

Ethical approval: Research and Ethics Committee of the Istituto Nazionale Tumori di Milan.

- Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Bruognatelli L, Brambilla C, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976;294:405-10.
- Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of randomised trials. *Lancet* 1998;352:930-42.
- Pritchard KI. Adjuvant therapy for premenopausal women with breast cancer: is it time for another paradigm shift? *J Clin Oncol* 2002; 20:4611-4.
- Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. *Stem Cells* 1998;16:413-28.
- Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med* 1995;332:901-6.
- Tancini G, Bonadonna G, Valagussa P, Marchini S, Veronesi U. Adjuvant CMF in breast cancer: comparative 5-year results of 12 versus 6 cycles. *J Clin Oncol* 1983;1:2-10.
- Zambetti M, Bonadonna G, Valagussa P, Daidone MG, Coradini D, Bignami P, et al. Adjuvant CMF for node-negative and estrogen receptor-negative breast cancer. *J Natl Cancer Inst Monogr* 1992;11:79-85.
- Jakesz R, Hausmaninger H, Kubista E, Gnant M, Menzel C, Bauernhofer T, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group trial 5. *J Clin Oncol* 2002;20:4621-7.
- Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex early breast cancer research association study. *J Clin Oncol* 2002; 20:4628-35.
- Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451-67.
- Ménard S, Valagussa P, Piloti S, Gianni L, Biganzoli E, Boracchi P, et al. Response to CMF in lymph-node positive breast cancer according to HER2 overexpression and other tumours biologic variables. *J Clin Oncol* 2001;19:329-35.

(Accepted 15 November 2004)

doi 10.1136/bmj.38314.622095.8F

Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study

Anne Helene Olsen, Sisse H Njor, Ilse Vejborg, Walter Schwartz, Peter Dalgaard, Maj-Britt Jensen, Ulla Brix Tange, Mogens Blichert-Toft, Fritz Rank, Henning Mouridsen, Elsebeth Lynge

Institute of Public Health, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark
Peter Dalgaard
associated professor
Elsebeth Lynge
professor
Sisse H Njor
statistician
Anne Helene Olsen
statistician

University Hospital Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark
Ilse Vejborg
chief physician, Centre of Diagnostic Imaging
Henning Mouridsen
professor, Department of Oncology

Ulla Brix Tange
staff specialist, Department of Oncology

Fritz Rank
chief physician, Department of Pathology

Mogens Blichert-Toft
professor, Danish Breast Cancer Cooperative Group
Maj-Britt Jensen
statistician, Danish Breast Cancer Cooperative Group

continued over
BMJ 2005;330:220-2

Abstract

Objectives To evaluate the effect on breast cancer mortality during the first 10 years of the mammography service screening programme that was introduced in Copenhagen in 1991.

Design Cohort study.

Setting The mammography service screening programme in Copenhagen, Denmark.

Participants All women ever invited to mammography screening in the first 10 years of the programme. Historical, national, and historical national control groups were used.

Main outcome measures The main outcome measure was breast cancer mortality. We compared breast cancer mortality in the study group with rates in the control groups, adjusting for age, time period, and region.

Results 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. For women actually participating in screening, breast cancer mortality was reduced by 37%.

Conclusions In the Copenhagen programme, breast cancer mortality was reduced without severe negative side effects for the participants.

Introduction

Organised, population based, mammography screening was introduced in Copenhagen in 1991. Since then the validity of the trial results and the justification of mammography screening have been debated intensively.¹⁻³ Mammography screening was introduced in only three out of 16 administrative regions, so the regions without a programme provide a natural

control group during the full period of follow up. In addition, opportunistic screening has been limited.³ Taking advantage of this “natural experiment,” and using the nationwide population and health registers in Denmark, we developed a method to determine the effect of mammography screening on breast cancer mortality.⁴ We present here the results of the first 10 years of screening in Copenhagen.

Methods

Model

We used a regression model with a study group, a historical control group, a national control group, and a historical national control group (table). We studied the effect of invitation to, as well as participation in, screening. The end point was mortality due to breast cancer.

The study group included women invited for screening in Copenhagen during the first five invitation rounds from 1 April 1991 to 31 March 2001. The screening interval was two years. The target group included about 40 000 women aged 50-69 at the start of each invitation round. Only the second invitation round included women aged 50-71. Women moving to Copenhagen received their invitation shortly after their arrival, unless their date of birth was scheduled for invitation later in the round. Invitations did not go to women if they moved out of Copenhagen before their scheduled date for invitation. Women invited for screening remained in the study group even if they moved to another region. We followed up all women from their first date of invitation until death,



This is the abridged version of an article that was posted on *bmj.com* on 13 January 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38313.639236.82>

Study areas and time periods of the study and control groups

Time period	Copenhagen	Denmark outside screening regions*
Pre-screening period 1981-91	Historical control group	Historical national control group
Screening period 1991-2001	Study group	National control group

*Three out of 16 administrative regions in Denmark—Copenhagen, Fyn, and Frederiksberg—had mammography screening in the 1990s. All three regions were excluded from the national and the historical national control groups.

emigration, or 31 March 2001. We excluded women with prevalent breast cancer before their first invitation date. In total 30 362 women, equivalent to 71% of women in the target population, participated in the first invitation round, a percentage that fell slightly over rounds as women could ask not to be reinvited to the programme.⁵

For all three control groups we constructed five, two year, “pseudo-invitation” rounds and allocated pseudo-invitation dates using the invitation system from the study group. We followed up women from their first pseudo-invitation date until death, emigration, or end of follow up, which was 31 March 1991 for the historical and the historical national control groups, and 31 March 2001 for the national control group. We excluded women with prevalent breast cancer before their first pseudo-invitation date.

