

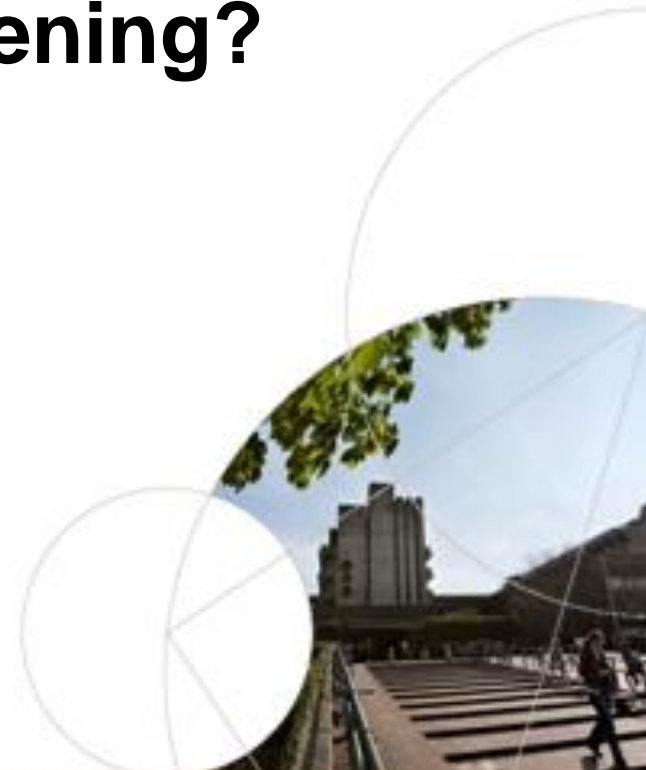


Danish Epidemiological Society
Odense, 7 April 2014

What is the evidence concerning the effects of breast cancer screening?

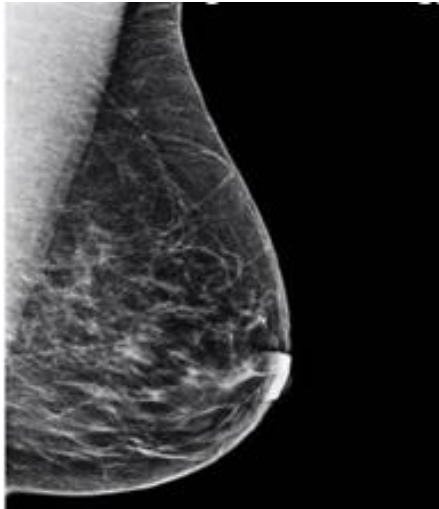
Elsebeth Lynge
elsebeth@sund.ku.dk

Elsebeth Lynge collaborates with Biomediq on evaluation of automated reading systems for mammography

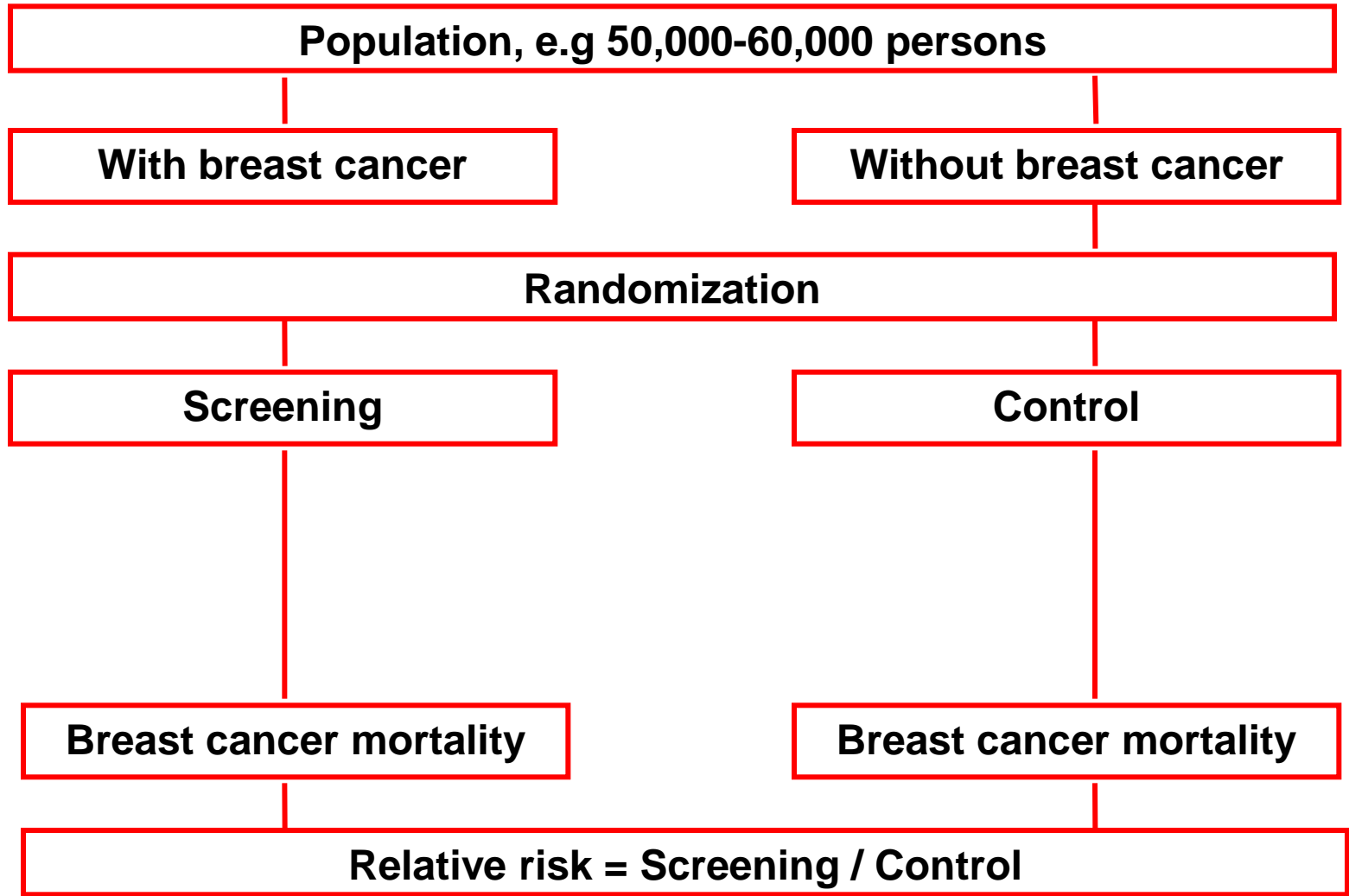


Breast cancer screening

- Purpose: To decrease mortality from breast cancer
- Method: Detect breast cancer before it gives rise to symptoms, because treatment is more effective in early than in late stages
- So far, radiology only feasible technology for screening
- Both benefits and harms of screening should be known



Golden standard: Randomized Controlled Trial



From RCTs to observational epidemiology

Why observational studies:

