Statistical Methods for Determining the Effect of Mammography Screening

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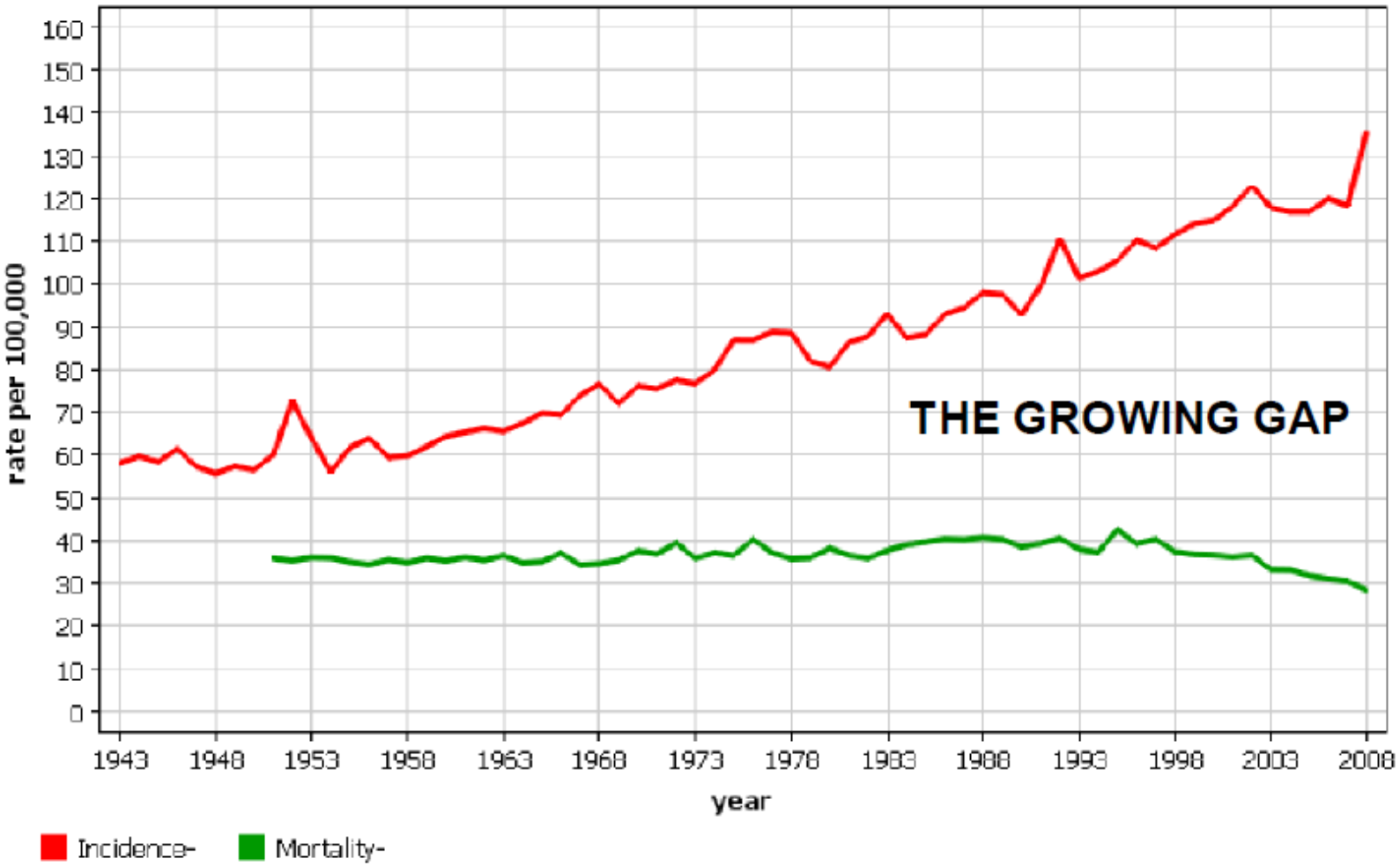
Agenda

