BIG DATA in Health Sciences

Innovations for health care, medical product development and regulatory science

Stochastic Model for Overdiagnosis in Disease Screening and Surveillance

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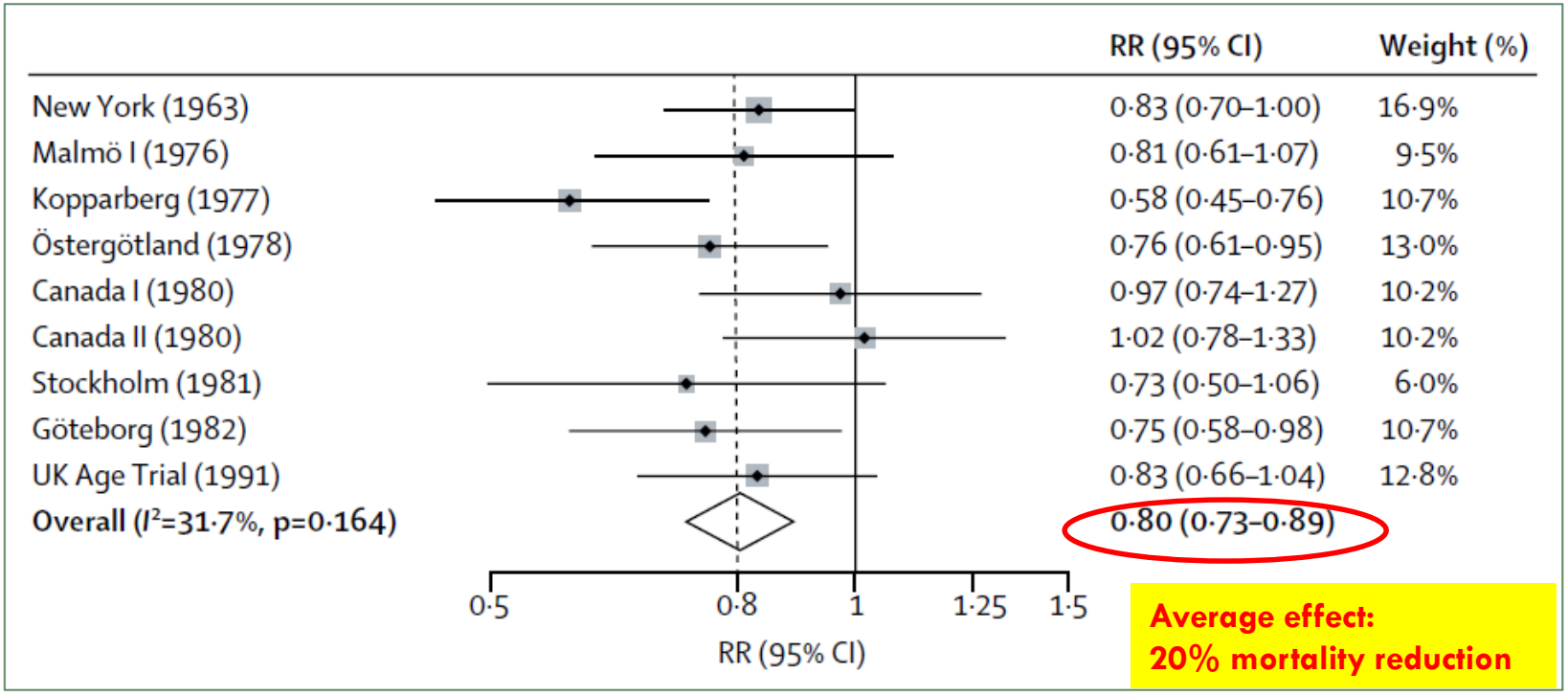
College of Public Health National Taiwan University

Meta-analyses: UK Independent

The benefits and harms of breast cancer screening: an independent review

*Independent UK Panel on Breast Cancer Screening**

2012 Lancet



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iWonder

Why isn't breast cancer screening totally reliable?

1. Catching a killer
2. False alarms
3. CLICKABLE: Harmless cancers
4. Unnecessary treatment?
5. Where next?

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Health

Breast cancer screens leads to 'unnecessary treatment'

By James Gallagher
Health and science reporter, BBC News

3 April 2012 | Health

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Up to one-in-four breast cancers detected by screening would never have gone on to be fatal or cause any symptoms, US researchers say.

Their study based on 39,888 women in Norway said between 15% and 25% of breast cancers were "overdiagnosed".

To screen or not to screen?

Health

Call for change to breast cancer screening approach

By Pippa Stephens
Health reporter, BBC News

22 March 2014 | Health

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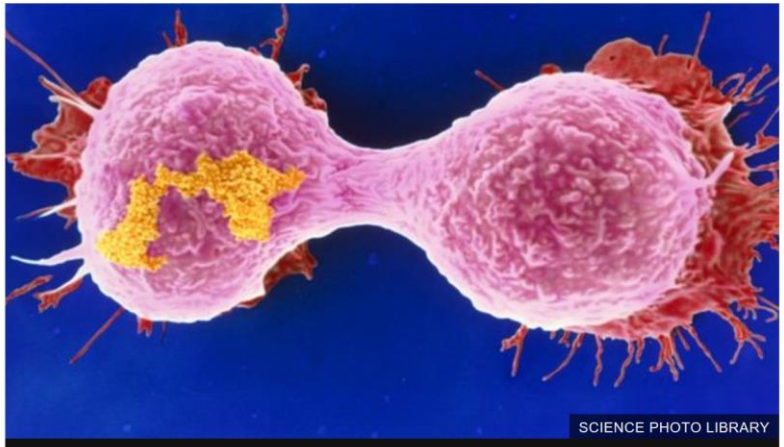

SCIENCE PHOTO LIBRARY

A different approach could help determine the severity of breast cancer cells, the study said

Almost one-third of women are at a higher risk of developing breast cancer and should be screened more than once every three years, a study says.


OP-ED CONTRIBUTOR
When Work Loses Its Dignity

EDITORIAL
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GAIL COLLINS
A Trumpian Silver Lining


NICHOLAS KRISTOF
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PAID POST: SOTHEBY'S REALTY
3 Ski Homes You'll Never Want to Come Down From

Cancer Survivor or Victim of Overdiagnosis?

By H. GILBERT WELCH NOV. 21, 2012

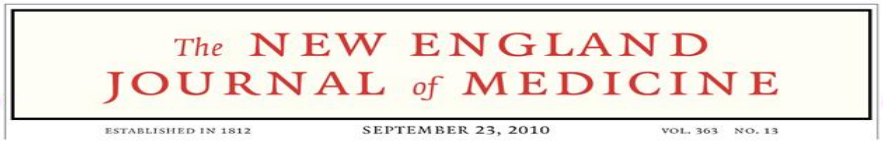
Hanover, N.H.

FOR decades women have been told that one of the most important things they can do to protect their health is to have regular mammograms. But over the past few years, it's become increasingly clear that these screenings are not all they're cracked up to be. The latest piece of evidence appears in a study in Wednesday's New England Journal of Medicine, conducted by the oncologist Archie Bleyer and me.

The study looks at the big picture, the effect of three decades of mammography screening in the United States. After correcting for underlying trends and the use of hormone replacement therapy, we found that the introduction of screening has been associated with about 1.5 million additional women receiving a diagnosis of early stage breast cancer.

