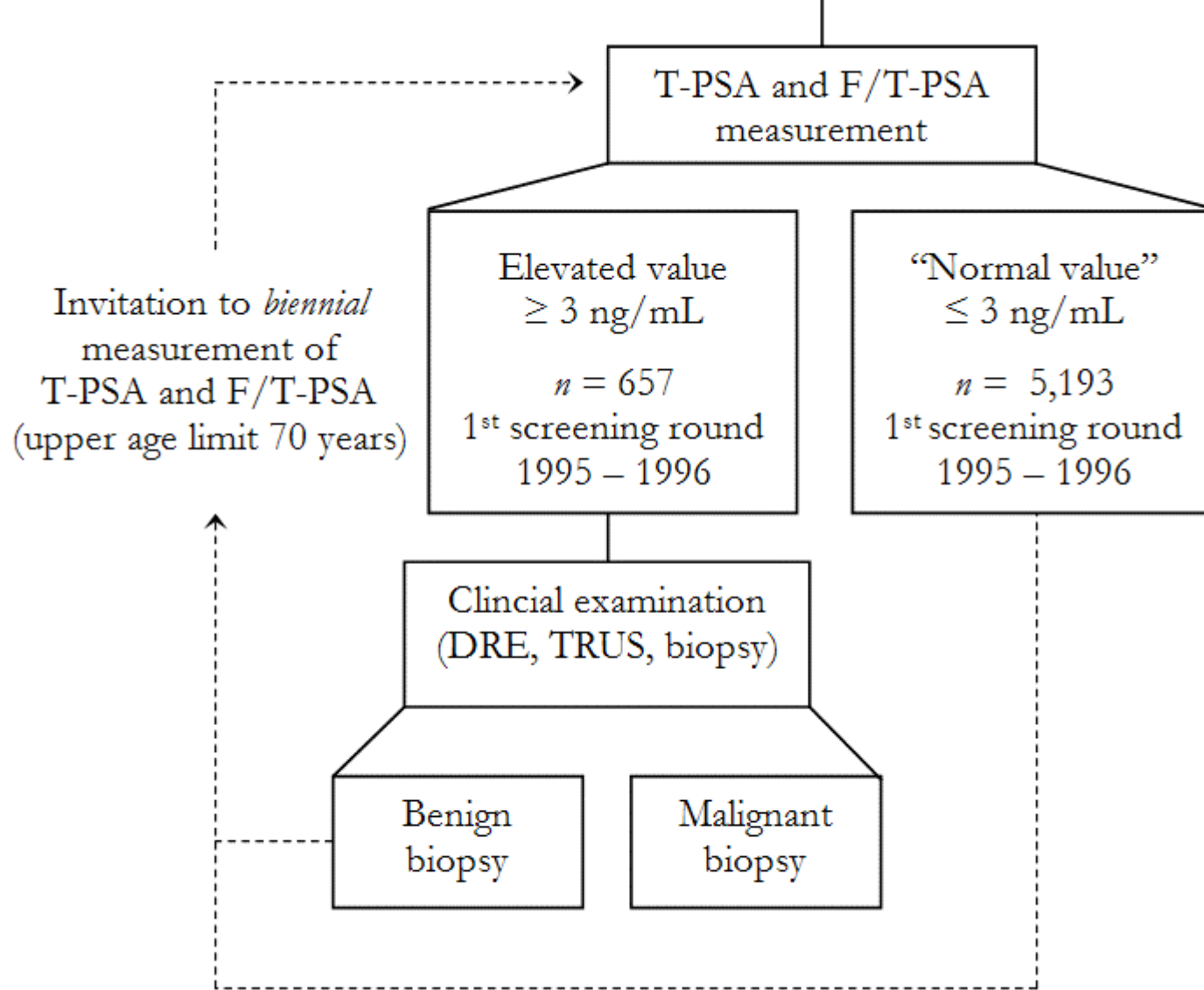
# Evaluation plan (Auvinen J med Screen 1996)

- 2004 year data, analysis designed to only detect very large differences. Finalized with negative results
  - 2006 years data, analysis which is currently carried out
  - 2008 year data, main analysis, data supposed to be collected and analyzed 2009-2010
- 

# Consort diagram

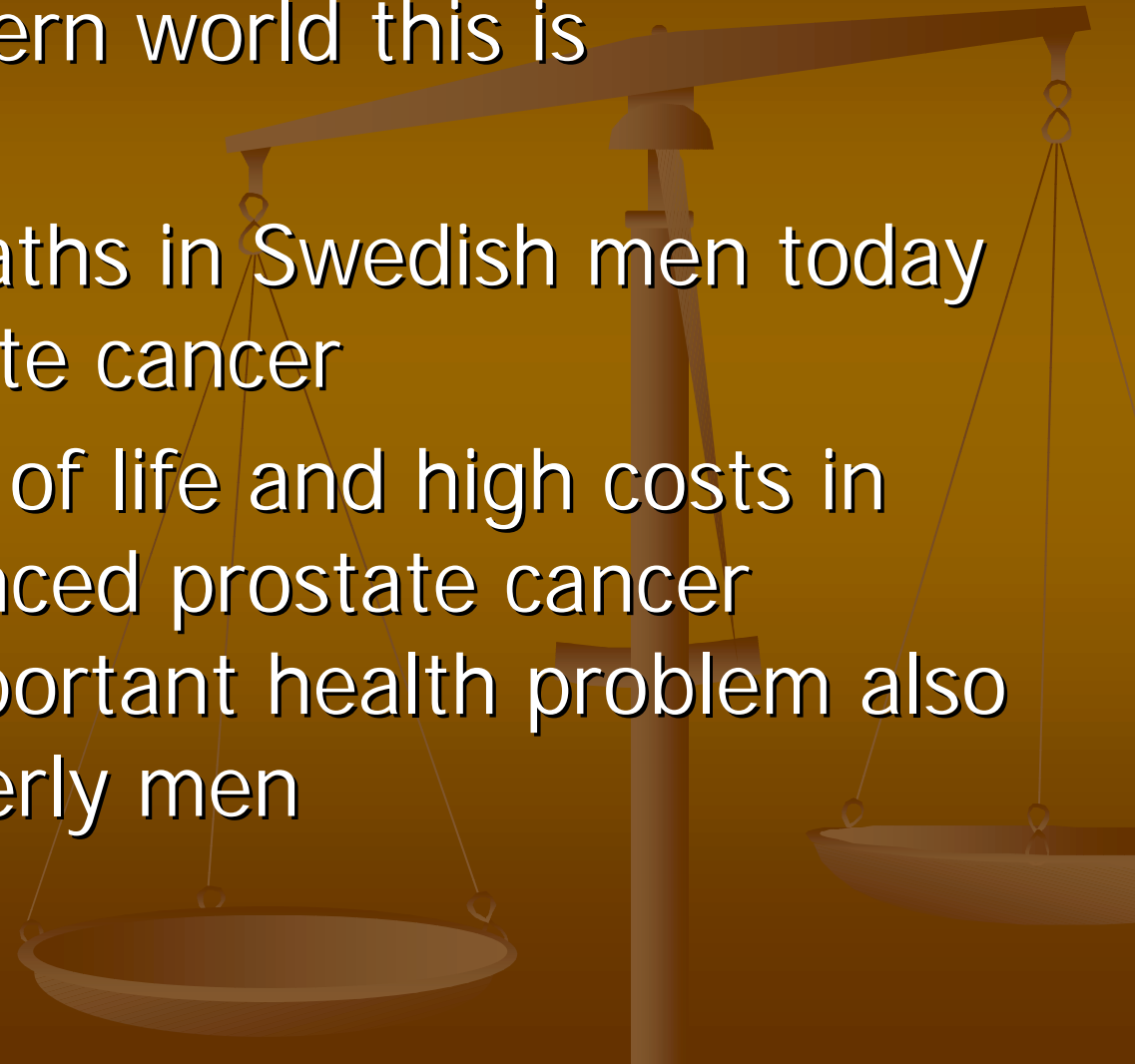
## Screening in Göteborg (1995 – 2008)



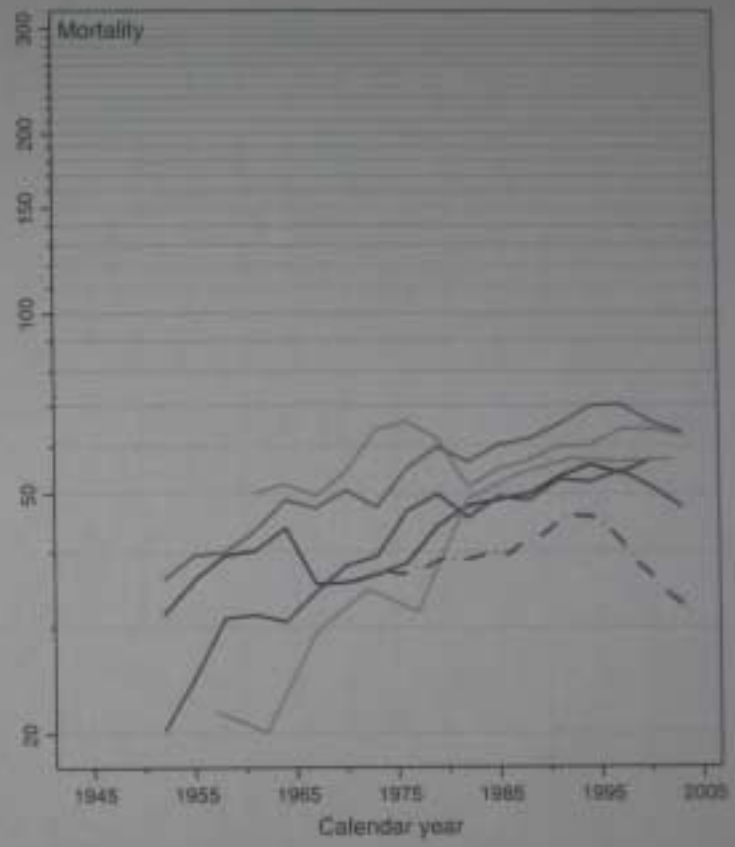
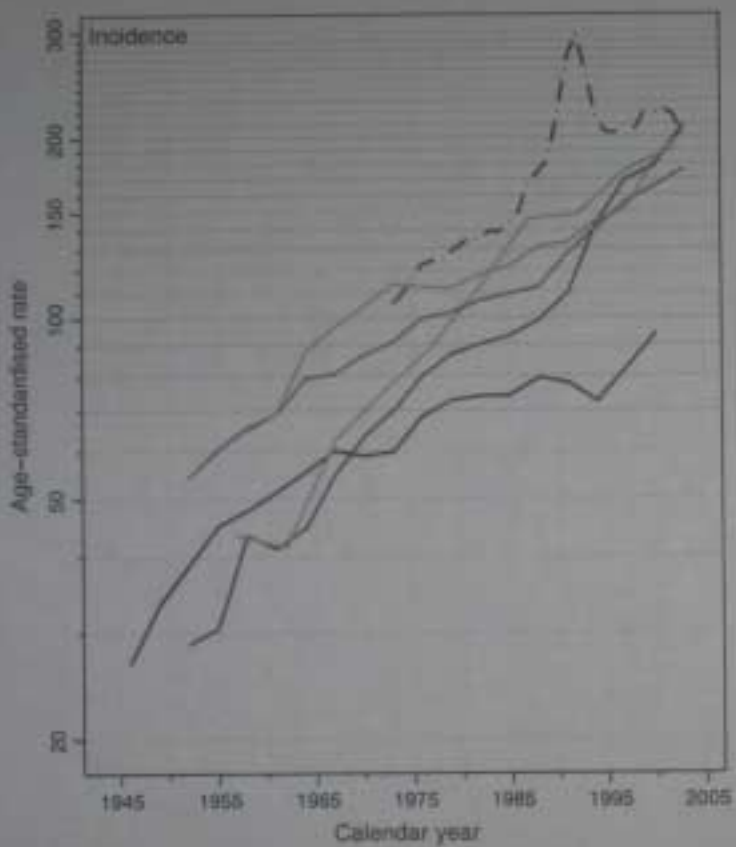


# The condition should be an important health problem (criteria 1)

- At least in western world this is indisputable
- 5-6 % of all deaths in Swedish men today is due to prostate cancer
- The low quality of life and high costs in men with advanced prostate cancer render it an important health problem also in the most elderly men



