# **Screening for cancer** When to screen and how to inform?

## Karsten Juhl Jørgensen The Nordic Cochrane Centre



### Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals (Review)

Holme Ø, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G





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### • Reduced incidence carries great weight

- Mechanism of effect differs fundamentally between programmes
- Which screening programmes we use is as much about timing and politics as about science and the benefit/harm balance



### General health checks in adults for reducing morbidity and mortality from disease (Review)

Krogsbøll LT, Jørgensen KJ, Grønhøj Larsen C, Gøtzsche PC





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A Department of Health representative told BBC News: "By spotting people who are at risk of heart attacks, diabetes, stroke and kidney disease we can help prevent them. The NHS Health Check programme is based on expert guidance."<sup>1</sup>

"...I have put our original suggestion of systematic health checks on ice. Because it did not have the desired effect." *Astrid Krag, Danish Minister of Health*<sup>2</sup>



### The Benefits and Harms of Breast Cancer Screening:

### An Independent Review

Authors: The Independent UK Panel on Breast Cancer Screening



A report jointly commissioned by Cancer Research UK and the Department of Health (England).

October 2012



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# Main results:

1 woman avoids a breast cancer death for every 3 overdiagnosed; 1 300 and 4 000 women per year, respectively, in the UK.



# Breast screening should continue

But would the Panel also have recomended to implement breast screening if it did not already exist?







# 2.7 million women invited in 2009<sup>1</sup>.

- False positives: 65,094
- Benign core biopsies: 19,467
- Benign open biopsies: 1,539
- False negatives: ~33% of cases in a screened population were not detected
- Direct cost: £ 96 million



# New UK leaflet - improvements

- Clearly states that there is a choice
- Clear presentation of the most important harm
- No direct encouragement to attend
- No indication that breast screening reduce the risk of mastectomy



# New UK leaflet – pending improvements

- Remaining harms must also be clearly presented using absolute numbers
- The importance and long-term consequences of false positive findings must be clearly stated
- Harms are not risks
- Pre-assigned appointments must be abandonned



# Evidence from current programmes

• Kalager et al. (NEJM 2010): 10% (CI: 0.78 to 1.04) average 6.6 years of follow-up

Olsen et al. (Int J Cancer 2012): 11% (CI: 0.77 to 1.12) "up to 13 years of follow-up"



# Tumour size and breast screening

- Average tumour size in Denmark was reduced from 33 mm in 1978-9 to 24 mm in 1988-9.
- Average size reduction in the trials was 5 mm.







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Pharoah P, Professor of Cancer Epidemiology, Univ. of Cambridge.





"The Panel's primary conclusions about breast cancer mortality are based on data reported in the Cochrane review..."



# How was the benefit estimated?

- **Assumption 1:** The randomised trials are equally reliable.
- **Assumption 2:** The effect can be extrapolated as unchanged 8-17 years beyond trial duration.
- Assumption 3: Identical effect today as then.
- **Assumption 4:** The effect remains unchanged 10 years beyond the screening age.
- Calculation: 20% fewer breast cancer deaths today than without screening in the age group 55-79 years (5843<sup>1</sup>) = 1461 fewer breast cancer deaths.



Α	В
100% participation	~80% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month



Α	В
100% participation	~70% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month
A finds smaller avera	ge size tumors than B



Α	B
100% participation	~70% participation
4-5 rounds	2-4 rounds
2 view	1 view
2 readers	1 reader
Screening every 12 month	Screening every 24-33 month
A finds smaller avera	ge size tumors than B
Individual randomisation	Cluster-randomisation (45)
Presents demographic data	Do not present demographic data
Consistent, transparent reporting	Inconsistent, unclear reporting
Blinded, external cause of death evaluation	No blinded cause of death evaluation



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3% reduction (-26% to +27%)*	42% reduction (-55% to -3%)*
2% increase(-22% to + 33%)*	24% reduction (-39% til -5%)*

\* Thirteen years follow-up



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"Between the late 1980s and 2008-2010, breast cancer mortality rates fell by 50% in the 15-39 age group, by 47% in the 40-49 age group, 45% in the 50-64 age group, 40% in the 65-69 age group and by 26% in women aged over 70 years."<sup>1</sup>





#### Breast cancer mortality rates for screened and non-screened areas in Denmark



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Jørgensen KJ, Zahl PH, Gøtzsche PC. BMJ 2010;340:c1241



A: Excess cancers as a proportion of cancers diagnosed over long-term follow- up. B: Excess cancers as a proportion of cancers diagnosed during the screening period.



