

Screening for Cancer



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Cancer Screening and Public Policy

- President Obama on cancer screening. From address to joint session of congress, September 9, 2009

The Cancer Screening Paradox

- There is high public enthusiasm for cancer screening
- But.....
-little evidence that some screening tests offer public health benefit

On local TV.....

- 38 year old woman decided to be screened for breast cancer
- Suspicious area identified
- Needle biopsy-- diagnosis DCIS
- Mastectomy
- Result
 - Woman happy
 - Surgeon happy
 - Reporter recommends mammography to all women (age not factor)

Enthusiasm for Cancer Screening in the United States (Schwartz et al, JAMA Jan 7, 2004)

- National survey
- Random digit dialing
- N=500 Age >40
- Questions
 - Total-body scanning
 - Pap smear
 - Mammography
 - PSA
 - Sigmoidoscopy or colonoscopy

Schwartz et al results

- Cancer screening is almost always a good idea -- 87%
- Finding cancer early saves lives--74%
- An 80 year old woman who decides not to get a mammogram is irresponsible --41%
- Had a false positive, but still glad I was tested -- 98%

American Cancer Society On Women Who Question Screening

If you haven't had a mammogram, you need more than your breasts examined.



A mammogram is a safe, low-dose X-ray that can detect breast cancer before there's a lump. In other words, it could save your life and your breast.

If you're a woman over 35, be sure to schedule a mammogram. Unless you're still not convinced of its importance.

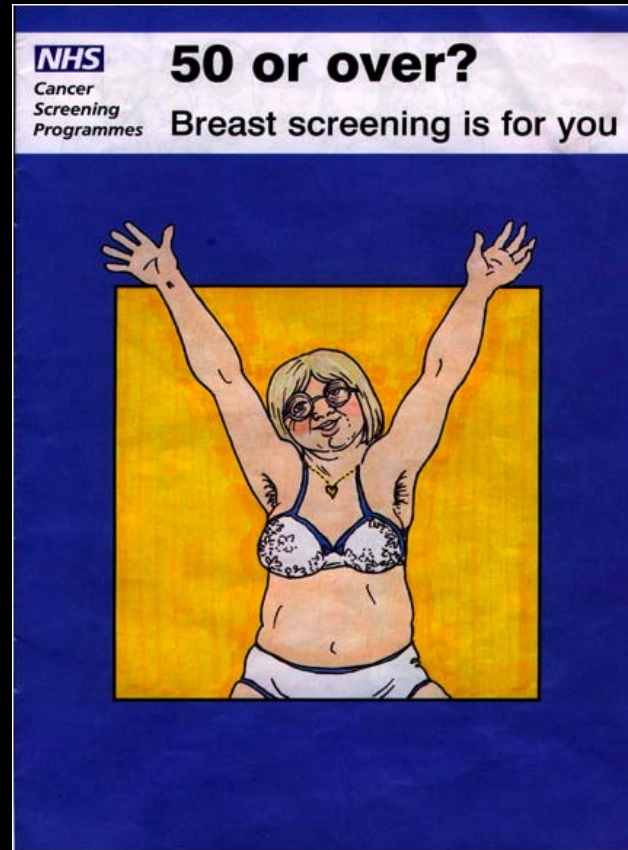
In which case, you may need more than your breasts examined.

Find the time.
Have a mammogram.



Give yourself the chance of a lifetime.

British National Health Service: “Informational Campaign”

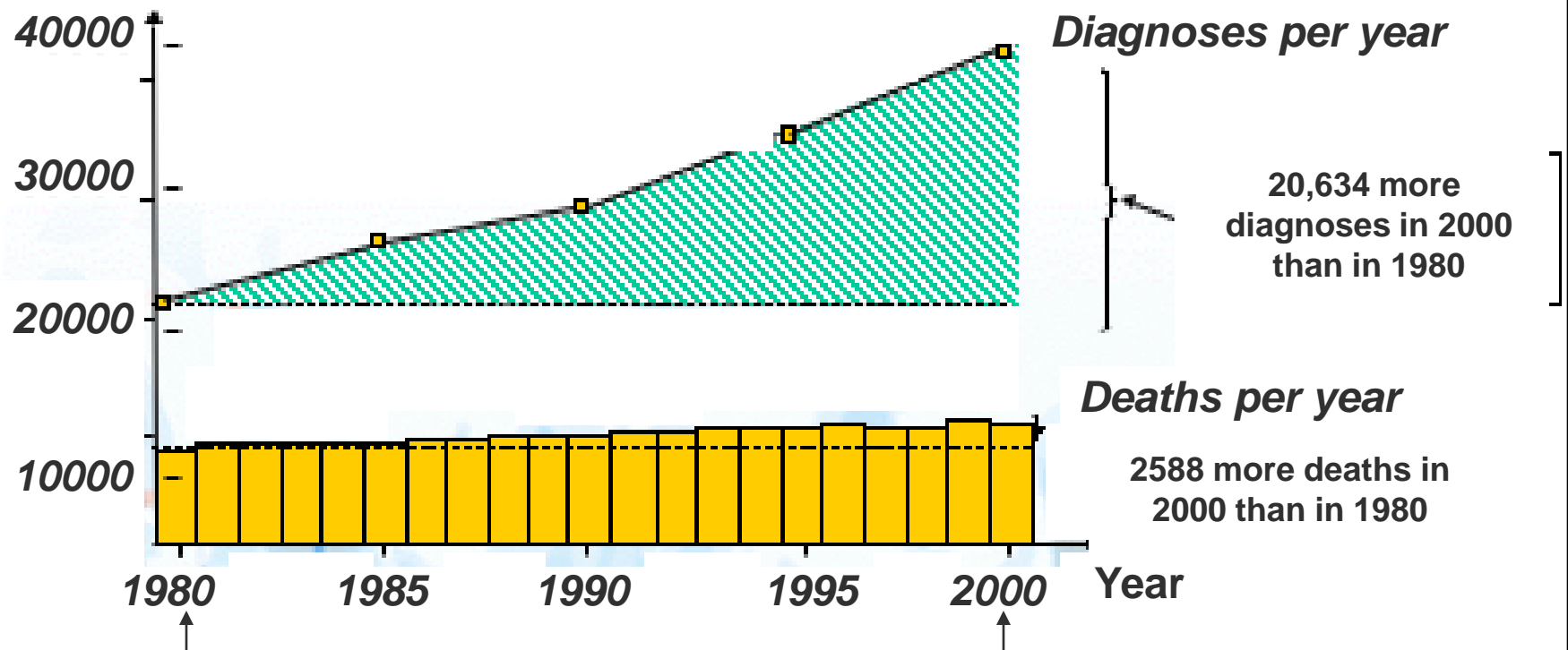


What Are the Issues

- Do guidelines agree on screening rules?
- Does breast cancer incidence increase with age?
- Is there evidence that mammography saves lives (reduces total mortality) in older women?
- How large is the effect?
- Can screening produce harm?
- Do we understand the natural history of breast cancer?
- Are there non-experimental opportunities to study these problems?
- What should patients be told?

Breast cancer diagnoses and deaths, 1980 – 2000 France (Junod, Olsen, Kaplan et al, 2009)

Number affected/yr



N=308
mammography
machines

N=2511
mammography
machines

Do guidelines agree
on screening rules?

Guidelines for Screening Older Women Using Mammography

US Preventive Services Task Force	Biennial mammography 50-70, no evidence for screening beyond 70
ACP	Screen until 74 (based on oldest participants in RCTs)
ACS/NCI	Annual mammography starting age 40, no upper limit
AGS	Biennial mammography until 75, every third year thereafter, no upper limit

Evaluation of a Disease Reservoir Hypothesis

- Disease is common, particularly in older adults
- If you look hard for disease, you will find it
- Much of the disease is “pseudo-disease” - if left alone, would have no clinical significance

SCREENING WILL:

- lead to more treatment
- increase cost
- not add health benefit and may cause harm



Received

Pseudodisease

If there is a reservoir...

- The better the technology for looking, the more you will find.

Question 3

Will Better Testing Methods Make
the Problem Better?

If there is a reservoir...

- The better the technology for looking, the more you will find.

How many people have cancer?

■ <u>Site</u>	Deaths	Autopsy
■ Breast	3%	39%
■ Prostate	3%	46%
■ Thyroid	0.1%	100%

Prevalence of DCIS by number of slides per breast

<u>Reference</u>	<u>Slides</u>	<u>% DCIS</u>
Bartow et al, 1987	9	0
Kramer et al, 1973	40	4.3
Neilsen et al, 1984	95	14.3
Neilson et al, 1987	275	39