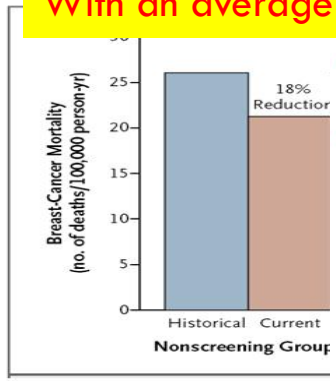
Fallacy in BC mass screening

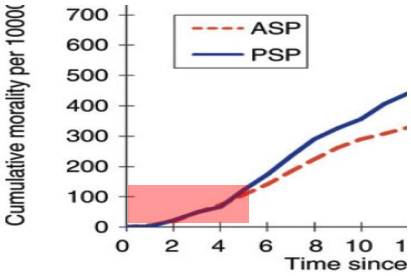
1. Short follow-up time: without lead-time consideration



Effect of Screening Mammography on Breast-Cancer Mortality in Norway

With an average follow-up of 2.2 years

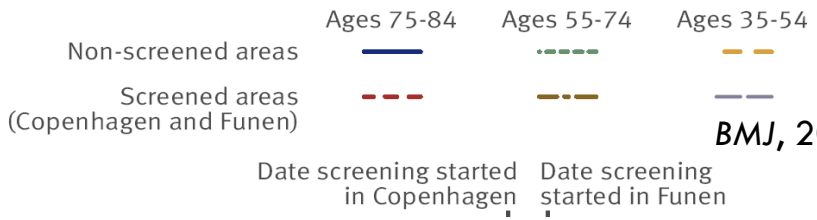




Lead-time period

前導期偏差(lead-tim

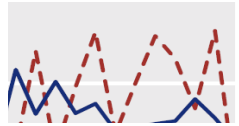
2. Breast Cancer mixed: diagnosed before screening program, but died after program implementation



BMJ, 2010

BMJ **RESEARCH**

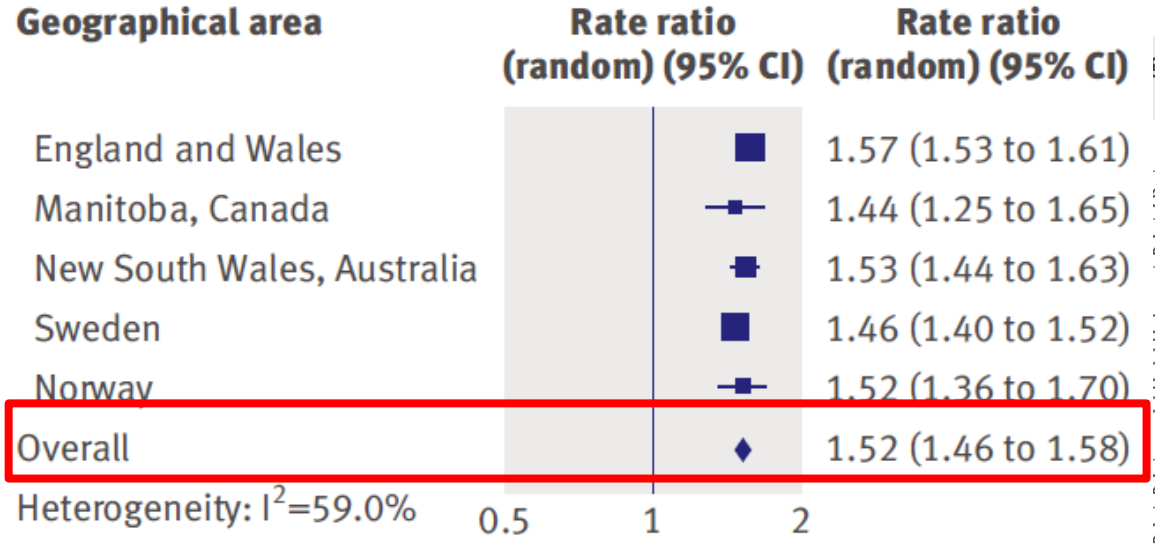
Mixed up lead-time and over-detection

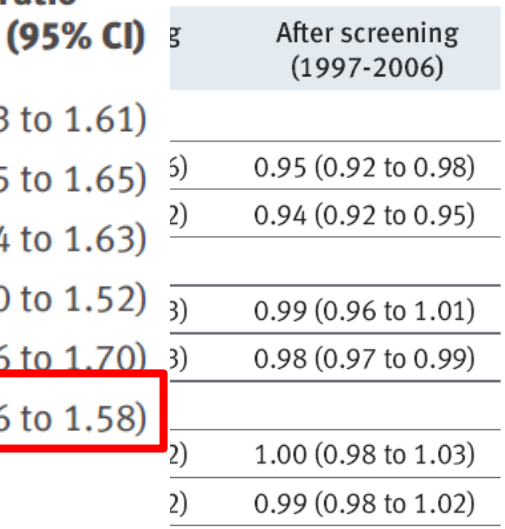


risk of breast cancer
10 years before
s during which
breast cancer

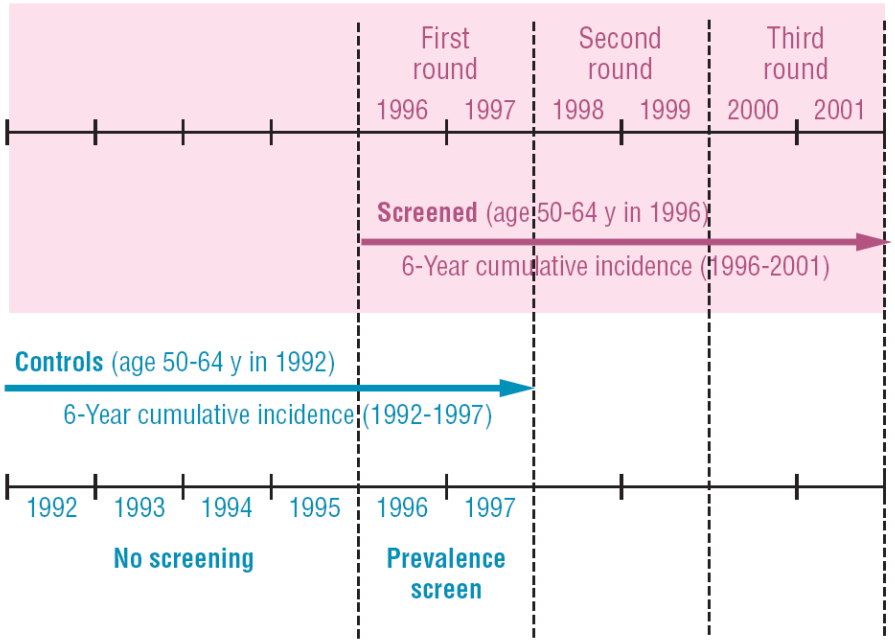
Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends

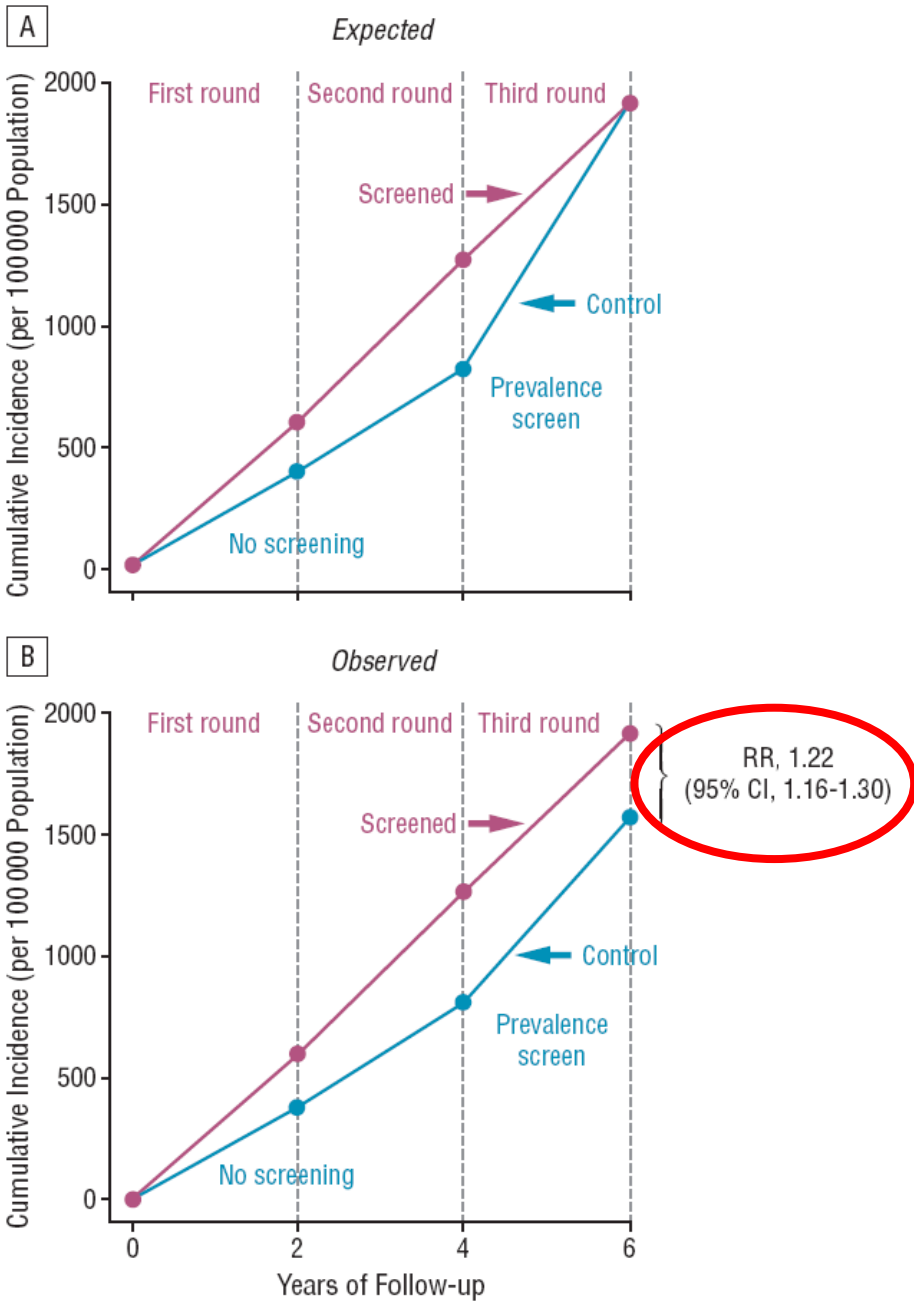
Jørgensen et al., 2009





Norwegian Study





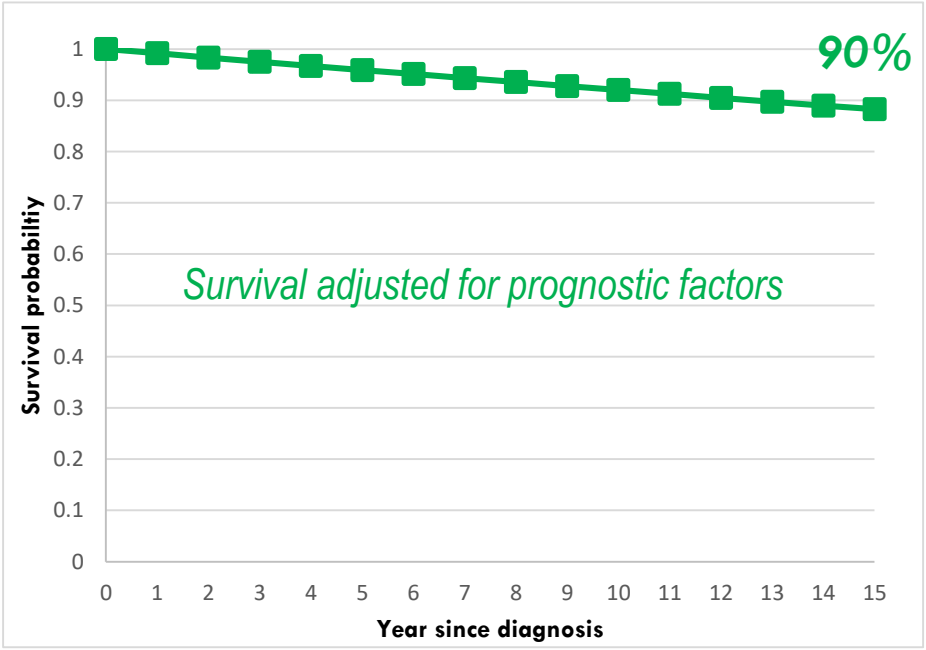
Zahl et al, Arch Intern Med. 2008;168:2311-2316

Survival of Breast Cancer, Darlana, Sweden

		aRR (95% CI)	P value
Tumor size, mm			<0.001
10-14 vs. 1-9		**1.01** (0.45 to 2.24)	
15-19 vs. 1-9		**1.12** (0.52 to 2.43)	
20-29 vs. 1-9		**2.63** (1.38 to 5.02)	
30+ vs. 1-9		**2.39** (1.19 to 4.80)	
Node (+) vs (-)		**1.86** (1.18 to 2.94)	0.007
Grade 3 vs. 1/2		**1.32** (0.84 to 2.07)	0.228
Triple negative	**Yes vs. No**	**1.53** (0.89 to 2.63)	0.132
Surgery	**MA vs. BCS**	**2.79** (1.56 to 4.98)	<0.001
Chemotherapy	**Yes vs. no**	**0.83** (0.51 to 1.38)	0.474
Radiotherapy	**Yes vs. no**	**1.39** (0.82 to 2.37)	0.215
Tamoxifen	**Yes vs. no**	**0.89** (0.56 to 1.42)	0.633

Abbreviations: aRR: adjusted relative risk; cRR: crude relative risk; df.: degree of freedom; MA: Mastectomy; BCS: Breast-conserving surgery

Without consideration of over-diagnosis

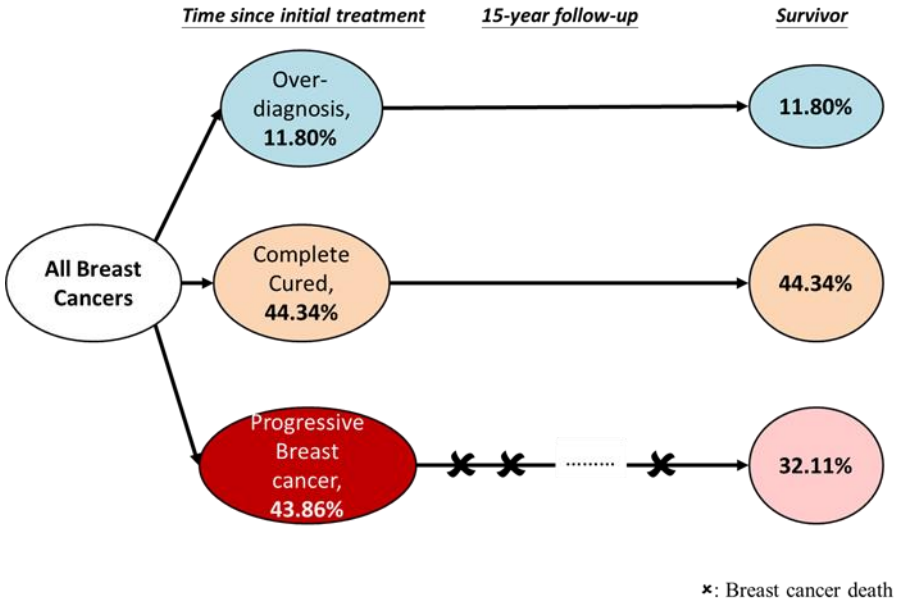


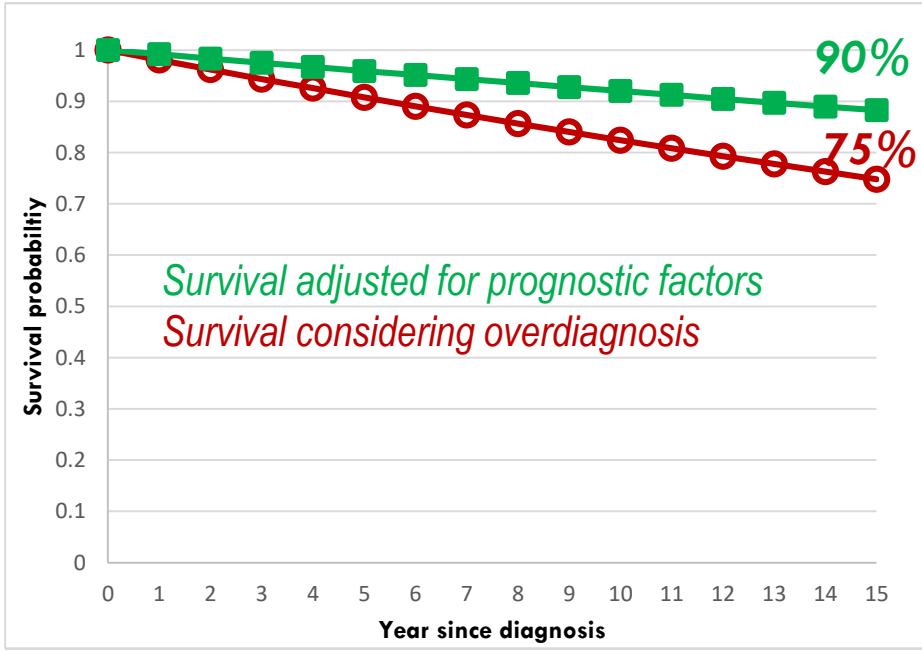
Zero-inflated Poisson regression model and overdiagnosis rate

