Overdiagnosis in Mammography Screening

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Outline

- **Mammographic Screening for Breast Cancer**
- **Fallacy on Overdiagnosis**
- **Overdiagnosis in Taiwanese Randomized Controlled Trial**
- **Methodology for Estimating Overdiagnosis**
- **Personalized Probabilistic Cost-Effectiveness Analysis**

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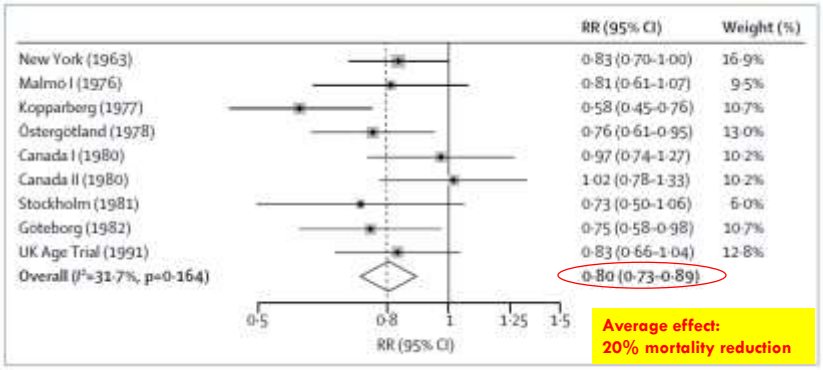
Meta-analyses: UK Independent

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

2012 Lancet



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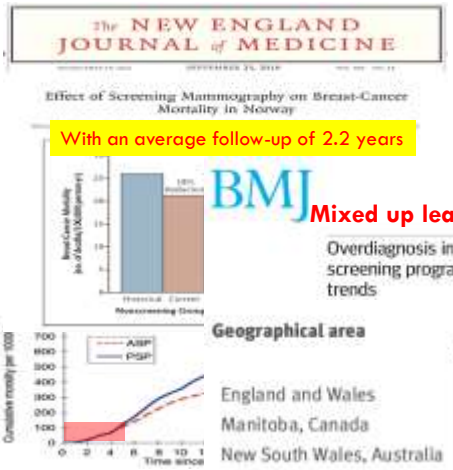
Fallacy in BC mass screening

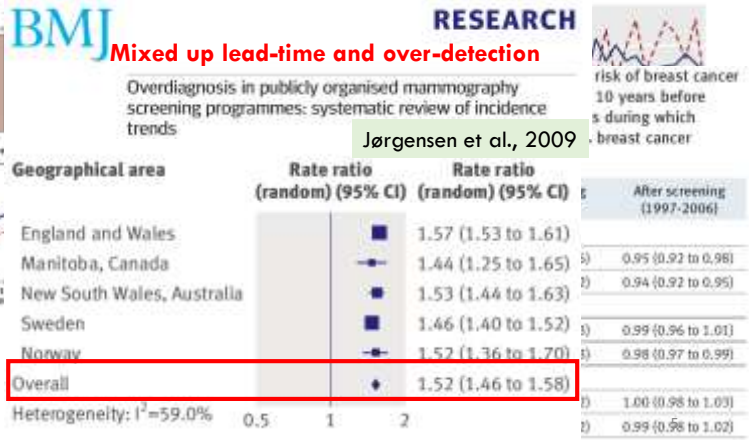
1. Short follow-up time: without lead-time consideration



(lead-time bias)

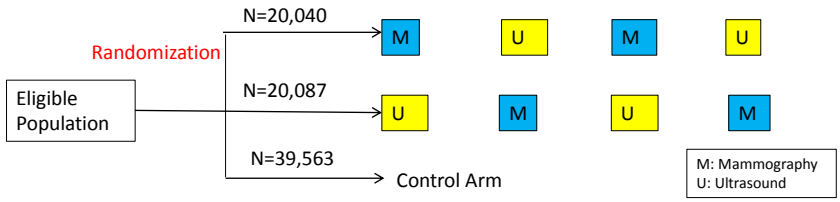
2. Breast Cancer mixed: diagnosed before screening program, but died after program implementation