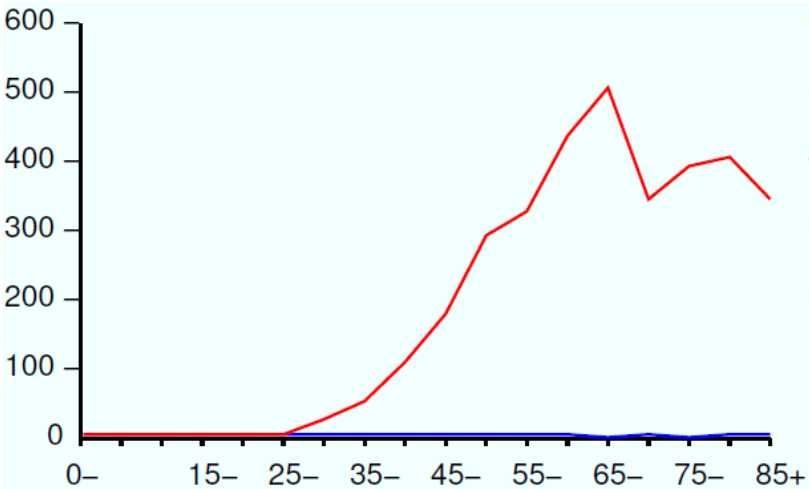
- Breast cancer
- What is screening?
- The breast cancer screening program in Denmark
- Statistical methods estimating the effect of breast cancer screening

Incidence by year

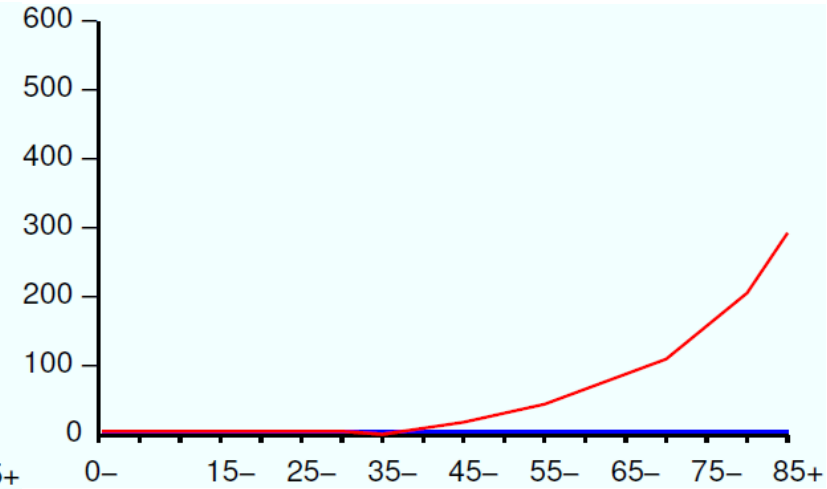


Incidence by age

New cases of breast cancer per year per 100000 persons (2009-2013)

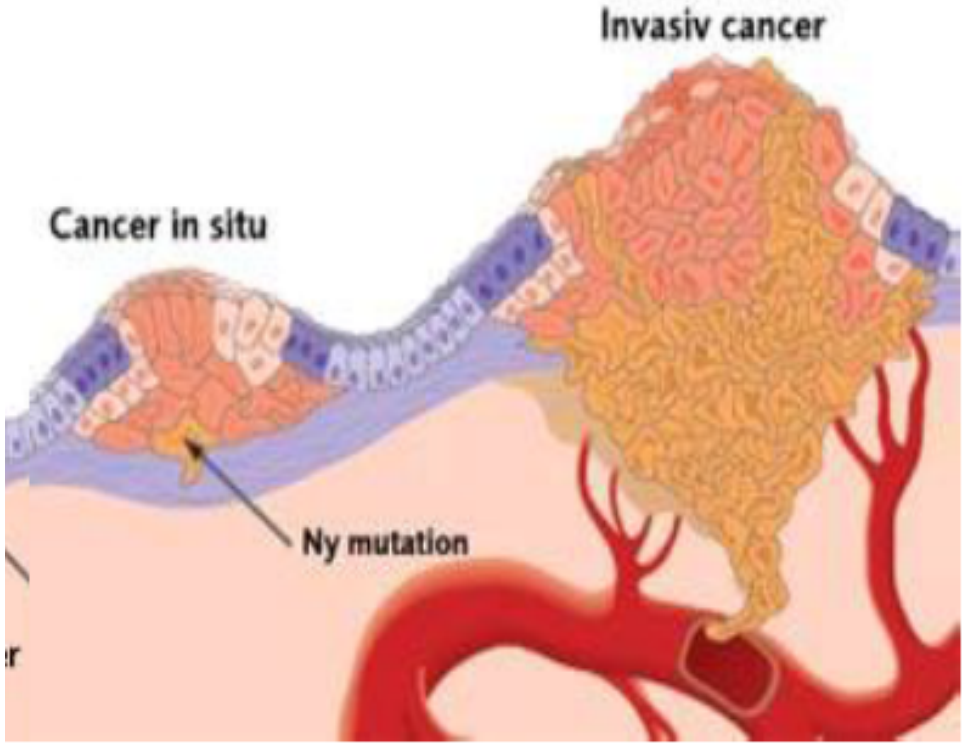


Deaths from breast cancer per year per 100000 persons (2009-2013)