Variable	RR/OR (95% CI)	P-value
Count part	**RR**	
Intercept		
Size, mm		0.015
10-14 vs. 1-9	3.69(0.76-18.01)	
15-19 vs. 1-9	3.85(0.80-18.53)	
20-29 vs. 1-9	10.26(2.27-46.33)	
30+ vs. 1-9	9.45(2.01-44.49)	
Node (+) vs. (-)	2.40(1.30-4.45)	0.005
Grade 3 vs 1/2	1.62(0.94-2.79)	0.080
Surgery MA vs. BCS	1.92(0.95-3.88)	0.071
Triple Negative Yes vs No	2.49(1.36-4.59)	0.003
Chemotherapy Yes vs. No	0.79(0.42-1.47)	0.456
Radiotherapy Yes vs. No	1.23(0.60-2.53)	0.568
Tamoxifen Yes vs. No	0.95(0.94-1.64)	0.847
Zero part	**OR**	
Intercept		
Detection mode		0.041
SD vs. RF	2.38(0.97-5.85)	
IC vs. RF	1.23(0.48-3.17)	

π = 56.14%

SD: 66.4% ↑ Overdiagnosis, 8.9%
IC: 50.5% ↑ Awareness, 2.9%
RE: 45.4% ➔ Treatment effect





QUANTIFY THE PROPORTION OF OVERDIAGNOSIS

DETERMINISTIC APPROACH

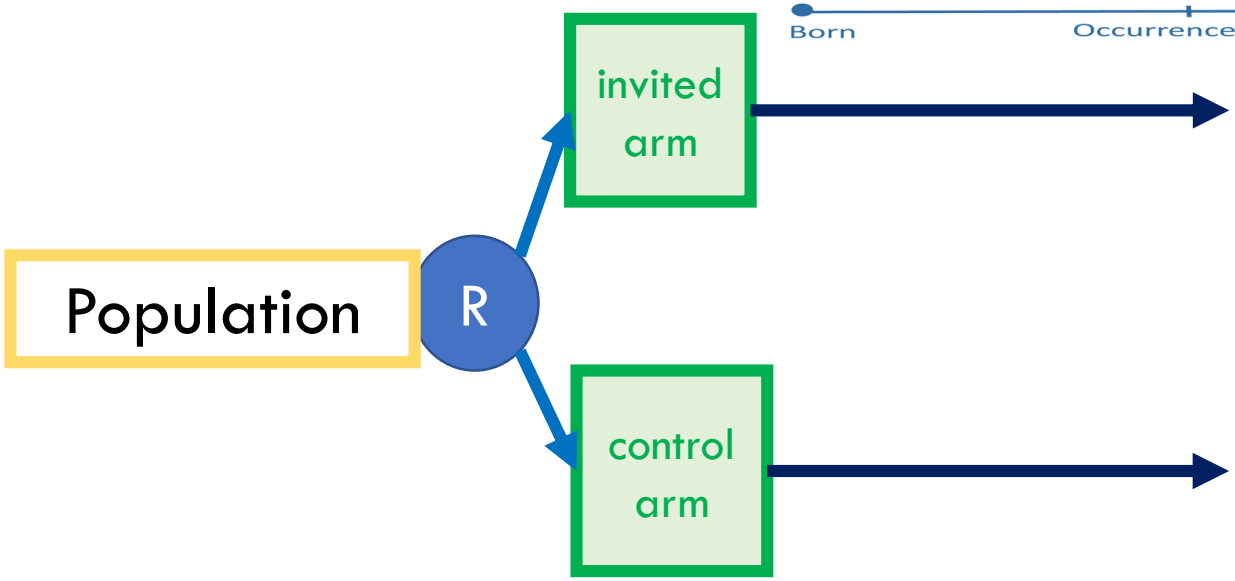
Natural disease progression and overdiagnosis

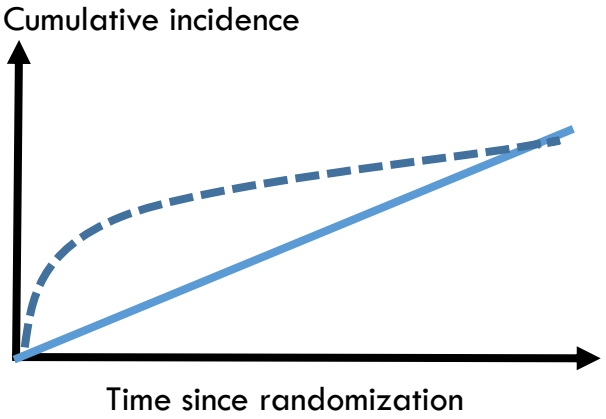
X歲時發病
(無症狀)

X+Y 歲時出現症狀
(就醫)

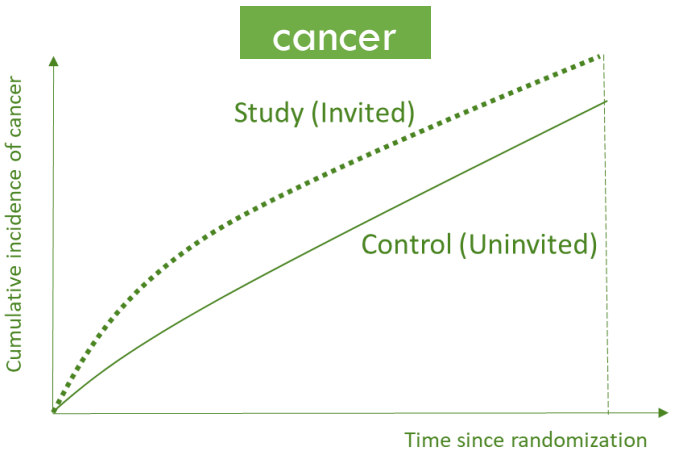
長得非常慢
不會有症狀
發病前死亡

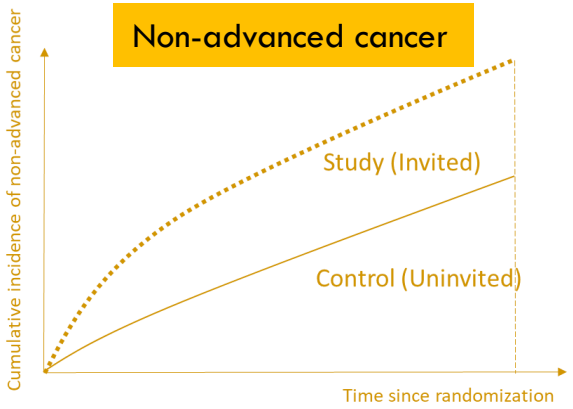
Y=∞

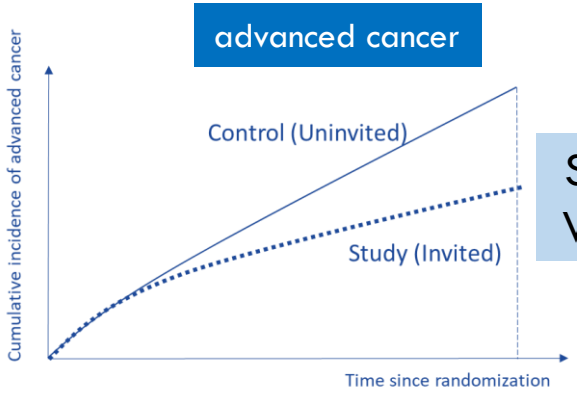




Curved method by comparing cumulative incidence of cancer







Screen Works!