# How was overdiagnosis estimated?

• Modelling based on observed invasive breast cancer incidence in the UK.

- 2250 linear and Poisson regression models applied to data from 1975-2004 with various assumptions.
- •Most model results estimated ~3000 overdiagnosed invasive breast cancers per year.
- •50-69 years: 23,297 invasive, 3,931 CIS. 19% ODX = 5,920 cases per year in the UK.<sup>1</sup>









# Conclusions on Marmot-report:

- The benefit was overestimated and not based on an observed effect in the UK, but extrapolations.
- The major harm is clearly visible in UK statistics, but was underestimated.
- •Improved treatment is the major cause of observed reductions in breast cancer mortality in the UK.
- An improvement in all cause or all cancer mortality has never been demonstrated.



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

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.



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### Breast screening controversy continues

"At what stage must we seriously consider whether this screening is a good use of £96m of the NHS budget?"

Fiona Godlee, Editor's Choice, BMJ.







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http://articles.timesofindia.indiatimes.com/2012-10-17/mumbai/34524140\_1\_preventive-checks-preventive-tests-public-health

"Preventive health check-ups are an irrational battery of tests carried out on healthy people whose main indication is that they have money in their pockets. It is not scientific and can be completely avoided," *Dr. Abhay Shukla, Centre for Enquiry in Health and Allied Themes (CEHAT), Pune.* 

"A hospital administrator said preventive cancer checks carried out in his hospital recently had revealed ovarian cancer in two of the 100 women who had signed up. "For them, it was a life-saving diagnosis," he said."





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• "..the UK breast screening programme confer significant benefit and should continue."

• "The Panel believes that overdiagnosis occurs"

• "Clear communication of these harms and benefits to women is essential and is the core of how a modern health system should function."

• "...the estimates provided are from studies with many limitations and [the] relevance to present-day screening programmes can be questioned, they have substantial uncertainty and should be regarded as only an approximate guide."

- "The Panel relied mainly on findings from randomised trials..."
- "Randomised trials that elucidate the appropriate treatment of screendetected ductal carcinoma of the breast are encouraged."
- "the overall cost-effectiveness of the UK breast cancer screening programme needs to be reassessed."



Cancer Screening Programmes

### NHS breast screening



"Designed to ensure that women are told what screening can and cannot achieve, the leaflet includes an explanation about false positive and false negative results [...]".

"This means that women should be able to make a genuinely informed choice based on an understanding about why they are attending for screening".



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Cancer Screening Programmes

### NHS breast screening



### Some statistics you might find helpful

- Breast cancer is the most common cancer in women. There are around 46,000 cases a year in the UK. Eight out of 10 breast cancers are found in women aged 50 and over.
- About 12,000 women die of breast cancer each year in the UK.
- For every 400 women screened regularly for 10 years, one less will die from breast cancer. This means that around 1,400 women are prevented from dying from breast cancer each year in England.



Cancer Screening Programmes

### NHS breast screening



What are the benefits of breast screening?

- Regular screening prevents deaths from breast cancer.
- If a breast cancer is found early, you are less likely to have a mastectomy (your breast removed) or chemotherapy.

# What are the downsides of being screened?

- Having a mammogram means your breasts are exposed to a small amount of radiation.
- Screening can find cancers which are treated but which may not otherwise have been found during your lifetime.





### Mastectomy use in sreened and non-screened areas in Denmark

Year



"Monitoring the effectiveness of screening.

This can be done approximately by examining trends in age-specific breast cancer mortality available from routine statistics."

The Forrest Report, 1986



# **BREAST CANCER IN UK WOMEN** 50 Deaths per 100 000 40 30 20 10 0

Mayor S. BMJ 2009; 338: b1710. Copyright ©2009 BMJ Publishing Group Ltd.



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#### Effect of Screening Mammography on Breast-Cancer Mortality in Norway

Mette Kalager, M.D., Marvin Zelen, Ph.D., Frøydis Langmark, M.D., and Hans-Olov Adami, M.D., Ph.D.

