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Limitations in the Effect of Screening on Breast Cancer Mortality

Anna-Belle Beau, Per Kragh Andersen, Ilse Vejborg, and Elsebeth Lynge

ABSTRACT

Purpose
Randomized, controlled trials showed that screening reduces breast cancer mortality rates, but some recent observational studies have concluded that programmatic screening has had minor effect on breast cancer mortality rates. This apparent contradiction might be explained by the use of aggregated data in observational studies. We assessed the long-term effect of screening using individual-level data.

Materials and Methods
Using data from mammography screening in the Copenhagen and Danish national registers, we compared the observed breast cancer mortality rate in women invited to screening with the expected rate in absence of screening. The effect was examined using the “naive model,” which included all breast cancer deaths; the “follow-up model,” which counted only breast cancer deaths in women diagnosed after their first invitation to screening; and the “evaluation model,” which is similar to the follow-up model during screening age, but after screening age, which counted only breast cancer deaths and person-years in women diagnosed during screening age.

Results
We included 18,781,292 person-years, 976,743 of which were from women invited to screening. The naive and follow-up models showed, respectively, 10% and 11% reduction in breast cancer mortality after invitation to screening. However, many breast cancer deaths occurred in women whose cancer was diagnosed when they were no longer eligible for screening. Accounting for this dilution, the evaluation model showed a 20% (95% CI, 10% to 29%) reduction in breast cancer mortality after invitation to screening.

Conclusion
Screening had a clear long-term beneficial effect with a 20% reduction in breast cancer–associated mortality in the invited population. However, this effect was, by nature, restricted to breast cancer deaths in women who could potentially benefit from screening. Our study highlights the complexity in evaluating the long-term effect of breast cancer screening from observational data.

INTRODUCTION

Breast cancer screening’s primary aim is to reduce the rate of breast cancer mortality. In the 1980s, several randomized controlled trials, first from Sweden, showed that screening with mammography only could help reduce breast cancer mortality rates. In one recent review, the combined evidence from the randomized controlled trials showed that screening delivered about a 20% reduction in breast cancer mortality rate; another review found that screening reduced the mortality rate associated with breast cancer by an average of 25%; and another found there was a mortality reduction across all ages varying from 12% in women aged 39 to 49 years, 14% in women aged 50 to 59 years, 33% in women aged 60 to 69 years, and 20% in women aged 70 to 74 years.

On this background, screening has been widely implemented in routine health care. Nevertheless, breast cancer screening is one of the most intensively debated health care interventions. During the same period that screening was introduced, breast cancer treatment improved, which makes it difficult to
separate the effect of screening from the effect of treatment. To address this problem, modeling studies based on US data concluded that both screening and treatment helped reduce the rate of death from breast cancer.5

Recent studies have focused on the incidence of late-stage breast cancer. The underlying assumption was that the effect of screening should result in a decrease in the incidence of late-stage breast cancer. If not observed, a decline in the breast cancer mortality rate would be attributable to treatment and not to screening. A study from the United States concluded that “the reduction in breast cancer mortality after the implementation of screening was predominantly the result of improved systemic therapy,”6 and another study, using Dutch data, concluded that the “screening program would have had little influence on the decrease in breast cancer mortality.”7 These studies analyzed data for all women above screening age, which is 40 years in the United States and 50 years in the Netherlands. However, not all women in these road age groups could have been affected by screening, and such studies, therefore, cannot correctly capture the possible effect of screening. For a proper evaluation of screening, it is necessary to avoid the use of broad age groups, to focus instead on the actual birth cohorts of women potentially affected by screening, and to use individual records instead of aggregated data.

In this study, we used individual-level data to analyze the long-term effect on breast cancer mortality rates of a population-based breast cancer screening program in Copenhagen, Denmark.

**MATERIALS AND METHODS**

**Breast Cancer Screening Program**

The Copenhagen screening program started with biennial screening on April 1, 1991. Women aged 50 to 69 years were invited every second year to screening. Other regional, organized programs were implemented in Funen in 1993, in Frederiksberg in 1994, in Bornholm in 2001, and in part of Vestjylland in 2004. Nationwide, organized screening in Denmark started at the end of 2007 and early 2008.

**Study Participants**

*Contemporary groups (screening period).* The Copenhagen study group included women invited to screening in the Copenhagen program between April 1, 1991 and December 31, 2007. The regional control group included women living in a nonscreening region (the rest of Denmark excluding Copenhagen, Funen, Frederiksberg, Bornholm, and Vestjylland) during the same period. In the regional control group, a first pseudo-invitation date was allocated to each woman following the scheme similar to the Danish Cancer Registry.