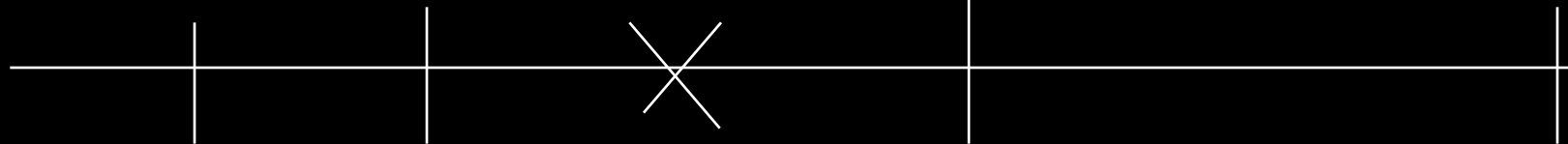
Natural History of Disease

Preclinical

Clinical

DPCP

Lead Time



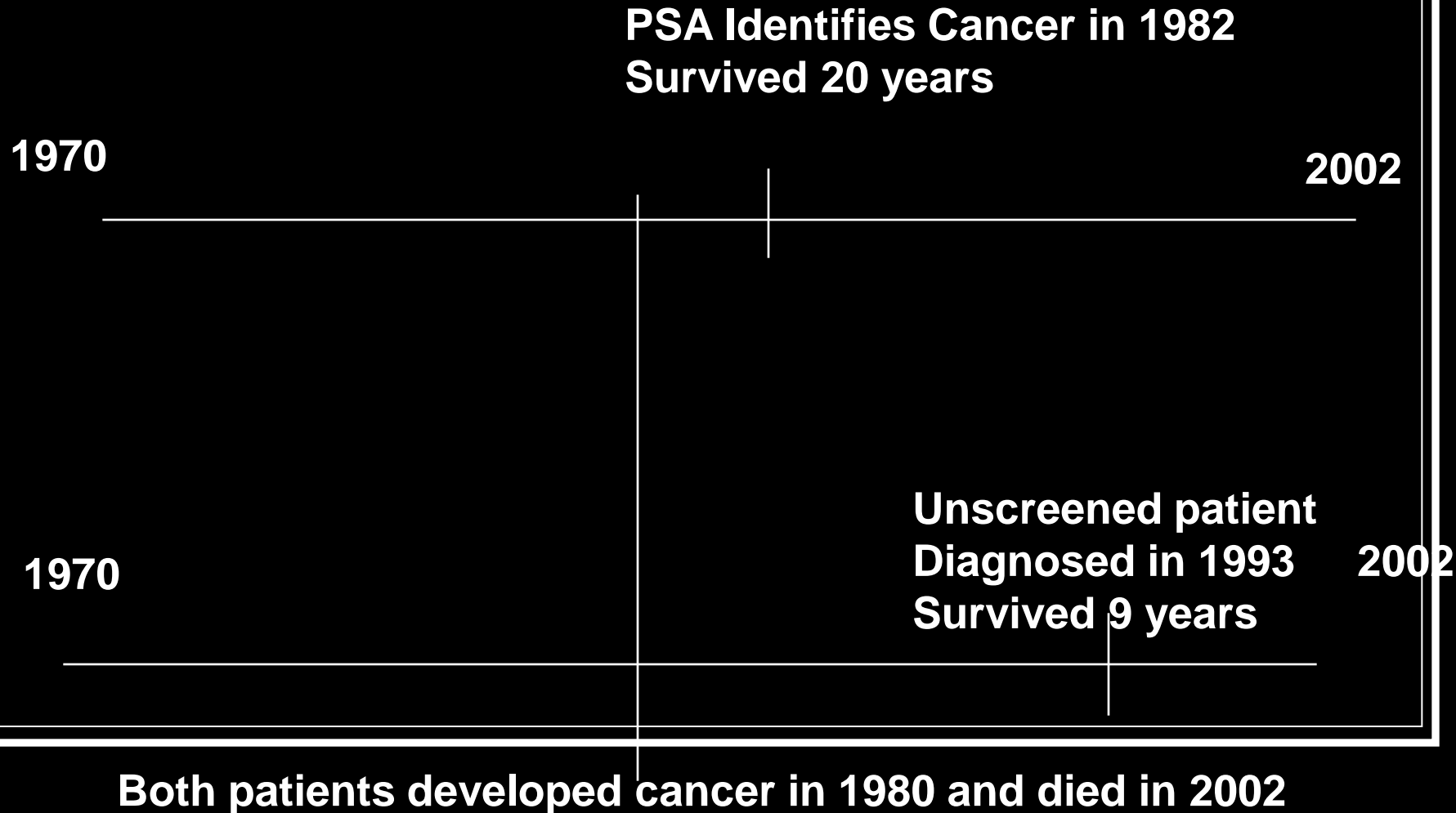
Onset of
of Disease

Test
Detects

signs or
Symptoms

Death
from disease
or other
cause

Lead Time Bias

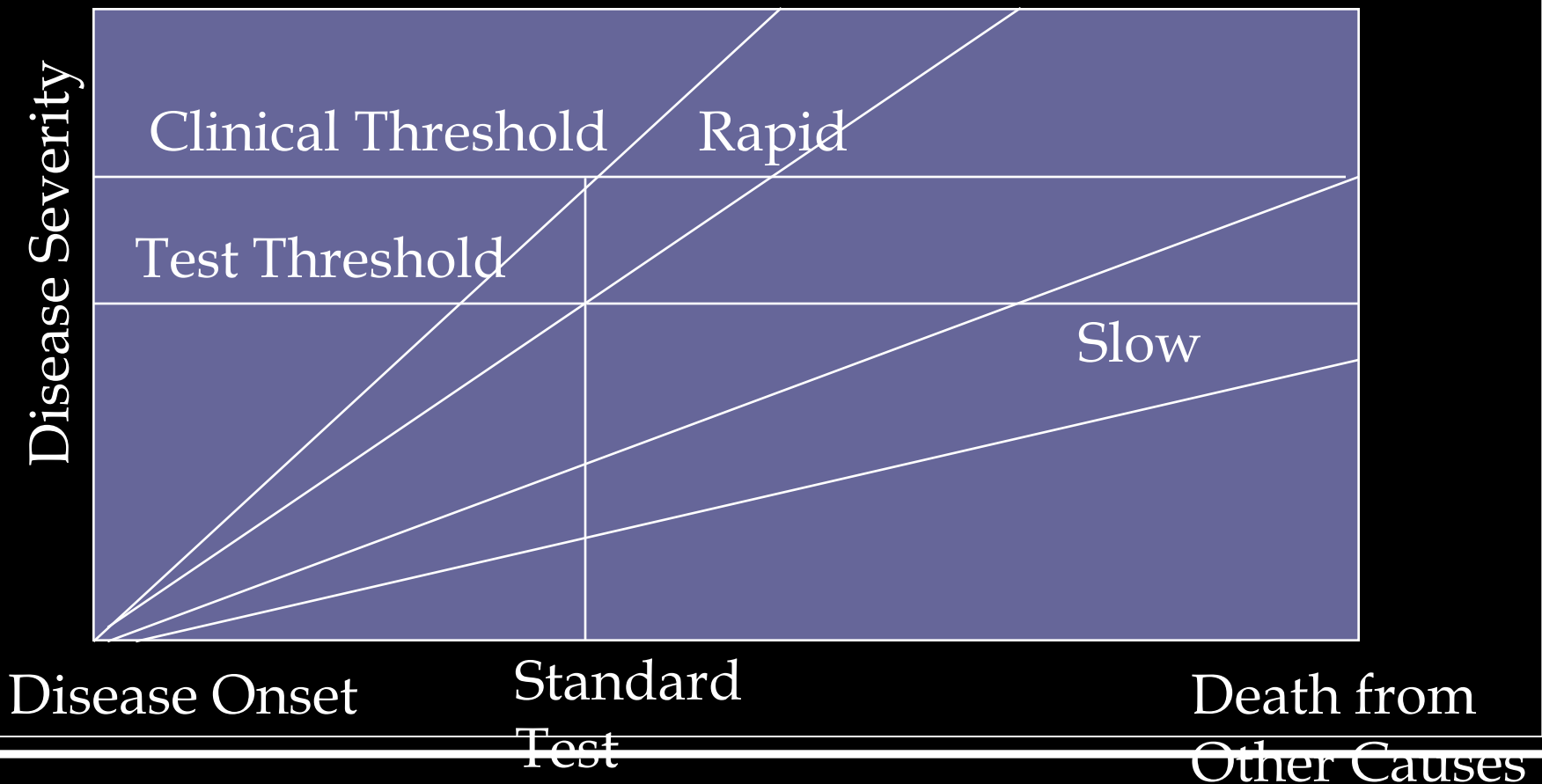


Five Year Survival Rates are Improving

Doesn't this mean we are winning the war on cancer?

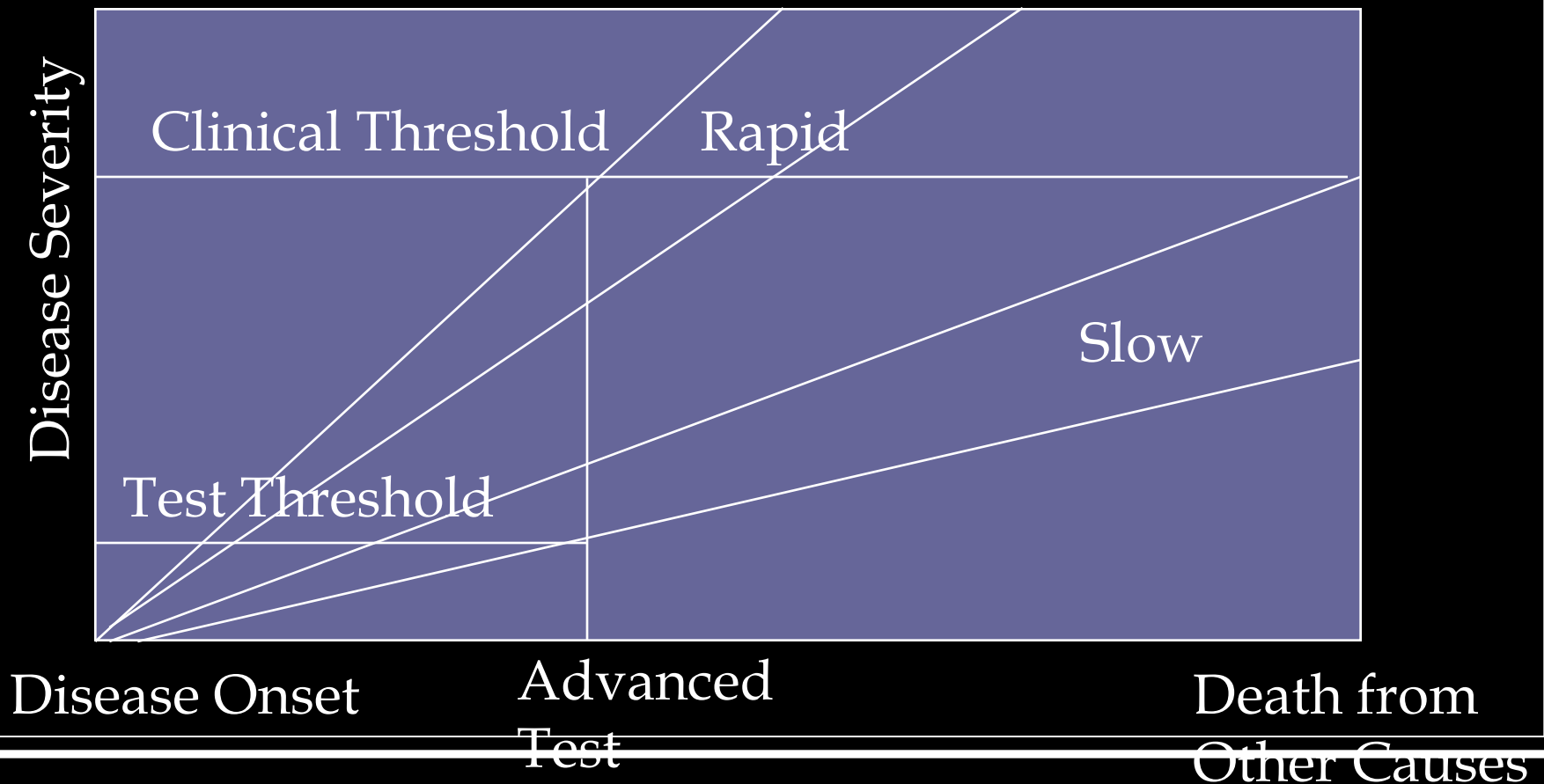
Length Bias: Standard Test (Black & Welch, 1993)

Death From Disease



Length Bias: Advanced Test (Black and Welch, 1993)

Death From Disease



Are There Problems With MD Judgment?

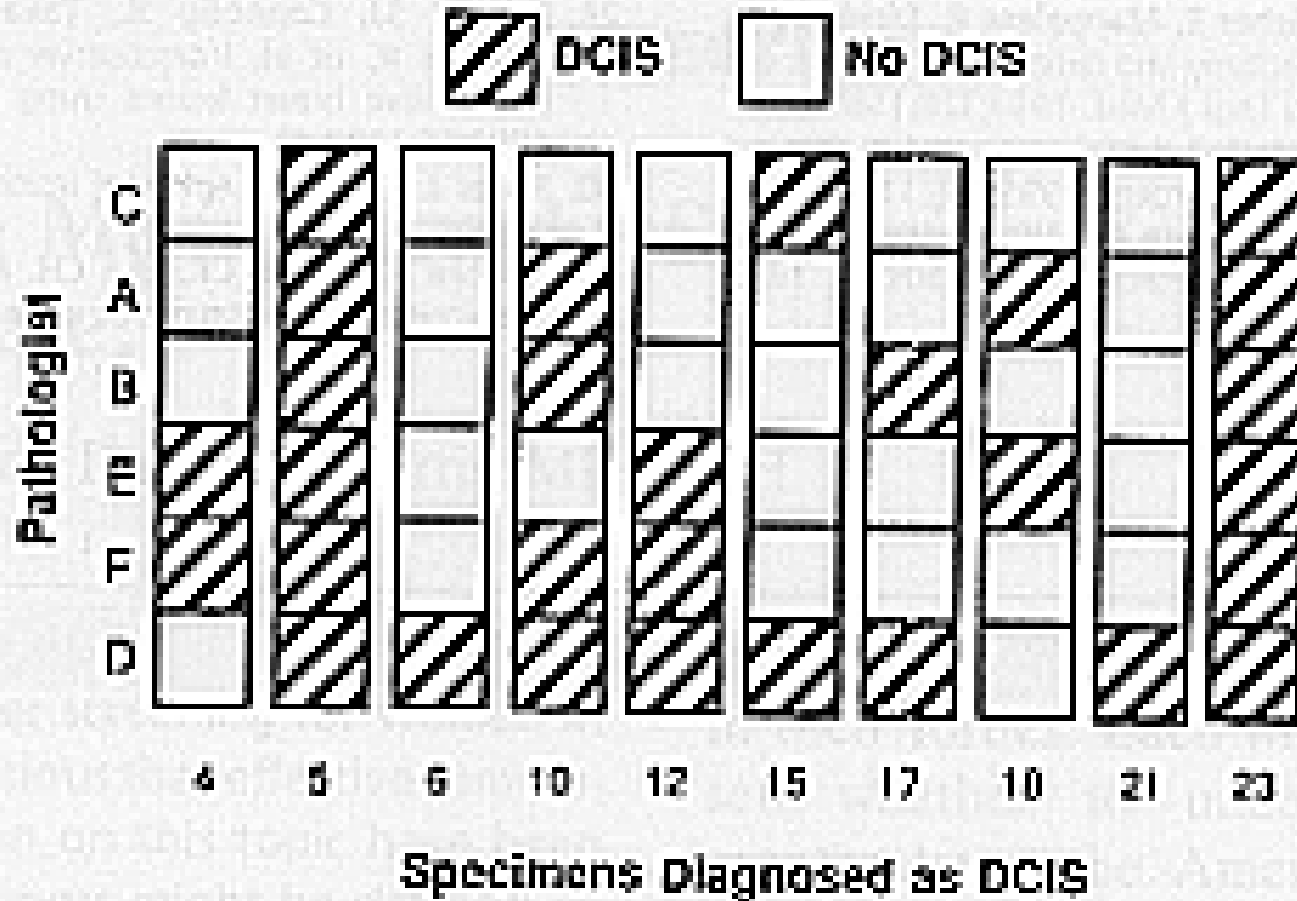
- MD decisions are highly variable
 - they disagree with their peers who have reviewed the same patient
 - they disagree with themselves when presented with the same patient records at two points in time.

Angiography Examples

- Four cardiologists given high-quality angiograms and asked to say if stenosis in the proximal or distal left anterior descending artery is >50%.
 - The cardiologists disagreed on 60% of the cases (Zir et al. Circulation, 1976,53,627)
 - Cardiologists looking at the same angiograms at two points in time disagree with themselves 8% to 37% of the time (Detre et al Circulation 1975, 52, 979)

Interobserver Agreement Among 6 Pathologists on DCIS for 10 Case

(Schnitt et al, 1992)



How common are false positive tests (cancer scares)

- 1st Mammogram 7% Kerilowske 1993
- 2nd Mammogram 3.5%
- PSA 7-11% Mettlin, 2001
- FOBT 8-16% Ransohoff, 1997

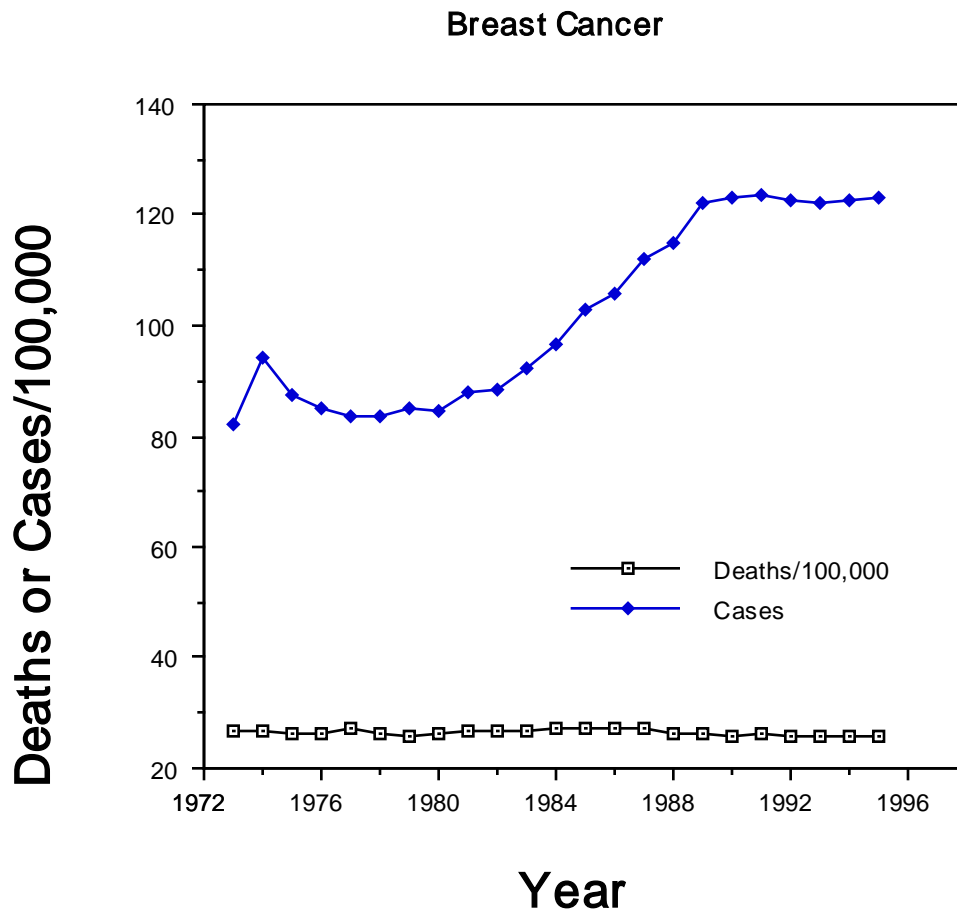
Chances of Having a False Positive over 10 Years if Screened Every Year or Every Other Year (Welch, 2003)

False Positive Rate	Annual	Every other Year
5%	40%	23%
10%	65%	41%

The Breast Cancer Screening Controversy

Should women age 40-50 be
screened?