Data

We retrieved data on women invited to the programme from the Copenhagen mammography screening register and checked them with the central population register. We “constructed” the control groups from individual records in the central population register. We identified all women with prevalent breast cancer from the Danish cancer register. We followed up the groups for deaths and emigrations in the central population register. Data on underlying cause of death came from the cause of death register. We used the personal identification number issued to all residents of Denmark to link registers.

Statistical analysis

To analyse the effect of invitation to screening, we compared breast cancer death rates in the study group and the control groups, adjusting for age, time period, and region. We used a Poisson regression model with the variables five year age group, exposure, period, and region.⁴ Although we were thereby able to control for time trends and regional differences, we were not able to separate out a potential effect of an interaction between the two from the effect of screening. We therefore had to take into consideration additional data on a potential interaction effect (see bmj.com).

Results

For the period before screening started, Copenhagen had a significantly higher mortality due to breast cancer than the rest of Denmark (relative risk 1.22, 95% confidence interval 1.10 to 1.35), although there was some variation by age group. This had changed in the screening period, where Copenhagen had a lower breast cancer mortality than the rest of Denmark (0.91, 0.80 to 1.05). When we compared Copenhagen in the screening period with the period before screening, the relative risk was significantly lower than 1 (0.80, 0.68 to

0.94). When we compared the rest of Denmark in the screening period with the period before screening, the relative risk was 1.05 (0.99 to 1.11), again with some variation by age group. When we estimated the effect of the combination of invitation to screening and the interaction term between period and region adjusted for age, period, and region, the relative risk was 0.75 (0.63 to 0.89) (see bmj.com for full table of results).

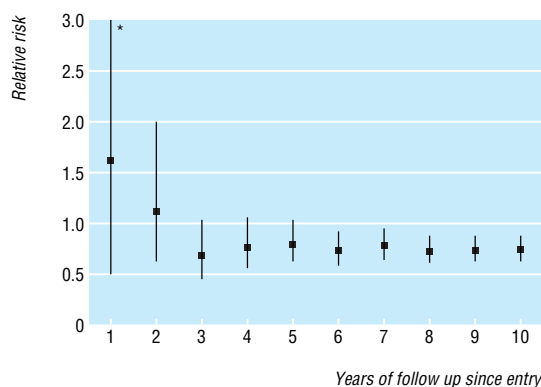
We estimated the cumulative effect of the combination of invitation for screening and the interaction term between period and region by year of follow up and adjusted for age at entry, period, and region (figure). Significance was reached after six years of follow up.

For the participants the estimated effect of combining participation in screening and the interaction term between period and region adjusted for age, period, and region resulted in a relative risk of 0.60 (0.49 to 0.74). On the other hand, women invited for screening who did not participate had a relative risk of 1.15 (0.91 to 1.46). On this basis, we estimated that in a situation without screening, participants would be a selected part of the population, with a relative risk of 0.95 compared with the total population. When we adjusted for this selection bias, the relative risk for the participants was 0.63.

When we used the same method as in the breast cancer mortality analysis, the invited population had a total cancer mortality (excluding breast cancer) close to that expected without screening (relative risk 0.96, 0.91 to 1.01).

Discussion

Breast cancer mortality in Copenhagen was reduced significantly after mammography screening had been introduced. A 25% reduction is the best possible estimate of the size of the mortality reduction achieved with mammography screening. However, the interaction term between period and region also inherent in the 25% estimate, could in theory reflect unsynchronised improvements in treatment. Since 1977, however, all hospital departments involved in diagnosis and treatment of breast cancer patients have used uniform guidelines for histopathology, surgery, radio-



* The 95% confidence interval after 1 year of follow up was 0.51 to 5.05

Estimated effect on breast cancer mortality of invitation to mammography screening in Copenhagen, cumulated over years of follow up

Mammography Screening Clinic, University Hospital Odense, Klørvænget 10, DK-5000 Odense, Denmark

Walter Schwartz
chief physician

Correspondence to:
A H Olsen
a.h.olsen@pubhealth.ku.dk

therapy, and systemic therapy.⁶ Survival from breast cancer has not differed between Copenhagen and the rest of Denmark since then.⁷ In addition, examination of time trends in breast cancer mortality in the pre-screening period found no interaction or only a negligible interaction between period and region.⁸ On this basis it is reasonable to expect the interaction term between period and region to be small. We also calculated the interaction term for the non-screening counties in Denmark. Copenhagen had the largest drop in mortality and was the only region where this reduction reached significance.