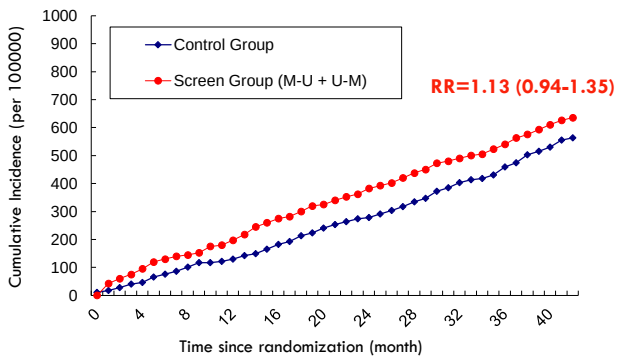
BMJ, 2010



Overdiagnosis with mammography in Taiwan

based on the Taiwanese randomized controlled trial for young women





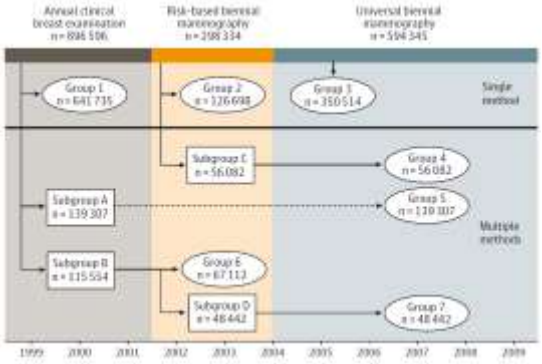
Overdiagnosis with mammography in Taiwan
based on the Taiwanese Population-based service screening

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; Hues-Shian Tsau, PhD; Jean Ching-Yuan Fann, PhD; Sam Li-Sheng Chen, PhD; Sherry Yueh-Hsia Chia, PhD; Yi-Chia Lee, PhD; Shin-Liang Pan, PhD; Han-Mo Chiu, PhD; Wen-Hsiang Kuo, PhD; King-Jon Chang, PhD; Yi-Ying Wu, PhD; Shu-Lin Chuang, PhD; Chen-Yang Hsu, PhD; Dan-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

Mammography vs CBE:

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

Over-detection: 13%

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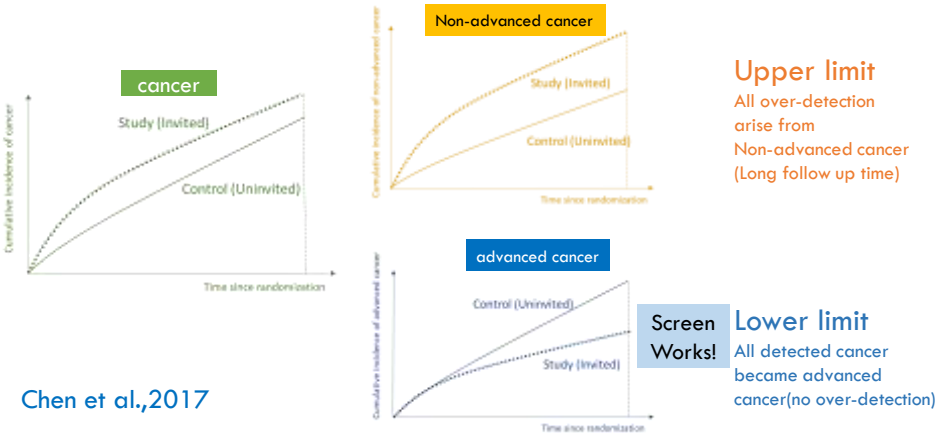
Methodology for Estimating Overdiagnosis

1. **Graphic method**
2. **Zero-inflated model**
3. **Coxian Phase-Type Markov Process**

1. Graphic method

Curved method by comparing cumulative incidence of cancer



Chen et al.,2017

Upper limit
All over-detection arise from Non-advanced cancer (Long follow up time)

Screen Works!

Lower limit
All detected cancer became advanced cancer(no over-detection)

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.

Trials	Women-years		Invasive breast cancer cases				Absolute rate of over-detection (per 10^5)			NSD			Percentage of over-detection		
	Study	Control	Study	Control	Study, adv	Control, adv	(Adv breast cancer)	Low	High	Average	Low*	High	Average	Low (%)	High (%)	Average (%)
HIP	179,672	180,016	504	352	162	200	Stage 2+	−0.09	0.76	0.34	0	1323	2983	1.4	39.1	17.5
Malmo	765,980	106,674	498	306	190	231	Stage 2+	0.49	1.38	0.93	727	2036	1072	33.5	65.1	44.3
Two-county	652,706	470,864	1303	906	524	555	Stage 2+	−0.09	0.83	0.37	0	1201	2703	0.3	40.0	17.8
Edinburg	157,946	147,864	355	261	226	221	Stage 2+	0.48	0.75	0.62	1331	3579	1823	37.7	43.1	39.4
CNBSS-1	124,621	124,943	288	232	96	83	Nodes +	0.44	1.79	1.11	558	2264	898	24.1	97.0	60.5
CNBSS-2	96,626	97,061	341	274	92	98	Nodes +	0.71	2.64	1.68	379	1415	597	25.5	94.1	59.8
Stockholm	201,990	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	80,335	124	164	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	51913	962	4.8	70.3	35.7
Age trial	312,957	622,127	409	750	134	276	Nodes +	0.09	0.86	0.48	1158	10686	2087	8.3	71.3	39.6
Overall								0.19	1.21	0.70				0.9	62.4	

HIP = Health Insurance Plan; NSD = number of screenees required for over detecting.
* The low estimate of NSD is truncated to 0 while the absolute rate is negative.