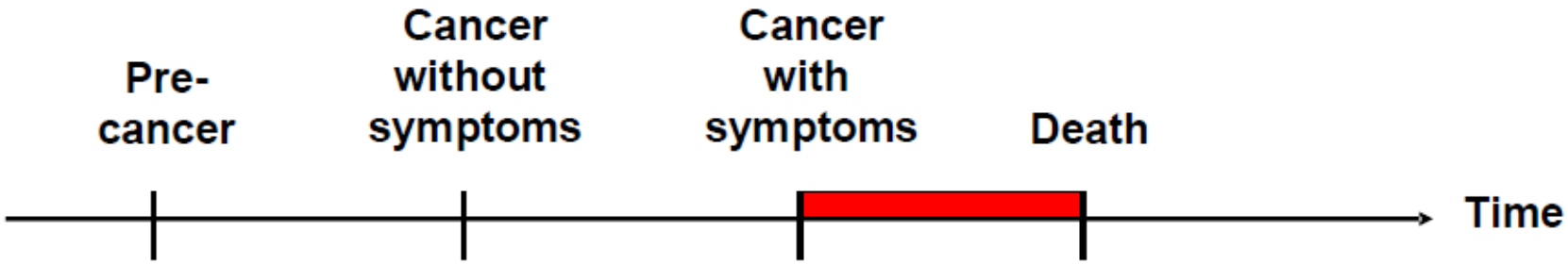
Breast cancer screening

- Purpose: To decrease mortality from breast cancer
- Method: Detect breast cancer before it give rise to symptoms, because treatment is more effective in early than in late stages

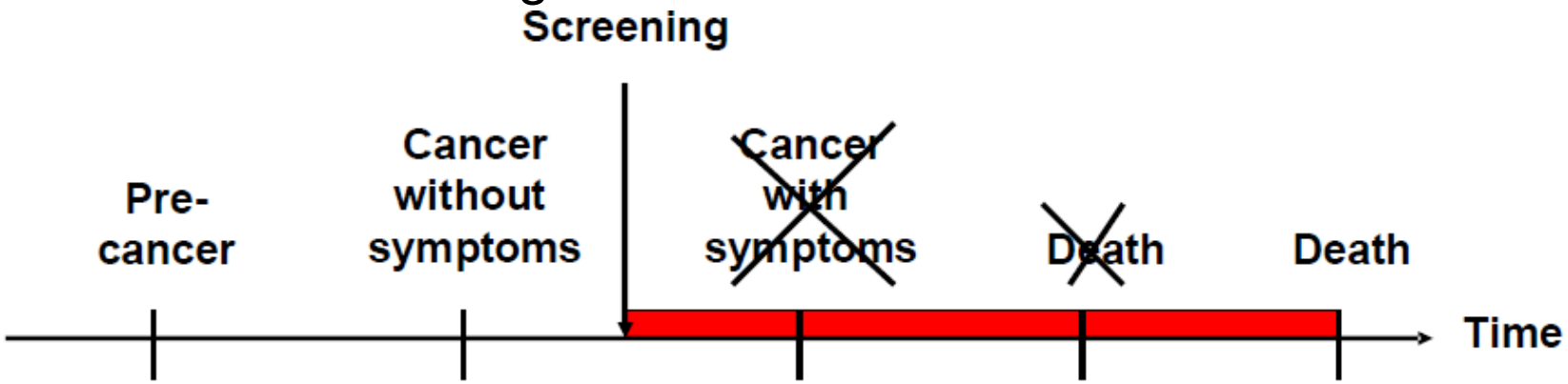


What is screening?