- RCTs undertaken long time ago, much has changed in the meantime
- RCTs, apart from the Malmö trial, not suitable for evaluation of overdiagnosis
- Need to know the outcome of screening in routine health care services

From RCTs to observational epidemiology

How to undertake observational studies:

- Mimic the RCTs
- Intention-to-treat analysis
- Exclude women with breast cancer before they were offered screening
- Compare groups equal apart from the screening
- Estimate relative risk for screening group versus control group

From RCTs to observational epidemiology

How to undertake observational studies

- Mimic the RCTs
- Intention-to-treat analysis
- Exclude women with breast cancer before they were screened

These rules are violated in many observational studies of breast cancer screening

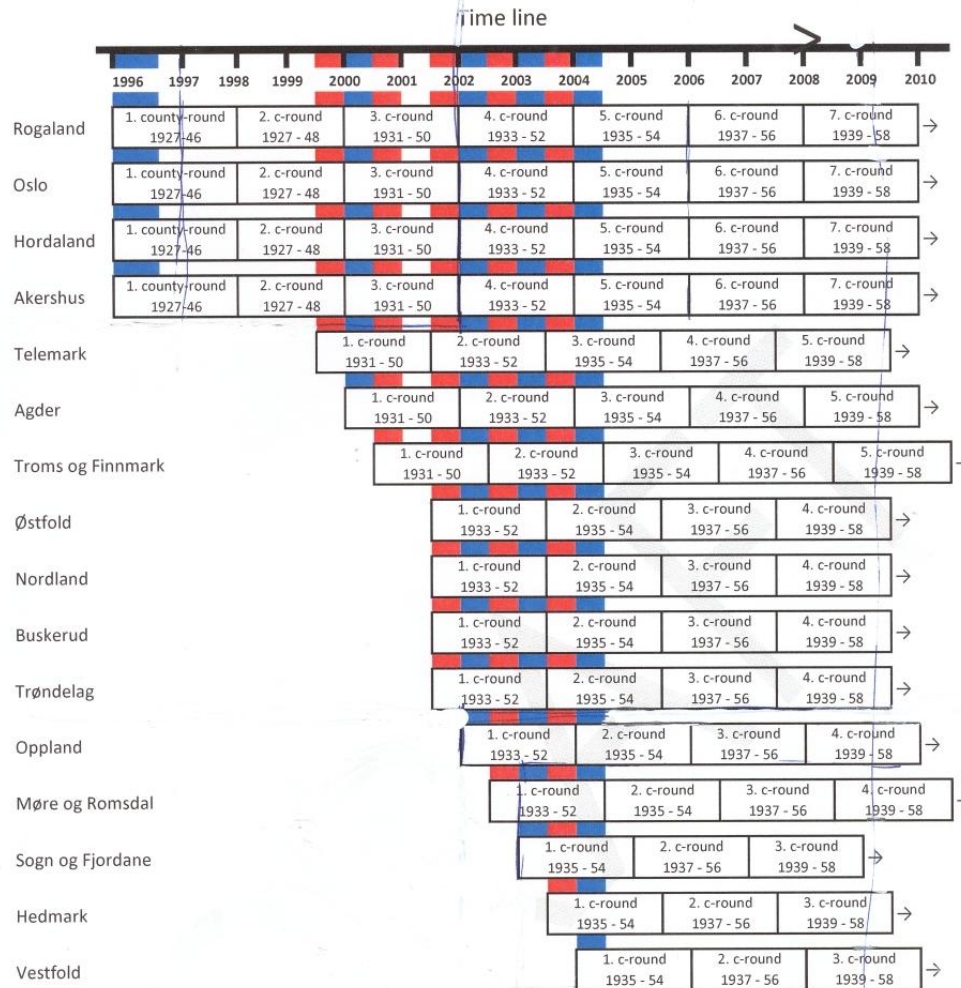
- Assume that the two groups are equal apart from the screening
- Calculate relative risk for screening group versus control group

From RCTs to observational epidemiology

How to undertake observational studies:

- Mimic the RCTs – **Do not study participants versus non-participants**
- Intention-to-treat analysis – **Follow the cohorts**
- Exclude women with breast cancer before they were offered screening – **Use incidence based breast cancer mortality**
- Compare groups equal apart from the screening – **Do not compare women offered screening with women in younger age groups not offered screening**
- Estimate relative risk for screening group versus control group – **Do not use data from older women not offered screening to estimate incidence after screening**

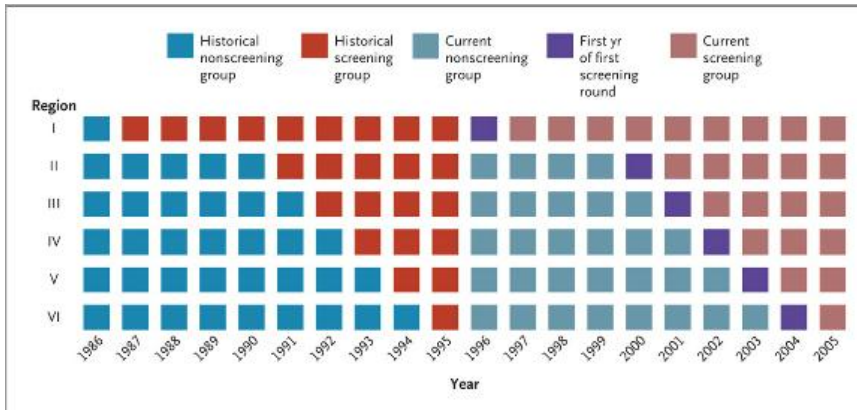
Possibility for observational study depends on setting



- Short implementation period for program
- Considerable opportunistic screening prior to program

Breast cancer mortality in Norway

Kalager et al., 2010



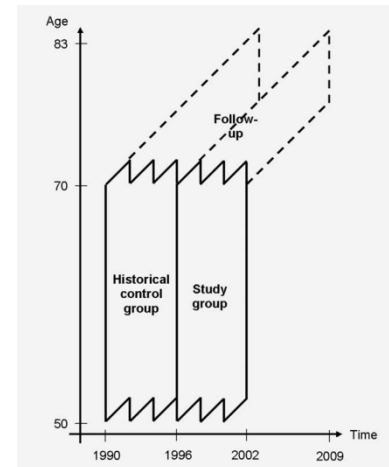
Result: 0.72 in screen vs. historical, 0.82 in non-screen vs. historical,

Conclusion: 10% reduction

Interpretation: Limited effect of screening. Treatment matters

Critics: Not balanced in calendar time and birth cohorts and affected by lead time