Comparison with other countries

The 25% reduction estimated in our study is consistent with that found in the evaluation of breast cancer screening programmes in England and Wales, Netherlands, and Sweden, although none of these studies is completely unbiased (see bmj.com for details).

Specific considerations

Breast cancer mortality was significantly higher in Copenhagen than in the rest of Denmark in the pre-screening period. This is probably due to regional differences in risk factors since diagnostic procedures and treatment have been organised nationwide since 1977.⁶

The age group 55-59 differed from the remaining age groups with a relative risk of 1.08 (0.68 to 1.72). Although the confidence interval is broad, this is in line with the lack of an effect for women aged 50-54 at randomisation found in other studies.^{9 10} Hormonal factors could play a part.⁹

Mortality reduction in participants

The non-participants in our study had a slightly, although not significantly, higher breast cancer mortality than the general population. The resulting selection bias does not affect the results for all invited women but merely the results for the participants. Adjusting for this selection bias resulted in a relative risk for the participants of 0.63—that is, a mortality that is 37% lower than that expected without screening was seen among participants in the Copenhagen screening programme.

Possible negative effects of mammography screening

Severe negative side effects for the participants were avoided; the introduction of mammography screening in Copenhagen did not lead to an increase in breast cancer incidence apart from the expected prevalence peak.³ In the first four invitation rounds, ductal carcinoma in situ constituted only 11% of the detected cases, owing to a deliberately conservative attitude towards supposedly benign microcalcifications.⁵ The false positive rate has been relatively high—5.6% after the first screen, 2.9% after the second screen, and 1-2% after subsequent screens.⁵ Most are sorted out at the assessment, and by now, about 80% of women having surgery had invasive breast cancer or ductal carcinoma in situ.⁵ The proportionate interval cancer rate after the first invitation round in Copenhagen was low compared with that of other European programmes.¹¹

Contributors: See bmj.com

Funding: Danish Medical Research Council; Centre for Evaluation and Medical Technology Assessment in the Danish

What is already known on this topic

Most studies of randomised controlled trials have indicated that mammography screening leads to a reduction in breast cancer mortality for certain age groups

Evidence is now starting to emerge on the effect of mammography screening in routine healthcare settings, such as service screening

What this study adds

This study of mammography service screening controlled for regional and historical differences

Patients with breast cancers diagnosed before they had received the first invitation to screening were excluded

The 25% reduction of breast cancer mortality found in this study therefore indicates that mammography service screening can reduce breast cancer mortality

National Board of Health; the European Commission, Directorate-General SANCO, and Copenhagen Hospital Corporation.

Competing interests: None declared.

Ethical approval: Not required.

- 1 Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000;355:131-6.
- 2 Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001;358:1340-2.
- 3 Olsen AH, Jensen A, Njor SH, Villadsen E, Schwartz W, Vejborg I, et al. Breast cancer incidence after the start of mammography screening in Denmark. *Br J Cancer* 2003;88:362-5.
- 4 Olsen AH, Njor SH, Vejborg I, Schwartz W, Dalgaard P, Jensen M-B, et al. A model for determining the effect of mammography service screening. *Acta Oncologica* 2005 (in press).
- 5 Vejborg I, Olsen AH, Jensen M-B, Rank F, Tange UB, Lyng E. Early outcome of mammography screening in Copenhagen 1991-99. *J Med Screen* 2002;9:115-9.
- 6 Fischerman K, Mouridsen HT. Danish Breast Cancer Cooperative Group (DBCG). Structure and results of the organisation. *Acta Oncologica* 1988;27:593-6.
- 7 Andreasen AH, Mouridsen HT, Andersen KW, Lyng E, Madsen M, Olesen KP. Improved prognosis of breast cancer. *Ugeskr Læger* 1994;156:6512-7.
- 8 Andreasen AH, Andersen KW, Madsen M, Mouridsen H, Olesen KP, Lyng E. Regional trends in breast cancer incidence and mortality in Denmark prior to mammographic screening. *Br J Cancer* 1994;70:133-7.
- 9 Nyström L, Andersson I, Bjurström N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002;359:909-19.
- 10 Alexander F, Anderson TJ, Brown HK, Forrest APM, Hepburn W, Kirkpatrick AE, et al. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet* 1999;353:1903-8.
- 11 Njor SH, Olsen AH, Bellstrøm T, Dyreborg U, Bak M, Axelsson C, et al. Mammography screening in the county of Fyn, November 1993-December 1999. *APMS* 2003;111(suppl 110):1-33.

(Accepted 15 November 2004)

doi 10.1136/bmj.38313.639236.82

Endpiece

The ideal diagnosis

One finger in the throat and one in the rectum makes a good diagnostician.

Sir William Osler (1849-1919), Canadian born British physician and educator

Fred Charatan, retired geriatric physician, Florida