Cancer without screening:

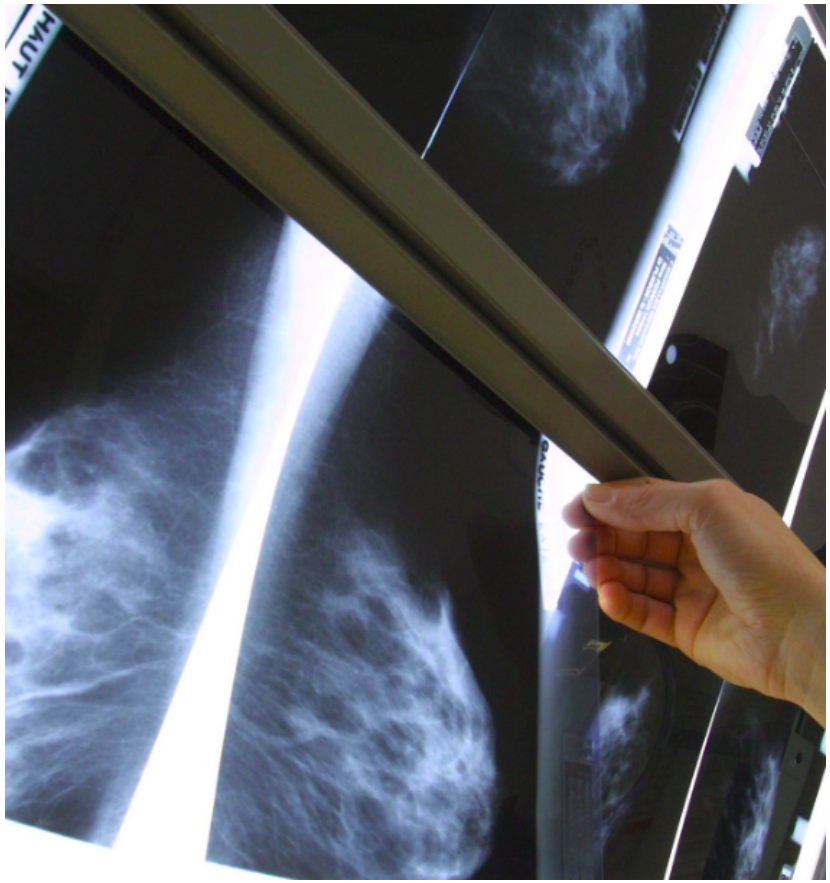


Cancer with screening:



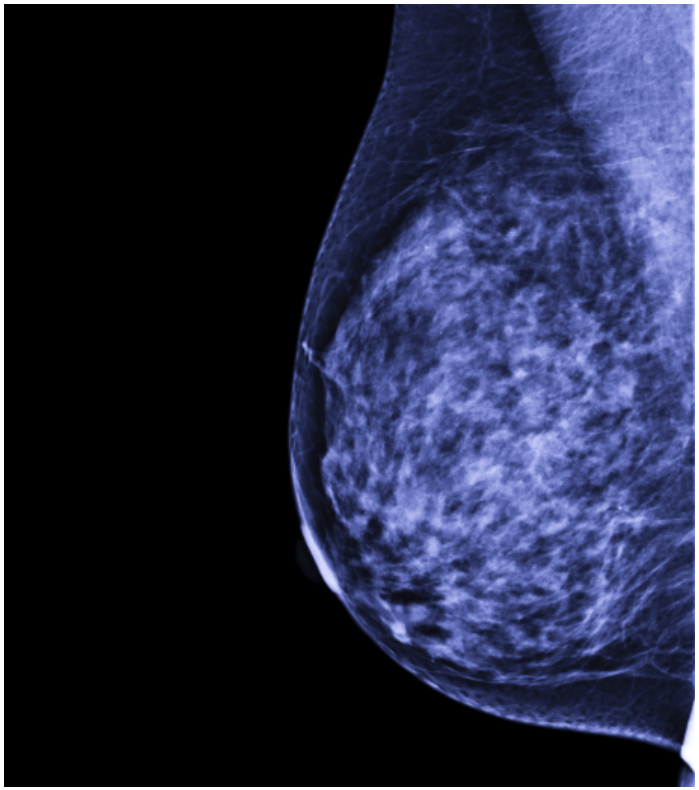
Did we do any good?

- Manipulation of time of diagnosis $\Longrightarrow$ made women cancer patients earlier in life
- Psychological effects
- Risk of overdiagnosis: the breast cancer detected would never have caused symptoms or death during a patient's lifetime