Olsen et al., 2012



Result: 0.93 (follow-up); 0.89

(evaluation) screen vs. historical

controlled for non-screen vs. historical

Conclusion: 7-11% reduction

Interpretation: Limited effect of

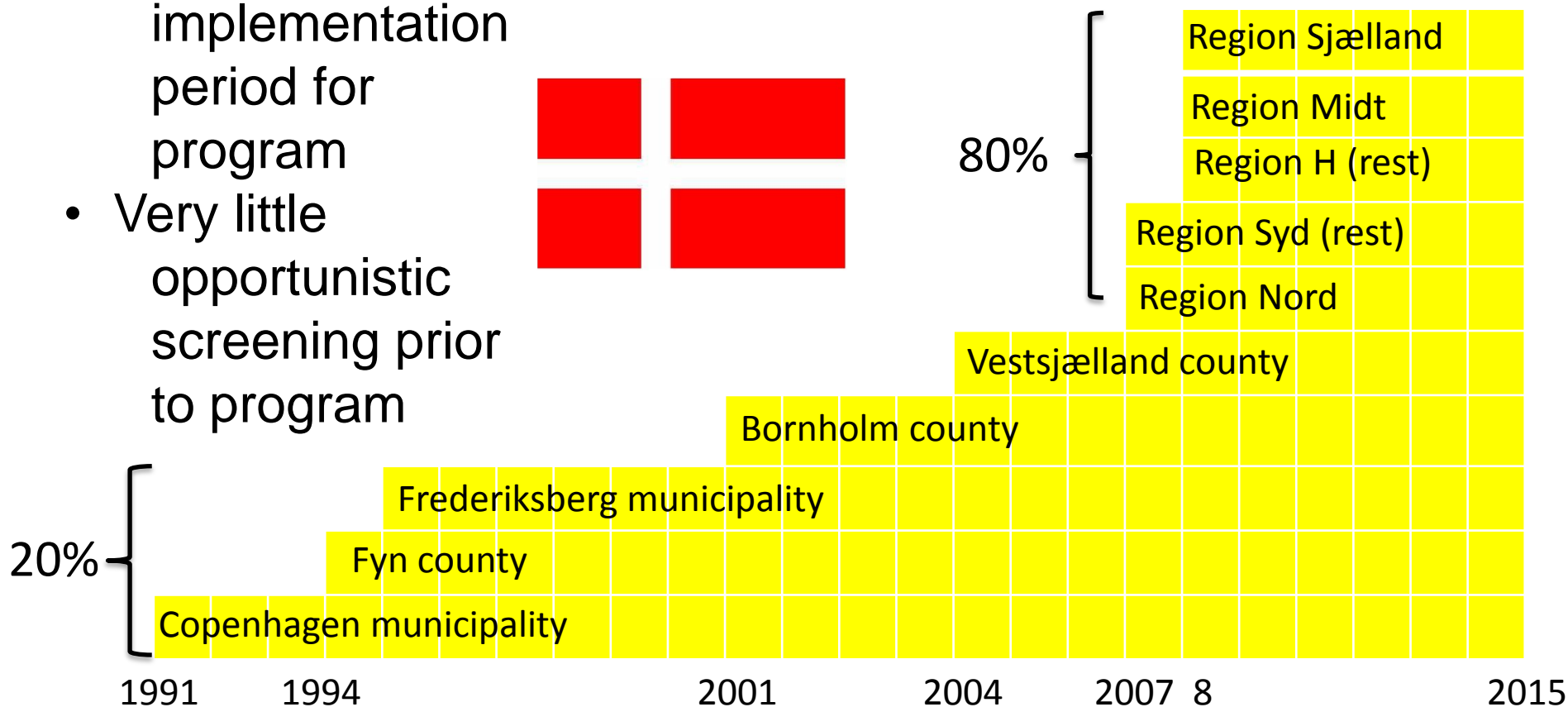
screening due to pre-program

mammography

Critics: Does not reflect long-term effect

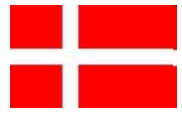
Possibility for observational study depends on setting

- Long implementation period for program
- Very little opportunistic screening prior to program



Possibility for observational studies in Denmark

	Before screening	During screening	During/Before
Study area	Historical control group	Study group	Study area: During/before
Denmark without screening	Historical regional control group	Regional control group	Control area: During/before
Study area/ Control area	Historical: Study area/ Control area	During: Study area/ Control area	(Study area: During/before)/ (Control area: during/before)



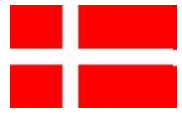
Effect of mammography screening in Denmark

Olsen et al, BMJ, 2005:

”Breast cancer mortality was reduced by 25% in the screening period compared with what would have been expected in the absence of screening.”

Jørgensen et al, BMJ, 2010:

”We were unable to detect any effect of the Danish screening programmes on breast cancer mortality”



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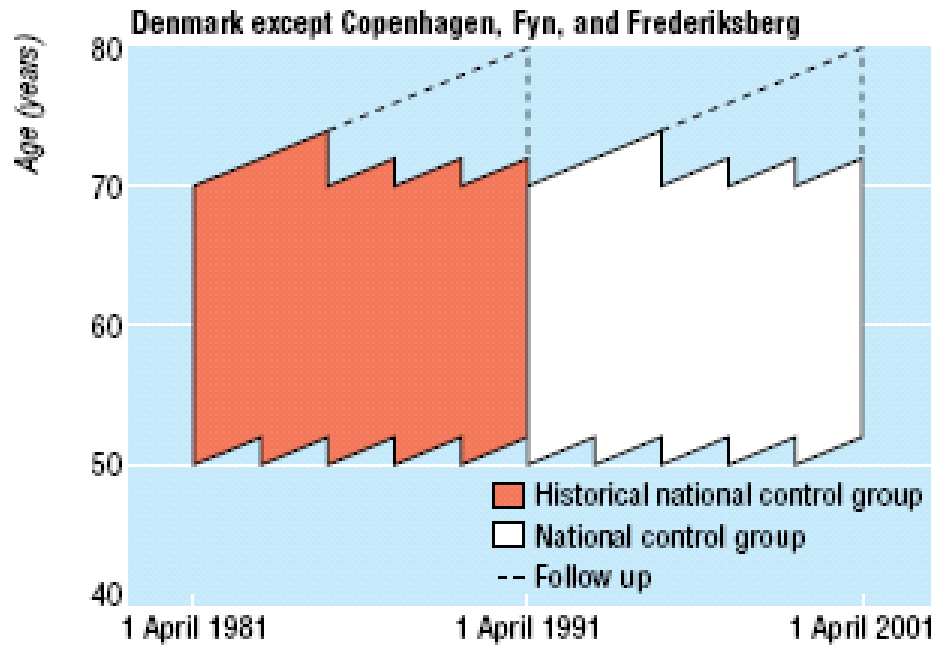
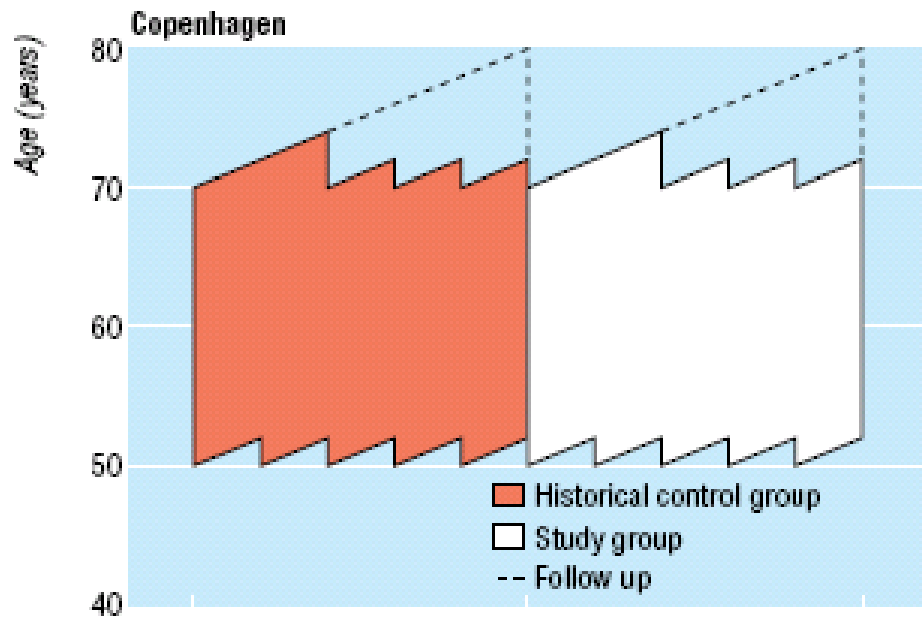
Olsen et al, 2005