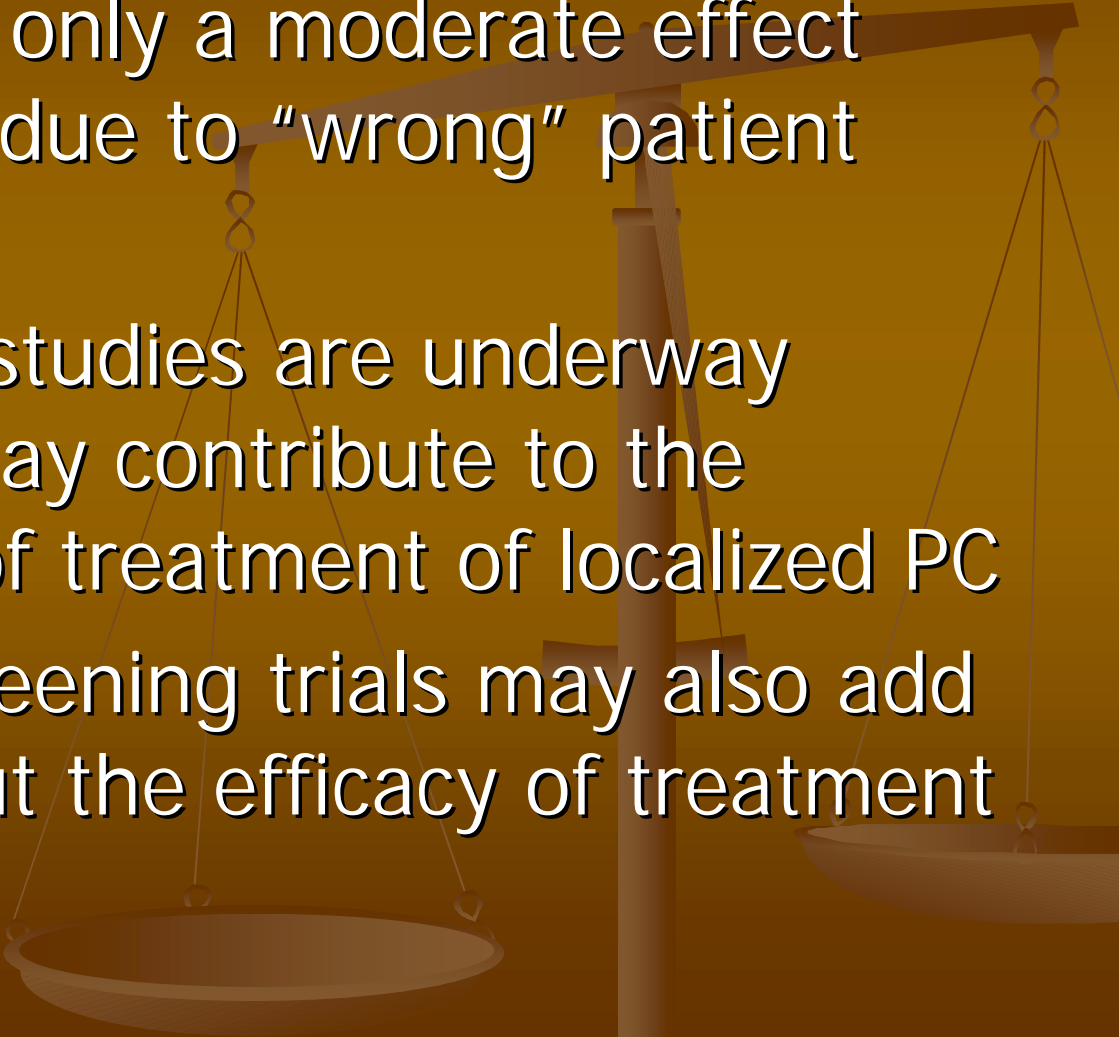




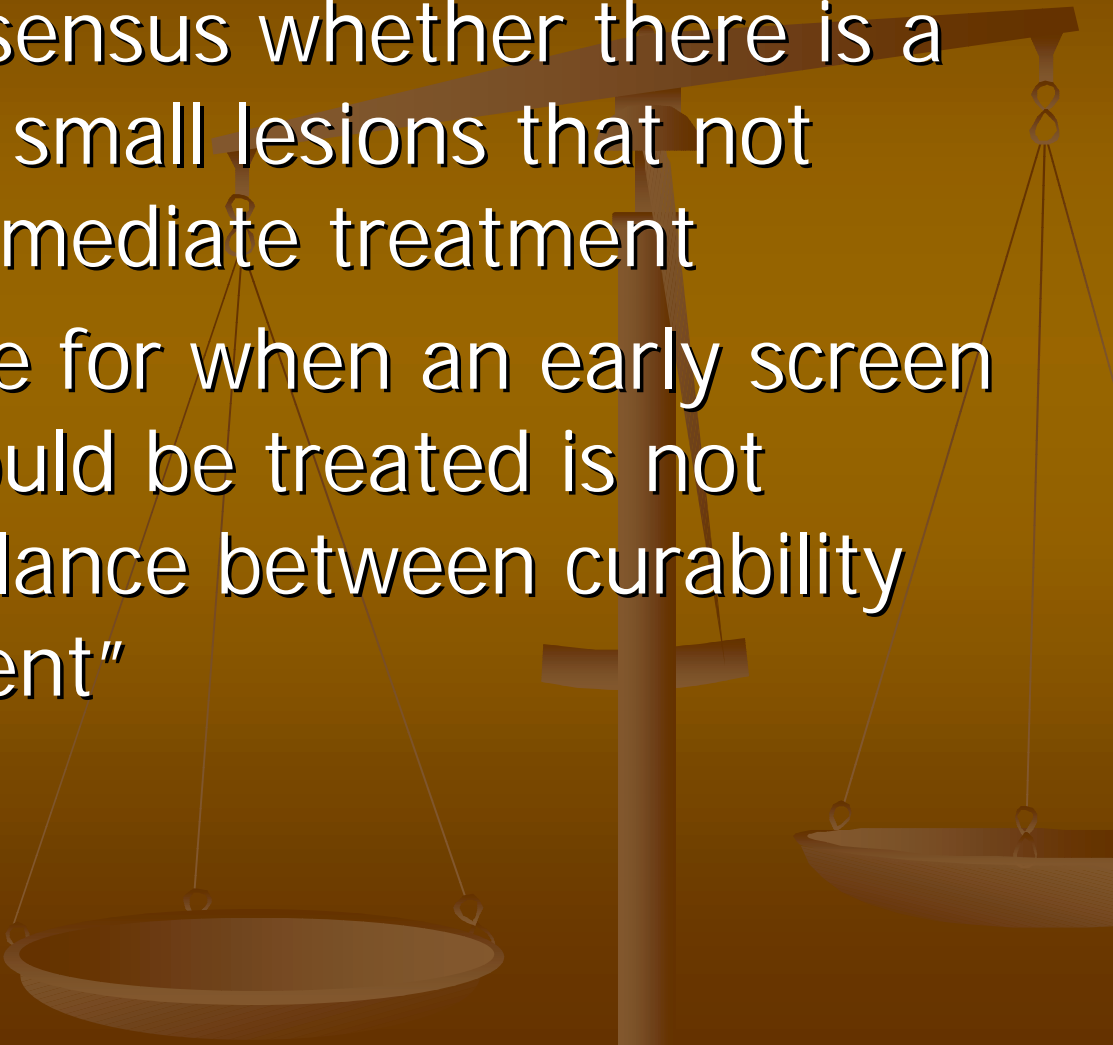
— Denmark	— Norway
— Finland	— Sweden
— Iceland	- - - SEER white

Fig. 1. Observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in the Nordic countries and the United States (all ages).

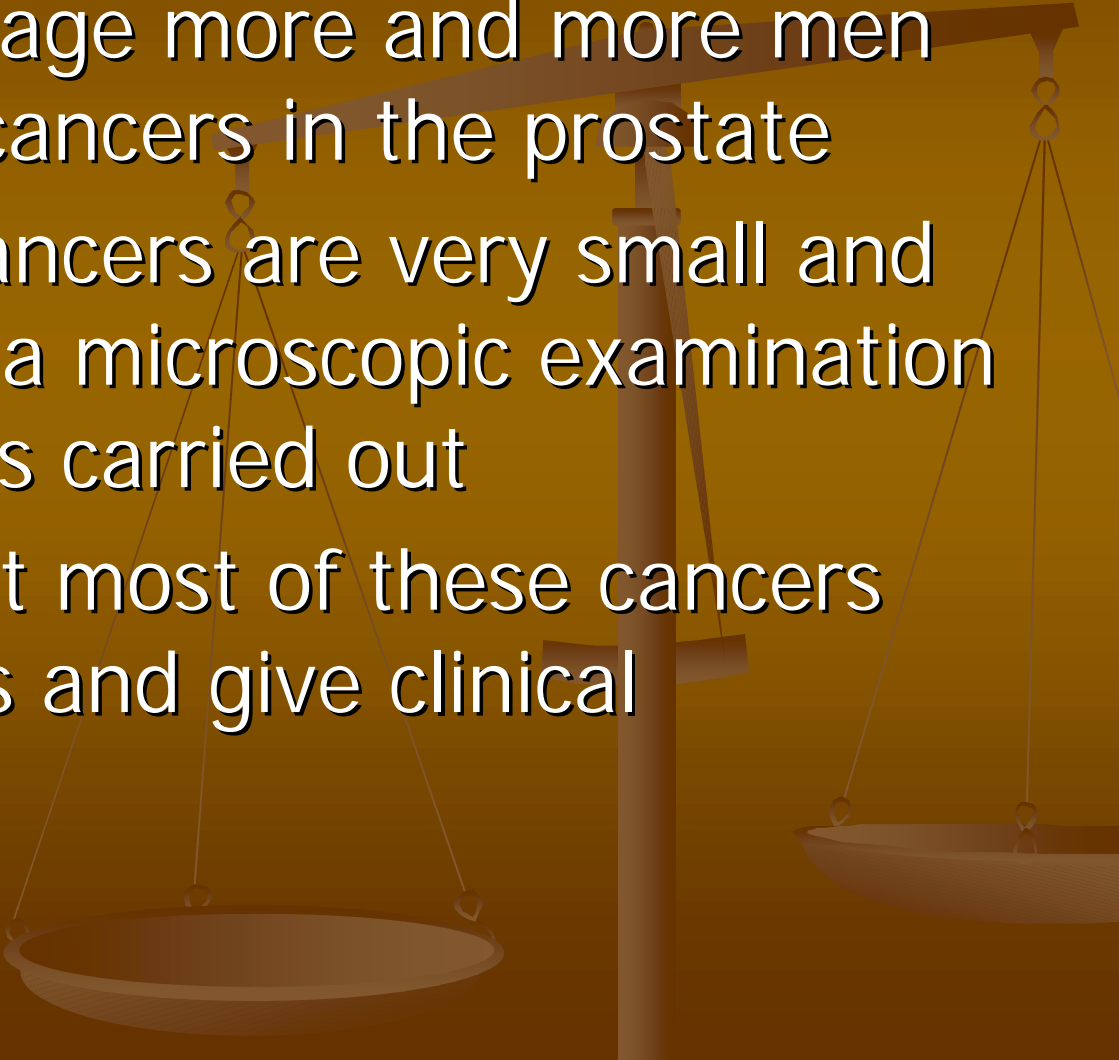
# There should be an accepted treatment (criteria 2)

- SPCG 4 showed only a moderate effect which might be due to “wrong” patient selection
  - New treatment studies are underway (SPCG 7) and may contribute to the understanding of treatment of localized PC
  - Randomized screening trials may also add knowledge about the efficacy of treatment
- 

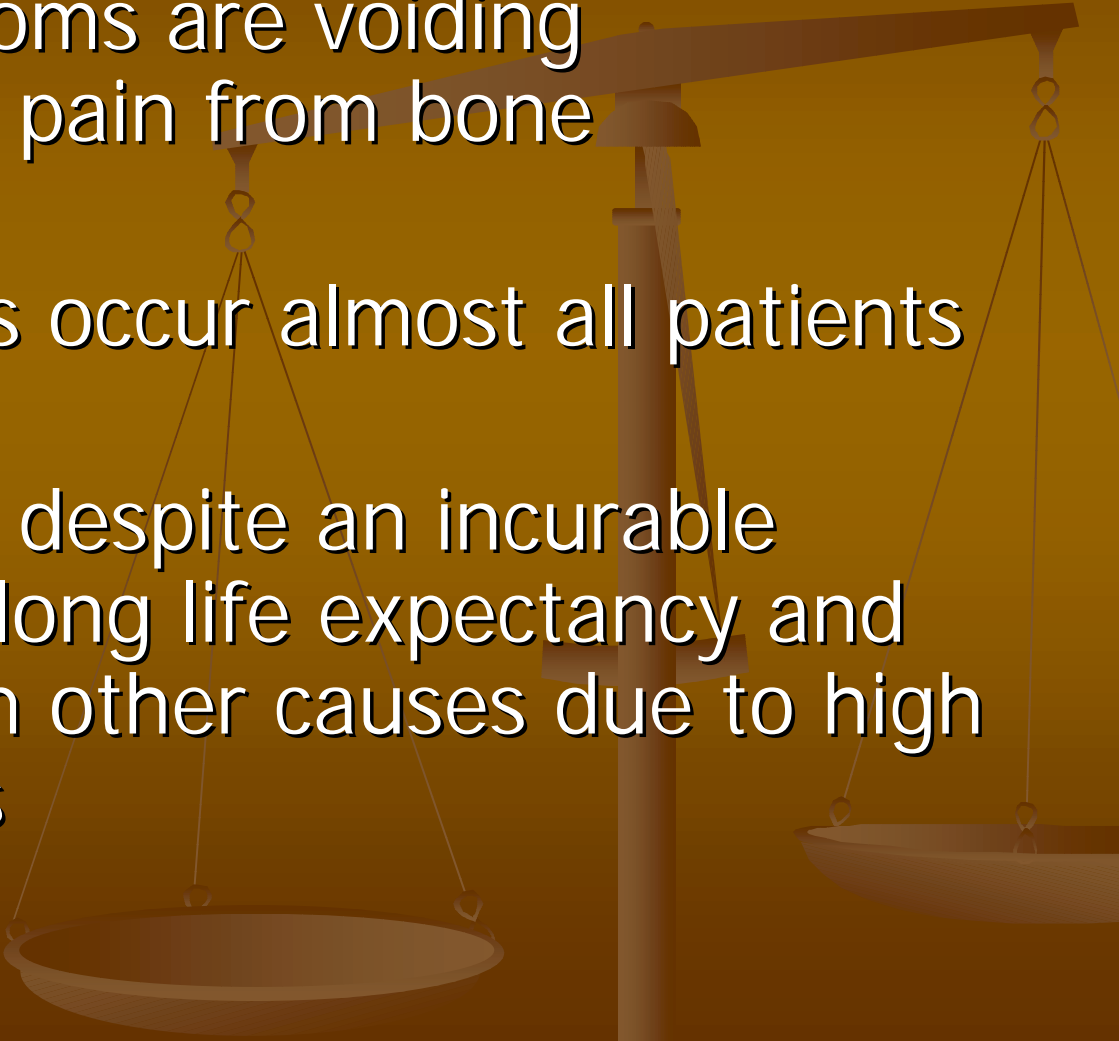
There should be an agreed policy of whom to treat as patients (criteria 8)

- There is no consensus whether there is a group with very small lesions that not need at least immediate treatment
  - The optimal time for when an early screen detected PC should be treated is not established, “balance between curability and overtreatment”
- 