#### RESULTS

We analyzed data from 40,075 women with breast cancer. The rate of death was reduced by 7.2 deaths per 100,000 person-years in the screening group as compared with the historical screening group (rate ratio, 0.72; 95% confidence interval [CI], 0.63 to 0.81) and by 4.8 deaths per 100,000 person-years in the nonscreening group as compared with the historical nonscreening group (rate ratio, 0.82; 95% CI, 0.71 to 0.93; P<0.001 for both comparisons), for a relative reduction in mortality of 10% in the screening group (P=0.13). Thus, the difference in the reduction in mortality between the current and historical groups that could be attributed to screening alone was 2.4 deaths per 100,000 person-years, or a third of the total reduction of 7.2 deaths.

#### CONCLUSIONS

The availability of screening mammography was associated with a reduction in the rate of death from breast cancer, but the screening itself accounted for only about a third of the total reduction. (Funded by the Cancer Registry of Norway and the Research Council of Norway.)



### Why does vehement opposition to screening come from Denmark, which has one of Europe's highest breast cancer mortality rates?

Denmark still has one of the highest breast cancer mortality rates in Europe, similar to that of Serbia. On the other hand, Finland and Sweden have among the lowest breast cancer mortality rates in Europe, although all the Nordic countries use identical breast cancer treatment guidelines. The health care systems among these countries are similar in most other aspects as well, except that Finland and Sweden introduced nationwide screening more than two decades ago. The implementation of organized nationwide screening should dramatically decrease breast cancer mortality throughout Denmark, as has already happened in Sweden and Finland.



			Mort	Mortality change for all ages (%)				Mortality change 1989-2006 by age group (%)					
	Meann	nortality*	For 1989	-2006	Veen fer	Annual		Annual chang	ge	0	)verall cha	nge	Quality
Country	1987-9	2004-6†	Annual	Overall	Year for start of decline‡	change 1999- 2006	<50	50-69	≥70	<50	50-69	≥70	of data on cause of death§
Iceland	33.1	23.5	-3.4	-44.5	1995	1.1	-8.1	-2.5	-3.1	-76.3	-35.0	-41.5	High
England and Wales	41.9	28.1	-2.5	-34.9	1989	-2.0	-3.2	-3.0	-1.5	-42.1	-40.1	-22.6	High
Luxembourg	36.3	22.9	-2.4	-34.1	1988	-2.8	-5.3	-2.5	-1.3	-60.0	-34.9	-19.9	Medium
Scotland	39.3	29.0	-2.1	-29.9	1990	-1.4	-2.9	-2.7	-0.7	-39.1	-37.2	-11.9	High
Northern Ireland	37.0	28.1	-2.0	-29.2	1991	-1.2	-3.8	-2.6	0.0	-48.2	-36.2	-0.7	High
Austria	31.8	24.5	-1.8	-26.8	1990	-1.6	-4.0	-1.7	-1.1	-50.3	-25.3	-16.9	Medium
Spain	23.7	18.9	-1.8	-26.8	1992	-2.2	-3.4	-2.1	-0.3	-44.7	-30.3	-4.6	Medium
Ireland	40.3	30.5	-1.8	-26.4	1991	-2.3	-3.2	-1.9	-1.0	-42.7	-27.2	-15.7	High
Netherlands	39.0	30.1	-1.7	-25.1	1993	-2.7	-1.7	-1.9	-1.4	-25.3	-27.8	-20.9	Medium
Norway	27.4	21.5	-1.6	-24.3	1995	-2.2	-2.5	-1.5	-1.4	-35.2	-22.6	-20.8	Medium
Italy	29.7	23.2	-1.5	-22.8	1991	-1.6	-2.7	-1.7	-0.7	-36.7	-24.9	-11.0	Medium
Switzerland¶	30.5	24.0	-1.5	-22.7	1985	-1.1	-2.2	-1.2	-1.7	-30.9	-18.5	-24.7	Medium
Germany	31.3	26.2	-1.4	-21.3	1999	-1.5	-3.5	-1.3	-0.5	-45.5	-20.2	-8.9	Medium
Denmark	40.5	32.0	-1.4	-20.8	1995	-2.6	-3.8	-1.7	0.1	-48.5	-25.7	1.3	Medium
Belgium	37.5	29.7	-1.3	-20.3	1986	-2.4	-2.7	-1.5	-0.4	-36.7	-22.0	-7.2	Medium
Portugal	23.9	NA	-1.1	-17.8	1992	-0.9	-2.7	-1.4	0.4	-36.9	-21.5	6.5	Low
Czech Republic	30.6	26.4	-1.1	-17.8	1994	-1.2	-3.7	-1.7	0.5	-47.2	-25.5	8.6	Medium
Slovenia	30.7	26.3	-1.0	-16.1	1993	-2.1	-4.1	-1.1	0.5	-51.3	-17.3	9.1	High
Sweden	25.6	22.0	-1.0	-16.0	1972	-0.6	-2.6	-1.0	-0.3	-35.7	-15.9	-4.3	Medium
Finland	24.5	21.4	-0.7	-11.7	1990	-1.5	-2.3	-0.7	0.0	-32.6	-10.8	0.1	High
Hungary	32.4	29.0	-0.7	-11.4	1994	-3.1	-2.4	-0.5	-0.1	-34.4	-8.3	-2.4	High
France	28.5	25.6	-0.7	-10.7	1994	-1.4	-0.9	-0.9	-0.1	-14.3	-14.9	-1.6	Medium
Poland	21.5	21.1	-0.4	-5.9	None	-0.1	-2.5	-0.3	0.8	-34.5	-4.3	14.6	Low
Slovakia	23.6	23.4	-0.1	-1.5	2000	-3.2	-2.1	-0.1	1.1	-30.7	-1.9	20.5	High