Register-based research where each woman is followed

STUDY GROUP

- **Cohorts**
- **Central Population Register: Identify women living in the municipality of Copenhagen at any time between 1991 and 2001 and aged 50 to 69 years**
- **Mammography Register: Date of first invitation to screening**
- **Cancer Register: Date of first breast cancer diagnosis (women with breast cancer prior to first date of invitation excluded)**
- **Central Population Register: Dates for death and emigration (women censored at these dates)**
- **Cause of Death Register: Breast cancer cause of death**

THE 3 CONTROL GROUPS FORMED IN THE SAME WAY



Time

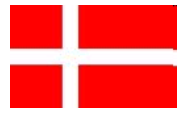
Olsen et al, 2005

Four cohorts

Olsen et al, 2005

	Before screening	During screening	During/Before
Copenhagen	69* per 100 000	52* per 100 000	
Denmark without screening	52* per 100 000	53* per 100 000	
CPH/DK			-25%** 0.75 (0.63-0.89)

* Crude rate, ** Age-adjusted ratio of rate ratios

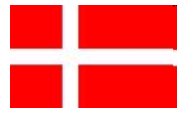


Effects of mammography screening in Denmark

Olsen et al, BMJ, 2005:

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CONCLUSION



Effects of mammography screening in Denmark

Jørgensen et al, BMJ, 2010:

”We were unable to detect any effect of the Danish screening programmes on breast cancer mortality”