# “Insignificant” prostate cancer

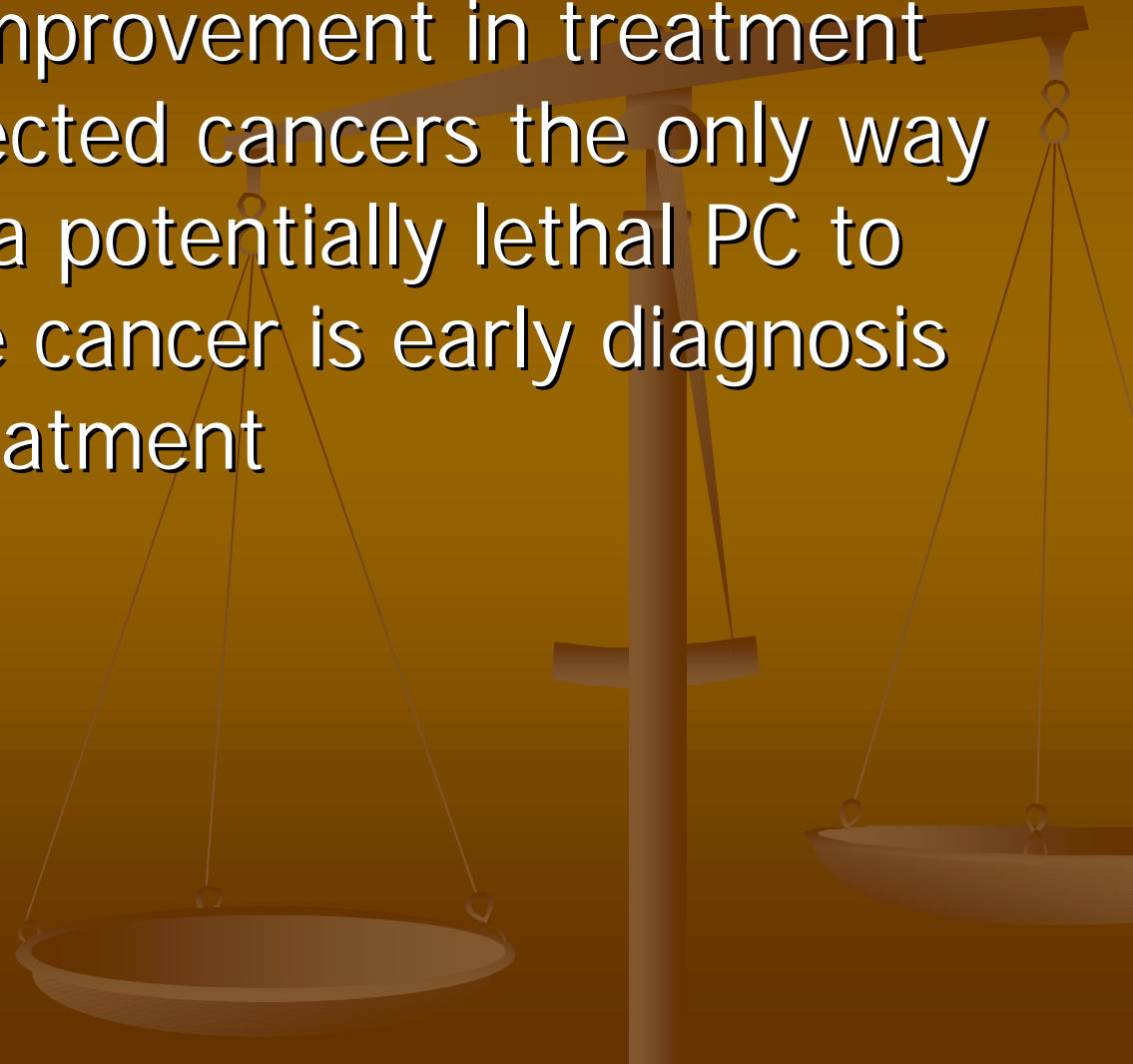
- With increasing age more and more men will have small cancers in the prostate
  - Most of these cancers are very small and only detected if a microscopic examination of the prostate is carried out
  - It is obvious that most of these cancers will not progress and give clinical symptoms
- 

# Clinical cancers

- Common symptoms are voiding dysfunction and pain from bone metastasis
  - When symptoms occur almost all patients are incurable
  - Many men have despite an incurable cancer a rather long life expectancy and half will die from other causes due to high age at diagnosis
- 

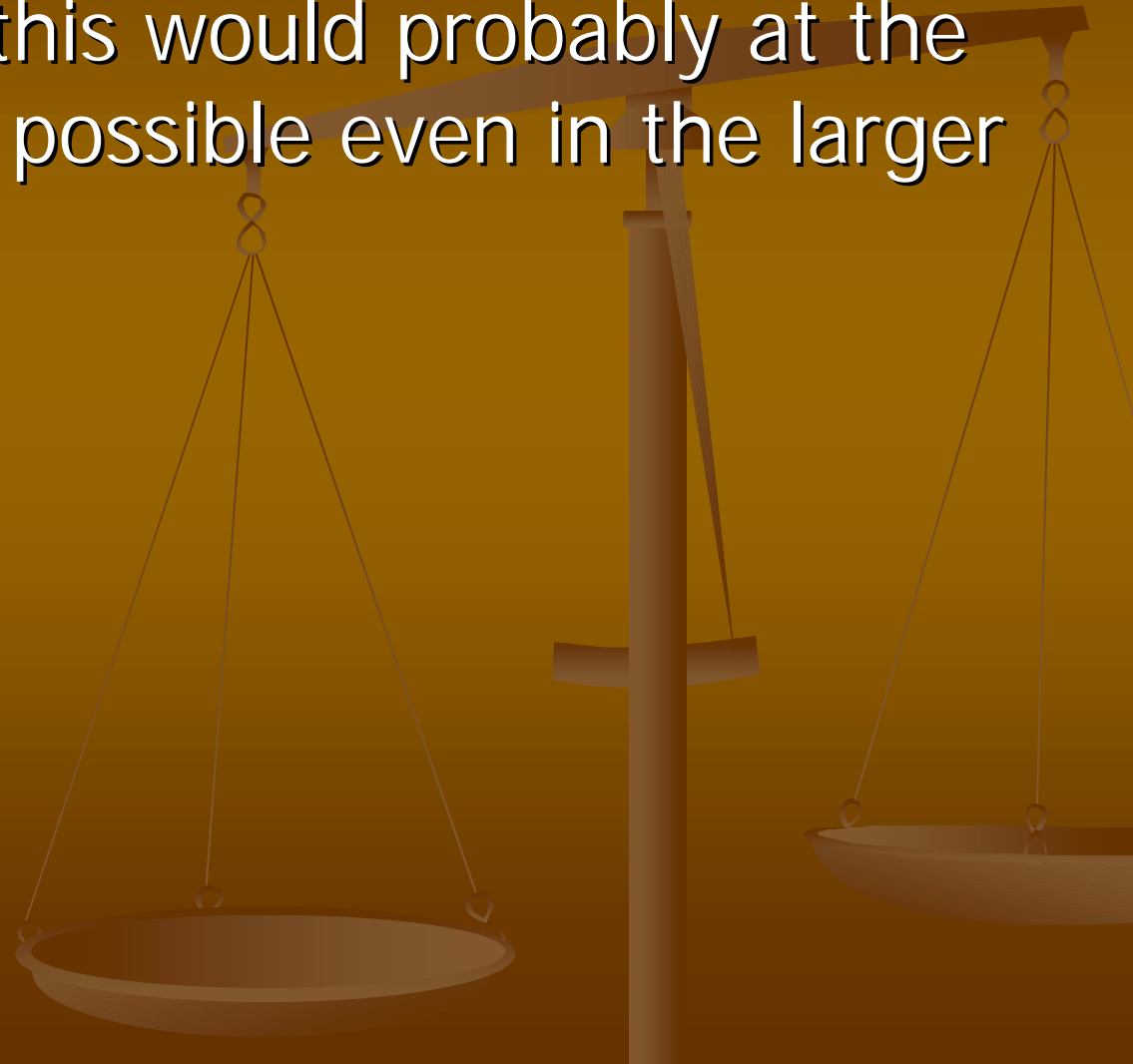
# Conclusion

- Despite some improvement in treatment of clinically detected cancers the only way for a man with a potentially lethal PC to survive prostate cancer is early diagnosis and curative treatment



# Facilities for treatment and diagnosis should be available (criteria 3)

- In Scandinavia this would probably at the moment not be possible even in the larger cities



There should be a recognizable latent or early symptomatic stage (criteria 4)

- Since long time it is known that many men have asymptomatic small tumors (latent carcinoma). The knowledge about the risk of progression from these early tumors is limited
- Today it is obvious that early detection program decrease the risk of being diagnosed with advanced prostate cancer (Aus et al 2007)

# Incidence of M1 disease in screened men compared to controls (Aus et al 2007)

**Table 2 - The use of and outcome from bone scans in relation to different serum PSA levels**

PSA level (ng/ml)	Screening group (n = 810)			Control group (n = 442)		
	M0	M1	Mx	M0	M1	Mx
0-4	36	1	240	7	0	35
4-10	107	3	260	38	0	138
10-20	47	0	41	58	2	39
20-50	36	4	5	47	6	12
50-100	7	2	0	8	2	7
≥100	3	10	1	7	27	3

In the screening arm, six PSA values are missing in the Mx group; in the control arm, one PSA value is missing in the M0 group and three in the Mx group.

PSA: prostate-specific antigen.

# Stage M1 at diagnosis

Van der Cruisjen-Koeter et al reported similar data from Rotterdam (J Urol 2005; 174: 121-125)

They reported extremely few men with stage M1, only 7 in the screening arm and 27 in the control arm

# There should be a suitable test (criteria 5)

- Is PSA good enough?



## Assessing Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial

Ian M. Thompson, Donna Pauler Ankerst, Chen Chi, Phyllis J. Goodman, Catherine M. Tangen, M. Scott Lucia, Ziding Feng, Howard L. Parnes, Charles A. Coltman, Jr.

**Background:** Prostate-specific antigen (PSA) testing is the primary method used to diagnose prostate cancer in the United States. Methods to integrate other risk factors associated with prostate cancer into individualized risk prediction are needed. We used prostate biopsy data from men who participated in the Prostate Cancer Prevention Trial (PCPT) to develop a predictive model of prostate cancer. **Methods:** We included 5519 men from the placebo group of the PCPT who underwent prostate biopsy, had at least one PSA measurement and a digital rectal examination (DRE) performed during the year before the biopsy, and had at least two PSA measurements performed during the 3 years before the prostate biopsy. Logistic regression was used to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy. Risk equations were created from the estimated logistic regression models. All statistical tests were two-sided. **Results:** A total of 1211 (21.9%) men were diagnosed with prostate cancer by prostate biopsy. Variables that predicted prostate cancer included higher PSA level, positive family history of prostate cancer, and abnormal DRE result, whereas a previous negative prostate biopsy was associated with reduced risk. Neither age at biopsy nor PSA velocity contributed independent prognostic information. **Higher PSA level, abnormal DRE result, older age at biopsy,**

**and African American race were predictive for high-grade disease (Gleason score  $\geq 7$ ) whereas a previous negative prostate biopsy reduced this risk. Conclusions:** This predictive model allows an individualized assessment of prostate cancer risk and risk of high-grade disease for men who undergo a prostate biopsy. [J Natl Cancer Inst 2006;98:529-34]

Since the advent of prostate-specific antigen (PSA) screening in the late 1980s, approximately 50% of U.S. men have had a PSA test performed regularly (1). Early large-scale prostate cancer screening studies used 4.0 ng/mL PSA as a threshold value to prompt a recommendation for prostate biopsy (2,3). Subsequent studies suggested that the risk of prostate cancer, as determined

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*Correspondence to:* Ian Thompson, MD, Department of Urology, UTHSCSA, University of Texas HSC at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78229 (e-mail: thompsoni@uthscsa.edu).

See "Notes" following "References."