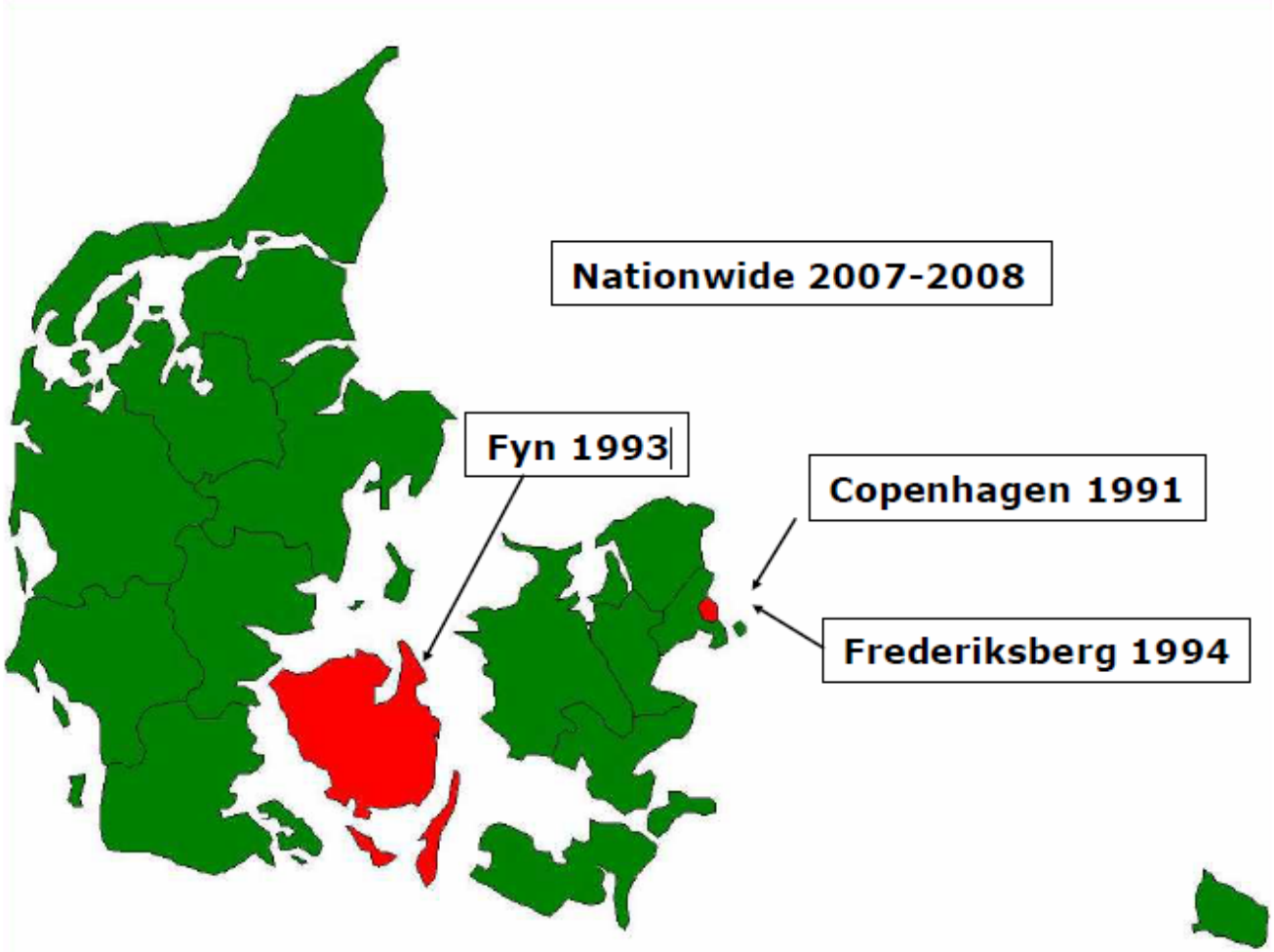
From randomised controlled trials to breast cancer screening

1. Randomised controlled trials showed good effect (screened versus non-screened women)
2. Breast cancer screening (women aged 50-69 years, invited every second year)