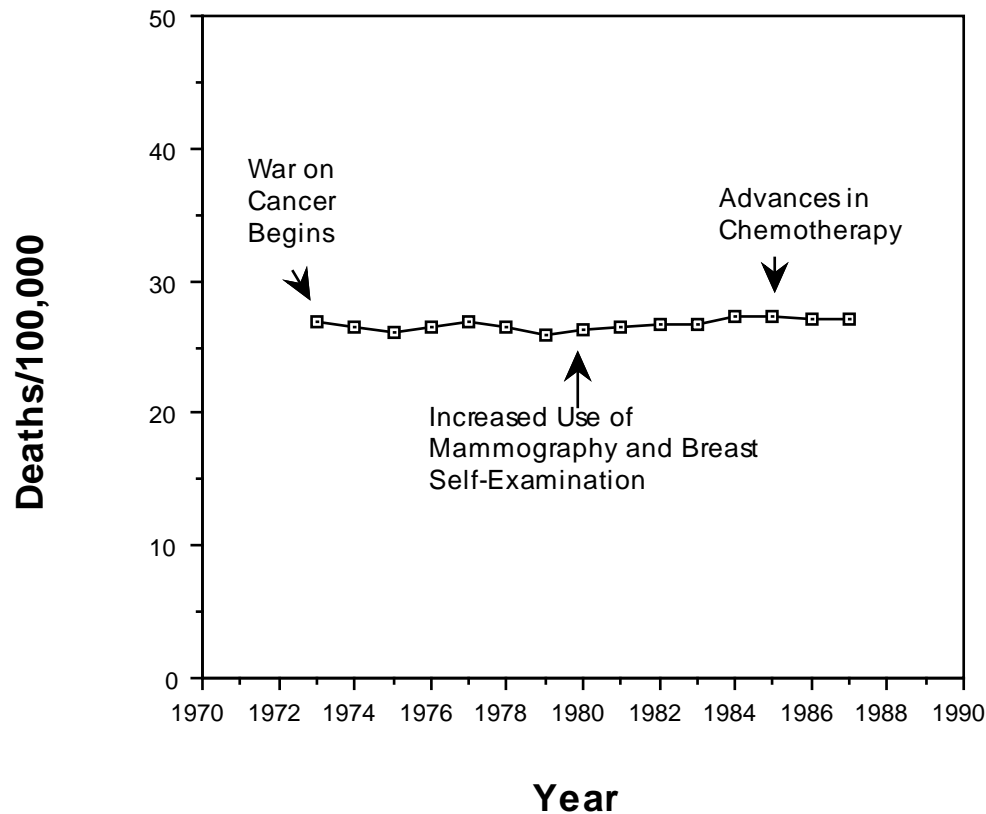
Breast Cancer Cases and Deaths: 1974-1995, SEER data



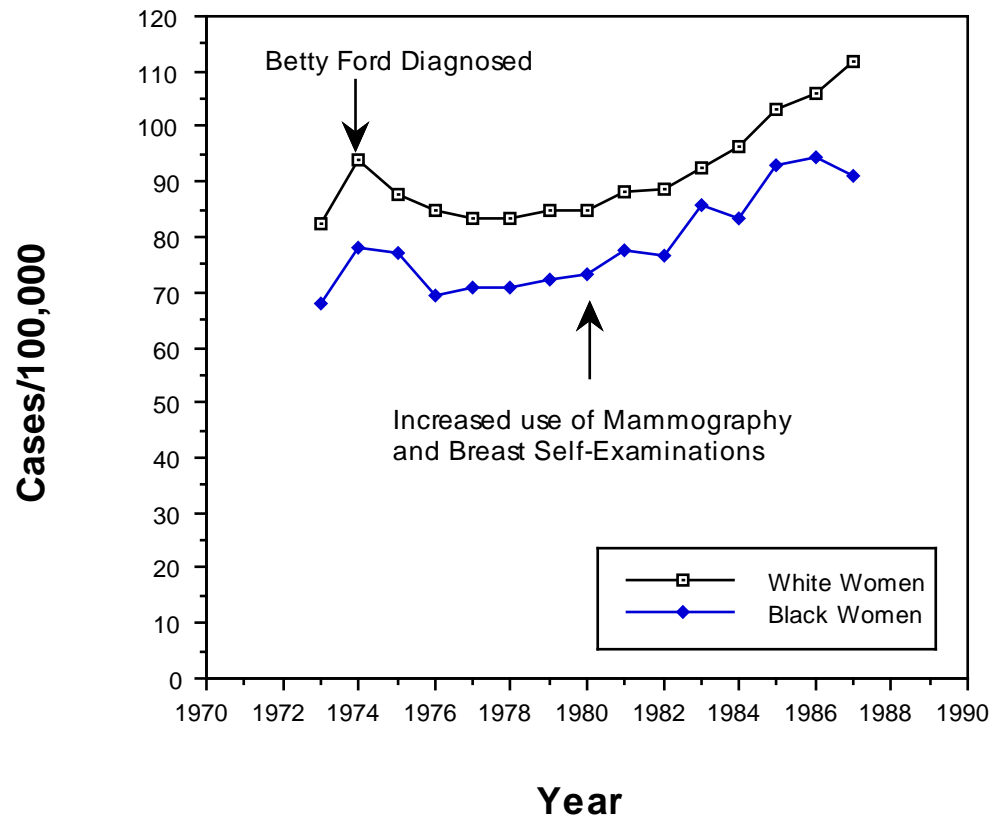
How many women die of breast cancer?: How many with breast cancer?

- ACS says 1 in nine women will be diagnosed with breast cancer
- About 3% of all women will die of breast cancer
- Autopsy studies show that about 39% of elderly women have some evidence of breast cancer

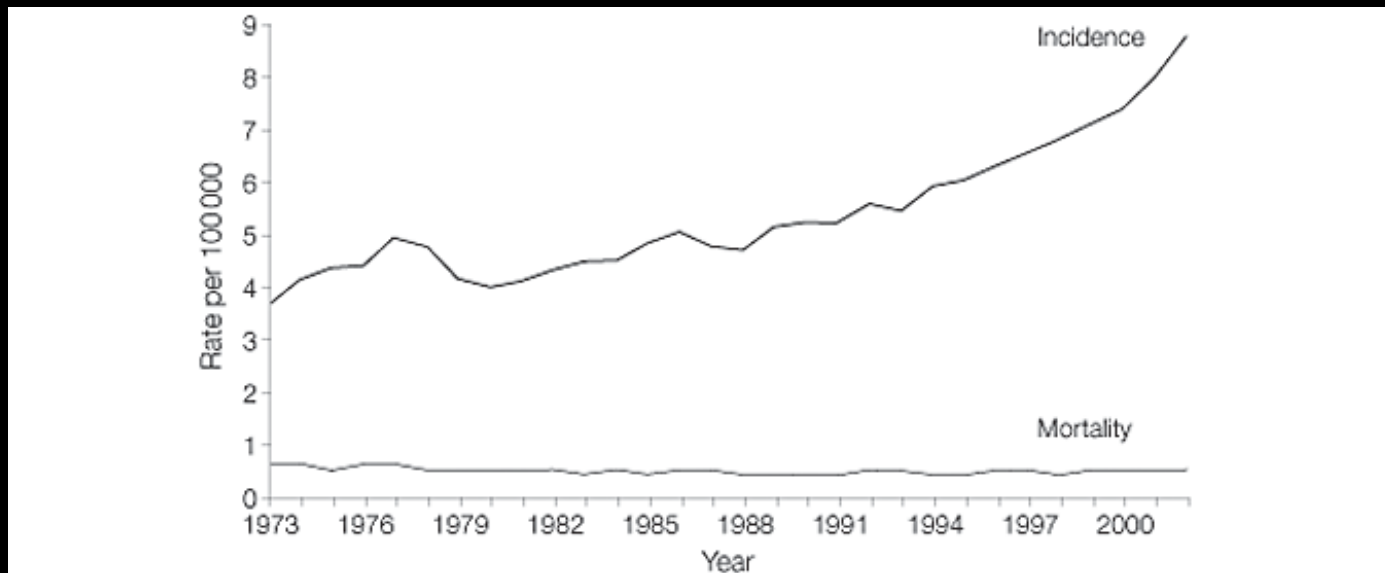
Breast Cancer Mortality (Kaplan, 1993, SEER Data)



Breast Cancer Incidence: 1972-1988 (Kaplan, 1993)



Thyroid Cancer Incidence and Mortality, 1973-2002



Davies, L. et al. JAMA 2006;295:2164-2167.

Incidence and mortality trends of potentially palpable head and neck cancers; rates are per million people-years

(Davies, L & Welch HG [Otolaryngology - Head and Neck Surgery Volume 135, Issue 3](#) , September 2006, P 457

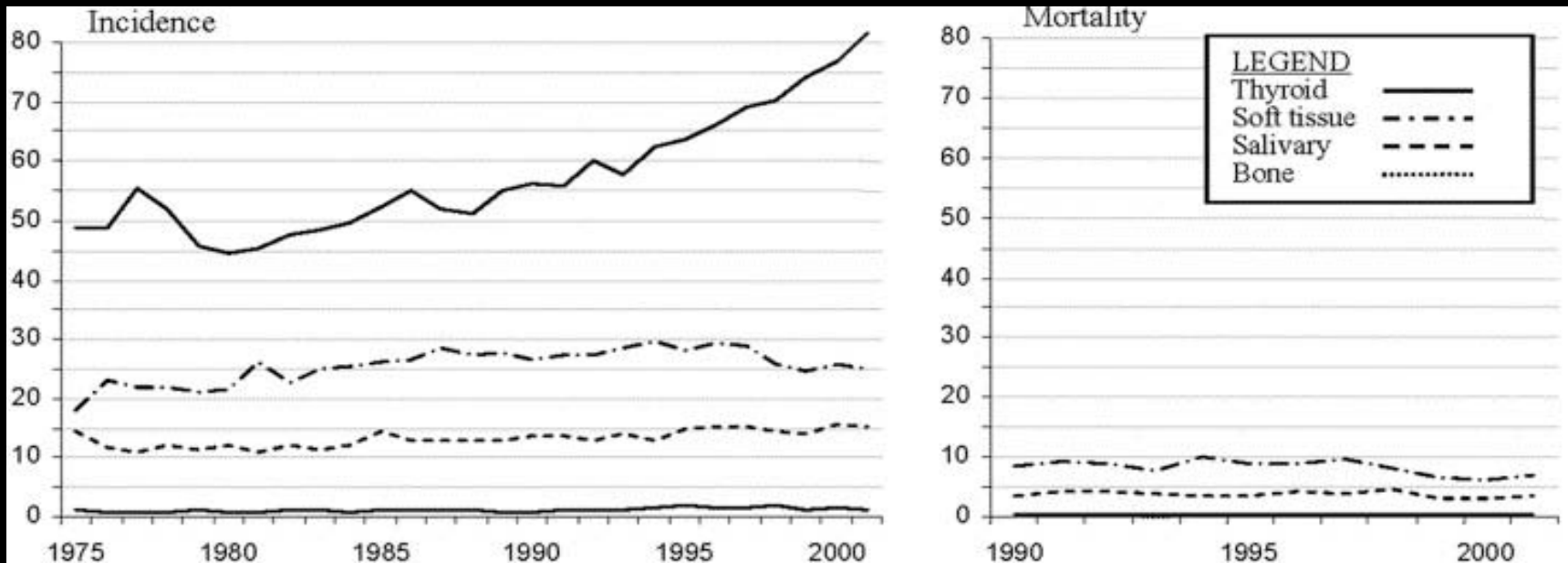


Figure 4.2 Skin biopsies and melanoma (per 100,000 population) in 1986, 2001 and the interval 1987-2000 (from Welch et al, 2005)