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**Table 3.** Numbers (percentages) of prostate cancers and high-grade prostate cancers by PSA level\*

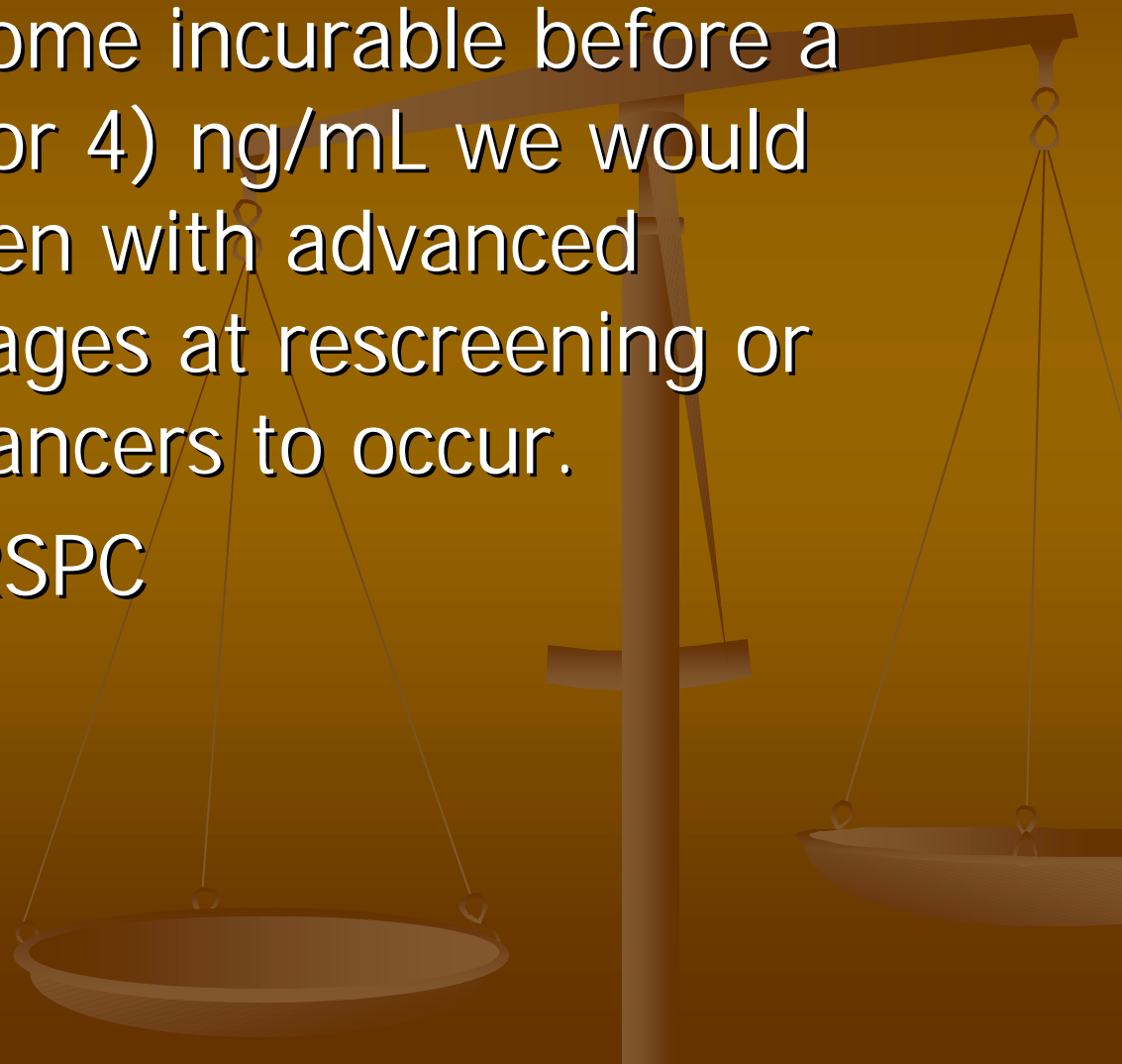
PSA level, ng/mL	<i>N</i>	No. of prostate cancers (%)	No. of high-grade prostate cancers† (%)
0–1	1963	217 (11.1)	19 (1.0)
1.1–2	1640	337 (20.5)	43 (2.6)
2.1–3	775	205 (26.5)	44 (5.7)
3.1–4	510	153 (30.0)	48 (9.4)
4.1–6	481	234 (48.6)	70 (14.6)
>6	150	65 (43.3)	33 (22.0)
Total	5519	1211 (21.9)	257 (4.7)

\*PSA = prostate-specific antigen.

†Gleason score of 7 or higher.

# Is it too late to detect PC if we wait until PSA > 3 (4) ng/mL

- If many PC become incurable before a PSA level of 3 (or 4) ng/mL we would expect many men with advanced (noncurable) stages at rescreening or many interval cancers to occur.
- Results from ERSPC



# Shift in TNM stage at repeated screening

**TABLE 3**  
T Category Distribution for All Patients with Detected Malignancies

T category	Screening group					Interval malignancies	Nonresponders*	Entire screening group	Control group
	Screening round				Total				
	First	Second	Third	Fourth					
T1a-b						10	1	11	11
T1c	124	100	110	70	404	15	14	433	90
T2	62	31	21	10	124	9	15	148	80
T3	8	1	1	1	11	0	3	14	19
T4	2	0	0	0	2	0	2	4	5
Tx	0	1	1	0	2	3	2	7	7
N1M0, any T	4	0	0	1	5	0	1	6	7
M1, any T, any N	2	0	0	0	2	5	9	17	25
Total	202	133	133	82	550	43	47	640	244

\* Patients who were randomized to undergo active screening but who did not adhere to the screening program.

# PSA shift in repeated screening

**TABLE 2**  
Detected Cases of Prostate Carcinoma by Prostate-Specific Antigen Interval

PSA interval (ng/mL)	Screening group				Interval malignancies	Nonresponders*	Entire screening group	Control group
	Screening round							
	First	Second	Third	Fourth				
0-2.53	0/6143	0/4987	0/3771	0/1055	4	0	4	4
2.54-2.99	6/265	8/203	32/206	29/132	0	1	76	0
3.0-3.99	47/348	43/299	52/257	31/169	1	3	177	15
4.0-9.99	95/450	70/366	46/275	19/161	19	14	263	81
10-19.99	30/67	9/43	3/30	2/15	9	9	62	58
20-99.9	22/36	2/5	0/1	1/2	5	13	43	58
≥ 100	2/3	1/1	0/0	0/0	2	6	11	22
Data unavailable	0	0	0	0	3	1	4	5
Total	202/7312	133/5904	133/4540	82/1534	43	47	640	244

PSA: prostate-specific antigen.

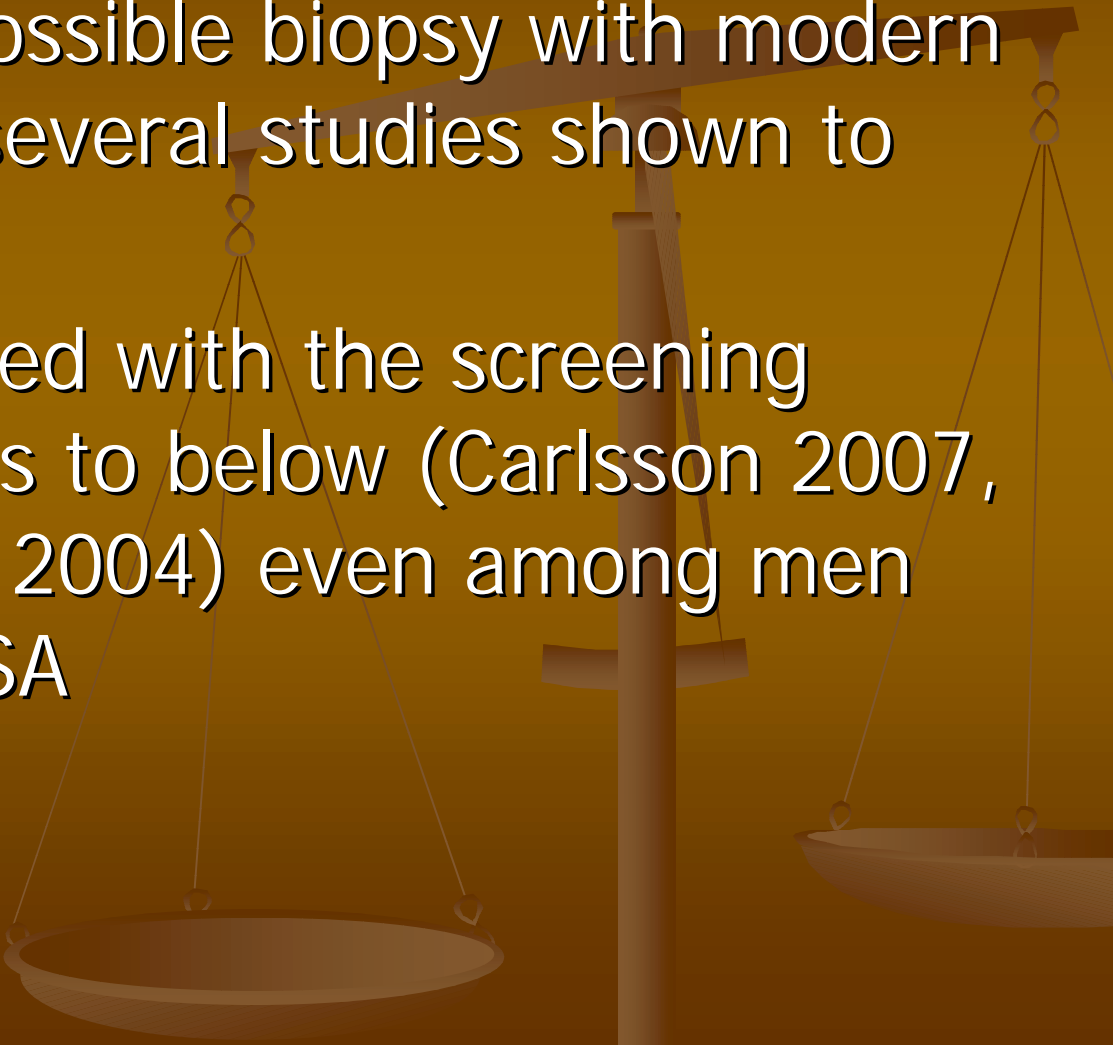
\* Patients who were randomized to undergo active screening but who did not adhere to the screening program.

# Interval cancers in Göteborg (2year) and Rotterdam (4 year)

Years after initial screening	Interval prostate cancer, all (N)		Interval prostate cancer, aggressive (N)	
	Rotterdam	Gothenburg	Rotterdam	Gothenburg
0-1	3	0	3	0
1-2	1	8	0	2
2-3	3	0	1	0
3-4	1	5	1	2
4-5	1	2	0	0
5-6	1	4	0	0
6-7	10	1	2	0
7-8	13	2	4	0
8-9	10	1	2	0
9-10	14	8	2	1
Total	57	31	15	5
Percentage of total screened	0.43	0.74	0.11	0.12
Percentage of total interval prostate cancers	NA	NA	26.3	16.1

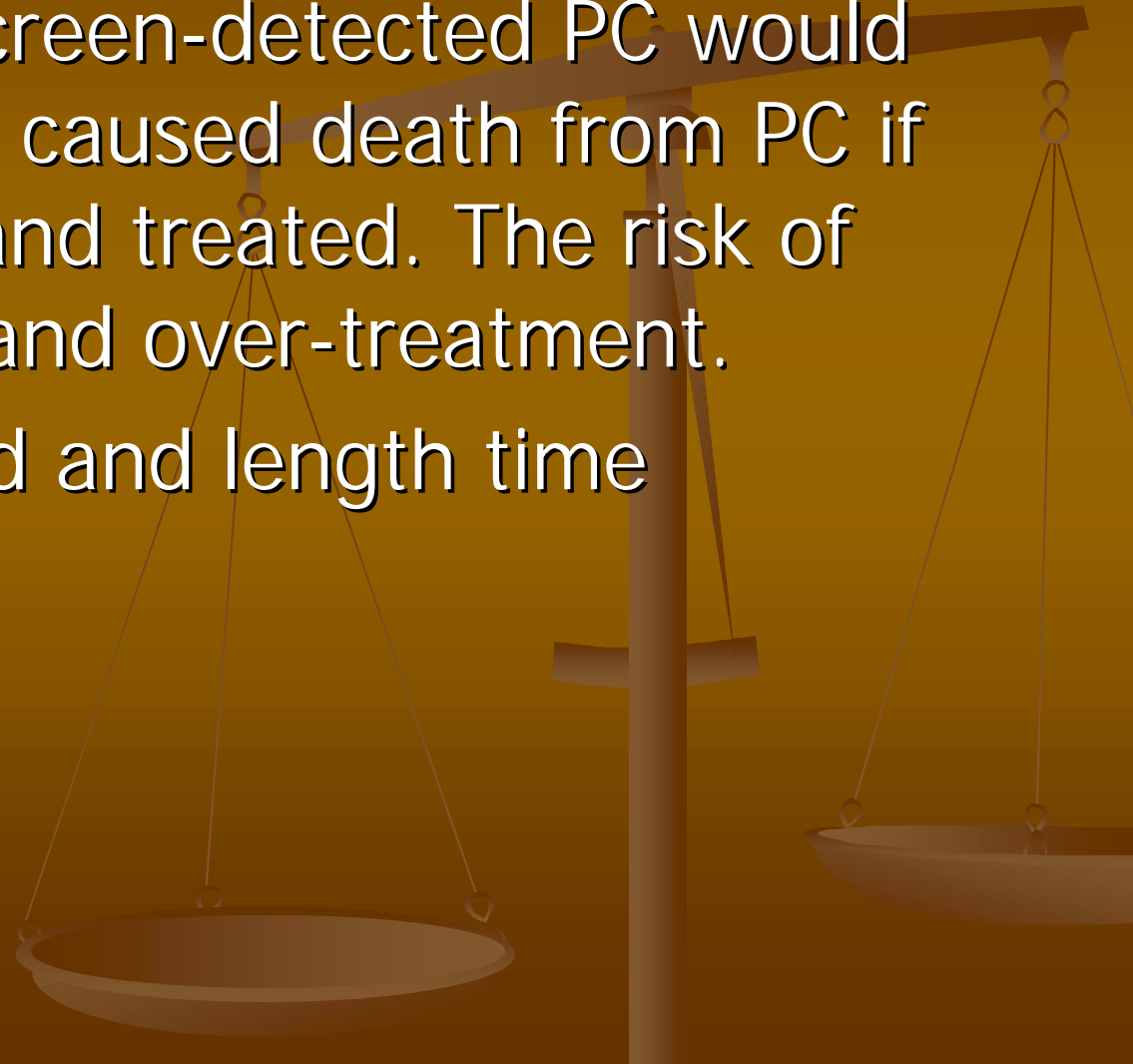
- \* Interval cancer = clinically diagnosed prostate cancer between two screening visits; aggressive interval cancer = interval cancer with at least one of the following characteristics: stage M1 or stage N1, prostate-specific antigen concentration greater than 20 ng/mL, or a Gleason score greater than 7; NA = not applicable.