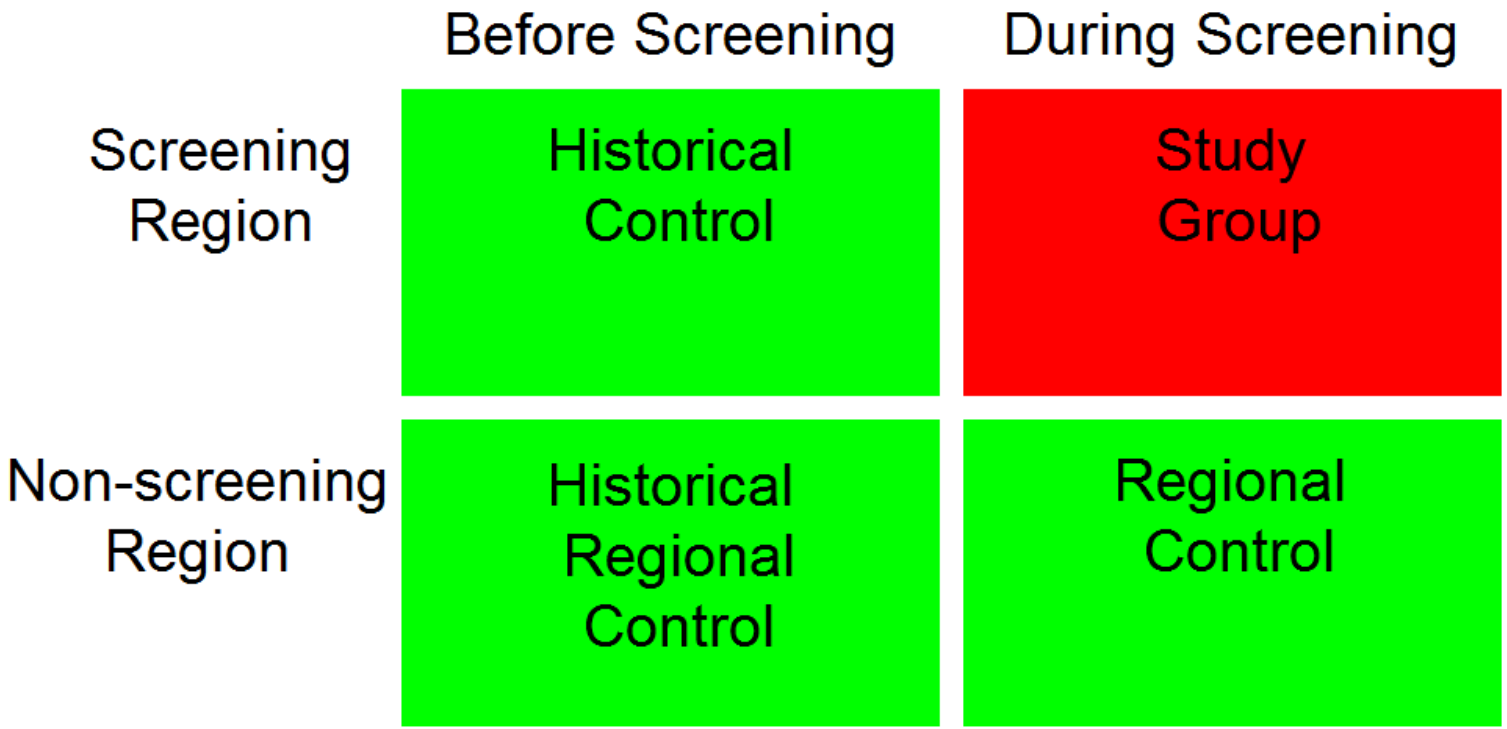
Implementation in Denmark

The implementation of the breast cancer screening program in Denmark form a natural experiment