Follow-up time

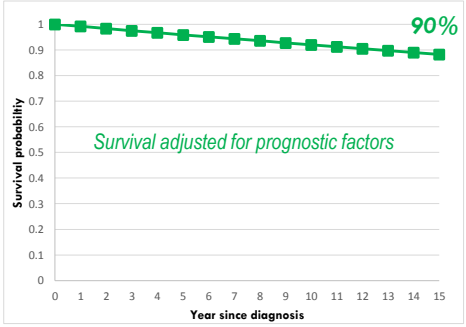
2. Zero-inflated model

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

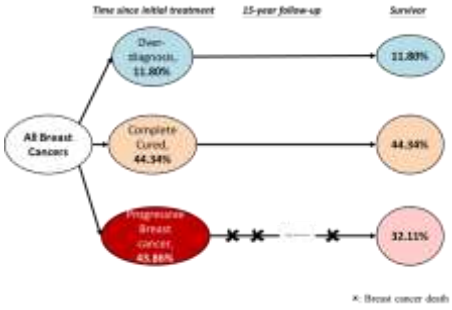


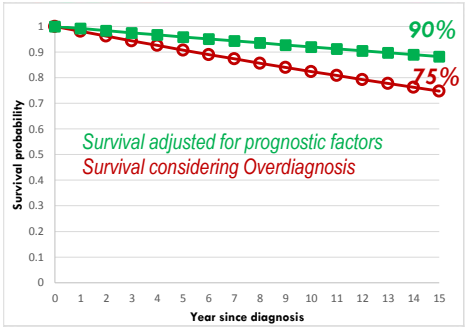
Zero-inflated Poisson regression model and overdiagnosis rate

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)	

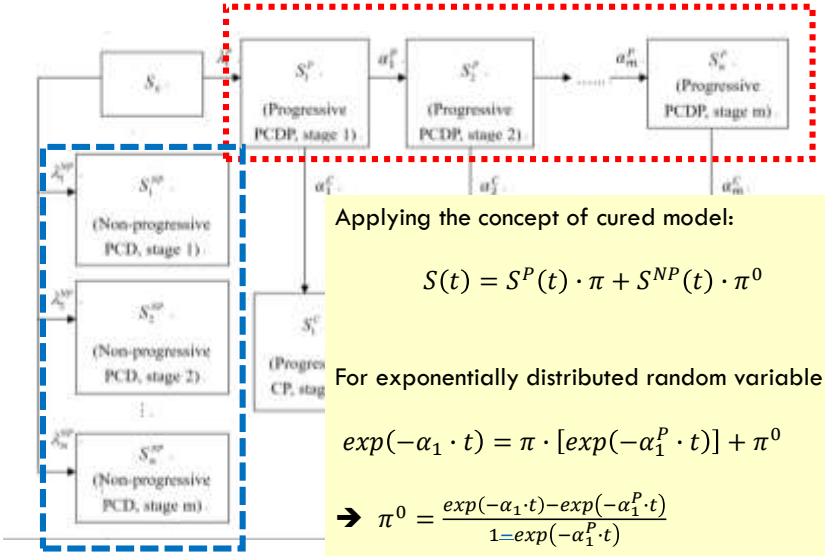
π = 56.14%

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





3. 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)				
Transition rate	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 ($S_{T^P} = S_{T^{NP}}$)	82.6%	75.6% - 89.5%	83.1%	76.5%-89.7%

➔ $\pi^0 = 2.6\%$

MST: mean sojourn time

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Probabilistic CEA of Personalized Breast Cancer Screening

- Population risk stratification for trade-off between harm and benefit
- Time preference for screening policy and outcome