## The test should be acceptable to the population (criteria 6)

- Both PSA and possible biopsy with modern technique is in several studies shown to be accepted
  - Anxiety associated with the screening procedure seems to be below (Carlsson 2007, van der Cruisen 2004) even among men with elevated PSA
- 

# The natural history of the disease should be adequately understood (criteria 7)

- How many of screen-detected PC would eventually have caused death from PC if not diagnosed and treated. The risk of over-diagnosis and over-treatment.
- It relates to lead and length time calculations

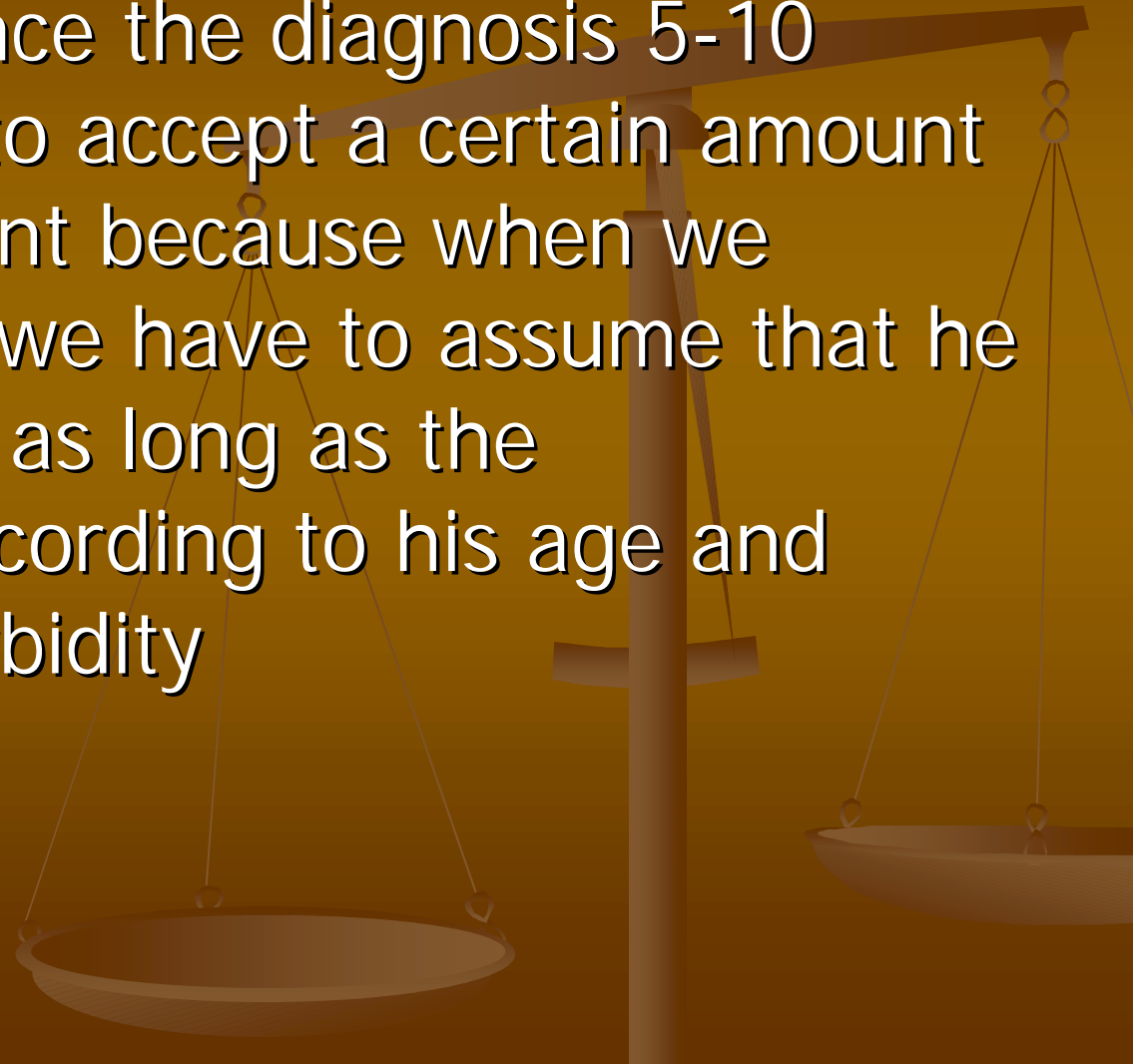


# Over treatment?

- A 56 year old man with positive family history (brother died from PC 62 years old) was discovered in 2000 with a PSA of 4.2 and T1c Gleason 4+3. He had a RRP and a pT3 but negative margins. He had a PSA < 0.01 after 52 months.
- In Dec 2004 he died in the Tsunami in Thailand

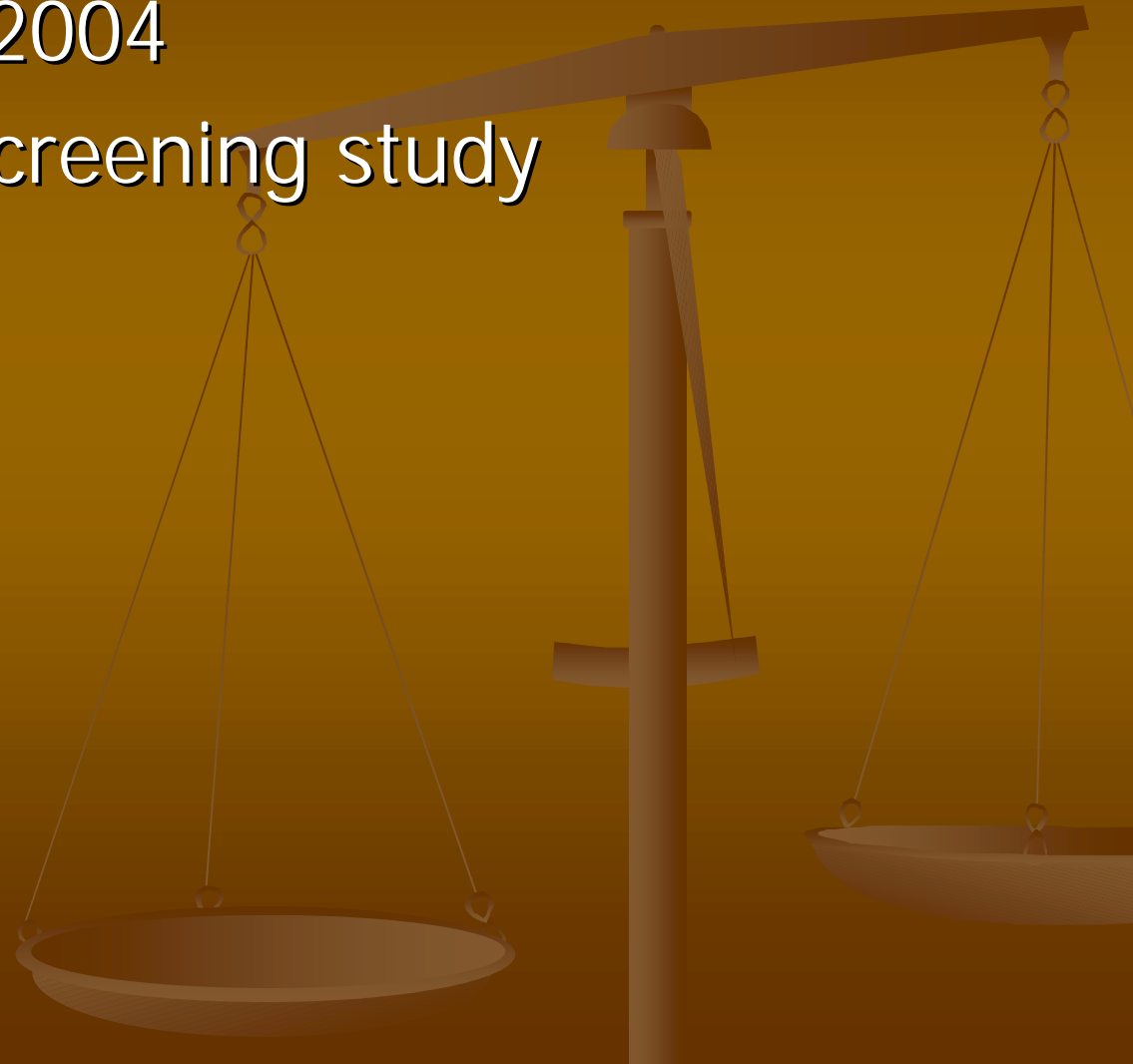
# Overtreatment unavoidable?

- When we advance the diagnosis 5-10 years we have to accept a certain amount of over-treatment because when we advise patients we have to assume that he will live at least as long as the expectations according to his age and possible co-morbidity



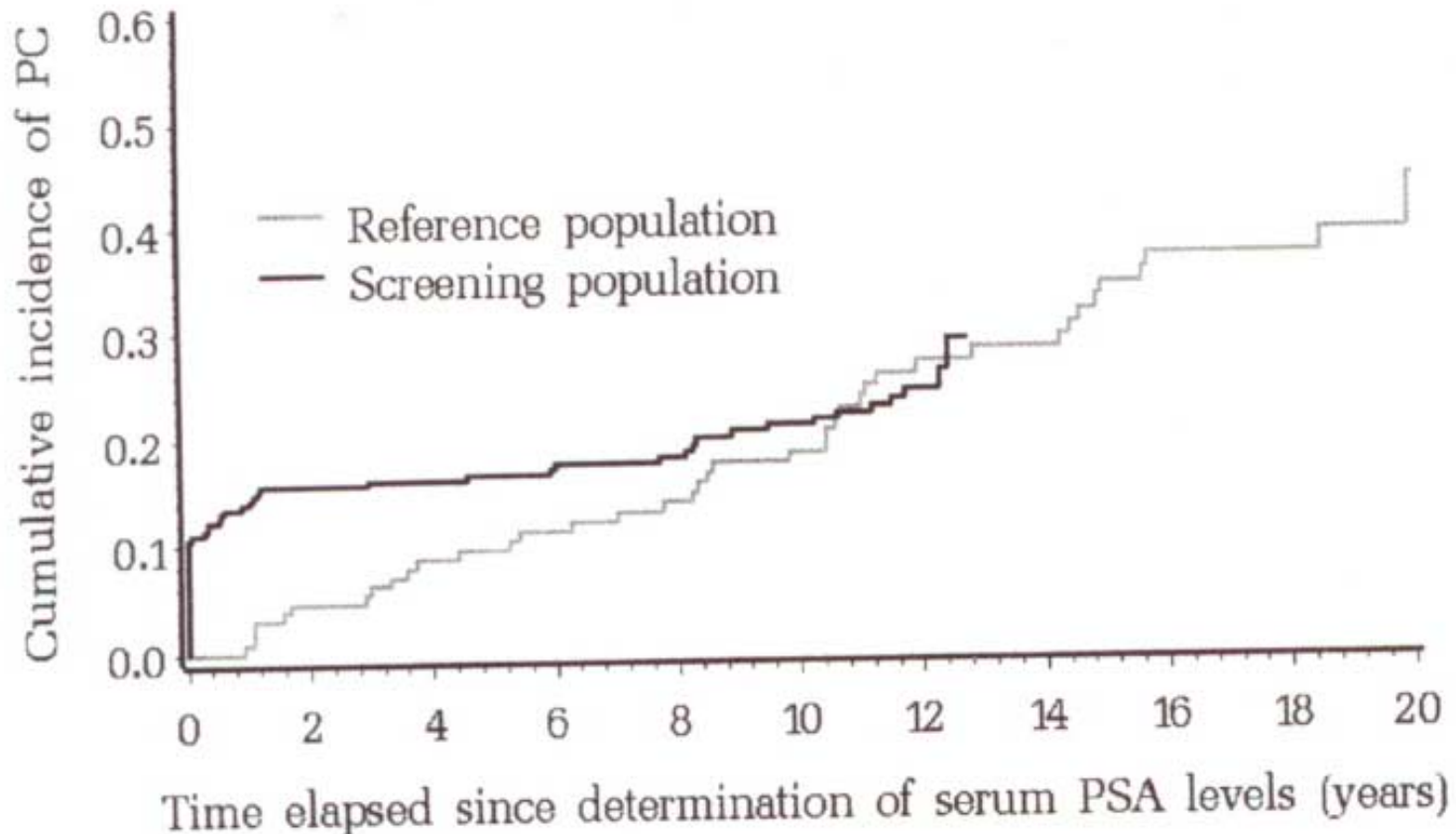
# How many men with screen detected PC have a disease that not will progress?