Table 1| Changes in breast cancer mortality between 1989 and 2006 in European countries ranked according to overall decline in mortality



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Page 1 of 10

### RESEARCH

### Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database

Philippe Autier *research director*<sup>1</sup>, Mathieu Boniol *senior statistician*<sup>1</sup>, Anna Gavin *director*<sup>2</sup>, Lars J Vatten *professor*<sup>3</sup>

<sup>1</sup>International Prevention Research Institute, 95 Cours Lafayette, 69006 Lyon, France; <sup>2</sup>Northern Ireland Cancer Registry, Belfast, Northern Ireland, UK; <sup>3</sup>Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway

**Conclusions** The contrast between the time differences in implementation of mammography screening and the similarity in reductions in mortality between the country pairs suggest that screening did not play a direct part in the reductions in breast cancer mortality.



"The 10-year fatality of screendetected tumours is 50% lower than that of symptomatic tumours"

Steven Duffy, Professor of Statistics, St. Barts & the London Medical and Dental Schools. NHS BSP Annual Review 2008.



Sündhedsstyrelsen	Porside wyneuscenter odgivelser Job og kamere om styrelsen English	۳ <b>۹</b>
Emneoversigt   Mest læste em	ner   Emner alfabetisk   🗛 🖂 📮	
Forside / Nyhedscenter / Nyheder /	2013 / Lavere overlevelse for danske kvinder med brystkræft	
	Lavere overlevelse for danske kvinder med brystkræft 01. marts 2013 Link til artiklen i British Journal of Cancer	
Nyhedscenter	Kvinder i Danmark og Storbritannien har haft en lavere overlevelse efter brystkræft, end kvinder i Australien, Canada, Norge og Sverige i perioden 2000-2007. Det viser et nyt videnskabeligt studie, som offentliggøres i dag i British Journal of Cancer. Studiet er udført af International Cancer Benchmarking Partnership, som Sundhedsstyrelsen deltager i og har medfinancieret.	eft
Nyheder - 2013 - 2012 - 2011 - 2010	<ul> <li>Tre-års overlevelsen for danske kvinder var 89 procent, hvilket var på niveau med Storbritannien, men lavere end i de andre fire lande, der lå på 91-94 procent.</li> <li>Studiet undersøgte, om forskellene mellem landene kunne forklares ved forskelle i sygdomsstadie på diagnosetidspunktet, og fandt at kun 30 procent af danske kvinder blev diagnosticeret i tidligt sygdomsstadie (stadium I), sammenlignet med 42-45 procent i de andre fem lande.</li> </ul>	er se et øre et
- 2009 - 2008 - 2007 - 2007	Ifølge forskerne kan en medvirkende forklaring på den lavere overlevelse blandt danske kvinder være, at kvinderne bliver diagnosticeret i senere stadier, formentlig på grund af at Danmark, som det eneste land i undersøgelsen, ikke havde udrullet et nationalt screeningsprogram for brystkræft før 2007.	e.
2005 2004 2003 2002	Kvaliteten af behandlingen kan også forklare noget af forskellen mellem landene, men studiet peger på, at det først er fremmeste er tilfældet for Storbritannien, hvor den specifikke overlevelse for de enkelte sygdomsstadier generelt lå lavere end de øvrige seks lande.	ndt
2001 2000 Alle nyheder Nyheder på Widget	Studiet er baseret på data fra 257.362 kvinder, der fik diagnosticeret brystkræft i årene 2000-2007, for danske kvinders vedkommende dog kun data for fire-års perioden 2004-2007.	- - en
Abonnement Nyhedsbreve Sundhedsfaolio kommentar	Information om brystkræftscreening Sundhedsstyrelsens hjemmeside	på
	Kontakt Enhedschef Søren Brostrøm Sundhedsstyrelsen Telefon: 72 22 78 67	
	Abonnér på nyheder og nyhedsbreve	
	Her kan du abonnere på nyheder og opdateringer fra sst.dk	