Upper limit

All overdetetion arise from Non-advanced cancer (Long follow up time)

Lower limit

All detected cancer became advanced cancer(no overdetection)

Chen et al.,2017

11

Assessing overdetection in breast cancer screening using data on randomized controlled trial

Chen et al.,2017 *Medicine*

The estimated results of over-detection and number needed to screen for one over-detected case in the population-based screening for breast cancer with mammography.

	Women-years		Invasive breast cancer cases					Absolute rate of over-detection (per 10^3)			NSO			Percentage of over-detection		
Trials	Study	Control	Study	Control	Study, adv	Control, adv	(Adv breast cancer)	Low	High	Average	Low*	High	Average	Low (%)	High (%)	Average (%)
HIP	179,472	180,816	334	352	162	200	Stage 2+	−0.09	0.76	0.34	0	1323	2983	1.4	39.1	17.5
Malmo	185,983	186,674	486	396	190	231	Stage 2+	0.49	1.38	0.93	727	2036	1072	23.5	65.1	44.3
Two-county	652,706	476,864	1303	996	524	555	Stage 2+	−0.09	0.83	0.37	0	1201	2703	0.3	40.0	17.8
Edinburg	157,946	147,854	355	261	228	221	Stage 2+	0.48	0.75	0.62	1331	2079	1623	27.7	43.1	35.4
CNBSS-1	124,621	124,943	286	232	96	63	Nodes +	0.44	1.79	1.11	558	2284	898	24.1	97.0	60.5
CNBSS-2	96,626	97,061	341	274	92	86	Nodes +	0.71	2.64	1.68	379	1415	597	25.5	94.1	59.8
Stockholm	201,590	99,715	385	203	172	97	Stage 2+	−0.13	0.94	0.41	0	1068	2468	1.2	46.5	20.4
Gothenburg, 39–49	81,750	99,335	124	184	39	73	Nodes +	−0.33	0.78	0.22	0	1280	4482	0.2	42.6	12.5
Gothenburg, 40–59	49,564	78,369	147	231	46	71	Nodes +	0.02	2.06	1.04	486	51813	962	4.8	70.3	35.7
Age trial	312,957	622,127	409	755	124	276	Nodes +	0.09	0.86	0.48	1158	10595	2087	8.3	71.3	39.6
Overall								0.19	1.21	0.70				9.9	62.4	

HIP = Health Insurance Plan, NSO = number of screenee required for over-detecting.
* The low estimate of NSO is truncated to 0 while the absolute rate is negative.

QUANTIFY THE PROPORTION OF OVERDIAGNOSIS

STOCHASTIC APPROACH

STOCHASTIC APPROACHES FOR OVERDIAGNOSIS

1. Progressive Markov Model
2. Coxian Phase-Type Markov Process
3. Mover-Stayer Model

Progressive Markov Model

Expected number

$$SOR = \left(\frac{C(t)}{D(t)} - 1\right) \times 100\%$$

Obsered data From Controlled arm

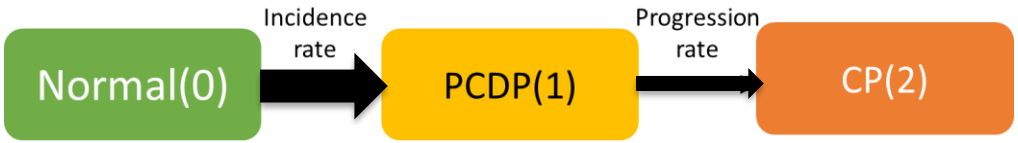
Randomized Controlled Design

Population

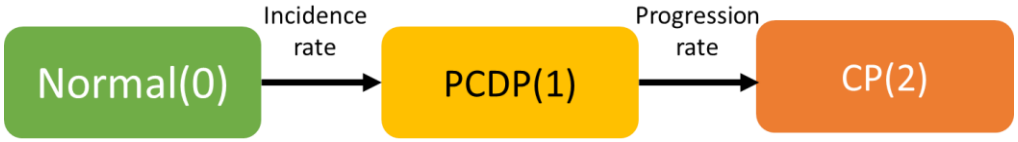
R

Projected Screen arm (Expected) C(t)

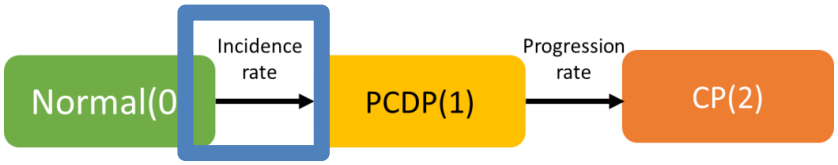
control arm (Observed) D(t)



three-state Markov model



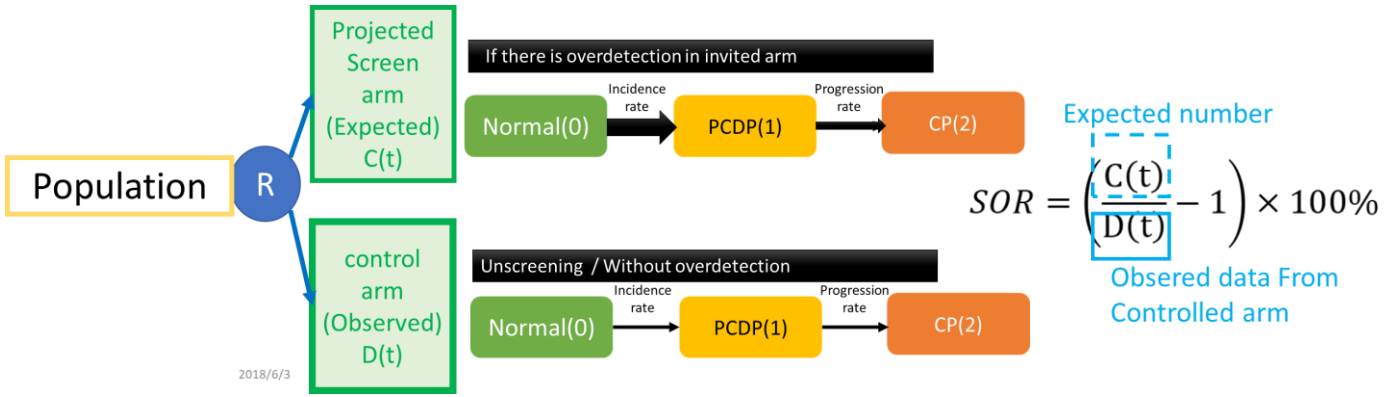
PCDP is unobservable in the control arm!



Estimated results on the transition rates of CRC based on three-state Markov model

Parameters	**UK** (Nottingham)	**Demark** (Funen)	**Taiwan**
Incidence rate	0.00147	0.00172	0.00096
(Normal→PCDP) (per person-year)	(0.00136, 0.00159)	(0.00155, 0.00189)	(0.00085, 0.00107)
Progression rate	0.3475	0.4433	0.1858
(PCDP →Clinical) (per year)	(0.2437, 0.4513)	(0.3226, 0.5639)	(0.0488, 0.7068)
Sensitivity of PCDP CRC	53.40%	52.05%	82.23%
	(34.26%, 69.55%)	(35.53%, 68.56%)	(46.82%, 96.05%)