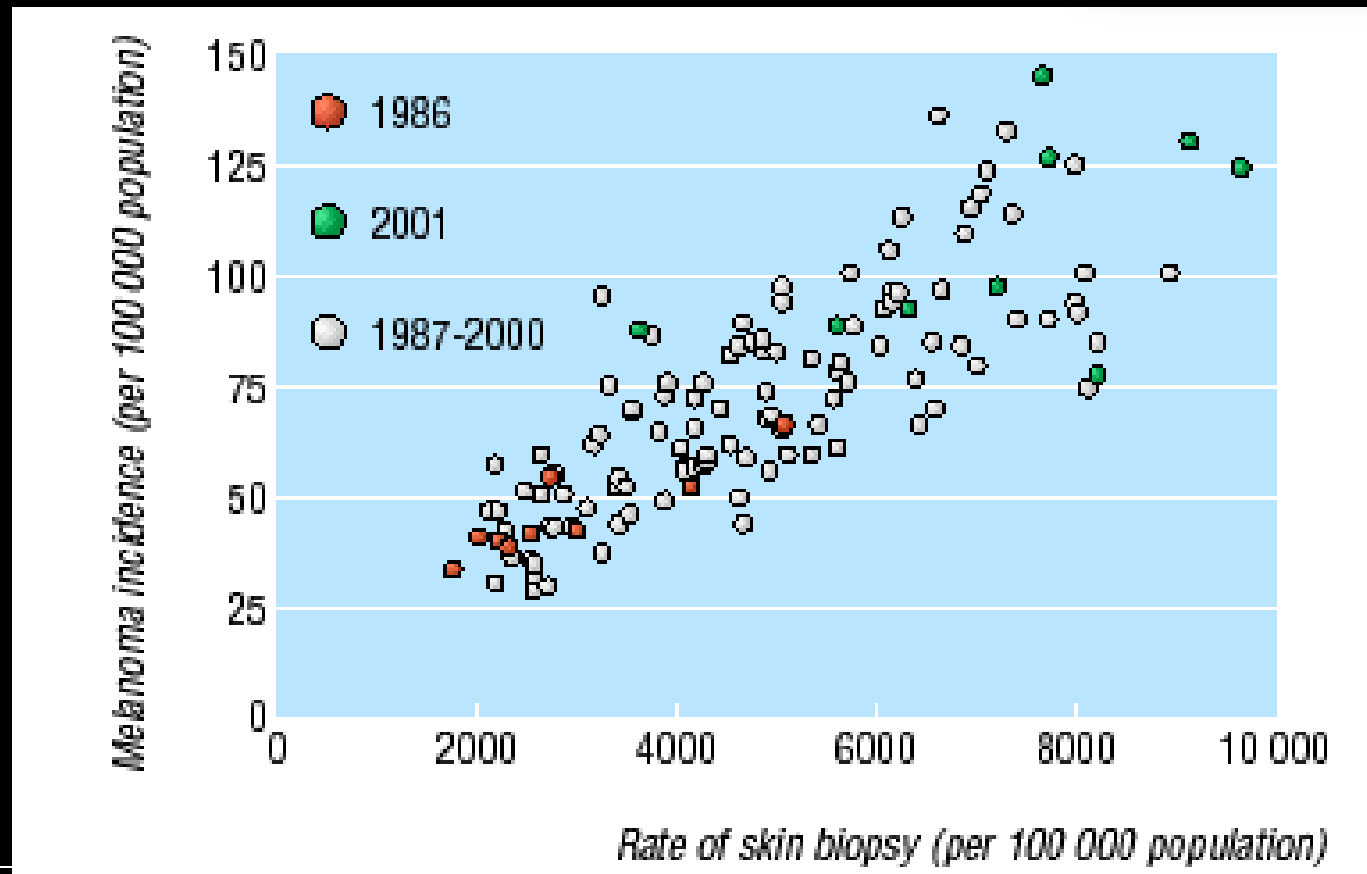
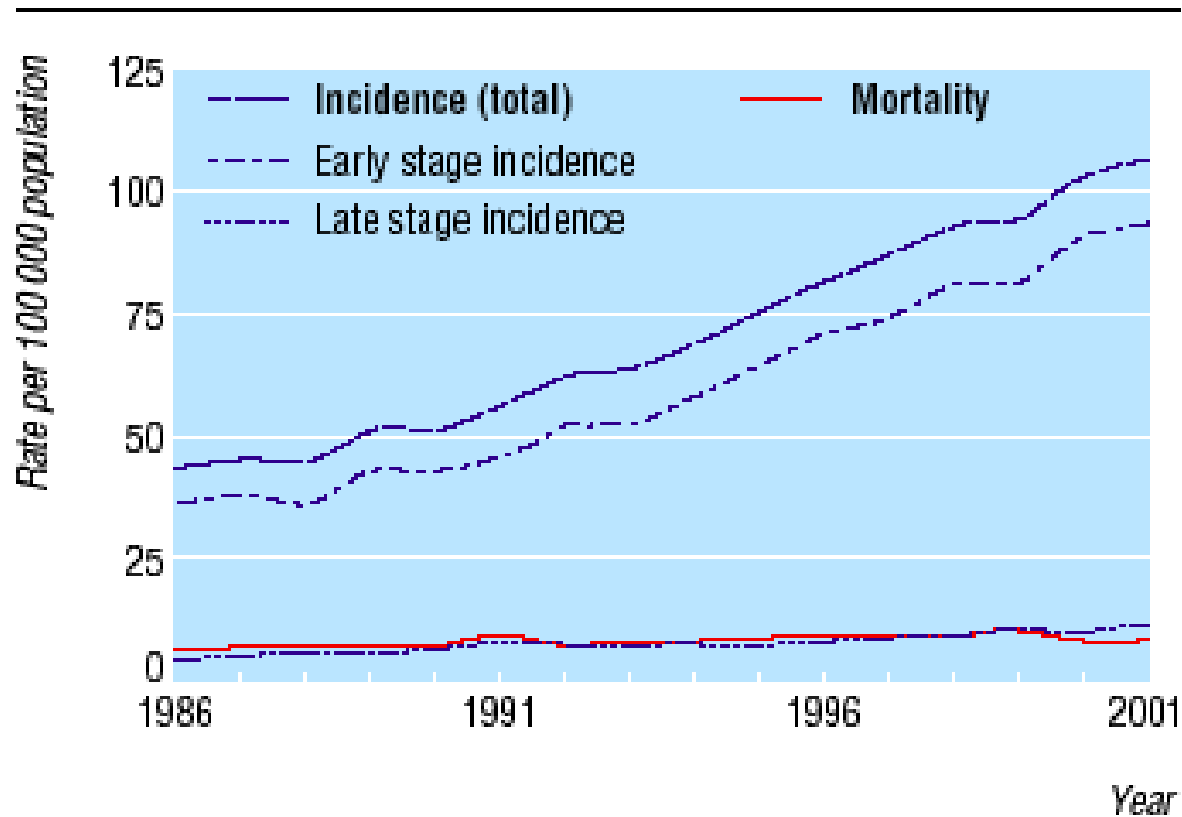
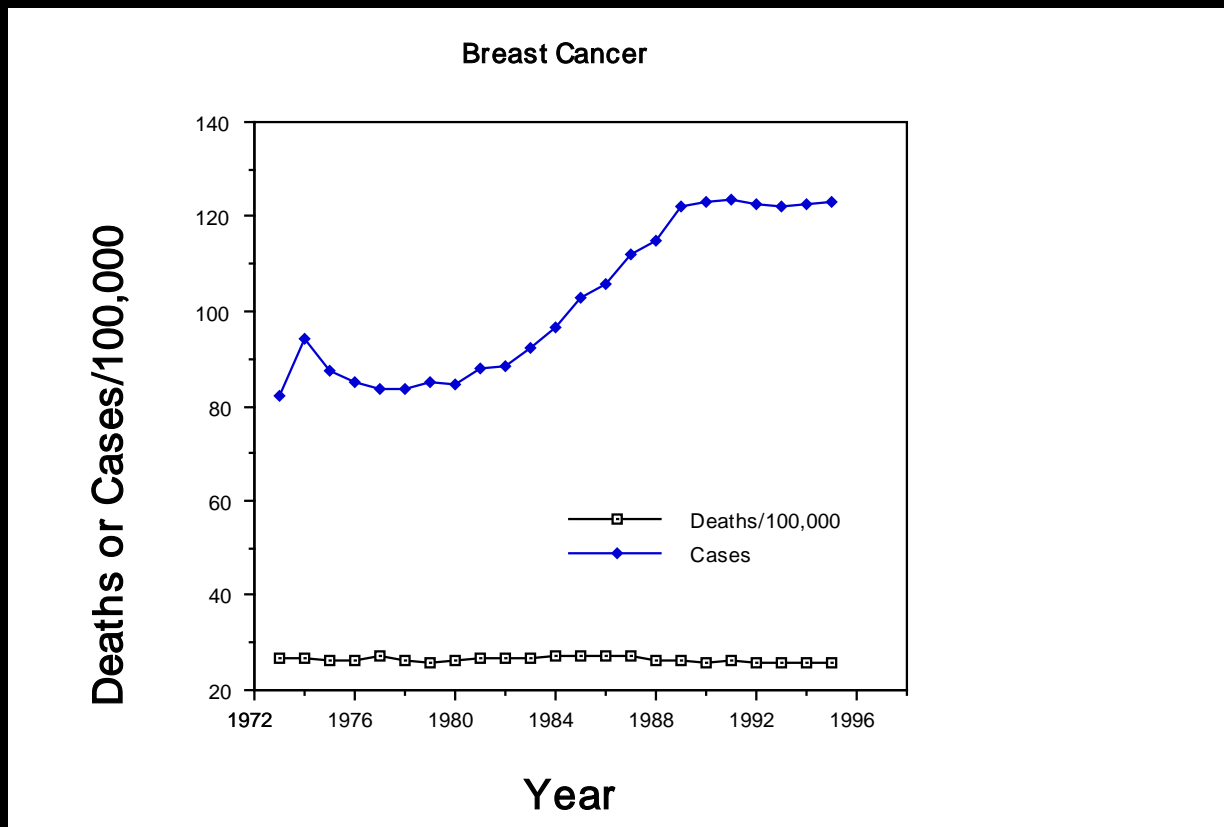


Figure 4.1 Incidence of melanoma and death from melanoma between 1986 and 2001 (From Welch et al, 2005)

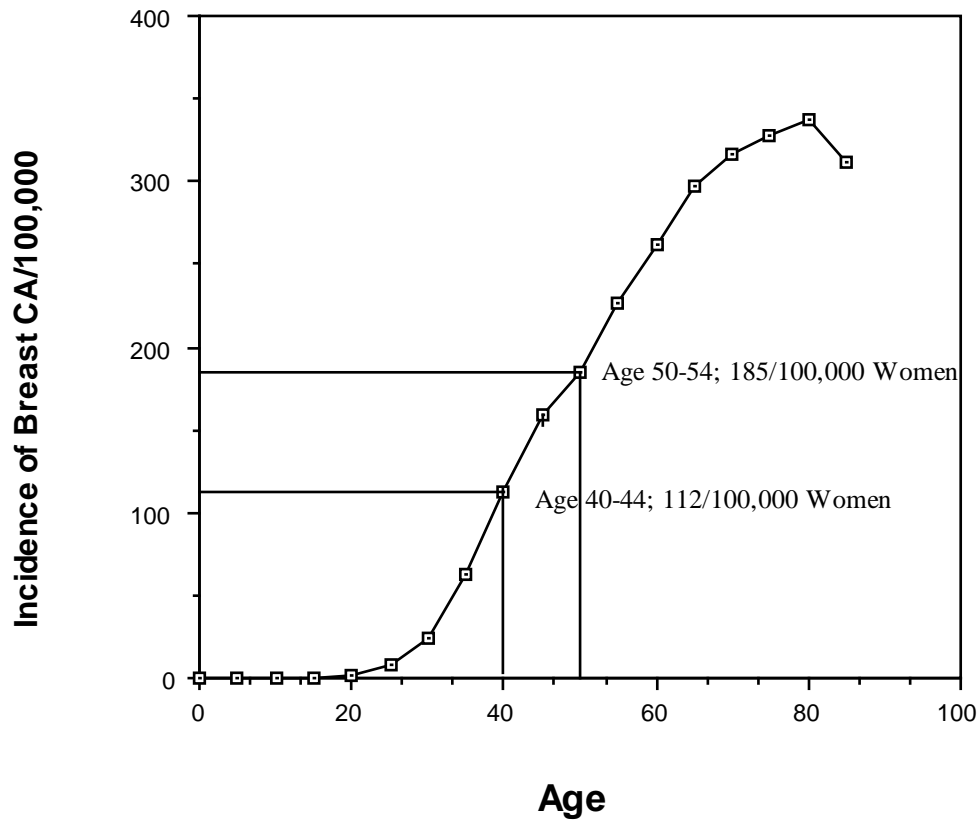


Breast Cancer Cases and Deaths: 1974-1995, SEER data

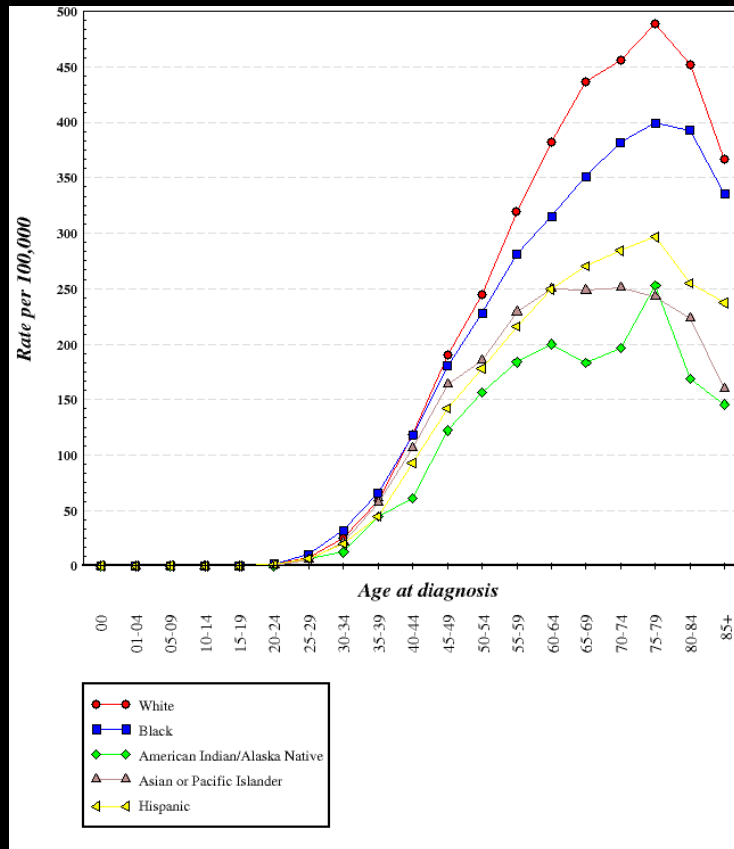


Does breast cancer
incidence increase
with age?