### **Lead-time bias**



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#### ARCHIVES OF INTERNAL MEDICINE



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### **Length bias**



Dx = Time when disease is clinically obvious without testing.



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Welch HG et al. Arch Intern Med 2007;167:2289-2295.

# Healthy Screenee effect.

"The screenees are the healthy, well-educated, affluent, physically fit, fruit and vegetable eating, nonsmokers with long-lived parents."

J. A. Muir Gray, former Programmes Director, National Screening Commitee, UK.



### Tumor diameter (cm) vs. cell doublings



THE COCHRANE

### review

Annals of Oncology doi:10.1093/annonc/mdq633

### Advanced breast cancer incidence following populationbased mammographic screening

P. Autier<sup>1</sup>\*, M. Boniol<sup>1</sup>, R. Middleton<sup>2</sup>, J.-F. Doré<sup>3</sup>, C. Héry<sup>3</sup>, T. Zheng<sup>4</sup> & A. Gavin<sup>2</sup>

<sup>1</sup>Department of Epidemiology and Biostatistics, International Prevention Research Institute (iPRI), Lyon, France; <sup>2</sup>Direction and Data Department, Northern Ireland Cancer Registry (NICR), Queens University Belfast, Belfast, UK; <sup>3</sup>Unit of Molecular Epidemiology, INSERM U 590, Lyon, France; <sup>4</sup>Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, USA

Received 22 September 2010; accepted 24 September 2010

**Conclusions:** In areas with widespread sustained mammographic screening, trends in advanced breast cancer incidence do not support a substantial role for screening in the decrease in mortality.





### Stage-related breast cancer incidence in the USA.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

#### Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.

ABSTRACT

#### BACKGROUND

From the Quality Department, St. Charles TO Health System, Central Oregon, and the Department of Radiation Medicine, Orgon Health and Science University, Port-Iand (A.B.); the University of Texas Medical School at Houston, (A.B.); and the Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Hanover, NH WK (H.G.W.). Address reprint requests to Dr. Bleyer at 2500 NE Neff Rd, Bend, OR Bloyer at 2500 NE Neff Rd, Standard

N Engl J Med 2012;367:1998-2005. DOI: 10.1056/NEJMoa1206809 Copyright © 2012 Massachusetts Medical Society. To reduce mortality, screening must detect life-threatening disease at an earlier, more curable stage. Effective cancer-screening programs therefore both increase the incidence of cancer detected at an early stage and decrease the incidence of cancer presenting at a late stage.

#### METHODS

We used Surveillance, Epidemiology, and End Results data to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women 40 years of age or older.

RESULTS

The introduction of screening mammography in the United States has been associated with a doubling in the number of cases of early-stage breast cancer that are detected each year, from 112 to 234 cases per 100,000 women — an absolute increase of 122 cases per 100,000 women. Concomitantly, the rate at which women present with late-stage cancer has decreased by 8%, from 102 to 94 cases per 100,000 women — an absolute decrease of 8 cases per 100,000 women. With the assumption of a constant underlying disease burden, only 8 of the 122 additional early-stage cancers diagnosed were expected to progress to advanced disease. After excluding the transient excess incidence associated with hormone-replacement therapy and adjusting for trends in the incidence of breast cancer among women younger than 40 years of age, we estimated that breast cancer was overdiagnosed (i.e., tumors were detected on screening that would never have led to clinical symptoms) in 1.3 million U.S. women in the past 30 years. We estimated that in 2008, breast cancer was overdiagnosed in more than 70,000 women; this accounted for 31% of all breast cancers diagnosed.

#### CONCLUSIONS

Despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with advanced cancer. Although it is not certain which women have been affected, the imbalance suggests that there is substantial overdiagnosis, accounting for nearly a third of all newly diagnosed breast cancers, and that screening is having, at best, only a small effect on the rate of death from breast cancer.