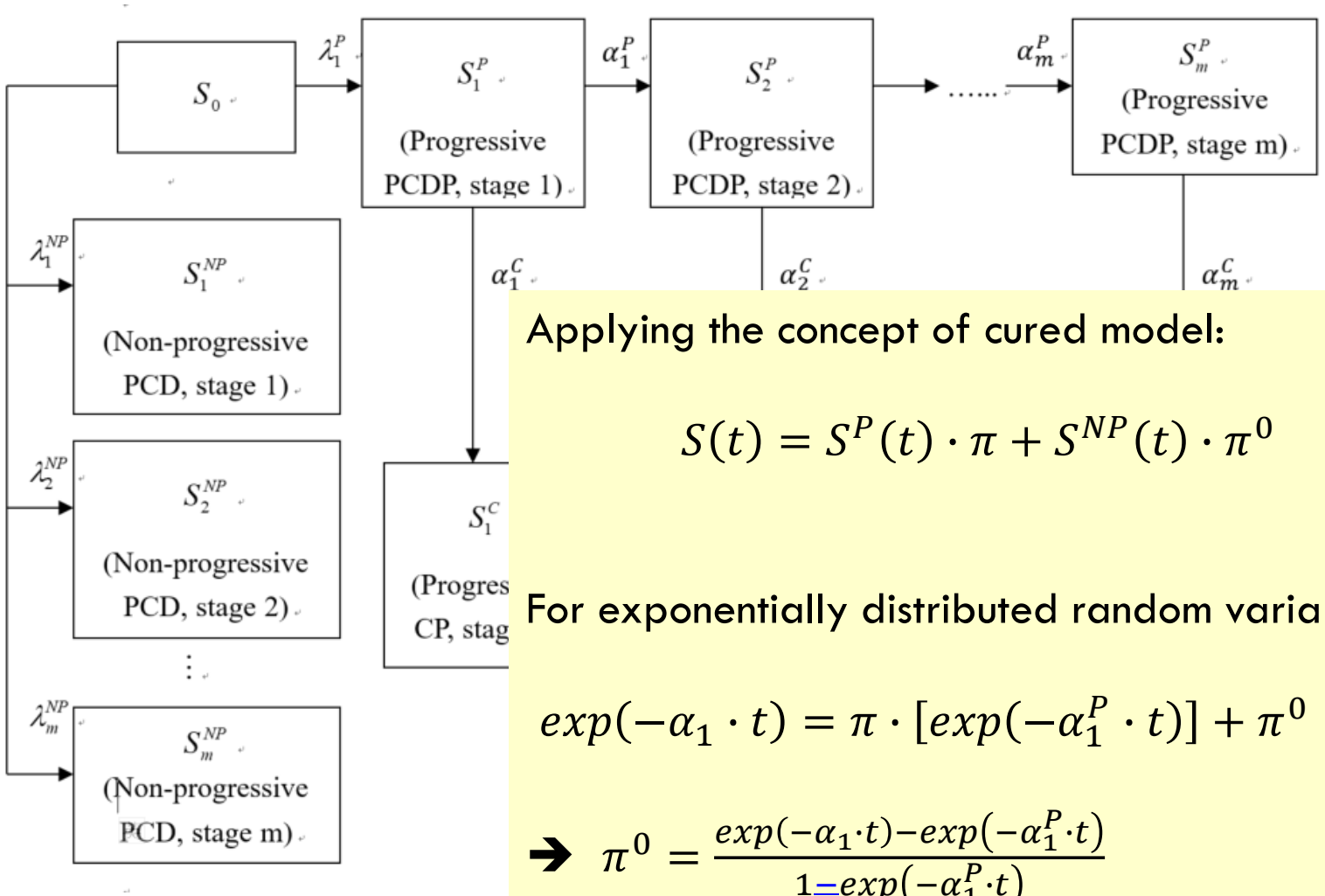
*CRC: colorectal cancer PCDP: pre-clinical detectable phase



Estimated results on standardized Over-detection ratio (SOR) based on the three-state Markov model and expected and observed frequencies of colorectal cancer for control group.

Study	Expected CRC, C(t)	Observed CRC, D(t)	SOR (%) (95% CI)
Nottingham, UK	931.26	856	8.79%(8.28,9.65)
Funen, Denmark	528.06	483	9.33%(8.81,10.20)
Taiwan	3656.63	3416	7.05%(6.56,7.89)

Coxian Phase-Type Markov Process



Applying the concept of cured model:

$$S(t) = S^P(t) \cdot \pi + S^{NP}(t) \cdot \pi^0$$

For exponentially distributed random variable

$$exp(-\alpha_1 \cdot t) = \pi \cdot [exp(-\alpha_1^P \cdot t)] + \pi^0$$

➔ $$\pi^0 = \frac{exp(-\alpha_1 \cdot t) - exp(-\alpha_1^P \cdot t)}{1 - exp(-\alpha_1^P \cdot t)}$$

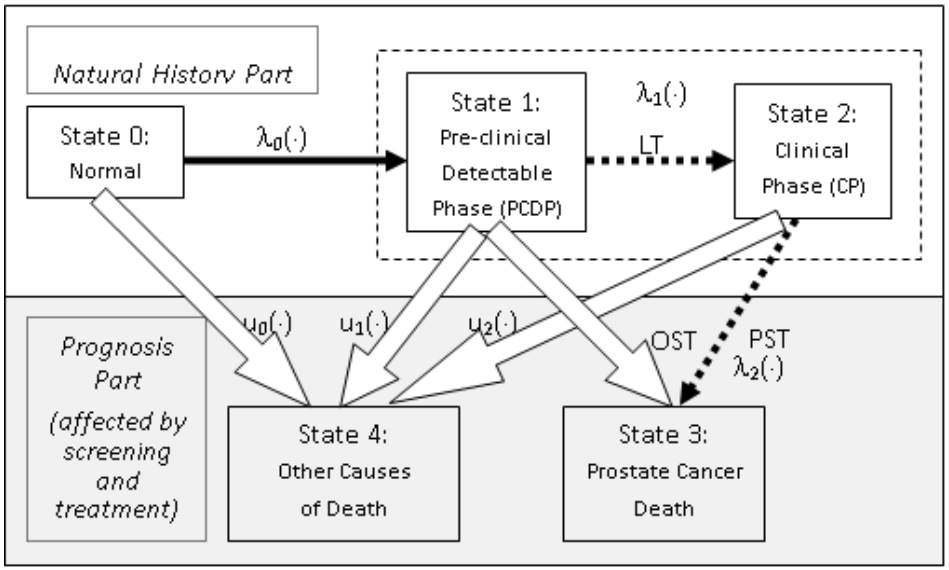
Estimated natural history of breast cancer with and without consideration of over-detection, Swedish Two-County Trial (Kopparberg) 1977-1985

Parameters	With consideration of over-detection		Without consideration of over-detection	
	Estimate	95% CI	Estimate	95% CI
No detectable disease → progressive PCDP (λ_1^P)				
	0. 00287	0.002677 - 0.003054	0.00293	0.002757-0.003105
No detectable disease → non-progressive PCDP (λ_1^{NP})				
	0.000017	0.000005 - 0.000057	---	
Progressive PCDP →CP (α_1^P)				
α_1^P	0.4189	0.3606 - 0.4772	0.3960	0.3467-0.4453
MST (years)	2.39	2.10 – 2.77	2.53	2.25-2.88
Sensitivity ($S_{q^P} = S_{q^{NP}}$)	82.6%	75.6% - 89.5%	83.1%	76.5%-89.7%
-2 log-likelihood	19325		19327	

➔ $\pi^0 = 2.6\%$

Mover-Stayer Model for Over-detection

(A)



(B)

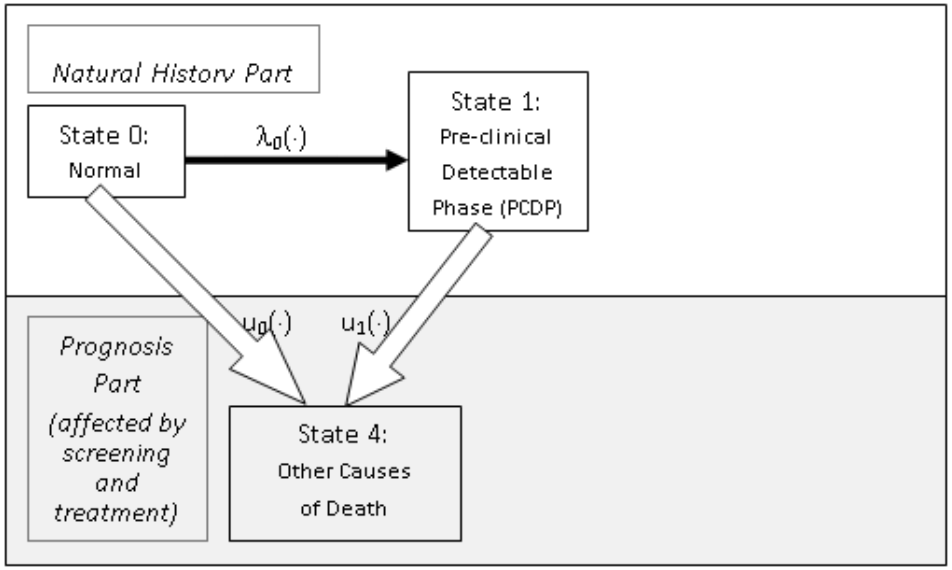


Fig. Diagrams of Markov models of natural history and prognosis of prostate cancer for lead-time, length bias, and overdetection adjustment.