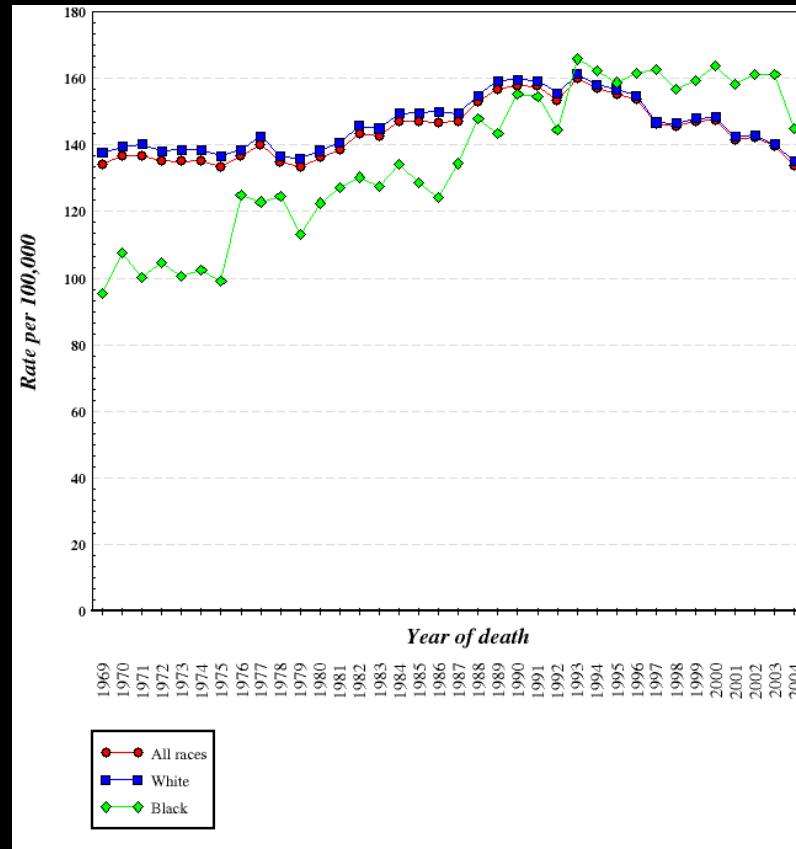
Relationship between age and breast cancer (Kaplan, 1993)



Breast Cancer Incidence By Age: SEER 1975-2006



Breast Cancer Mortality Women 75+: SEER 1969-2004

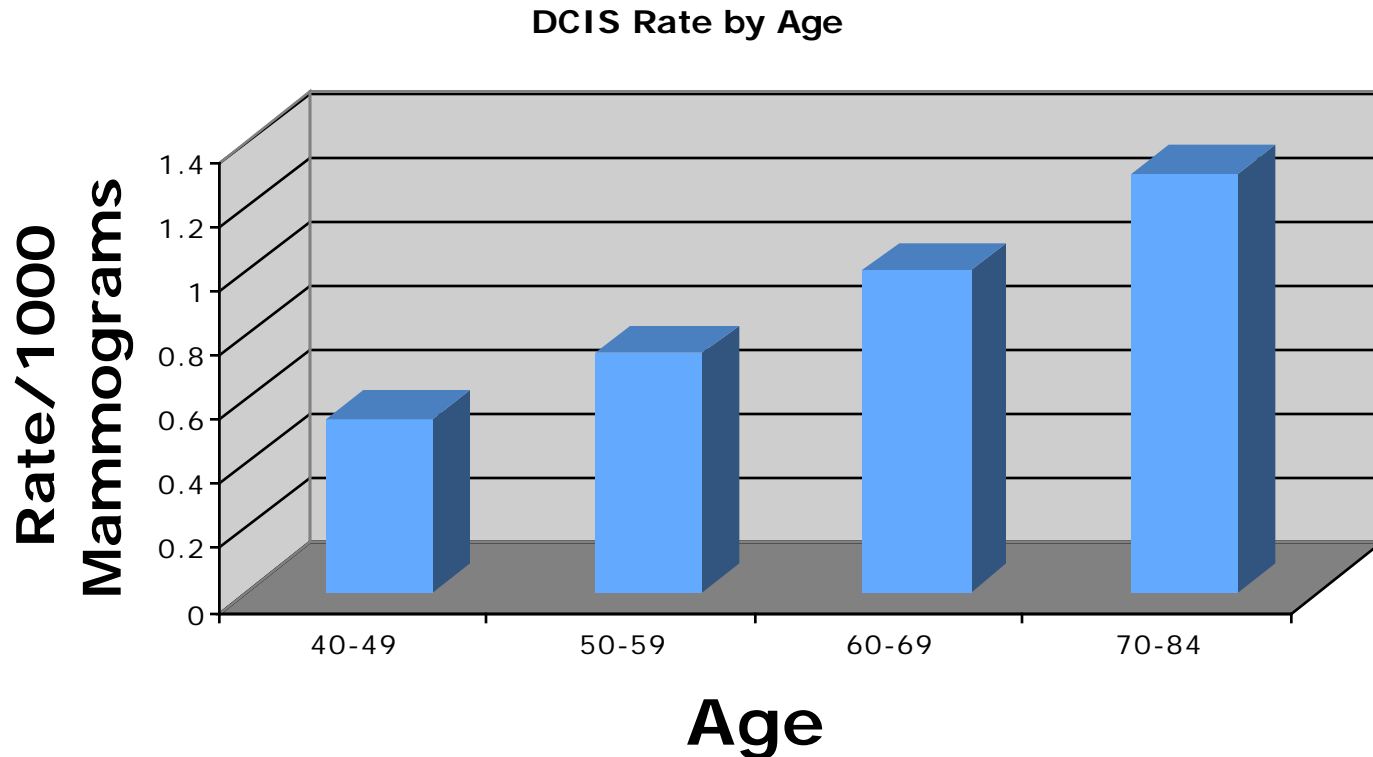


What Explains the Decline for Older Women?

Disease Reservoir Hypothesis:
The more you look, the more you
find

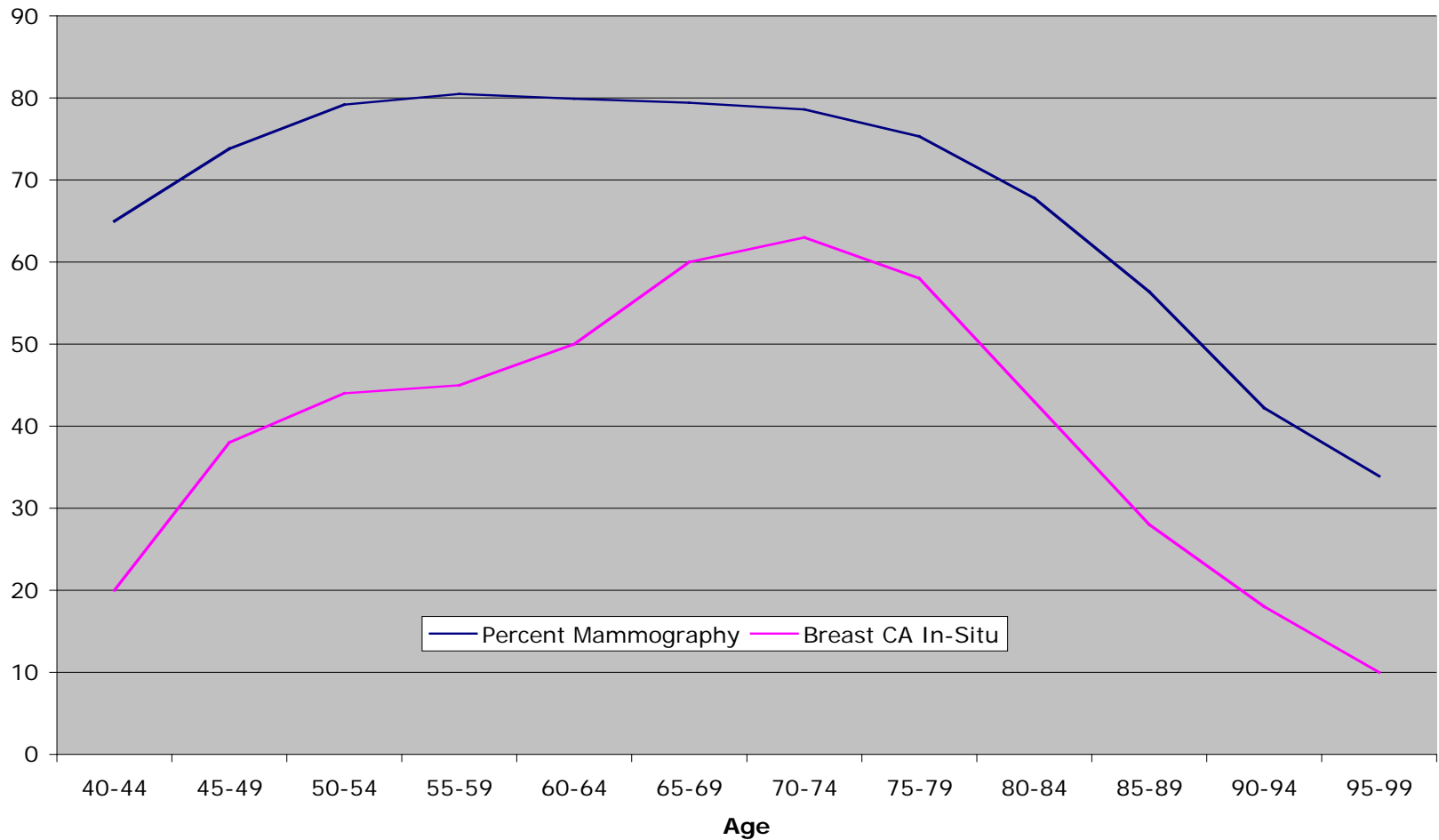
DCIS Rate by Age in NCI Breast Cancer Consortium

(pool of 7 registries, N = 540,738) (adapted from Ernster et al JNCI 2002, 94, 1546)

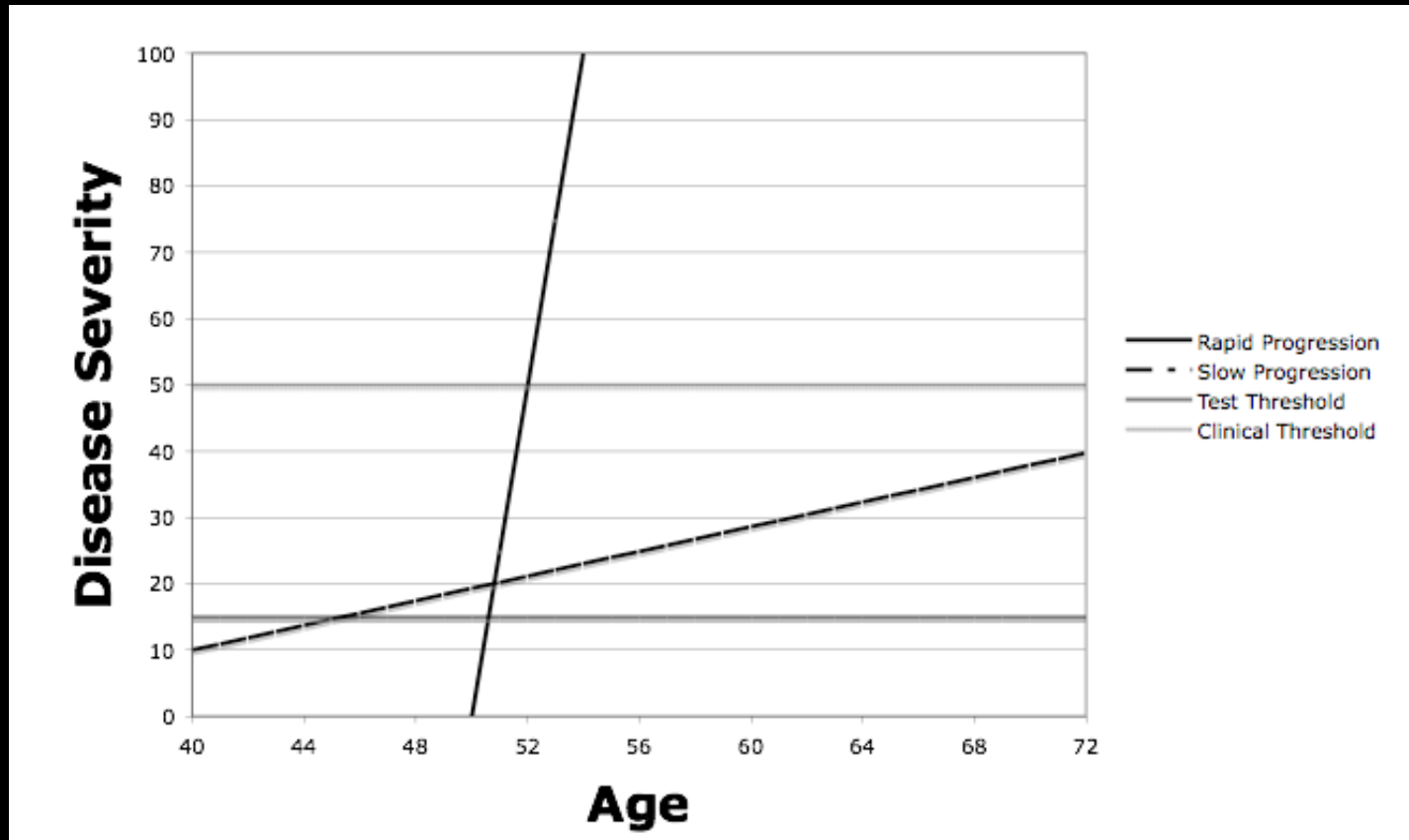


From Kaplan & Saltzstein, 2005

Figure 1. Mammography and Breast CIS by Age



Does screening detect the wrong cases? (Kaplan, 2007)