- Törnblom et al 2004
- The Göteborg screening study

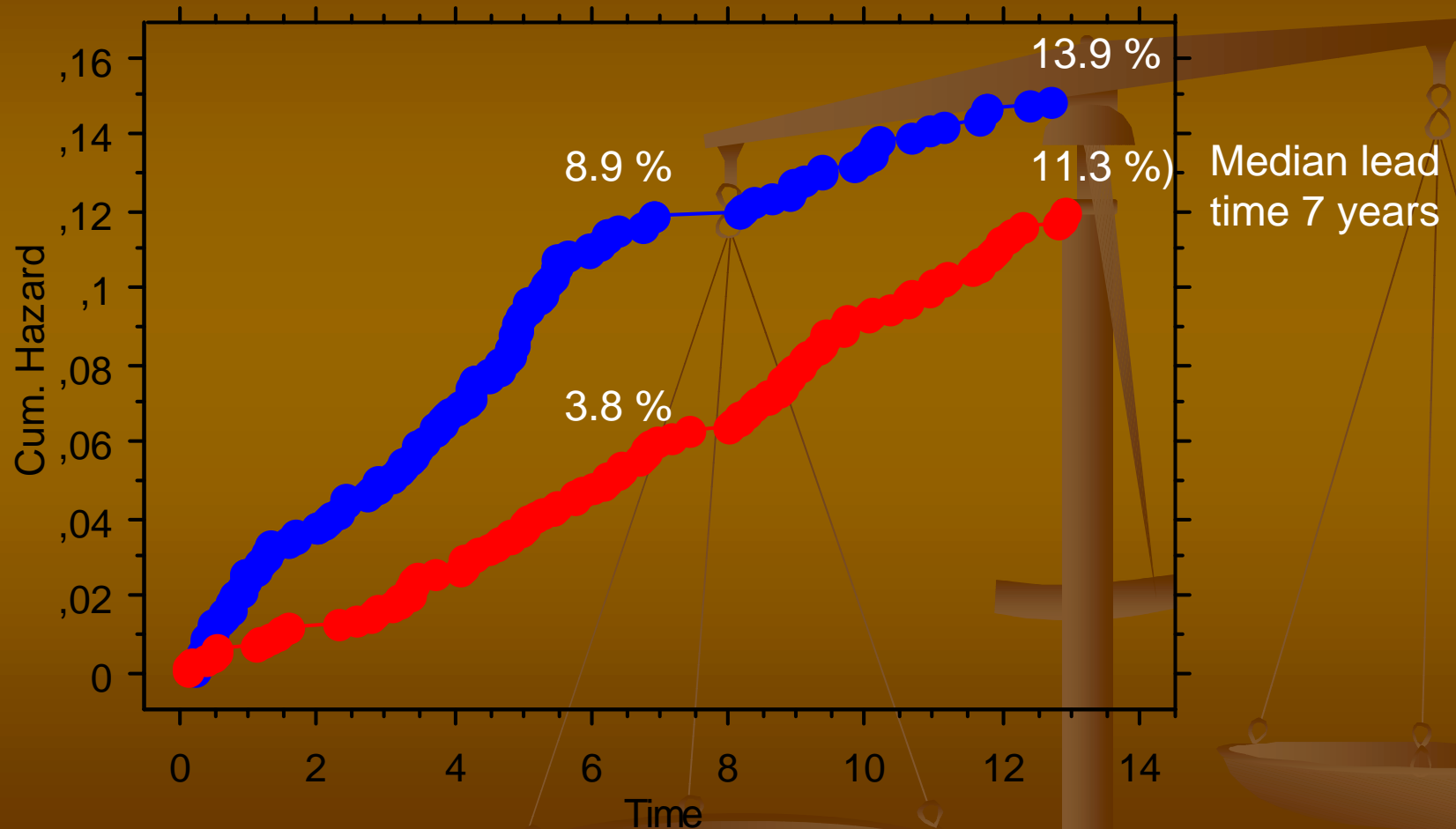


# Time to clinical diagnosis in men with PSA > 3 ng/mL (Törnblom et al 2004)

Median lead time approx 5 years

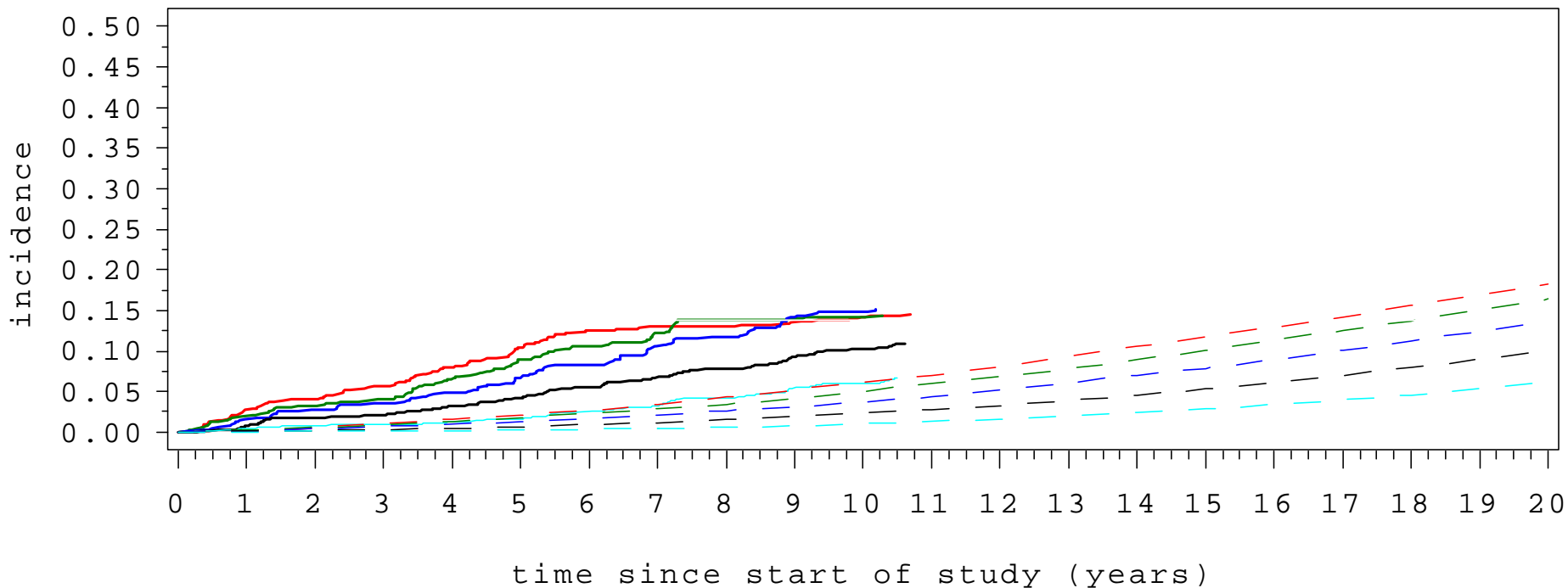


# Cumulative incidence of prostate cancer in screening and control group (only men born 1930-31)

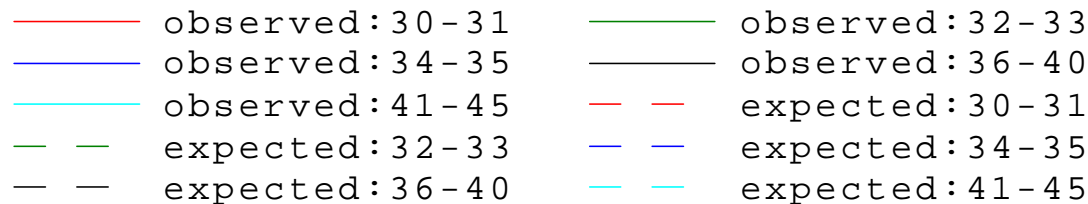


# Observed and expected prostate cancer incidence

Screening group by birth cohort

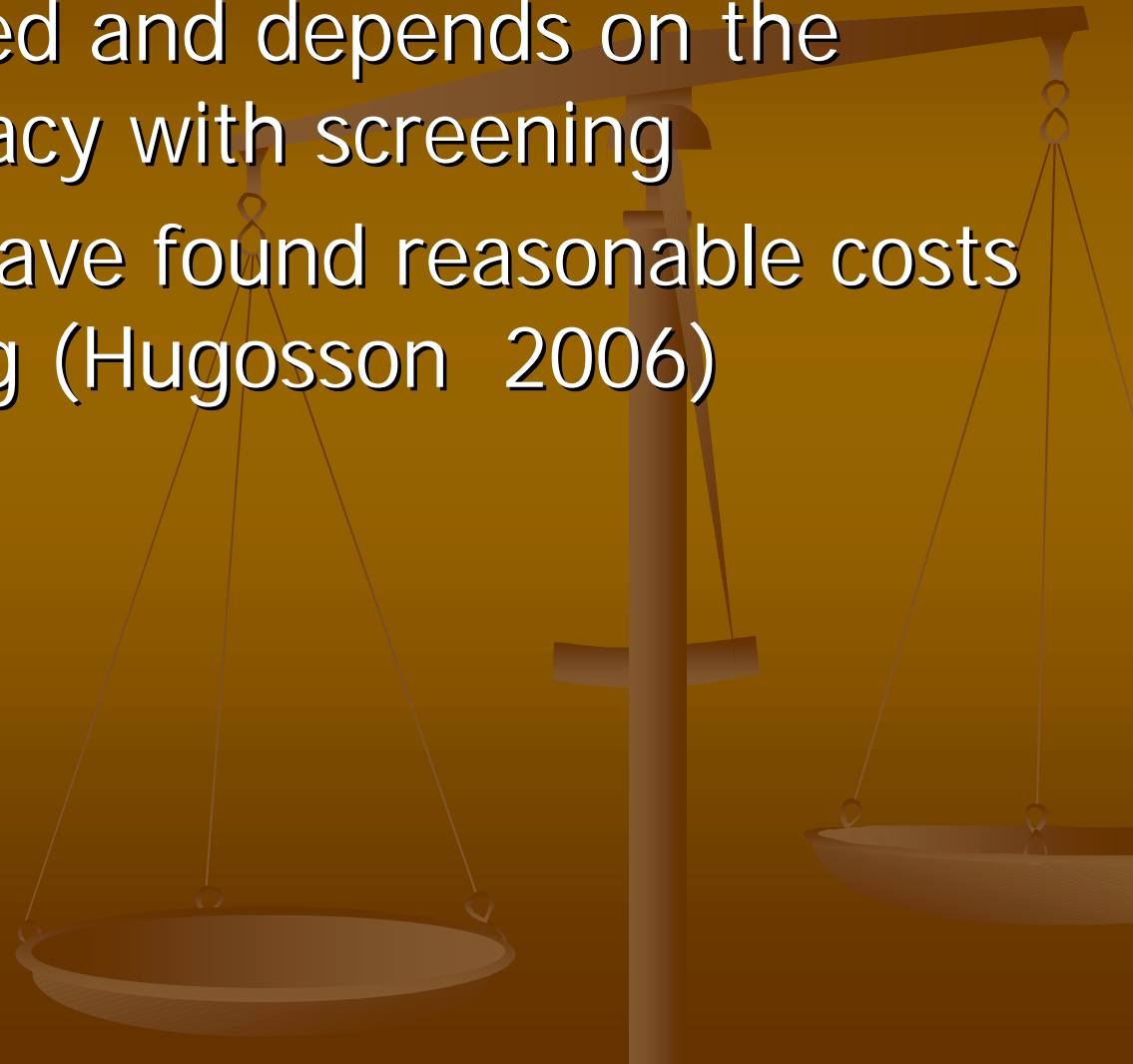


Incidence



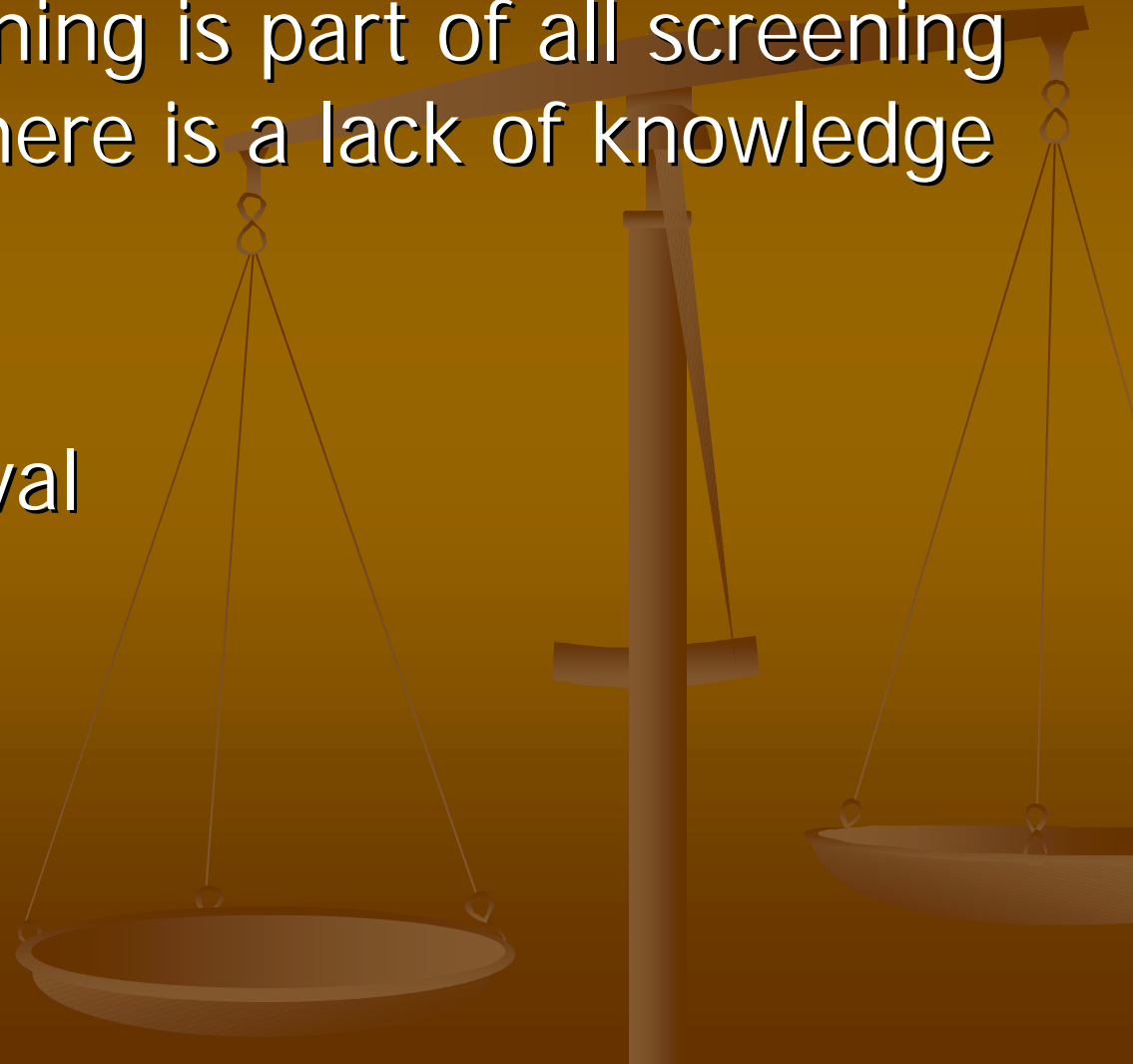
The cost should be balanced in relation to possible expenditure on medical care as a whole

- Very little studied and depends on the efficacy of efficacy with screening
- Studies so far have found reasonable costs for PC screening (Hugosson 2006)