Jørgensen et al, 2010

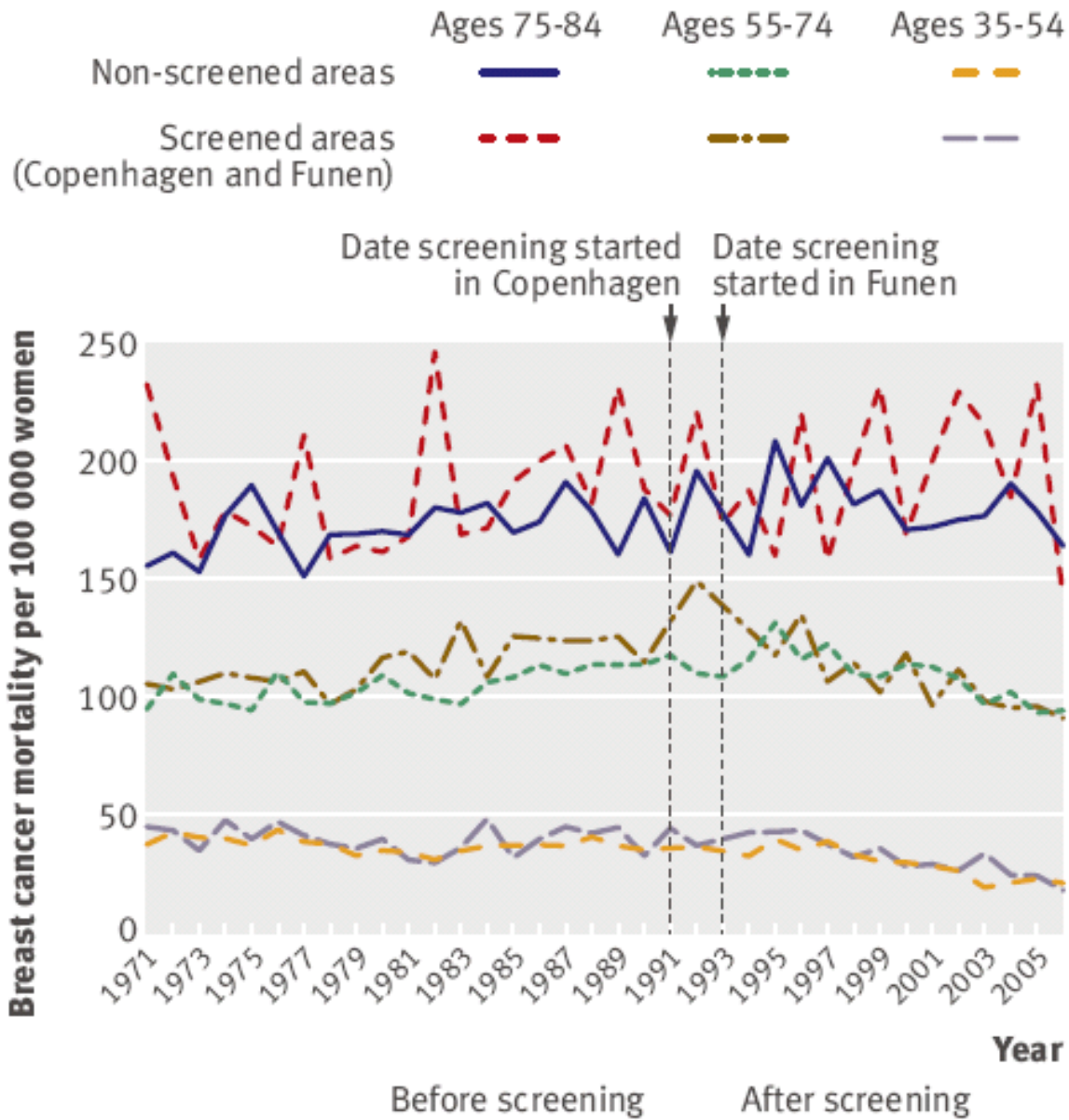
Routine statistics

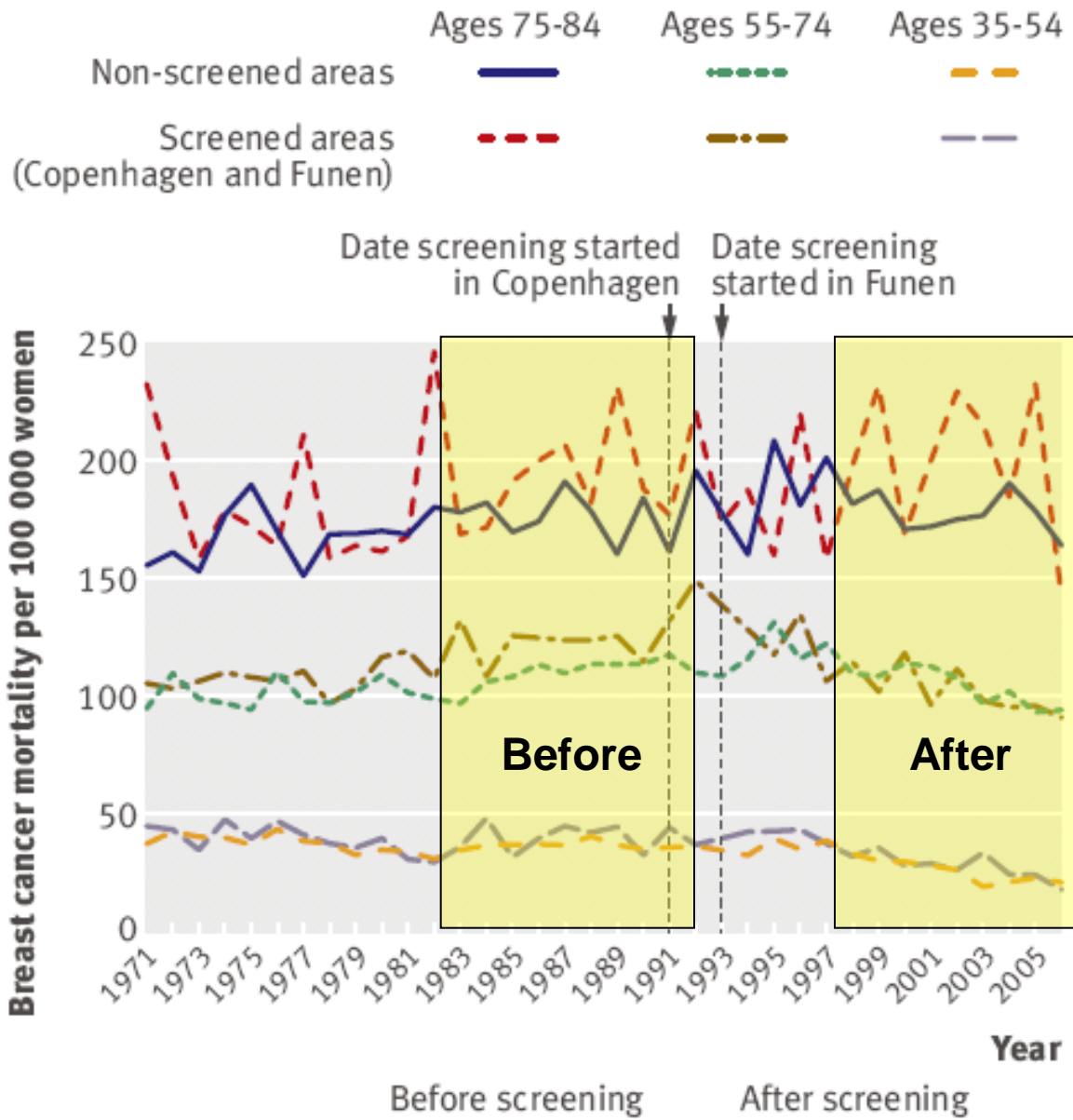
Average for population

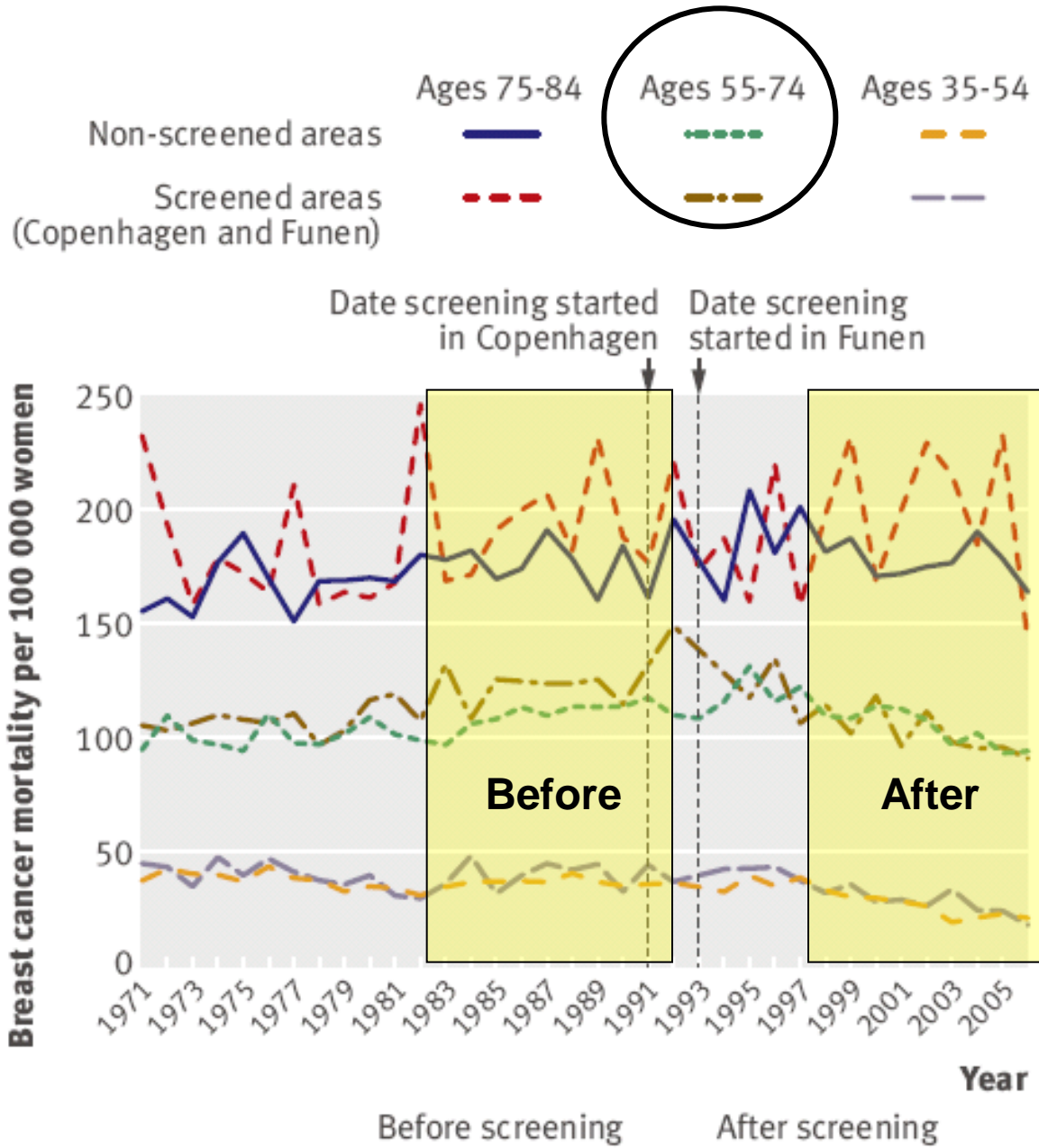
STUDY GROUP

- **Fixed age-groups**
- **Routine statistics: Number of women per year**
- **Routine statistics: Number of breast cancer deaths per year**