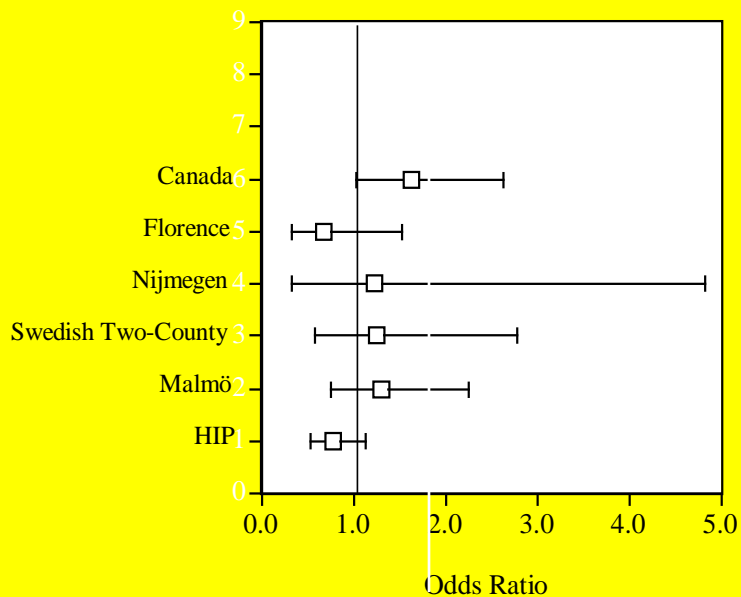


Is There Evidence
that Screening
Mammography
Saves Lives in

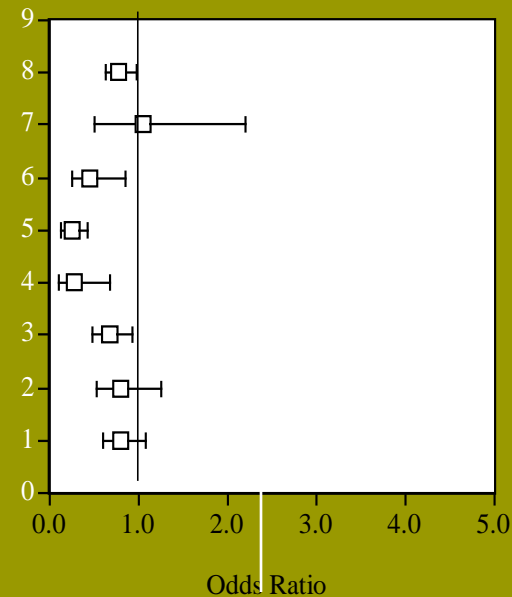
Among Older
Women?

Meta Analysis of Mammography Trials (Navarro and Kaplan, 1996)

Women less than 50 years old



Women over 50 years of age



Cancers detected: Cochrane Review October 2006

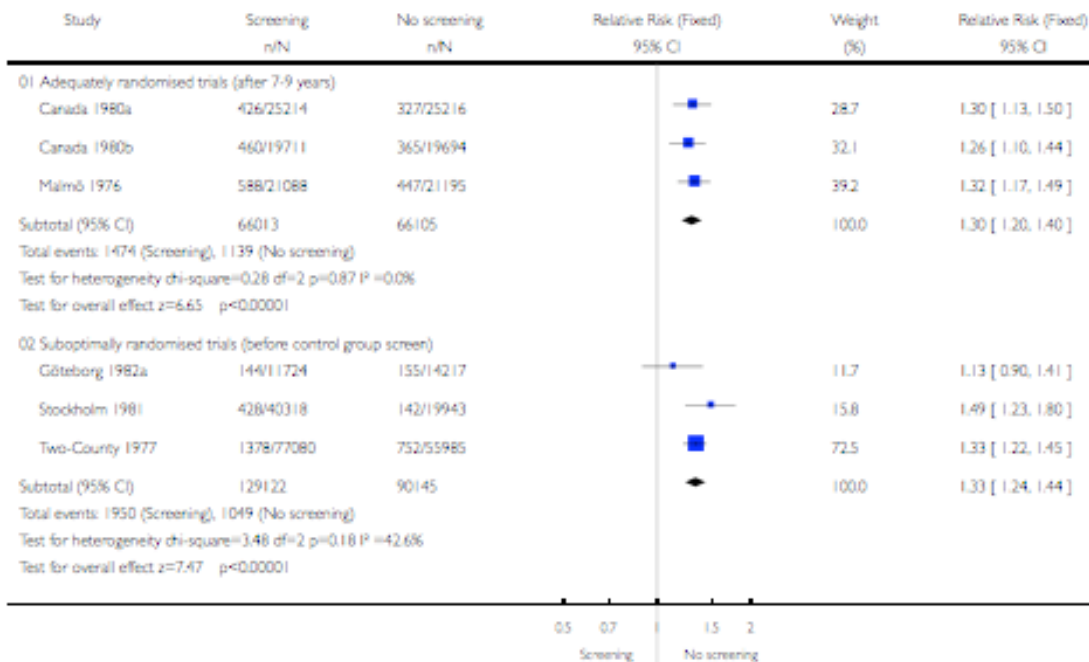
Gotzsche & Nielsen

Analysis 01.21. Comparison 01 Screening with mammography versus no screening, Outcome 21 Number of cancers

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 21 Number of cancers



Results of Randomized, Controlled Trials of Mammography among Women 39 to 74 Years of Age

Table 4. Results of Randomized, Controlled Trials of Mammography among Women 39 to 74 Years of Age*

Study (Reference)	Age	Median Follow-up	Breast Cancer Deaths/Total Women		Breast Cancer Death Rate per 1000 Women		Relative Risk for Death from Breast Cancer (95% CI)	Absolute Risk Reduction per 1000 Women	Number Needed To Invite to Screening†
			Screened Group	Control Group	Screened Group	Control Group			
	y		n/n						
Mammography alone									
Stockholm (23)	40–64	13.8	82/39 139	50/20 978	2.10	2.38	0.91 (0.65–1.27)	0.288	3468
Gothenburg (23)	39–59	12.8	62/20 724	113/29 200	2.99	3.87	0.76 (0.56–1.04)	0.878	1139
Malmö (23)	45–70	17.1	161/21 088	198/21 195	7.63	9.35	0.82 (0.67–1.00)	1.712	584
Swedish Two-County Trial (26)	40–74	17	319/77 080	333/55 985	4.14	5.95	0.68 (0.59–0.80)	1.809	553
Mammography plus CBE									
CNBSS-1 (22)	40–49	13	105/25 214	108/25 216	4.16	4.28	0.97 (0.74–1.27)	0.12	–
CNBSS-2 (20)	50–59	13	107/19 711	105/19 694	5.43	5.33	1.02 (0.78–1.33)	–0.097	–
HIP (19)	40–64	16	232/30 239	281/30 256	5.46	6.89	0.79	1.438	883
Edinburgh (18)	45–64	13	156/22 926	167/21 342	6.80	7.82	0.79 (0.60–1.02)	1.020	980

* CBE = clinical breast examination; CNBSS = Canadian National Breast Screening Study; HIP = Health Insurance Plan of Greater New York.

† Number needed to invite to screening to prevent one death from breast cancer 13–20 years after randomization.

Humphrey, L. L. et. al. Ann Intern Med 2002;137:34760-3

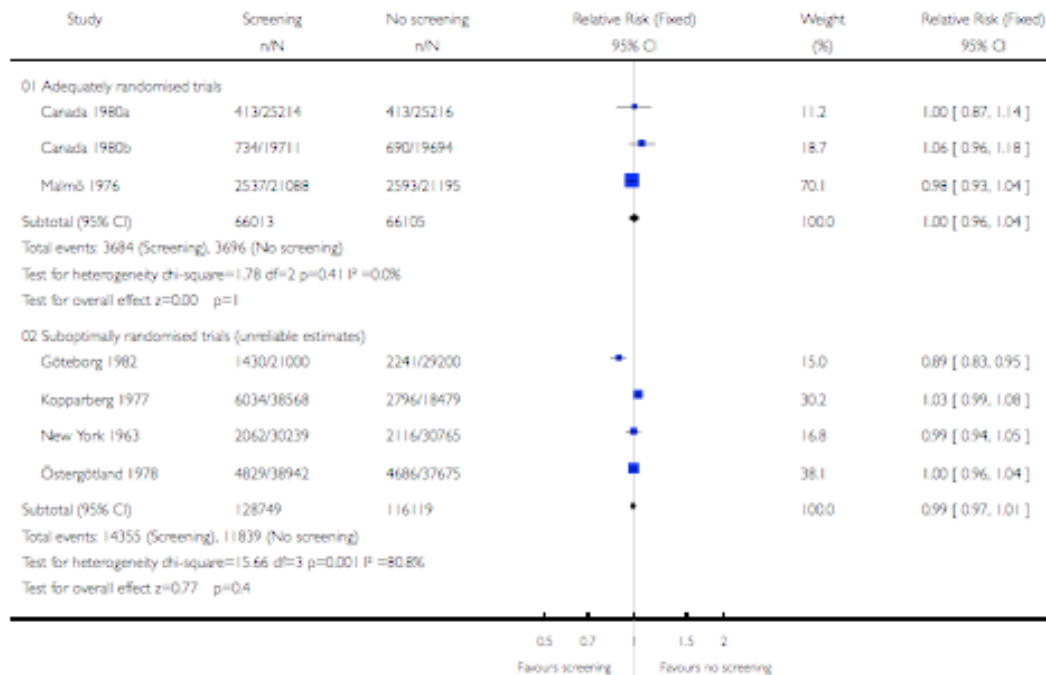
Cochrane Review October 2006 Gotzsche & Nielsen

Analysis 01.09. Comparison 01 Screening with mammography versus no screening, Outcome 09 Overall mortality, 13 years follow up

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 09 Overall mortality, 13 years follow up