(A) A Markov model combining the natural history and prognosis of prostate cancer. The model is also the same with the one for the **progressive** prostate cancer, "**mover**".

(B) A Markov model for the **non-progressive** prostate cancer, "**stayer**". White arrows denote the direct observation from the follow-up. Dotted arrows denote the unobserved transitions which decomposed the observed survival time into lead-time and post-lead-time survival time. OST: observed survival time; LT: lead-time; PST: post lead-time survival time.

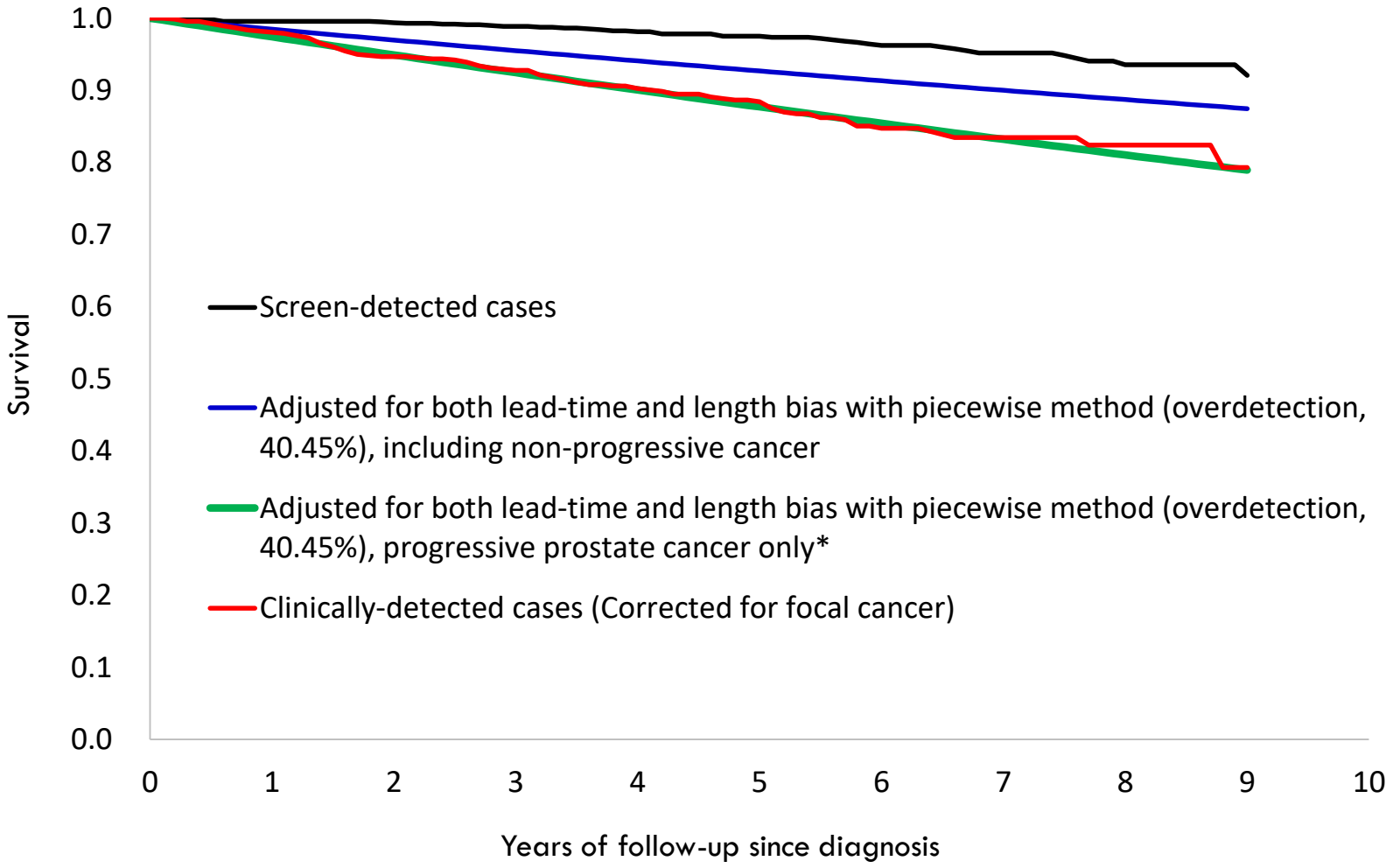
Estimated progression rates (per year) of prostate cancer cases, adjusted for both lead time and length bias, Finnish randomized controlled trial, 1996–2005.

Parameters	Estimate	95% CI[a)]
Extended model with over-detection adjustment[b)]		
The proportion of stayer	40.45%	31.95–48.95%
Pre-clinical incidence rate (λ_0) (Piecewise)		
55–58 y/o (λ_{01})	0.0009	0.0006–0.0013
59–62 y/o (λ_{02})	0.0047	0.0040–0.0054
63–66 y/o (λ_{03})	0.0069	0.0059–0.0078
67+ y/o (λ_{04})	0.0119	0.0108–0.0130
Annual progression rate (λ_1) (Piecewise)		
55–62 y/o (λ_{11}, λ_{12})	0.1376	0.0964–0.1787
63+ y/o (λ_{13}, λ_{14})	0.1340	0.1110–0.1570
Rate of prostate cancer death (λ_2) (Weibull)		
Scale (λ_{20})	2.01×10^{-5}	2.19×10^{-8}–4.02×10^{-5}
Shape (γ_2)	2.5086	2.2855–2.7318
Rate of other causes of death		
From normal (u_0)	0.0094	0.0087–0.0101
From PCDP (u_1)	0.0159	0.0127–0.0191
From CP (u_2)	0.0213	0.0164–0.0261

a) CI, confidence interval.
b) The proportion of over-detection, 40.45%, was estimated using a mover–stayer model.

Results. Finish PSA screening for prostate cancer

The estimated proportion of over-detection was 40.45% by using a mover-stayer model



Wu et al, 2012 *Biom J.*

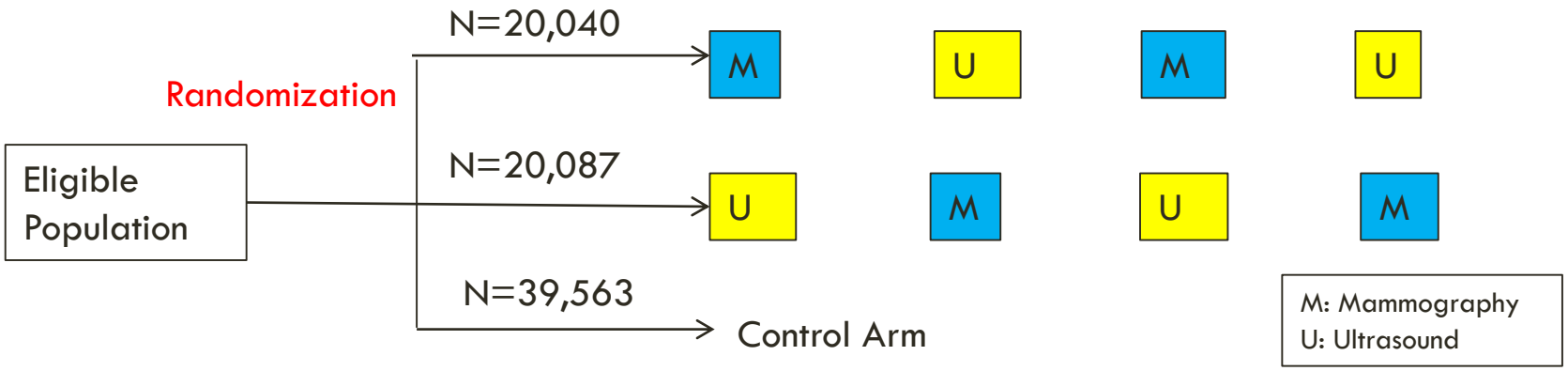
Impact of downstaging of breast tumor due to mammography screening on sensitivity and over-detection