![Fig 1. Study design illustrated in Lexis diagram.](image-url)
We conducted a population-based study using individual records investigating the long-term impact of breast cancer screening on breast cancer mortality rates. According to our study data, a substantial proportion of breast cancer deaths were among women whose breast cancer was diagnosed when the women were no longer eligible for screening. Inclusion of these breast cancer deaths...
### Table 1. Breast Cancer Deaths, Person-Years, Breast Cancer Mortality Rates, and Rate Ratio Estimate of the Copenhagen Mammography Screening Program

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of Breast Cancer Deaths/PY per 1,000/Rate per 100,000 PY</th>
<th>Expected Rate in the Absence of Screening*</th>
<th>Screening Effect†, Crude rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Copenhagen Study</td>
<td>Rest DK</td>
<td>Copenhagen, Historical</td>
</tr>
<tr>
<td>50-54</td>
<td>14/111/12.6</td>
<td>134/1,209/11.1</td>
<td>32/90/35.7</td>
</tr>
<tr>
<td>55-59</td>
<td>75/184/40.7</td>
<td>794/1,935/41.0</td>
<td>90/188/47.9</td>
</tr>
<tr>
<td>60-64</td>
<td>98/164/99.8</td>
<td>1,031/1,633/63.1</td>
<td>190/227/66.0</td>
</tr>
<tr>
<td>65-69</td>
<td>103/149/69.0</td>
<td>1,122/1,382/81.2</td>
<td>202/250/80.7</td>
</tr>
<tr>
<td>70-74</td>
<td>146</td>
<td>173.2</td>
<td>184</td>
</tr>
<tr>
<td>75-79</td>
<td>185</td>
<td>1,066</td>
<td>21</td>
</tr>
<tr>
<td>80-84</td>
<td>130</td>
<td>1,049</td>
<td>2</td>
</tr>
<tr>
<td>85-89</td>
<td>70</td>
<td>587</td>
<td>8</td>
</tr>
<tr>
<td>90-94</td>
<td>13</td>
<td>97</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>50-94</td>
<td>804</td>
<td>7,581</td>
<td>2,095.7</td>
</tr>
<tr>
<td></td>
<td>977</td>
<td>9,366</td>
<td>6,733</td>
</tr>
<tr>
<td>85.4</td>
<td>73.2</td>
<td>80.9</td>
<td>72.0</td>
</tr>
</tbody>
</table>

**NOTE.** For calculations, see Methods, Statistical analysis.

Abbreviations: —, no data; CI, confidence interval; DK, Denmark; PY, person-years; Rest DK, regions without screening.

*Expected Rate in the Absence of Screening = Rest DK x (Copenhagen, Historical/Rest DK Historical).
†Screening Effect = Copenhagen Study/Expected Rate in the Absence of Screening.
‡Adjusted by 5-year age groups.
in the analysis will inevitably dilute the measured effect of screening. When the analysis was restricted to the women who could have benefited from screening, our data showed a 20% reduction in breast cancer mortality after invitation to screening.

Comparison With Other Studies

Studies based on broad age groups showed no marked effect of screening on breast cancer mortality.6,7 In these studies, it was not possible to separate breast cancer deaths among women invited to screening from those among noninvited women. Hence, a substantial proportion of breast cancer deaths included in these analyses will be among women who received a breast cancer diagnosis when they were not eligible for screening (ie, either before the start or after the end of screening age), as seen also from Dalarna, Sweden.16 In contrast, in cohort studies with individual records, it is possible to separate women invited to screening from those not invited, and to link data from each woman to cancer and cause of death registries. Then, the analyses could be restricted to women and breast cancer cases that could potentially have benefited from screening.

The concept of the follow-up model and the evaluation model were first presented by Nyström et al13 in their overview of the Swedish randomized controlled trials. They found invitation to screening was associated with a 15% reduction in breast cancer mortality rate when the follow-up model was used, and a 21% reduction when using the evaluation model. These results are in line with ours, indicating the importance of dilution in long-term follow-up data. Therefore, in later updates, Nyström et al.17 (relative risk, 0.85; 95% CI, 0.73 to 0.98) and Tabár et al18 (relative risk, 0.69; 95% CI, 0.56 to 0.84) reported only results from the evaluation model. In the latter study, less than half of prevented breast cancer deaths were observed within the first 10 years of follow-up.

In the Swedish analyses,13 the evaluation model used the person-years from all women from randomization until the end of the follow-up. In our evaluation model, we restricted the person-years accumulated after the screening period only among women with breast cancer that was diagnosed during the pseudoscreening period.
person-years after screening age to the women diagnosed with breast cancer during screening age. This choice was motivated by the fact that in the evaluation model, only these women were at risk for dying of breast cancer after end of screening. It should be noted that this calculation will give high mortality rates in all groups after the end of screening.

Previously, the Copenhagen screening program was analyzed using the follow-up model for the first 10 years after the program started. The analysis showed a 25% (95% CI, 11%–37%) reduction in breast cancer mortality rates after invitation to screening. After a maximum of 23 years of follow-up since the start of the program, the reduction in breast cancer mortality rate was, as estimated from the follow-up model, only 11% (95% CI, 2%–18%). This difference was a result of the increasing dilution with time from breast cancer deaths in women who received a diagnosis after screening age. Hence, a long follow-up after end of screening permits evaluation of the long-term impact; however, the longer the postscreening follow-up, the greater the dilution.20 US mortality data from 2007 to 2011 showed that approximately one-third of breast cancer deaths in women were attributed to diagnoses after the age of 70 years.21 García-Albéniz et al22 highlighted the problems in using observational data in evaluation of cancer screening outcomes. Their data set was different from the one used in the current study. Where García-Albéniz et al compared colorectal cancer incidence between persons undergoing and not undergoing colonoscopy, we compared breast cancer mortality between populations offered and not offered screening mammography and adjusted for prescreening differences between these two populations. Thus, we avoided bias from selective participation and confounding from differences between geographical areas and/or time periods. García-Albéniz et al22 demonstrated the importance of never classifying screening status retrospectively; accordingly, screening status was classified only prospectively in our study.