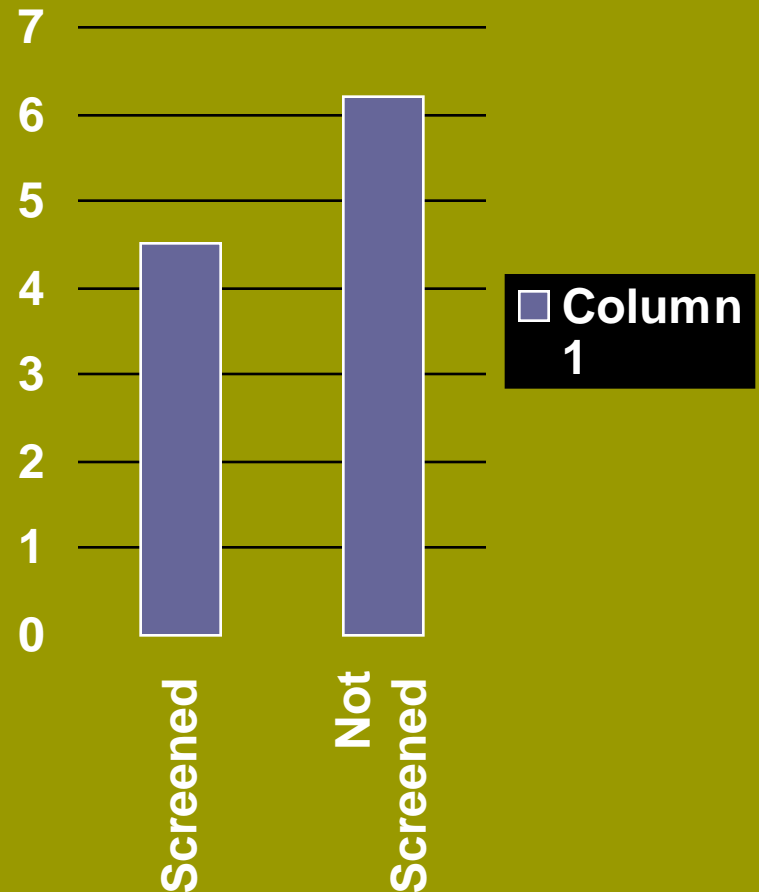


The total mortality problem

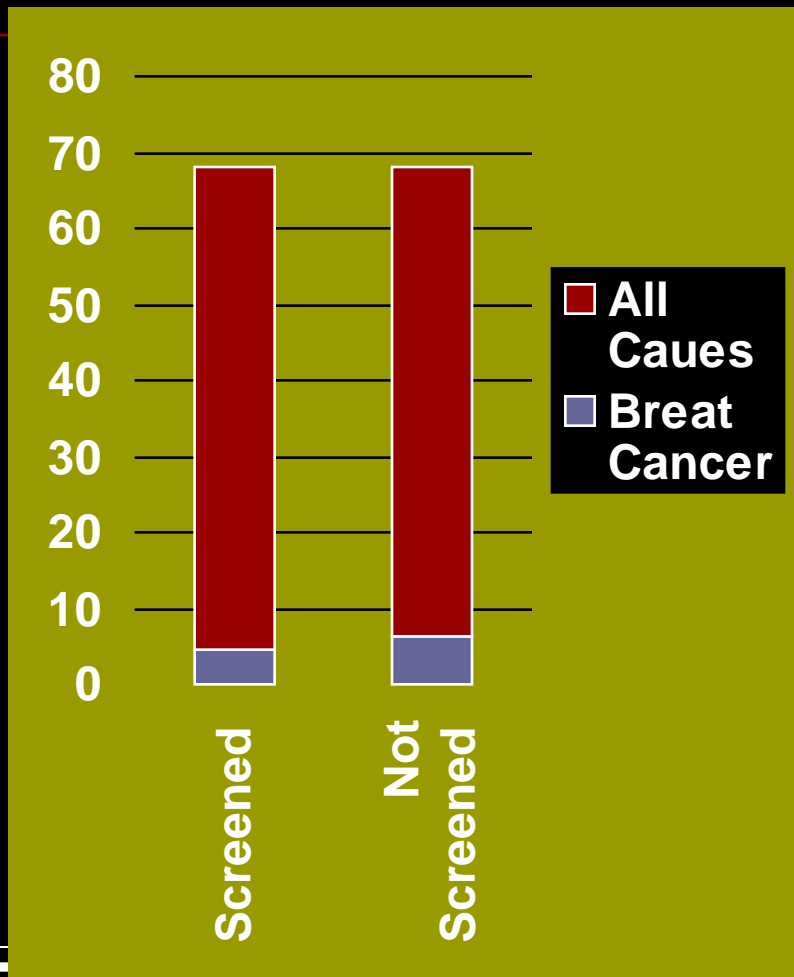
Is being dead from cancer worse
than being dead from something
else?

Cancer mortality in the Health Insurance Plan of New York

- 60,000 women assigned to mammography or usual care
- After 10 years 147 deaths in the mammography group and 192 deaths in usual care group
- 23% reduction in cancer deaths



Cancer mortality in the Health Insurance Plan of New York



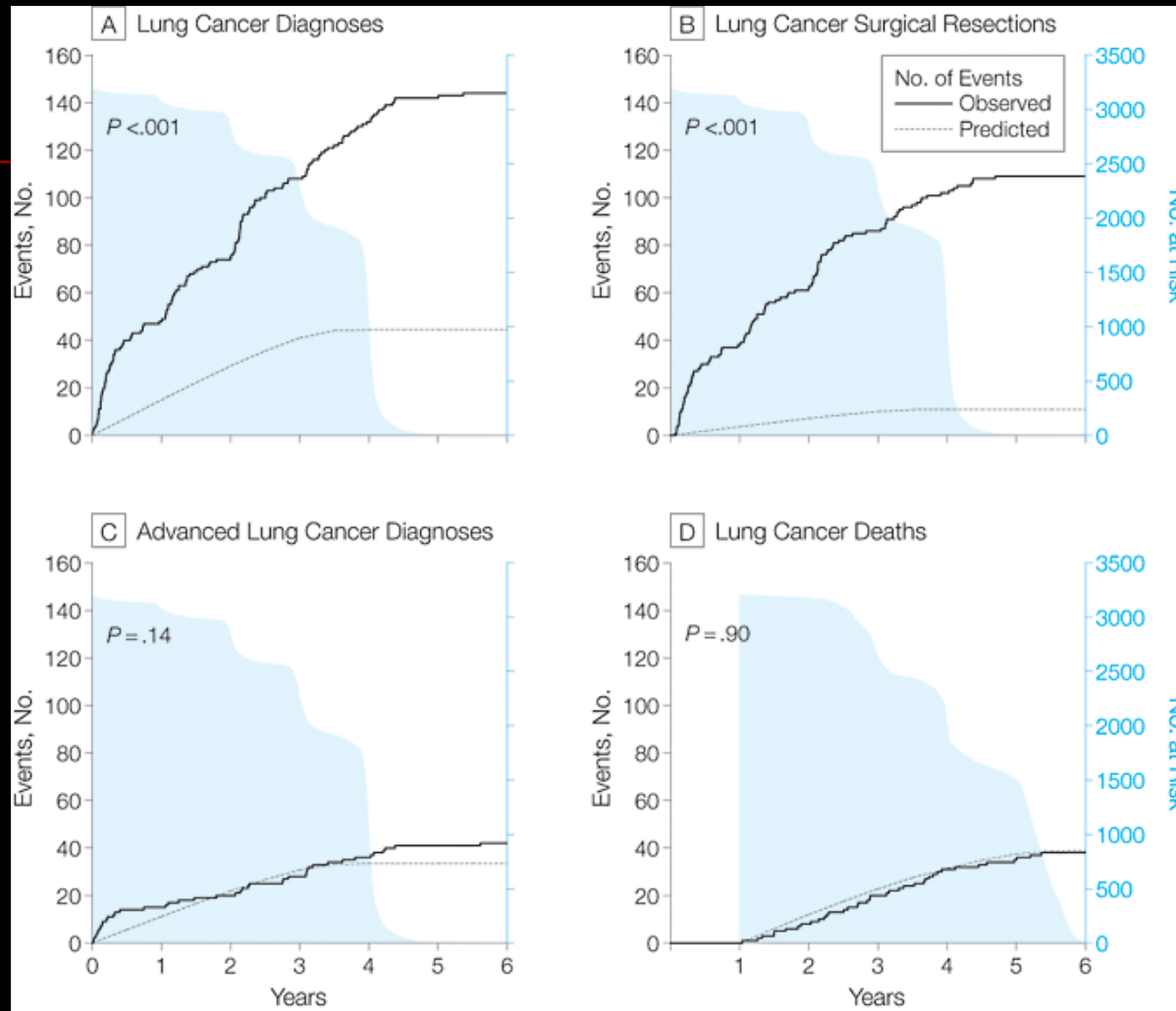
- Lower portion shows cancer deaths, upper shows non cancer deaths
- No difference is survival between screened and unscreened women

Summary of data on benefits and harms of screening mammography every 1-2 years for 10 year.

Adapted from Schwartz, BMJ, 2007;335:731-732

	40-49 Years	50-69 Years
Benefits- 10 year Survival		
No screening	3.3/1000 (0.33%)	8.9/1000 (0.89%)
Screening	2.5/1000 (0.25%)	6.0/1000 (0.6%)
Avoidance of death from breast cancer	0.8/1000 (0.08%)	3/1000 (0.30%)
Harms		
Patient has at least one false positive screening examination that results in additional testing ³	100-500/1000 (10-50%)	100-500/1000 (10-50%)
Patient has at least one false positive screening examination that results in unnecessary diagnosis and treatment for breast cancer	2-5/1000 (0.25-0.5%)	3-9/1000 (0.30-0.90%)

Combined Results for the Studies of Lung Cancer Screening With Computed Tomography



Bach, P. B. et al. JAMA 2007;297:953-961.

PLCO Prostate Study

NEJM 2009, 360 (13) 1310-19

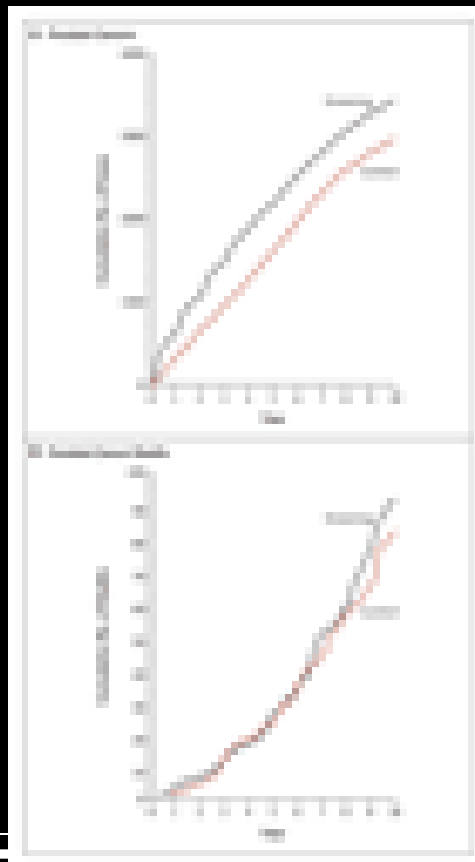
Table 1. Characteristics of the Subjects at Baseline.*

Variable	Screening Group (N=38,343)	Control Group (N=38,350)
	<i>percent</i>	
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.

PLCO Results for Cases and Deaths

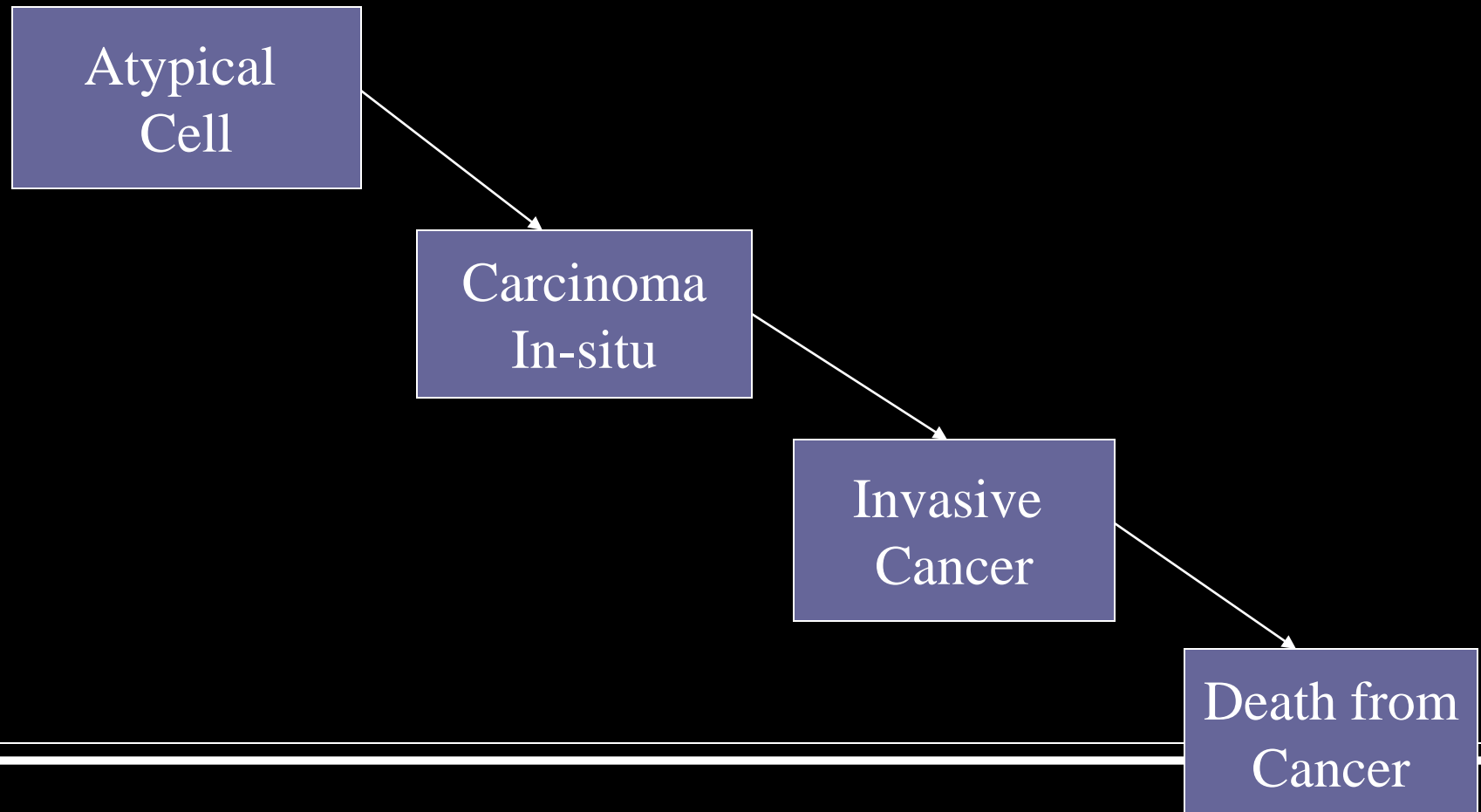


Do We Understand The Natural History of Breast Cancer?