#### The Nordic Cochrane Centre

BMJ 2013;346:11064 doi: 10.1136/bmj.11064 (Published 26 February 2013)

#### RESEARCH

#### Overdiagnosis in screening mammography in Denmark: population based cohort study

Sisse Helle Njor statistician<sup>1</sup>, Anne Helene Olsen statistician<sup>2</sup>, Mogens Blichert-Toft professor emeritus<sup>3</sup>, Walter Schwartz chief physician<sup>4</sup>, Ilse Vejborg chief physician<sup>5</sup>, Elsebeth Lynge professor<sup>1</sup>

<sup>1</sup>Department of Public Health, University of Copenhagen, Østre Farimagsgade 5, DK 1014 Copenhagen K, Denmark; <sup>2</sup>Institute of Community Medicine, University of Tromsø, Norway; <sup>3</sup>Danish Breast Cancer Cooperative Group, 2100 Copenhagen Ø, Denmark; <sup>4</sup>Mammography Screening Clinic, University Hospital Odense, 5000 Odense, Denmark; <sup>8</sup>Diagnostic Centre, University Hospital Copenhagen, Blegdamsvej, 2100 Copenhagen Ø, Denmark

#### Abstract

Objective To use data from two longstanding, population based screening programmes to study overdiagnosis in screening mammography.

Design Population based cohort study.

Setting Copenhagen municipality (from 1991) and Funen County (from 1993), Denmark.

Participants 57 763 women targeted by organised screening, aged 56-69 when the screening programmes started, and followed up to 2009.

Main outcome measures Overdiagnosis of breast cancer in women targeted by screening, assessed by relative risks compared with historical control groups from screening regions, national control groups from non-screening regions, and historical national control groups.

Results In total, 3279 invasive breast carcinomas and ductal carcinomas in situ occurred. The start of screening led to prevalence peaks in breast cancer incidence; relative risk 2.06 (95% confidence interval 1.64 to 2.59) for Copenhagen and 1.84 (1.46 to 2.32) for Euren, During subsequent screening rounds, relative risks were slightly above unity: 1.04 (0.85 to 1.27) for Copenhagen and 1.14 (0.98 to 1.32) for Funen. A compensatory dip was seen after the end of invitation to screening: relative risk 0.80 (0.65 to 0.98) for Copenhagen and 0.67 (0.55 to 0.81) for Funen during the first four years. The relative risk of breast cancer accumulated over the entire follow-up period was 1.06 (0.90 to 1.25) for Copenhagen and 1.01 (0.93 to 1.10) for Funen. Relative risks for participants corrected for selection bias were estimated to be 1.08 for Copenhagen and 1.02 for Funen; for participants followed for at least eight years after the end of screening, they were 1.05 and 1.01. A pooled estimate gave 1.040 (0.99 to 1.09) for all targeted women and 1.023 (0.97 to 1.08) for targeted women followed for at least eight years after the end of screening

Conclusions On the basis of combined data from the two screening programmes, this study indicated that overdiagnosis most likely amounted to 2.3% (95% confidence interval -3% to 8%) in targeted women. Among participants, it was most likely 1-5%. At least eight years after the end of screening were needed to compensate for the excess incidence during screening.

#### Introduction

The purpose of screening mammography is to reduce mortality from breast cancer without increasing mortality from other diseases. Preventive measures in healthcare might, however, also have unintended negative side effects, and the occurrence of these should be closely monitored. In screening mammography, the most serious concern is the risk of overdiagnosis—that is, diagnosis of breast cancer that would in the absence of screening not have led to clinically manifest disease in the woman's lifetime.<sup>1</sup> Overdiagnosis cannot be identified biologically, as distinguishing between progressive and non-progressive or slowly progressive cancers is not possible with current diagnostic tools. Overdiagnosis can therefore be investigated only epidemiologically.

Screening affects the incidence rate. Assuming a three year advancing of time of diagnosis (lead time) and screening of all women during a two year period, a doubling of the incidence rate is expected during the first round of screening.<sup>2</sup> As screening continues, the incidence rate should go down to the level before screening, apart from an increase caused by the artificial aging—that is, breast cancer diagnosed at age 55 in the absence of screening will during screening be diagnosed, for example, at age 52. A complementary dip in the incidence rate is expected after women leave the screening programme.<sup>34</sup> Overdiagnosis occurs if the cumulative incidence some years after the end of













Screening started 1991 in Copenhagen and 1994 in Funen

THE COCHRANE