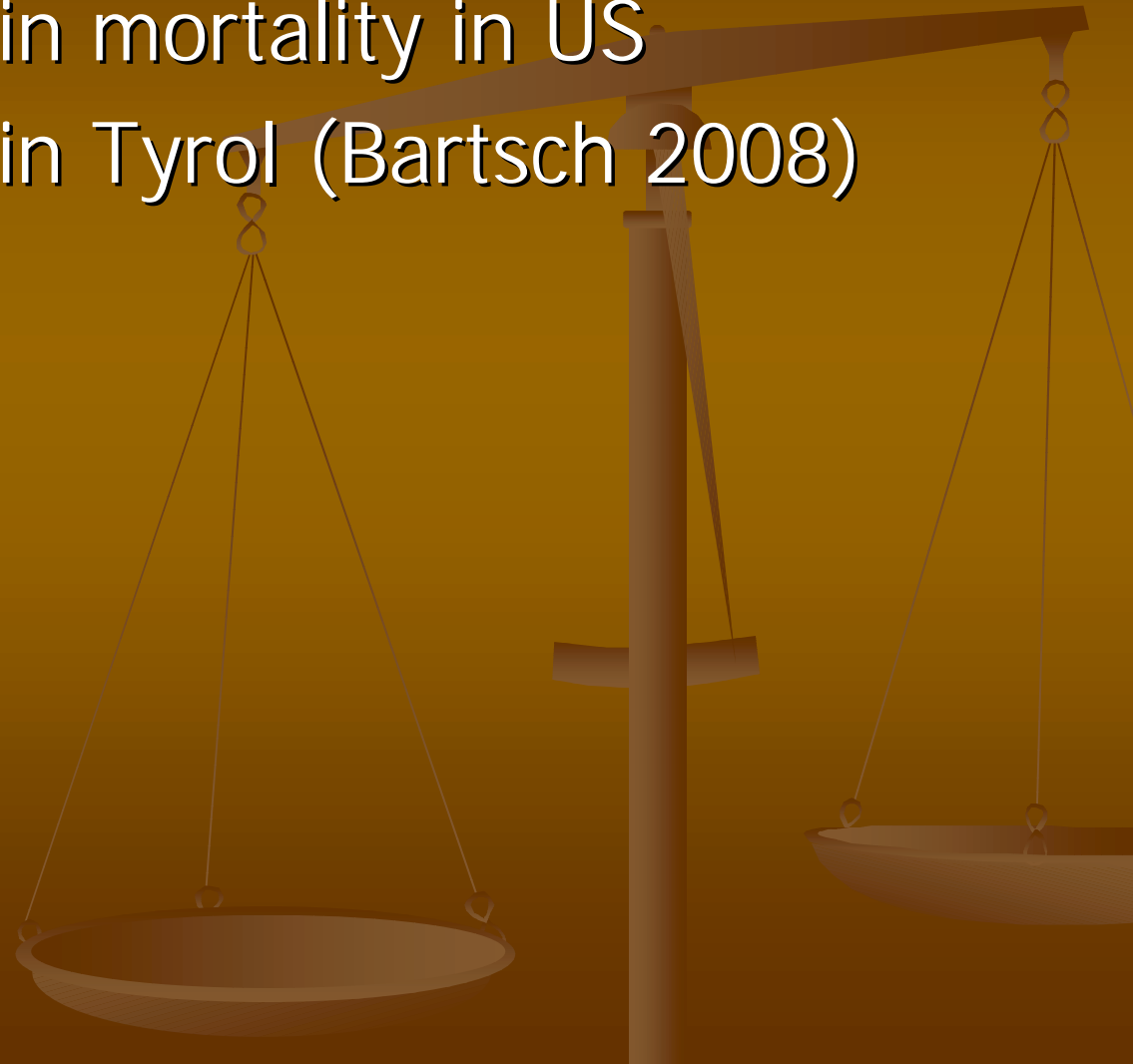
# Case-finding should be a continuing process and not a once for all project

- Repeated screening is part of all screening programs but there is a lack of knowledge about
  - Age to start
  - Screening interval
  - Age to stop



# Are randomized studies necessary?

- 30 % decrease in mortality in US
- 50 % decrease in Tyrol (Bartsch 2008)



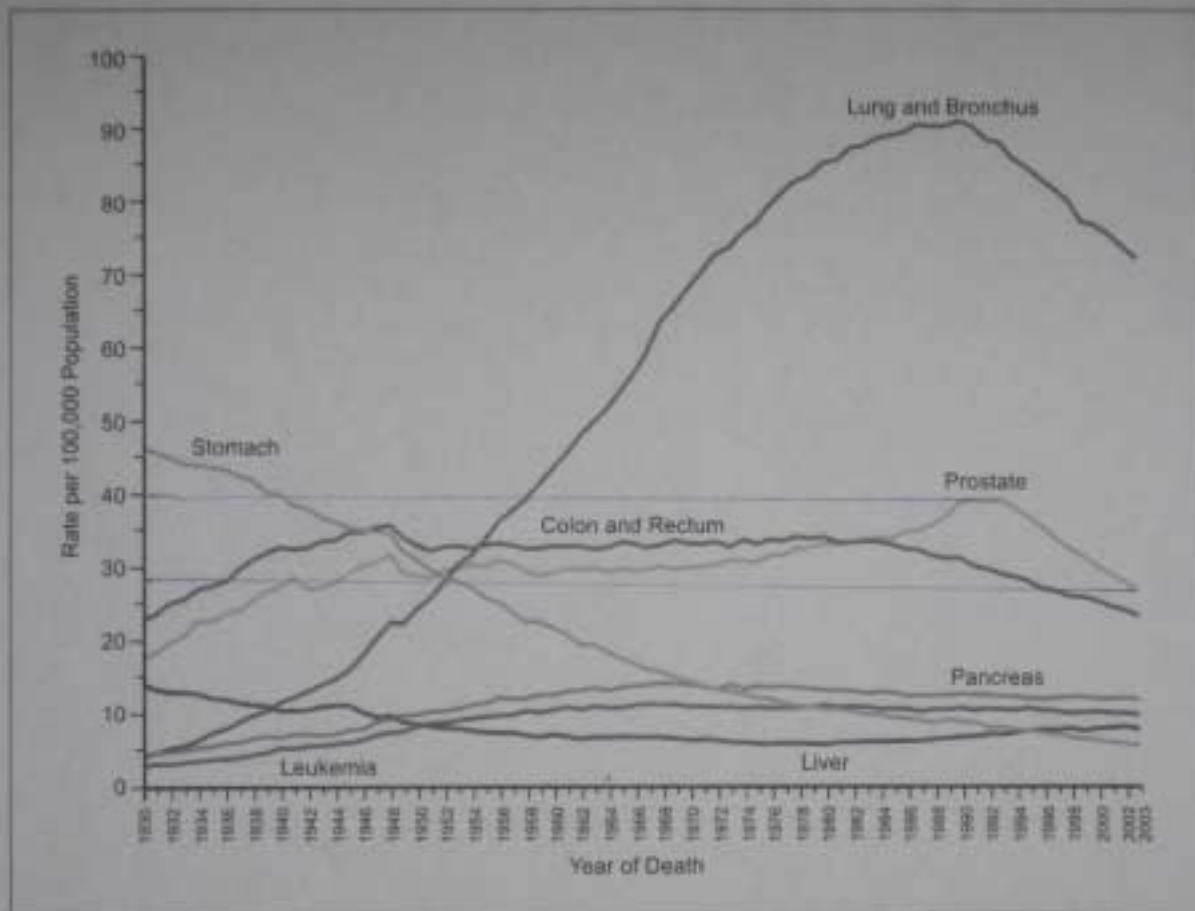
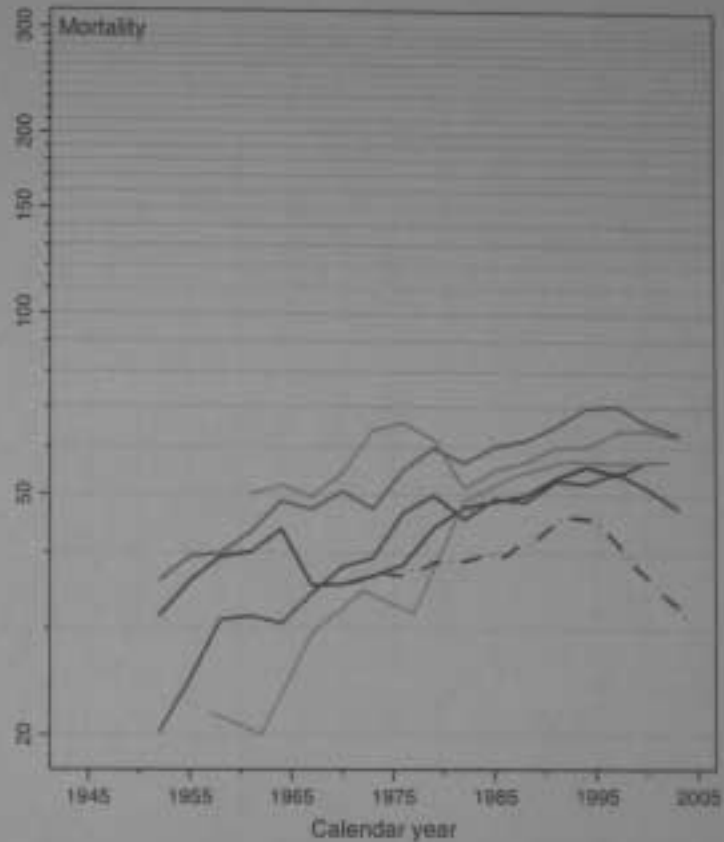
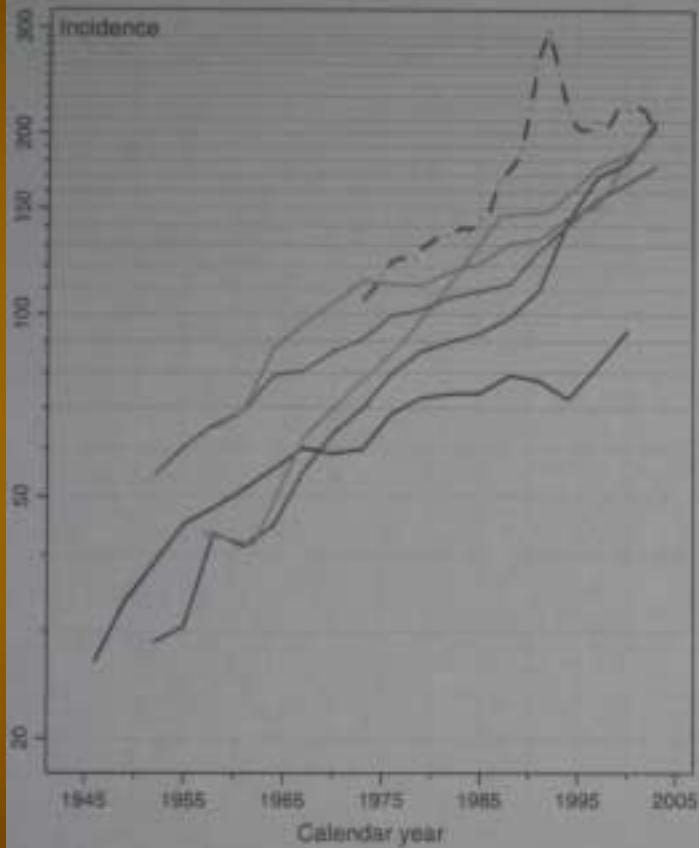


FIGURE 4 Annual Age-adjusted Cancer Death Rates\* Among Males for Selected Cancers, US, 1930 to 2003.  
 \*Rates are age-adjusted to the 2000 US standard population. Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes. Source: US Mortality Public Use Data Tapes, 1960 to 2003, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.



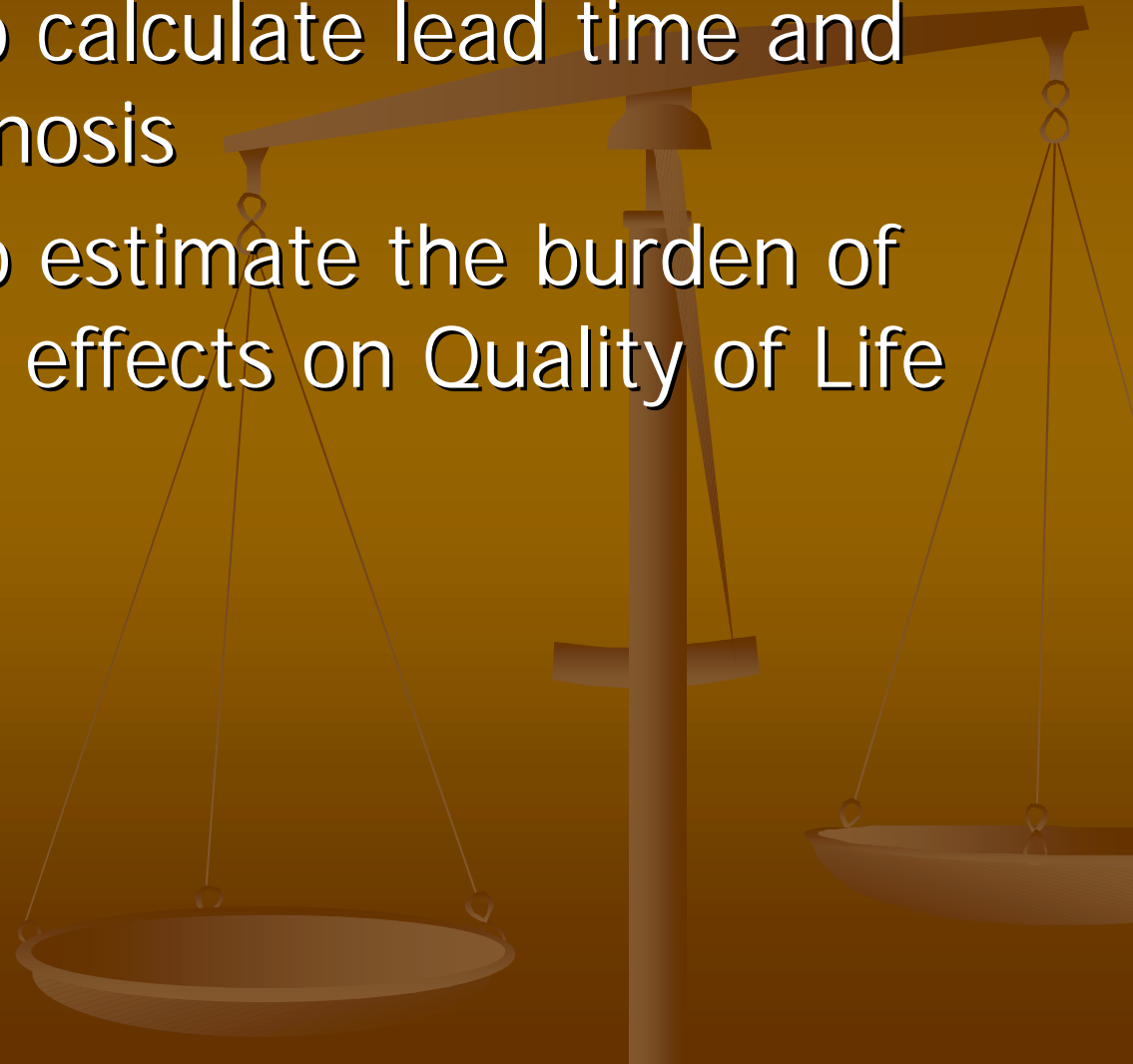
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1. Observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in the Nordic countries and the United States (all ages).