The Problem of Pseudodisease

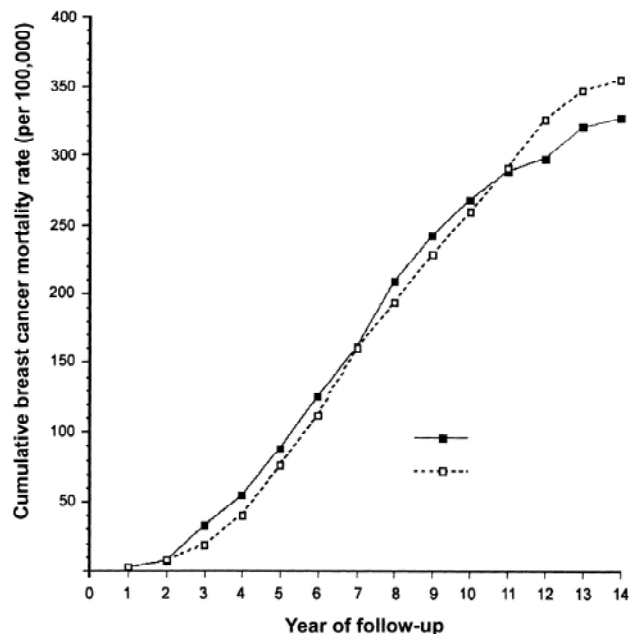
Cancer Progress

Welch, 2003



Summary of Results of Clinical Trials: Women 40-49 Years

Figure 5.8 Overall cumulative breast cancer mortality rates per 100 000 women aged 40-49 years in intervention and control groups from seven trials of breast screening



Baines, C. J. *J Natl Cancer Inst* 2003;95:1508-1511

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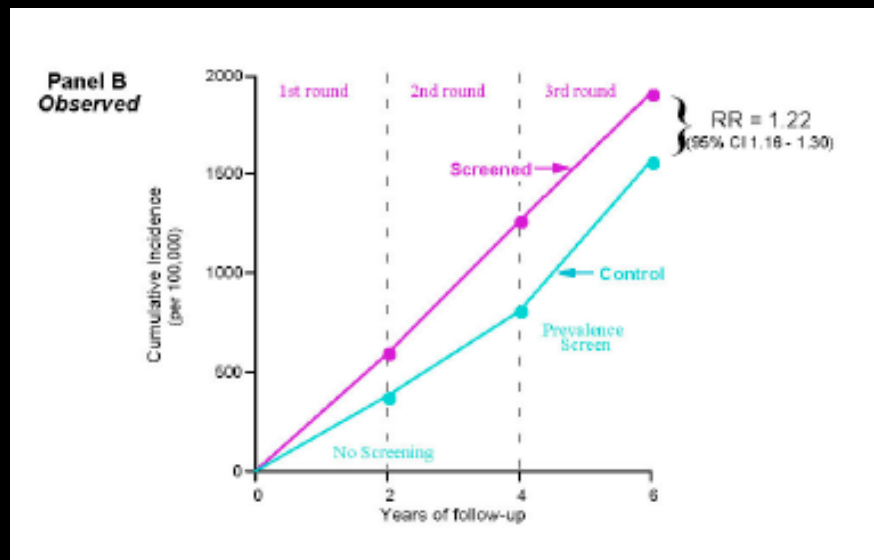
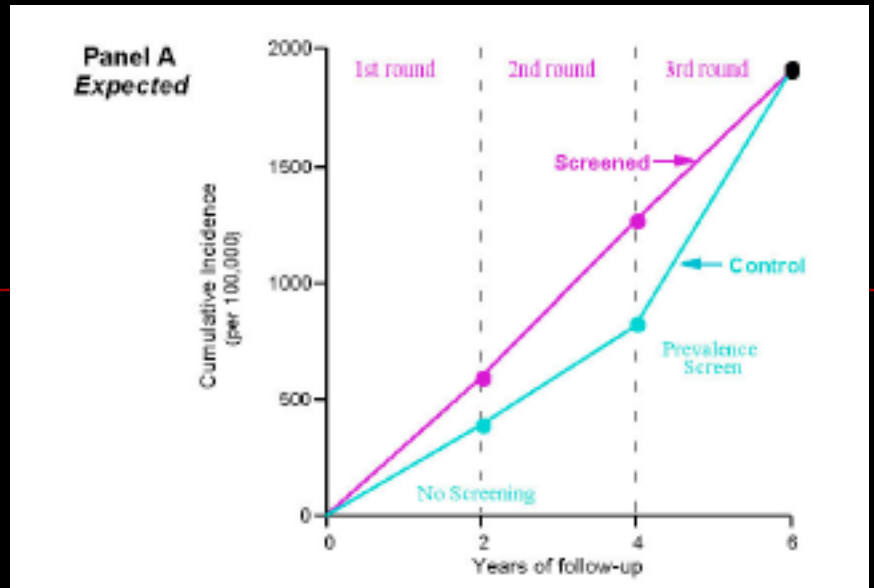
JNCI Journal of the
National
Cancer
Institute

Natural History of Breast Cancer

Zahl et al Archives of Int Med Nov 24, 2008

Repeated Screening Vs Prevalence Screening among Norwegian Women Age 40-64.

(From Zahl, Maehlen, & Welch, Archives of Int Med, Nov 2008)



Is there any evidence for spontaneous regression of advanced cancer?

- Metastatic melanoma (Printz JNCI, 2001)
- Metastatic renal cell (Gleave et al NEJM, 1998)
- National Polyp Study (Int J. Cancer, 2004)
- Pre-cancerous cervical lesions (Moscicki et al, Lancet, 2004)

Alternative Explanations

Were the samples comparable?

No differences between groups on any variable

	Screened Group (age 50-64 in 1996)	Control Group (age 50-64 in 1992)
N (start of observation period)	119,472	109,784
Starting age (mean)	56.8	57.4
Educational level (%)		
some high school	69.5%	74.0%
completed high school	10.8%	10.0%
some college	11.7%	10.4%
completed college	8.0%	5.7%
Family income* (mean)	266,000Kr (\$41,900)	239,000Kr (\$37,600)
Reproductive history		
Nulliparous (%)	15.6%	16.3%
Age at first birth (mean)	24.5	25.0
Number of births (mean)	2.17	2.20
Attendance at screening at the end of observation period (3rd round screened group; prevalence screen control group)	78.3%	79.5%

Evidence from Trials

- Malmö study estimated that there was 19% higher rate of diagnosis in the screened group 10 years after the trial ended (both groups got screened at exit)
- Canadian trials screen all women at end. Four years later cumulative rates remained 7% higher in the screened group

Evidence from simulation studies

- Wisconsin Breast Cancer Epidemiology Simulation Model (Fryback et al JNCI 2007)
 - Stochastic simulation to replicate breast cancer incidence and mortality in the US 1975-2000
 - Postulated that 40% initiated breast cancers were of “limited malignant potential”
 - “progress to a maximum of 1-cm, dwell at this size for 2 years, and then regress if untreated”

Ascertainment Bias

- Unlikely-- The Norwegian Cancer Registry had an almost perfect record (99%) of solid tumor ascertainment rates.
- Could it be improved sensitivity of Mammography?--
 - Mean diameter did not change (14.4 mm 1997 to 14.0 mm in 2001)
 - Incidence in 50-51 year olds did not change (281/100K in 1997 - 286/100K in 2001)

Could it be temporal change in incidence of cancer?

- Unlikely. No evidence for an epidemic of breast cancer in Norway at that time.

Could it be HRT?

- WHI did show a 24% increase in invasive cancer
- There was an increase in HRT use in Norway at the time, but N using HRT was only 14,000 out of 119,000 (2.8%)
- Assuming no use in the control group and 46,000 using in the screened group
 - $24\% \times 46,000 / 119,000 = 9.3\%$
 - So, HRT seems not to explain it

The multiple screen problem

- Between 20 and 30% of visible lesions are overlooked
- Detection rates are higher if films are reviewed by multiple radiologists.
- Among 108 radiologists, there was a range of 40% in the sensitivity for detecting breast lesions(Beam et al Arch Int Med, 1996)
- Women who have had three consecutive mammograms may be up to 20% more likely to have a positive result on one of the three tests

But.... There was one additional screen in each group

- If multiple vs single screen explanation is correct, we should have seen a narrowing of the difference between the two groups following the additional screen. That did not occur. Further, if we assume that tumors missed in early screens continue to progress, they should have showed up in the tumor registry. They did not.

What Harm Is Done?

Conclusions: Cochrane Review October 2006 Gotzsche & Nielsen

- ARR for mammography is 0.05%
- Screening will lead to a 30% increase in diagnosis
- For every 2000 women invited for screening, 1 will have her life prolonged
- Among the 2000 women, 10 healthy women will be treated unnecessarily

The BHS Leaflet

- Leaflet emphasizes the benefits of screening.
- It states, “If changes are found at an early stage, there is a good chance of a successful recovery, ”
- “Around half the cancers that are found at screening are still small . . . This means that the whole breast does not have to be removed.”
- Screening saves “an estimated 1400 lives each year in this country”(UK) and “reduces the risk of the women who attend dying from breast cancer.”

New Evidence-Based Leaflet

- It may be reasonable to attend for breast cancer screening with mammography, but it may also be reasonable not to attend because screening has both benefits and harms
- 2000 women are screened regularly for 10 years, one will benefit from the screening, as she will avoid dying from breast cancer
- At the same time, 10 healthy women will, as a consequence, become cancer patients and will be treated unnecessarily. These women will have either a part of their breast or the whole breast removed, and they will often receive radiotherapy and sometimes chemotherapy
- Furthermore, about 200 healthy women will experience a false alarm. The psychological strain until one knows whether it was cancer, and even afterwards, can be severe

London Times Controversy: Letter to times signed by 22 experts (including me)

- ... for every 2,000 women screened, one will benefit (by having her life saved), but 10 will have unnecessary treatment.
- One women in 10 will experience a false positive. This will be higher in the US, where the interval for screening is shorter and the age of initiation is earlier

Summary

- The public is highly enthusiastic about cancer screening
- Clinical trials show only limited benefits of cancer screening for breast, lung, and prostate screening
- New major clinical trials not likely to resolve the controversy in the near future

Contact Information

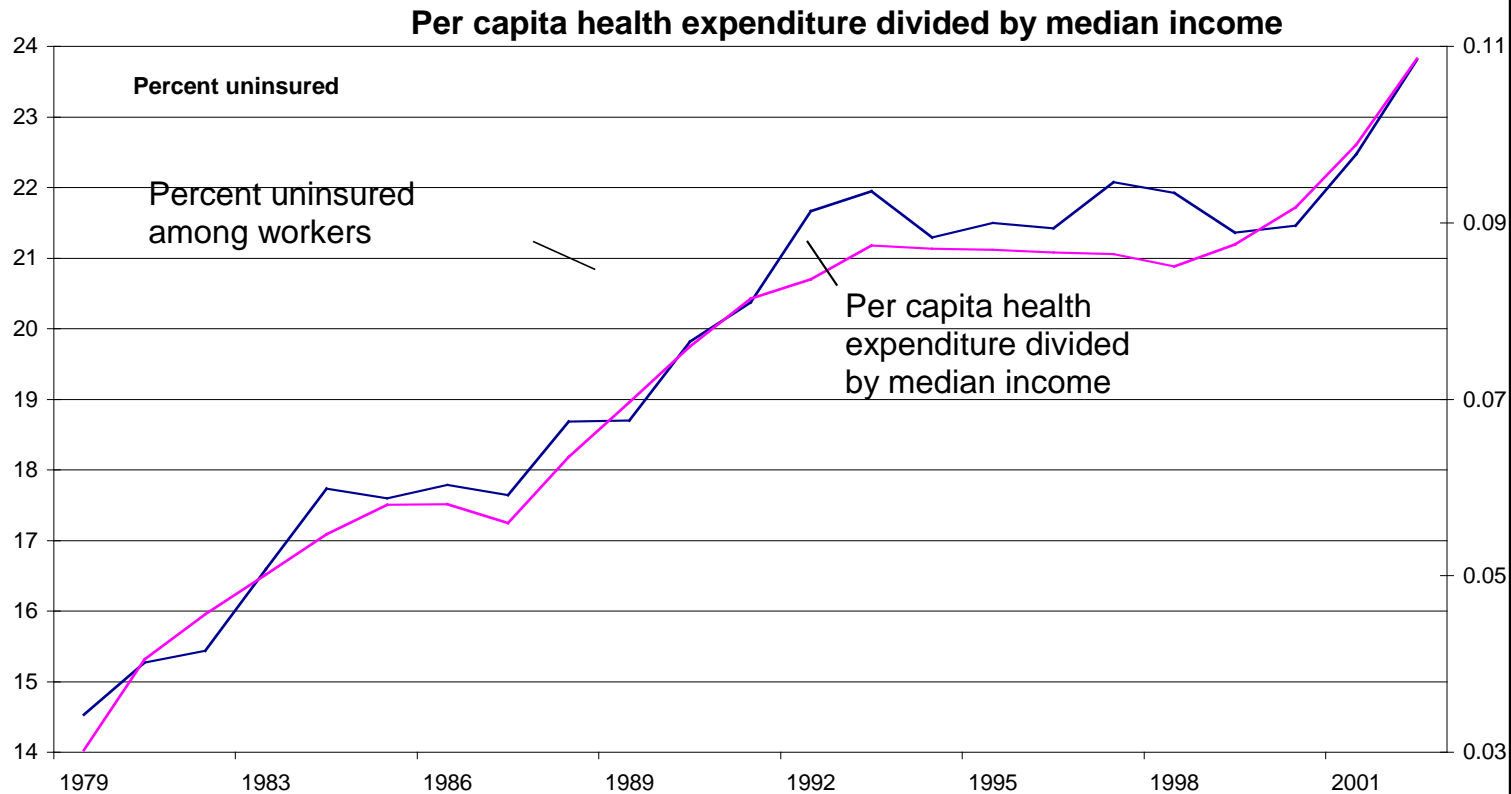
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A Final Thought

The Opportunity Cost Problem

EXHIBIT 2

Percentage Uninsured Among Workers And Per Capita Health Expenditure Divided by Median Income, 1979-2002



SOURCES: Authors' Analysis of Current Population Survey, March Supplements, Annual Demographics Files, 1980-2003, except 1981; and Health Care Financing Administration, National Health Accounts, 1979-2002.

NOTE: Percentage uninsured is scaled on the left axis and per capita health expenditure divided by median income is scaled on the right axis. Results from 1979-1999 have been adjusted to make them consistent with the insurance verification question that was added to the CPS in 2001. The series for workers is restricted to those not covered as a dependent or by a public program.