Choice of control groups

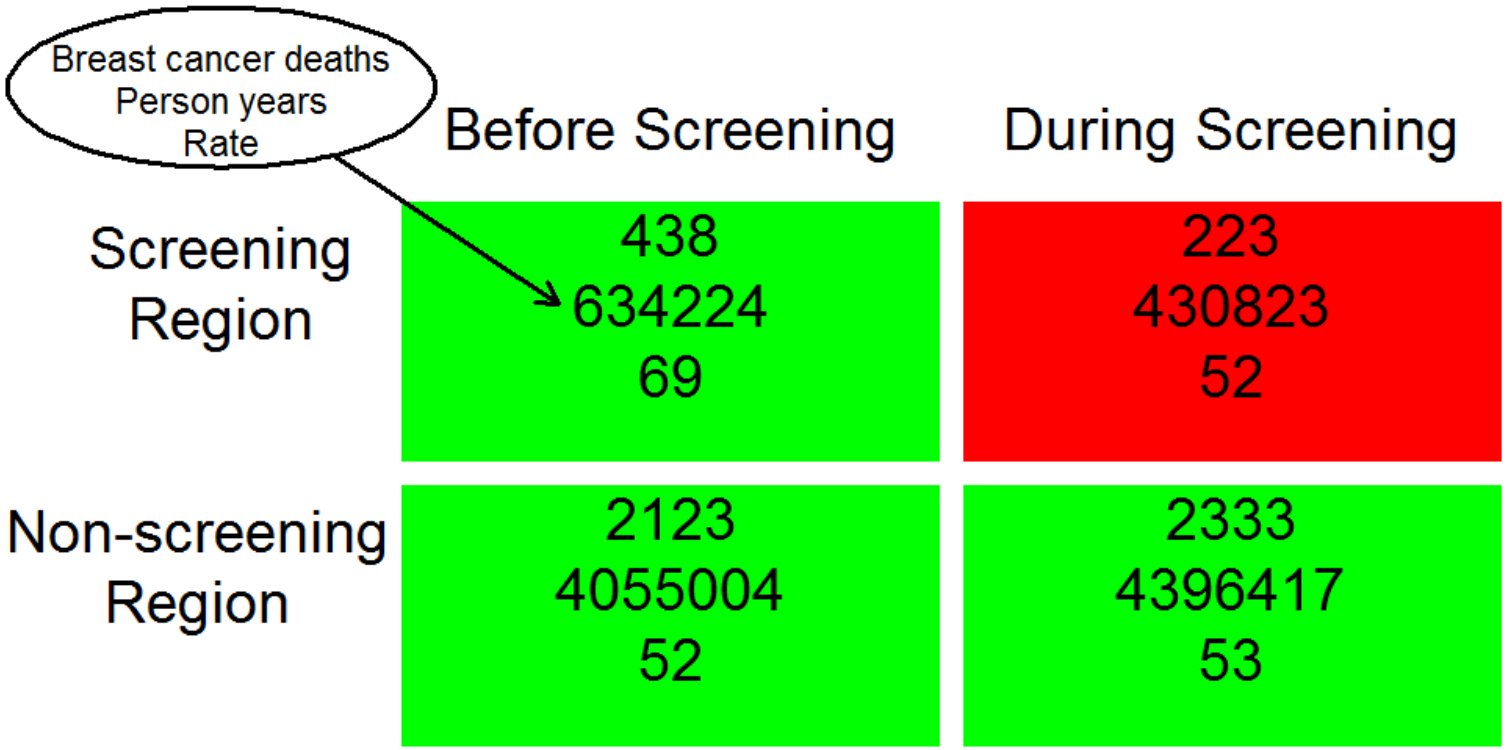
Taking advantage of the natural experiment



Choice of effect measure

- With screening we have determined the time of diagnosis
- Need an effect measure that is independent of the time of diagnosis
- Breast cancer mortality rate: Deaths from breast cancer / person years at risk

Crude breast cancer mortality rates



Poisson model

The breast cancer mortality rate:

$$\begin{aligned}\lambda_{epr} &= \theta \times (\theta_{exp})^{e} \times (\theta_{per})^{p} \times (\theta_{reg})^{r} \times (\theta_{exp,per})^{ep} \\ &\quad \times (\theta_{per,reg})^{pr} \times (\theta_{exp,reg})^{er} \times (\theta_{exp,per,reg})^{epr}\end{aligned}$$

where θ are main- and interaction effects of exposure (exp, 1=invitation to screening, 0=no invitation), period (per, 1=prior to screening, 0=during screening) and region (reg, 1=regions outside screening, 0=screening region)

- log(person years) included as offset
- age in 5-year age groups included as explanatory variable
- Intention-to-treat analysis: all women invited to screening
- Refined mortality: exclude women with breast cancer before they were offered screening
- Follow up women until death, emigration, or end of study

Poisson model

Estimate of interest:

$$\theta_{exp} = \frac{\lambda_{e=1,p=0,r=0}}{\lambda_{e=0,p=0,r=0}}$$

$\lambda_{e=0,p=0,r=0}$ is not directly available. Can directly estimate:

- Breast cancer mortality rate of the study group: $\lambda_{e=1,p=0,r=0}$
- Breast cancer mortality rate of the regional control group: $\lambda_{e=0,p=0,r=1}$
- Breast cancer mortality rate of the historical control group: $\lambda_{e=0,p=1,r=0}$
- Breast cancer mortality rate of the historical regional control group: $\lambda_{e=0,p=1,r=1}$

Poisson model

Can calculate study group rate/regional control group rate:

$$\frac{\lambda_{e=1,p=0,r=0}}{\lambda_{e=0,p=0,r=1}} = \frac{\theta_{exp}}{\theta_{reg}}$$

Historical control group rate/historical regional control group rate:

$$\frac{\lambda_{e=0,p=1,r=0}}{\lambda_{e=0,p=1,r=1}} = \frac{1}{\theta_{reg} \times \theta_{per,reg}}$$

Ratio of the two relative risks is:

$$\theta_{exp} \times \theta_{per,reg}$$

Not possible to estimate these two terms independently, i.e. the exposure effect is confounded by the interaction term between region and period