Furthermore, the potential impact of breast cancer screening on breast cancer mortality rates depends also on the coverage by examination (the number of participating women divided by the number of targeted women). A substantial proportion of the targeted population must be screened for screening to be effective in reducing mortality rates associated with breast cancer at the population level. In the Copenhagen program, the coverage by examination at first invitation was between 73% for the first targeted birth cohorts and 64% for the last birth cohorts.23 A drop in coverage was observed with the increasing invitation number.23 These differences in coverage are expected to have an impact on the outcome of breast cancer screening. Then, the true effectiveness of breast cancer screening might be underestimated.

**Limitations and Strengths**

Screening advances the date of diagnosis, and slow-growing and less aggressive tumors, or even nonaggressive tumors in terms of overdiagnosis, are more likely to be detected by screening, so the survival advantage of screening detection can be artificially inflated in the study group as compared with the control subjects. However, we expected the lead time bias to be limited in our evaluation model, because the number of deaths resulting from breast cancer and person-years would be affected by it. Screening, in particular the first screen, may lead to diagnosis of slow-growing tumors. But this potential time bias was not expected to affect our data set seriously, because most women attended screening several times, and all patients with breast cancer were followed up for breast cancer deaths for a minimum of 10 years. Moreover, the evaluation model relied on the fact that cases of breast cancer deaths were previously registered with a diagnosis of breast cancer. This was verified for 96% of the breast cancer deaths.

The breast cancer mortality rates in our follow-up model increased with age, similar to the pattern seen in routine breast cancer mortality statistics. The data in the follow-up model, however, do not give a proper presentation of a possible screening effect because the majority of the breast cancer deaths after the age of 70 years were diagnosed after the women stopped being offered screening. This problem was overcome in the evaluation model by including after the age of 70 years only breast cancer deaths in women whose cancer was diagnosed when they were still offered screening. It should be noted, however, that the breast cancer mortality rates in our evaluation model increased very rapidly after the age of 70 years. This may intuitively look strange, but it is explained by the fact that women diagnosed with breast cancer prior to the age of 70 years are at a very high risk of dying of breast cancer after the age of 70 years. This is true for women offered screening and women not offered screening. The rates in the evaluation model, therefore, should be used only for internal comparisons between the study group and three control groups.

The strengths of our study include the use of individual data with linkage between the exposure and outcome for each woman. Another strength of our study is that the study group included all women offered screening and not only those who attended screening. In this way, we avoided self-selection bias. In addition, this study took advantage of the use of three control groups; hence, the expected breast cancer mortality rate in the absence of screening was estimated by the rate in a nonscreening region, controlling for regional differences in a prescreening period. Both region and period were thus controlled for, but it was assumed that in the absence of screening, the breast cancer mortality rate changed identically over time in screening and nonscreening regions. It means no interaction between region and period (ie, no unsynchronized changes between screening and nonscreening regions). This assumption was considered realistic because, in Denmark, diagnostics and treatment of breast cancer have been organized nationwide since 1977.24 This assumption was further supported by regional trends in breast cancer mortality rates in the prescreening period.25 Last, our study was based on a long follow-up, with a 17-year screening period and 20 years of postscreening time. All patients with breast cancer were followed up for breast cancer–related mortality for a minimum of 10 years, ensuring a long follow-up time even for cases diagnosed at an early stage. Women screening positive in our study group underwent the same diagnostic procedures as women with symptoms of breast cancer.

Our findings highlight the complexity of evaluating the long-term impact of screening on breast cancer mortality rates. We found that screening had a clear, long-term, beneficial impact of a 20% reduction in breast cancer mortality rate in the
invited population. Nevertheless, this effect of screening is restricted to breast cancer deaths in women who could potentially benefit from screening. As women age, a rapidly increasing proportion of breast cancer deaths occur in women who received a breast cancer diagnosis after screening age. If this dilution is not adequately addressed, the effect of screening is inevitably underestimated. Thus, screening is clearly beneficial but, after screening age, only for a diminishing proportion of women.

REFERENCES


Affiliations

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AUTHOR CONTRIBUTIONS

Conception and design: Anna-Belle Beau, Per Kragh Andersen, Elsebeth Lynge
Collection and assembly of data: Anna-Belle Beau, Elsebeth Lynge
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors
Limitations of Screening Effects on Breast Cancer Mortality

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Anna-Belle Beau
No relationship to disclose

Per Kragh Andersen
No relationship to disclose

Ilse Vejborg
No relationship to disclose

Elsebeth Lynge
No relationship to disclose