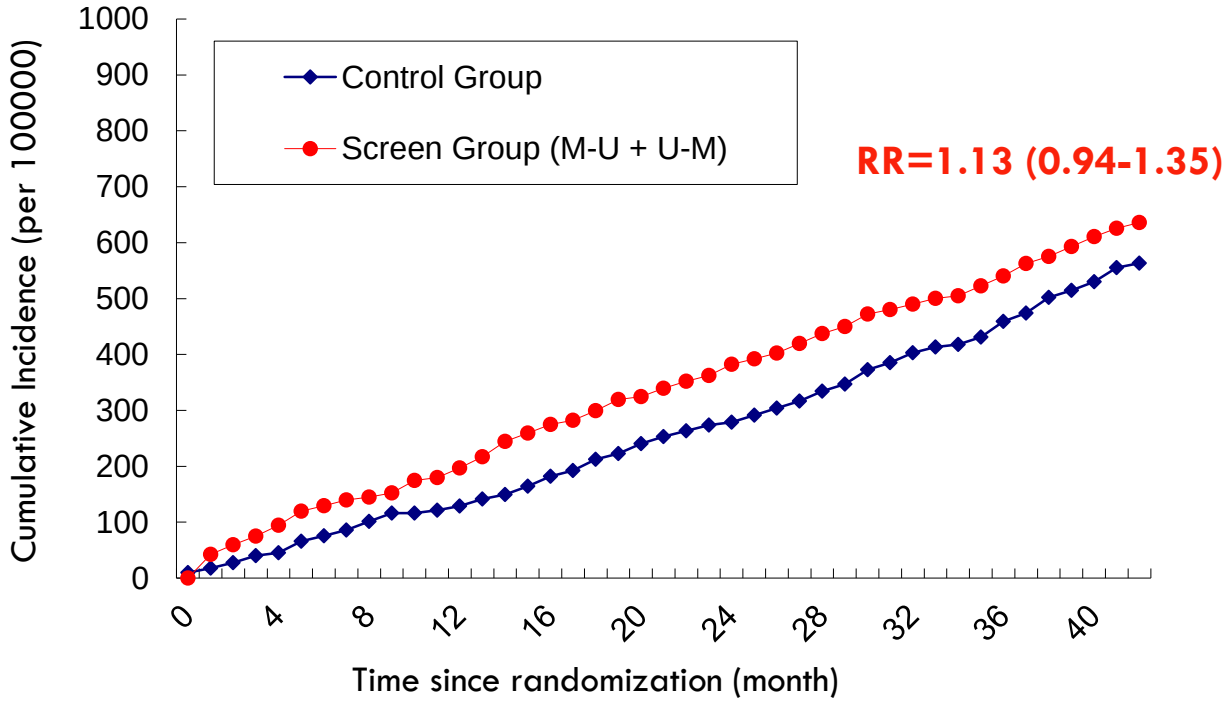
- Small tumor has a lower sensitivity than large tumor

- The proportion of overdiagnosis would be increased when the proportion of small breast tumour among screen-detected cases increase

Overdiagnosis with mammography in Taiwan

based on the Taiwanese randomized controlled trial for young women





Overdiagnosis with mammography in Taiwan

based on the Taiwanese Population-based service screening

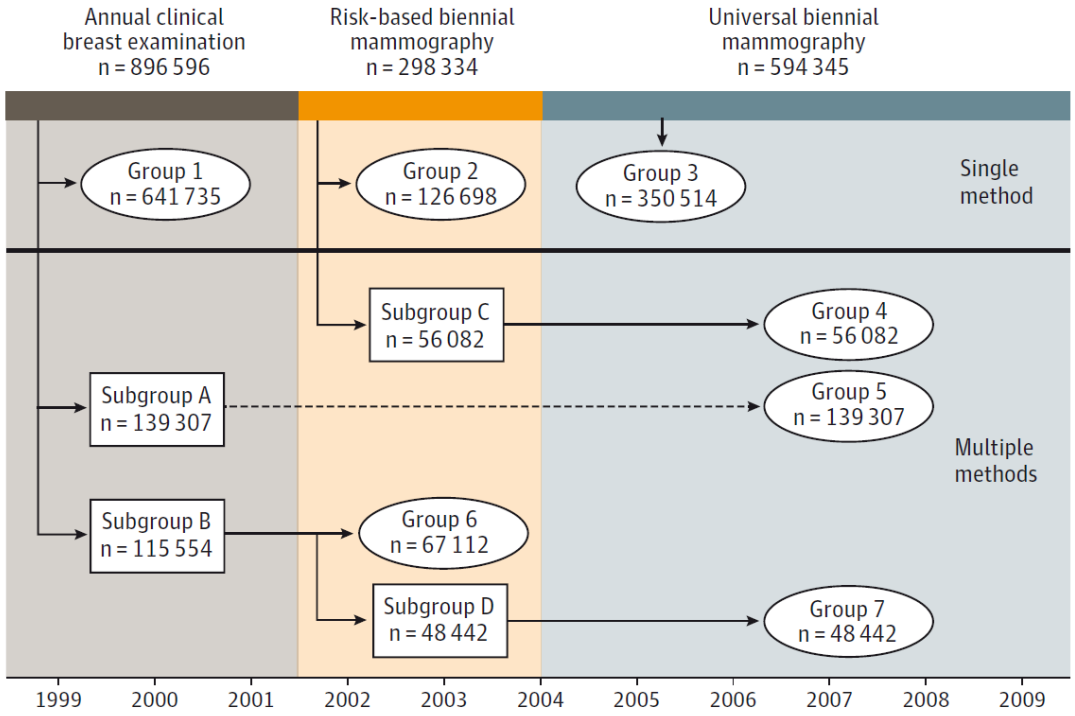
Original Investigation

Population-Based Breast Cancer Screening With Risk-Based and Universal Mammography Screening Compared With Clinical Breast Examination

A Propensity Score Analysis of 1 429 890 Taiwanese Women

2016 *JAMA Oncology*

Amy Ming-Fang Yen, PhD; Huei-Shian Tsau, PhD; Jean Ching-Yuan Fann, PhD; Sam Li-Sheng Chen, PhD; Sherry Yueh-Hsia Chiu, PhD; Yi-Chia Lee, PhD; Shin-Liang Pan, PhD; Han-Mo Chiu, PhD; Wen-Horng Kuo, PhD; King-Jen Chang, PhD; Yi-Ying Wu, PhD; Shu-Lin Chuang, PhD; Chen-Yang Hsu, PhD; Dun-Cheng Chang, PhD; Shing-Lang Koong, PhD; Chien-Yuan Wu, MS; Shu-Lih Chia, MS; Mei-Ju Chen, MS; Hsiu-Hsi Chen, PhD; Shu-Ti Chiou, PhD



Total Incidence of breast cancer

Risk-based vs CBE:

RR=0.97 (95% CI: 0.92-1.03)

Mammography vs CBE:

RR=1.13 (95% CI: 1.08-1.18)

Conclusion

- The estimated proportion of over-diagnosis cases is affected by lead-time, sensitivity, and changing incidence, which causes the large disparity of over-detection.
- We clarified the estimation of over-diagnosis by the application of stochastic approaches taking three factors into account.
- Attention to over-diagnosis should be paid given a full-grown mature screening program.

THANKS FOR YOUR ATTENTION!