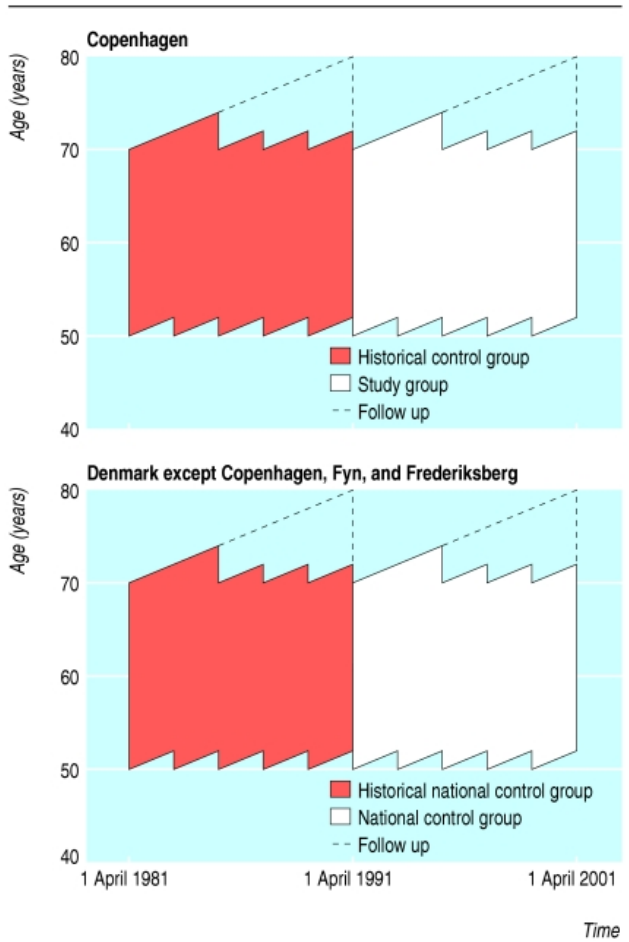
Registers to be used

- Population register: right age group, right place of living
- Mammography screening register: Date of first invitation
- Cancer register: Date of diagnosis of breast cancer (cases diagnosed before date of first invitation to be excluded)
- Population register: Dates of death or emigration (women to be censored from follow-up on these dates)
- Cause of death register: Death from breast cancer (effect measure)

The effect of breast cancer screening in Copenhagen (Olsen et al, 2005)

Conclusion:

"Breast cancer mortality in the screening period was reduced by 25% (relative risk 0.75, 95% confidence interval 0.63 to 0.89) compared with what we would expect in the absence of screening."



Other studies (Jørgensen et al, 2010)

Conclusion:
"We were unable to find an effect of the Danish screening programmes on breast cancer mortality"

Modifying the Poisson model (Olsen et al, 2007)

TABLE 1. Relative Risk for Breast Cancer Mortality in the Copenhagen Program, by Degree of Adjustment

Degree of Adjustment	Study Group		Control Groups		RR (95% CI)
	No. Deaths	Person-Years	No. Deaths	Person-Years	
Invited cohort: all ages, time, region, refined mortality	223	430,823	4894	9,085,645	0.75 (0.63–0.89)
Invited cohort: all ages, time, refined mortality	223	430,823	438	634,224*	0.80 (0.68–0.94)
Invited cohort: all ages, region, refined mortality	223	430,823	2333	4,396,417	0.91 (0.80–1.05)
Invited cohort: all ages, time, region	506	440,824	9983	9,244,489	0.79 (0.70–0.89)
Invited cohort: truncated age group (50–69), time, region, refined mortality	139	327,796	3350	7,297,832	0.85 (0.68–1.05)
Invited cohort: truncated age group (50–69), time, refined mortality	139	327,796	253	465,574*	0.84 (0.68–1.03)
Invited cohort: truncated age group (50–69), region, refined mortality	139	327,796	1574	3,568,086	0.93 (0.78–1.11)
Invited cohort: truncated age group (50–69), time, region	347	334,800	7284	7,418,815	0.86 (0.75–0.99)
Age group 50–69, time, region	405	405,446	8912	9,483,216	0.87 (0.77–1.00)
Age group 50–69, time	405	405,446	673	580,312*	0.90 (0.79–1.02)
Age group 50–69, region	405	405,446	4358	4,712,489	1.06 (0.96–1.17)

*The high number of person-years in the historical control groups compared with the study groups is due to a decrease in population size in Copenhagen in the relevant age group.

Thank you for your attention