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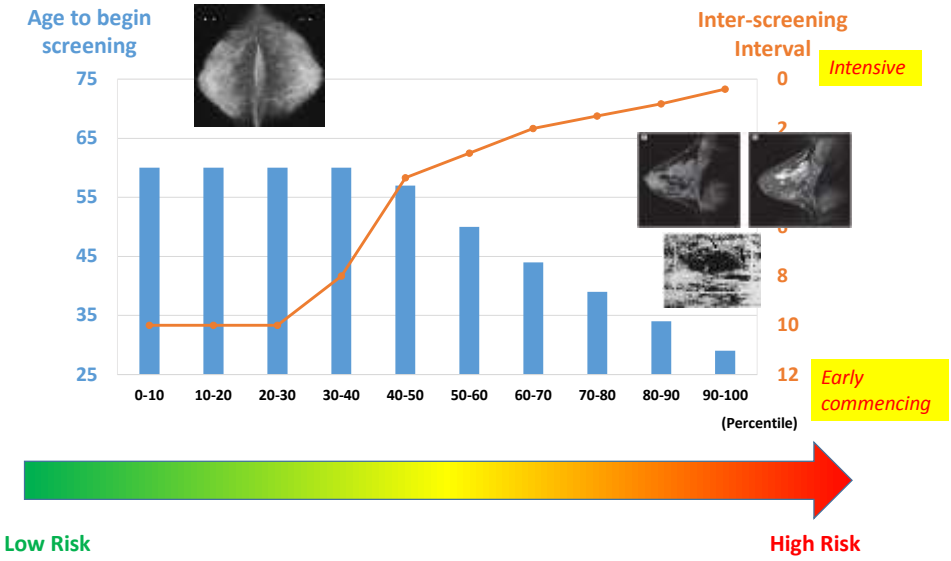
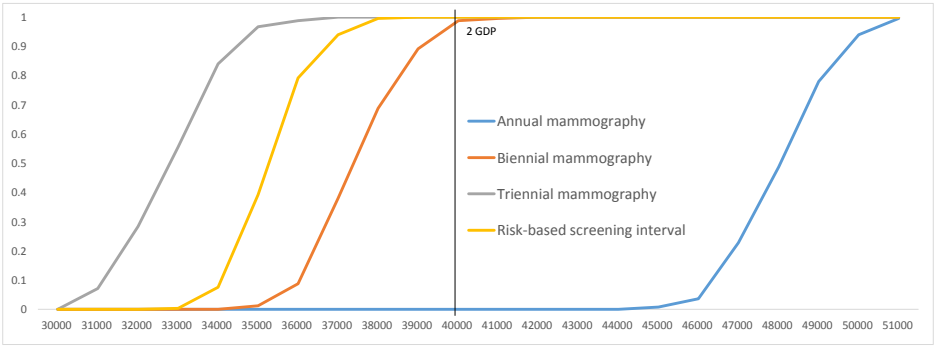
Risk stratification:

The recommend age to begin screening and inter-screening interval for screening by percentiles of risk score



Economic Evaluation

Acceptability curve of primary and secondary breast cancer prevention for **non-BRCA Carrier**



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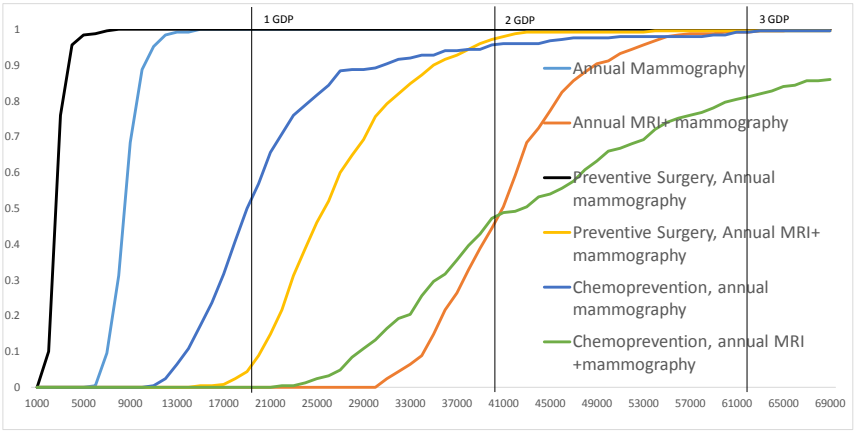
Acceptability curve of primary and secondary prevention of breast cancer for **BRCA-carrier** women



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Conclusion

- The estimated proportion of over-diagnosis cases is affected by lead-time, sensitivity, and follow-up time, which causes the large disparity of over-detection across studies.

  - Methodological flaws

- Use high-quality design-based study and model-based approach

- Probabilistic CEA for personalized screening policy is strongly recommended

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Taiwan
花東縱谷
East Rift Valley
Thanks for your attention!