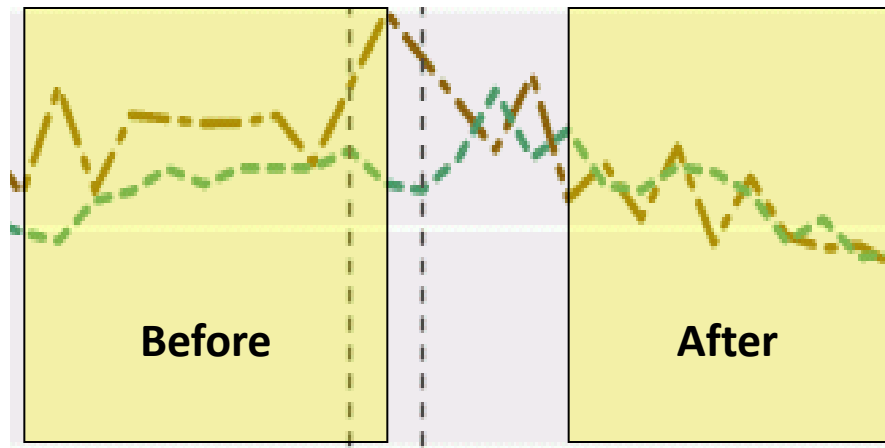
THE 3 CONTROL GROUPS WERE MADE IN THE SAME WAY







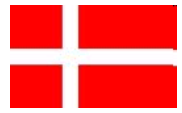
Jørgensen et al, 2010



Jørgensen et al, 2010: Analysed average annual change (= slope of line):

	Before	After
Copenhagen etc. (olive green)	+ 1%	- 1 %
Rest of Denmark (green)	+ 2%	- 2 %

There was little difference between the two slopes both before and after start of screening

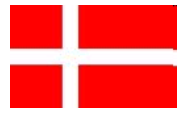


Effects of mammography screening in Denmark

CONCLUSION

Jørgensen et al, BMJ, 2010:

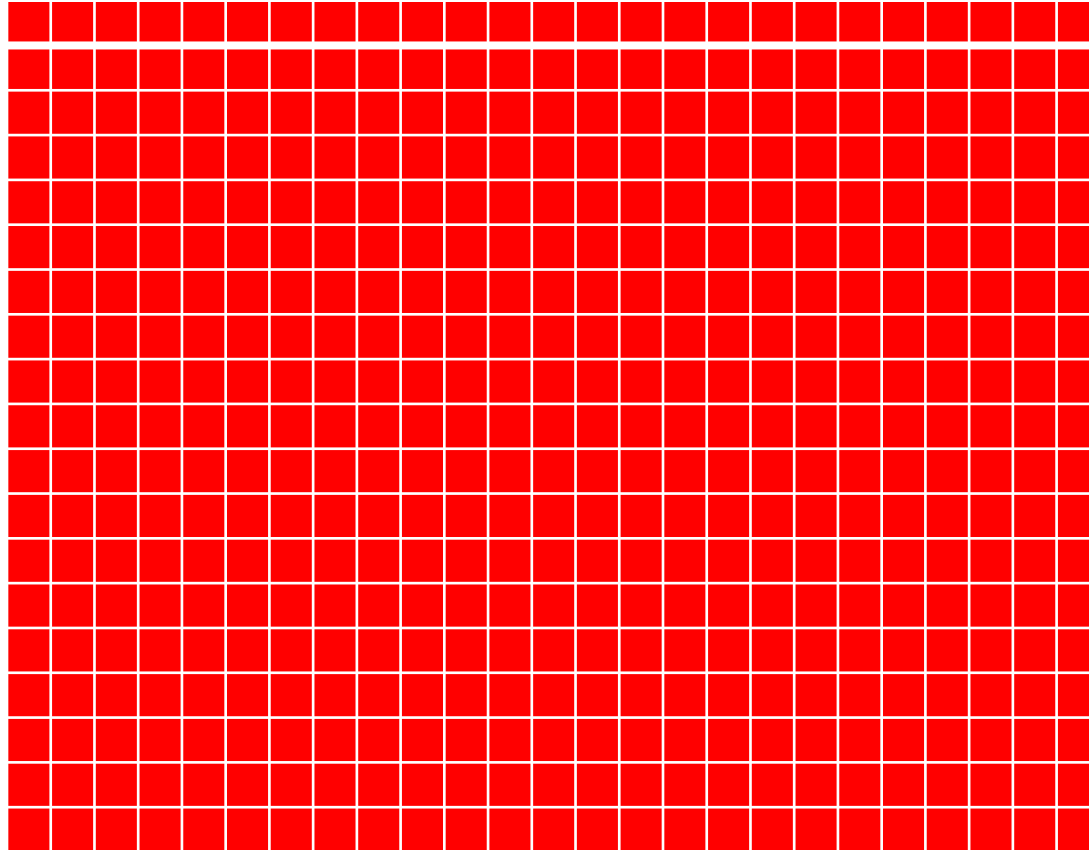
”We were unable to detect any effect of the Danish screening programmes on breast cancer mortality”