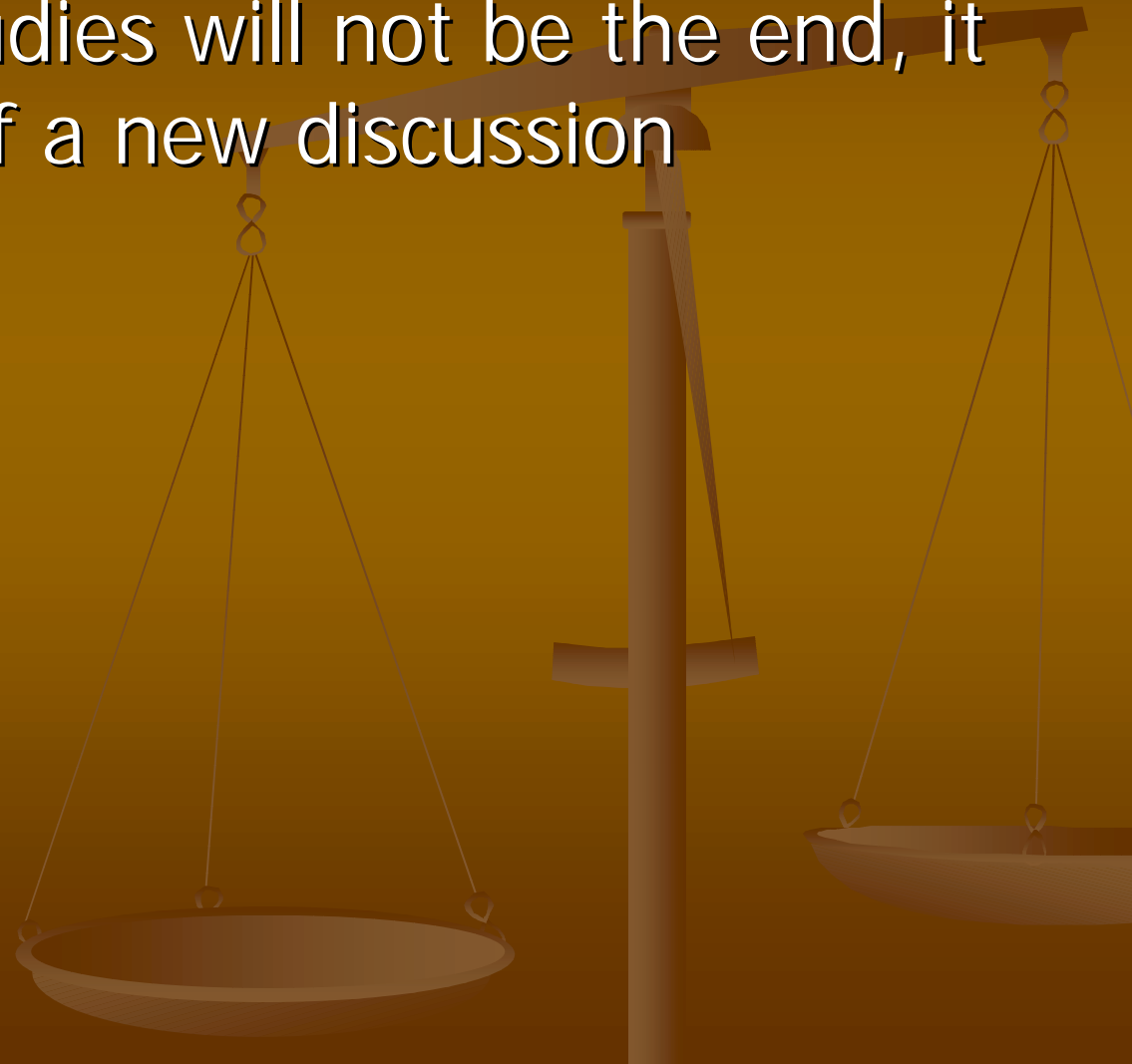
# Why randomized screening studies are necessary

- The only way to calculate lead time and risk of overdiagnosis
- The best way to estimate the burden of side effects and effects on Quality of Life

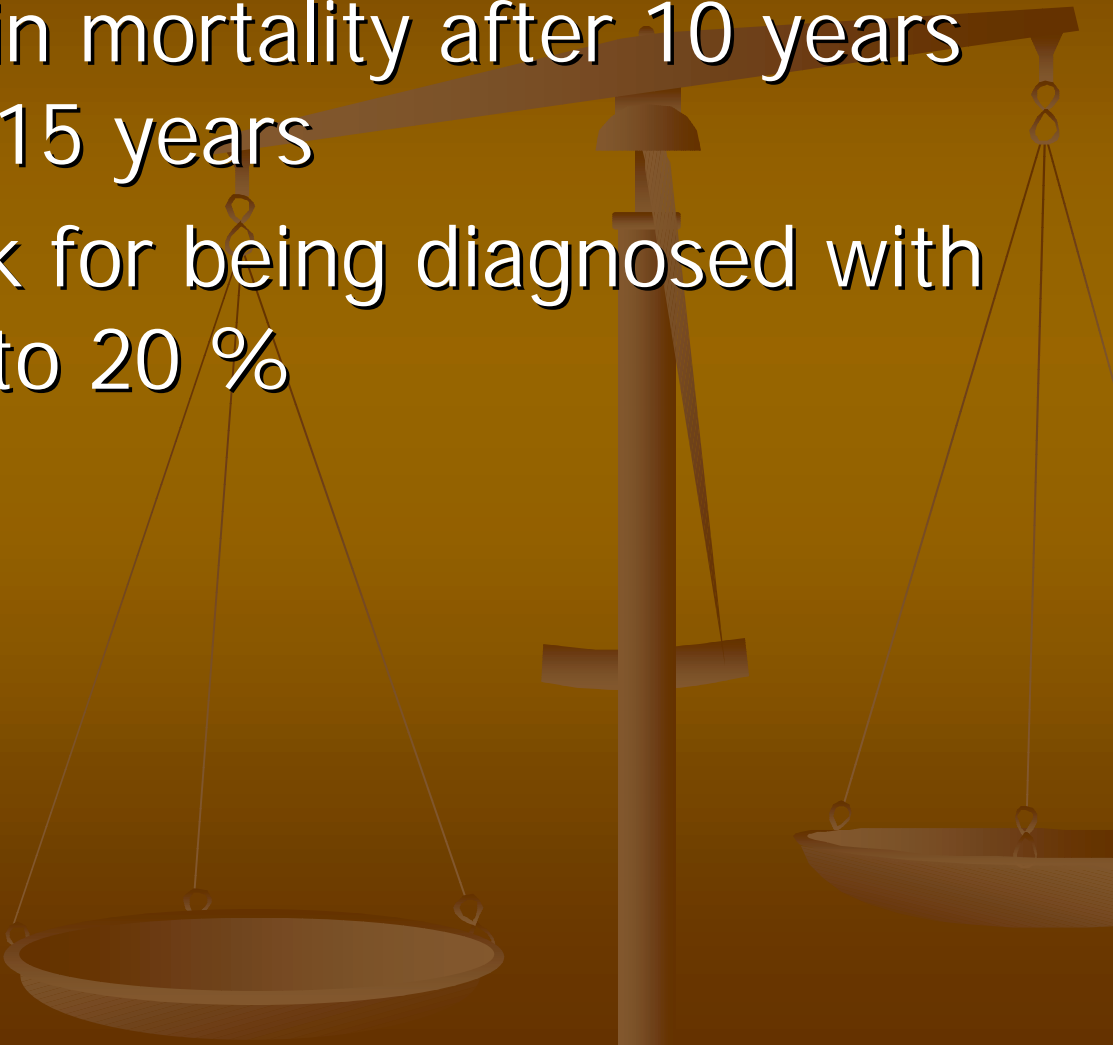


# But...

- Randomized studies will not be the end, it will be a start of a new discussion



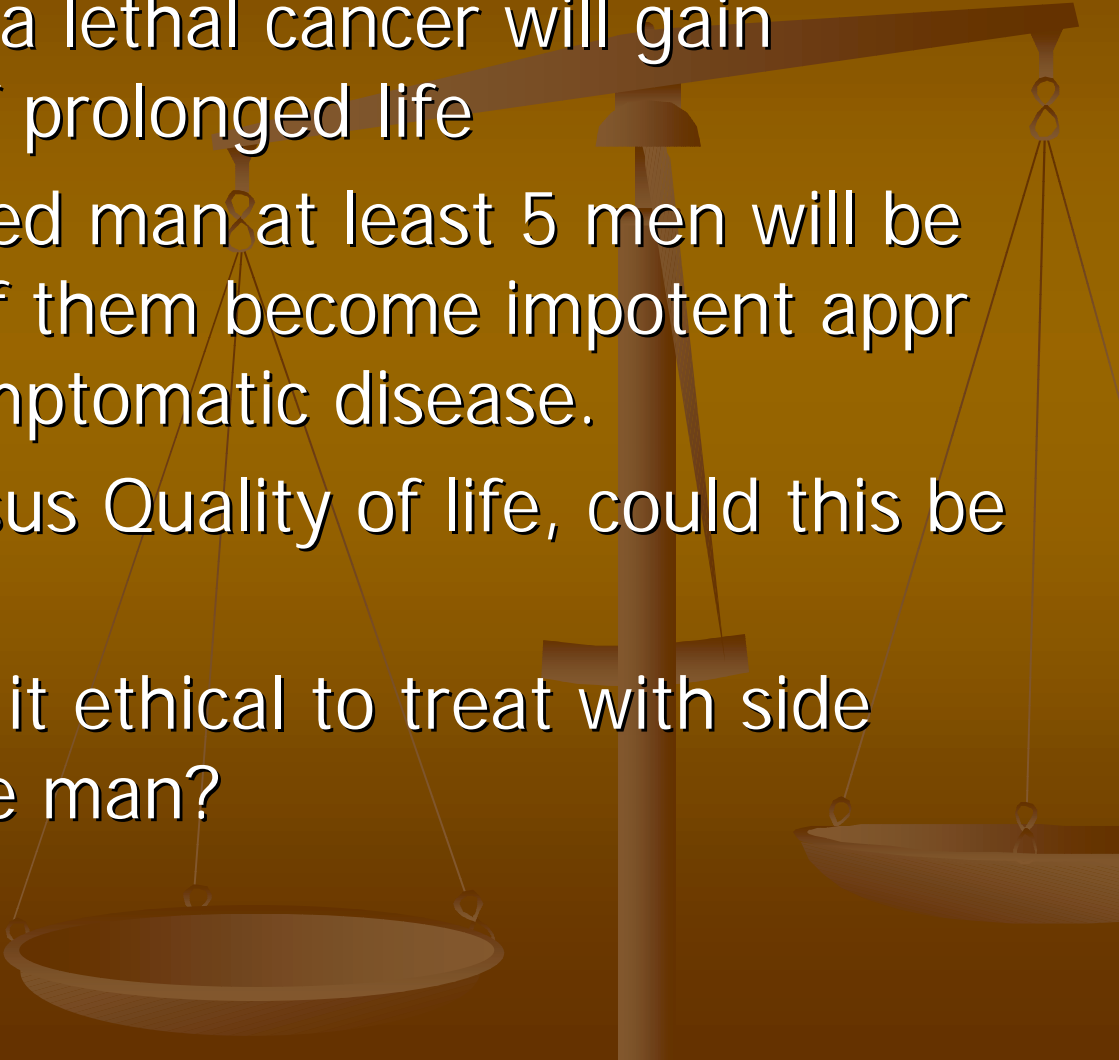
# Calculated survival benefits from M1 data

- 30 % decrease in mortality after 10 years and 50 % after 15 years
  - The life time risk for being diagnosed with PC is increased to 20 %
- 

# Or

- Of those detected with screening 1 out of 8 will be cured instead of dying from PC
- 1 out of 8 will die anyhow
- 6 out of 8 will be diagnosed but would not have died of PC even in the absence of screening
- Men will be treated on an average 5-10 years before they would have become symptomatic in the absence of treatment

# Or

- Those cured from a lethal cancer will gain another 5 years of prolonged life
  - But... for each cured man at least 5 men will be treated and half of them become impotent approx 7 years before symptomatic disease.
  - Prolonged life versus Quality of life, could this be measured?
  - How many men is it ethical to treat with side effects to save one man?
- 

# Conclusion

- Screening for prostate cancer will remain to be a controversial subject for a long time.
  - The randomized studies will be extremely important to judge benefits and harm with early detection
  - Even if ERSPC will show a survival benefit we still lack a lot of knowledge about optimal design of a screening program
- 