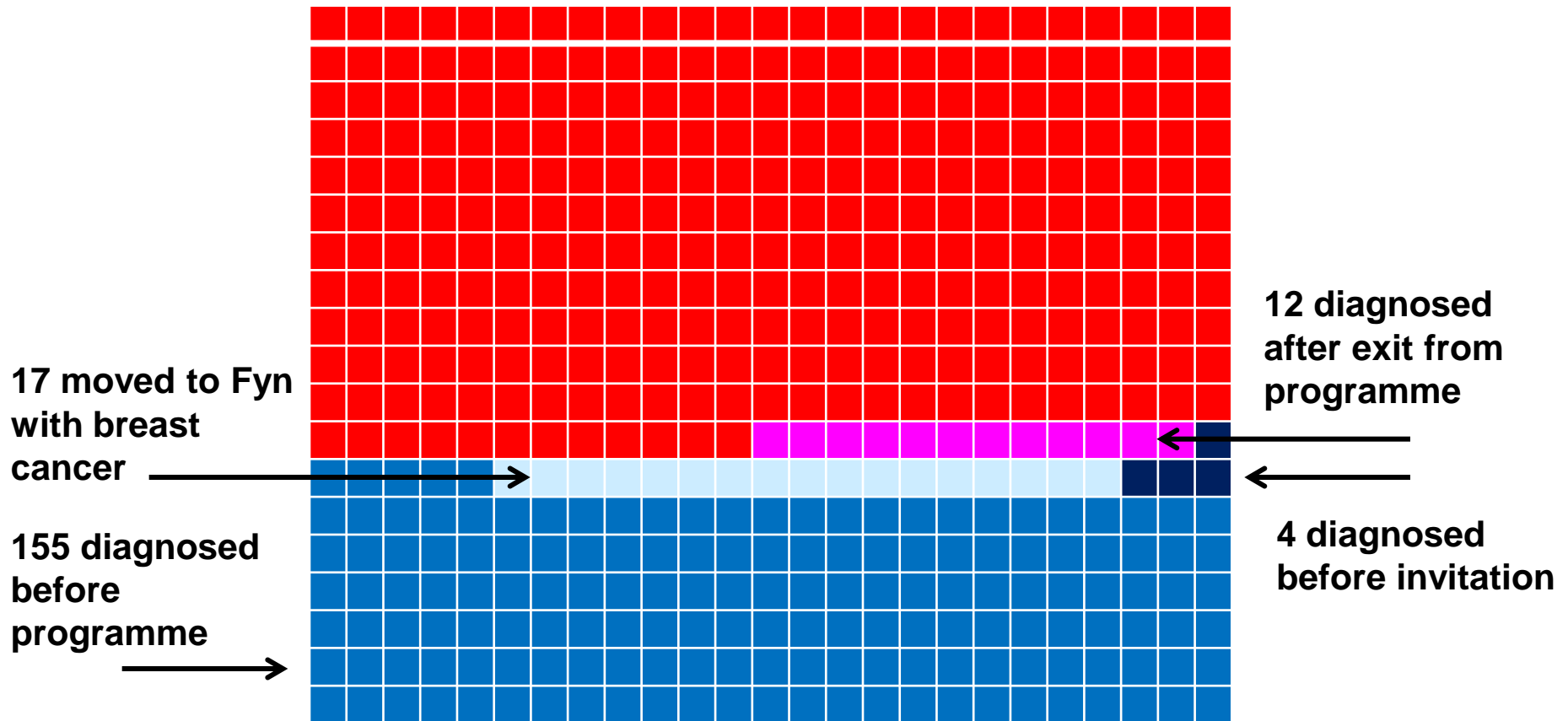
Effects of mammography screening in Denmark

- **Olsen et al, BMJ, 2005
and Jørgensen et al, BMJ, 2010**
- **Do we have conflicting results?**
- **Actually not, if we take the methodological limitations into consideration**
- **Routine data versus incidence-based mortality data**
- **Slope of lines versus level of lines**

476 breast cancer deaths in women aged 55-74 from Fyn after start of screening

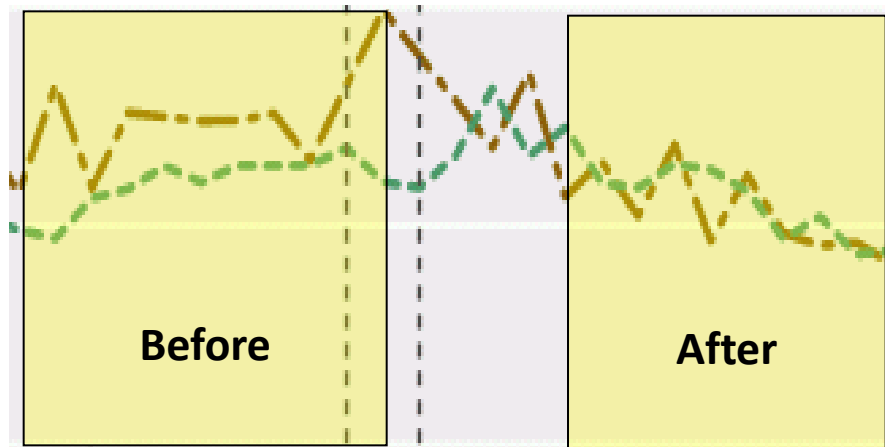


From 476 to 288 deaths = 61%



■ 288 deaths ■ 155 deaths ■ 17 deaths ■ 4 deaths ■ 12 deaths

Slope versus level of lines

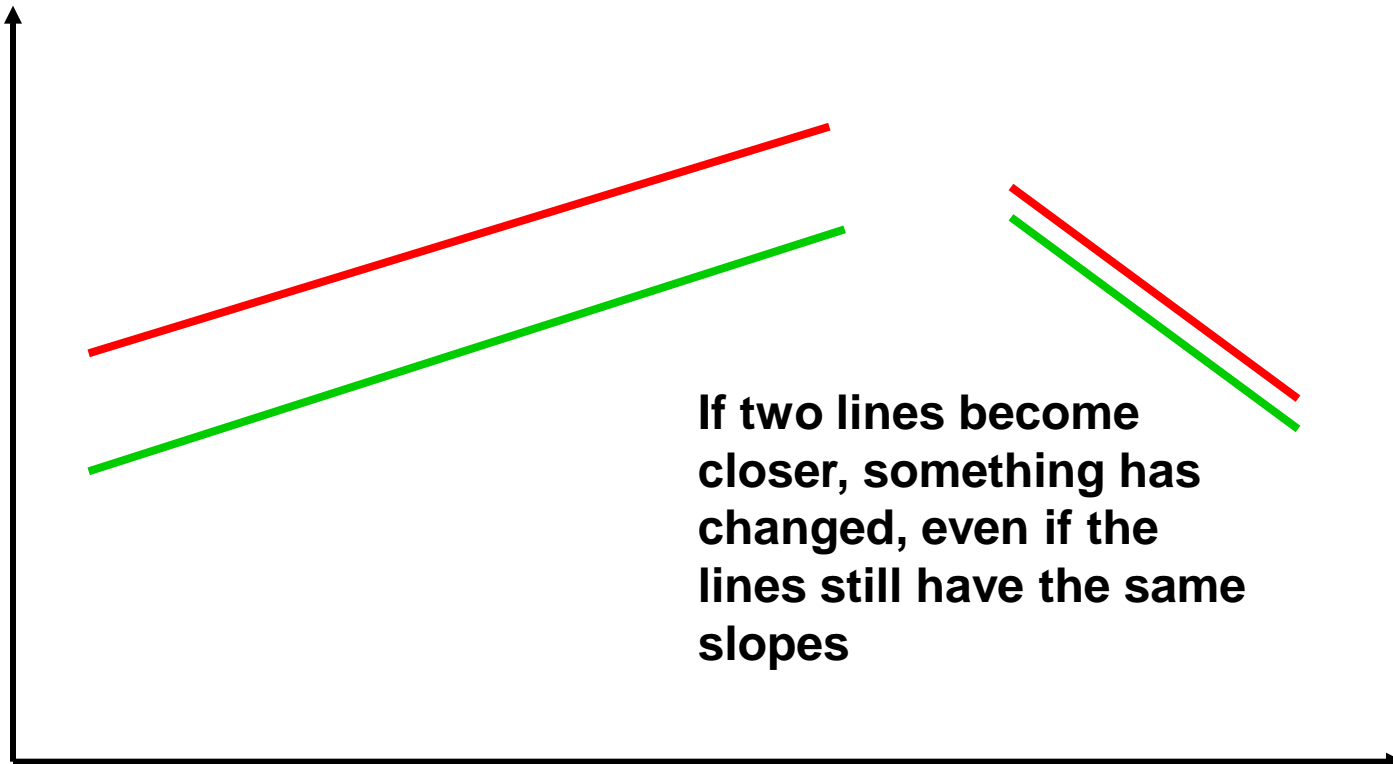


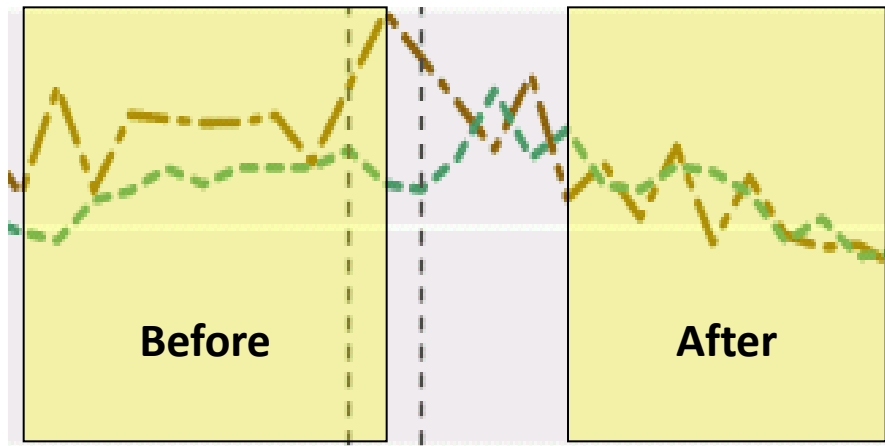
When the transition period is omitted from the analysis, it is more relevant to look at the **levels** of the lines than at the **slopes** of the lines

Copenhagen, Frederiksberg, Fyn: Olive green

Rest of Denmark: Green

Analysis of lines





$$\left(\frac{\text{Death rate}_{\text{CPH after}}}{\text{Death rate}_{\text{CPH before}}}\right) / \left(\frac{\text{Death rate}_{\text{DK after}}}{\text{Death rate}_{\text{DK before}}}\right)$$

Age group	RR (95% CI)
35-54 years	1.00 (0.86-1.17)
55-74 years	0.87 (0.79-0.95)
75-84 years	0.97 (0.87-1.09)

Copenhagen, Frederiksberg, Fyn: Olive green
Rest of Denmark: Green



Effects of mammography screening in Denmark

Olsen et al, BMJ, 2005:

25% reduction in breast cancer mortality

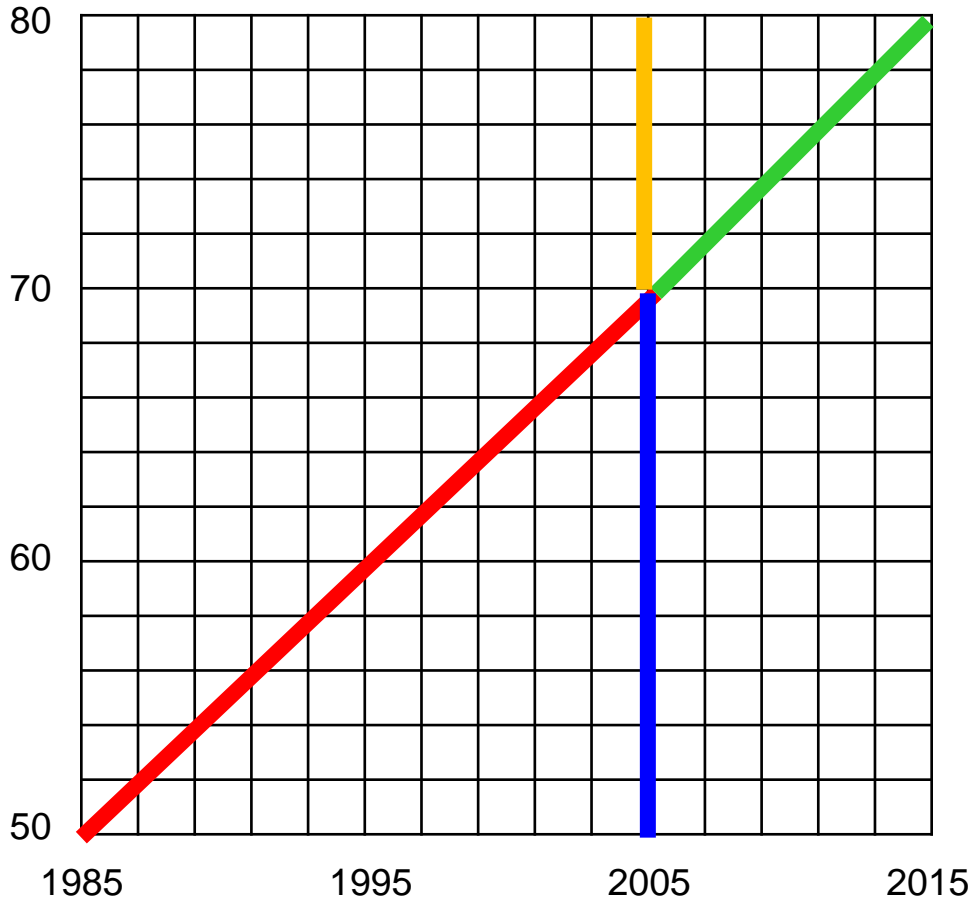
- **Copenhagen**
- **1991-2001**
- **Register-based research**

Our conclusion from Jørgensen et al, BMJ, 2010:

13% reduction in breast cancer mortality

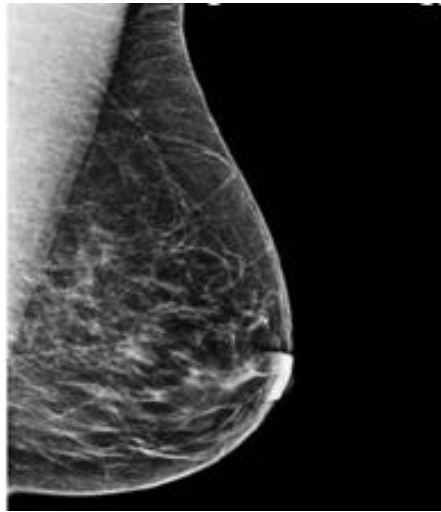
- **Copenhagen, Frederiksberg, Fyn**
- **1997-2006**
- **Routine statistics**

Lexis' diagram



- Jørgensen et al, 2010 used for illustration
- It is not a stand-alone example
 - Many studies have methodological shortcomings
- Many mistakes derive from the simple misunderstanding that it should be possible to replace cohort data by cross-sectional data

Why have epidemiological virtues been forgotten, when it comes to evaluation of mammography screening?



Thank you for your attention



Copenhagen Old Municipality Hospital, now part of University of Copenhagen