Comparative analysis of breast cancer mortality following mammography screening in Denmark and Norway

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Background: Denmark and Norway are the best countries to study effects of mammography screening, because they are the only countries with stepwise introduction of nationwide mammography screening, enabling comparative effectiveness studies of high quality. Although Denmark and Norway are countries with similar populations and health care systems, reported reductions in breast cancer mortality (incidence-based) caused by screening differed vastly; 25% in Denmark versus 10% in Norway. This study explores reasons for this difference.

Patients and Methods: We compared two published studies from the Danish and Norwegian screening programs (Olsen et al., 2005; Kalager et al., 2010) investigating biennial mammography screening for women age 50–69 years. Four comparison groups of women were constructed (‘current’ and ‘historical screening groups’; ‘current’ and ‘historical nonscreening groups’) based on county of residence. We calculated incidence-based cancer mortality in the current versus the historical period for screening and nonscreening groups, using mortality rate ratios (MRR) in the two countries, accounting for concomitant changes in breast cancer mortality.

Results: In the screening groups, similar reductions in breast cancer mortality were found when periods preceding and following start of screening were compared, in Denmark [25%; MRR 0.75; 95% confidence interval (CI) 0.64% to 0.88%] and in Norway (28%; MRR 0.72; 95% CI 0.63% to 0.81%). However, mortality increased in Denmark in the current nonscreening group compared with the historical nonscreening group; for women >59 years, breast cancer mortality increased by 14% (MRR 1.14, 95% CI 1.07–1.22), whereas in Norway a 19% reduction was seen (MRR 0.81, 95% CI 0.72–0.92). This increase accounts for the different relative effect of screening in Denmark and Norway; 25% breast cancer mortality reduction in Denmark, 10% in Norway.

Conclusions: The seemingly larger effect of screening in Denmark may not be solely attributable to screening itself, but to increased breast cancer mortality in women older than 50 years not invited to screening.

Key words: mammography, screening, mortality, effectiveness

introduction

Widely recommended and promoted in the western world, mammography screening is currently considered also in developing countries due to high fatality rates and increasing incidence of breast cancer [1]. Since the late 1980s, mortality from breast cancer has been declining in many western countries, probably chiefly due to mammography screening and improved therapy [2–6]. The precise contribution of screening and treatment has, however, been a matter of heated debate [7–9]. Recent studies indicate that the effect of mammography screening on breast cancer mortality may be smaller than previously anticipated; increased awareness and effective adjuvant therapy might indeed have reduced breast cancer mortality more than screening [6, 9–11].

Denmark and Norway are unique countries when it comes to evaluation of mammography screening and are often referred to as ‘model countries’ in this respect, because their geographically staggered implementation of screening over a long time period provides valid control groups. An exploration of the observed variations in effectiveness of screening between these two countries is therefore highly relevant for medicine in general.
Denmark and Norway are neighboring countries with similar socioeconomic standards and health care systems. In Denmark, a population-based screening program with biennial mammography for women aged 50–69 years covering ~20% of the total Danish population was launched in 1991 [12] and became nationwide from 2008/2009. In 1996, a similar program was launched in four Norwegian counties and expanded gradually to reach nationwide coverage from 2005 [9]. Due to the gradual expansion of the mammography screening programs in these two countries, concomitant changes in breast cancer mortality can be accounted for among women not invited to screening.

Notwithstanding similar organization and design, the effect of these two programs, evaluated after at least 10 years of follow-up [9, 12], differed vastly; the estimated (incidence-based) mortality reduction ranged from a statistically nonsignificant 10% in Norway to 25% in Denmark [9, 11, 12]. To this end, our aim was to explore reasons for these paradoxical differences in the estimated benefit of mammography screening.

methods

Denmark and Norway have public health care systems with high-quality population-based registries. In both countries, all individuals are assigned an individually unique national registration number. Thus, individual information on breast cancer incidence, death and screening data can be linked.

the danish screening program

The Danish breast cancer screening program began in 1991 in the municipality of Copenhagen [13] and was expanded in 1993 to the county of Funen [14] covering ~20% of the entire Danish population. In 2008/2009, the program expanded to all Danish counties, inviting all women aged 50–69 years to mammography screening every second year [15]. At the initial screening, two-view mammograms are taken. For women with dense breasts, all subsequent mammograms were two-viewed whereas for women with low-density breasts, mammograms were one-viewed until 2004 and two-viewed after that [16]. Two radiologists read all mammograms independently, and the final decision is based on consensus in accordance to European guidelines [17]. In the initial screening round, the attendance rate was 71% in Copenhagen and 88% in Funen, declining over time [13, 14].

Unlike in Norway, multidisciplinary teams of radiologists, pathologists, surgeons and oncologists, were established independent of the screening program, and these teams were not fully functioning in hospitals treating breast cancer patients in Copenhagen when screening was implemented in 1991 (personal communication; P. M. Christiansen). Instead, multidisciplinary teams were created over a 20 years period from 1990 in different counties, following no geographical pattern.

the norwegian screening program

The Norwegian breast cancer screening program started in 1996 in four counties covering about 40% of the total Norwegian population. From 2000, the program gradually expanded, county by county. Since 2005, all women aged 50–69 years are invited to biennial mammography. Two-view mammograms are read independently by two radiologists; the final decision is based on consensus in accordance with European guidelines [17] and classified according to a 5-point scale reflecting the probability of cancer [18]. The average attendance rate from the start of the program to 2005 was 77% [19].

Unlike in Denmark, before enrollment in the program, each county was required to establish multidisciplinary breast cancer management teams [18]. As a result, breast cancer care became centralized for all residents within each county, and dedicated teams of radiologists, pathologist, surgeon and oncologists manage the care of all patients, regardless of age and method of detection [9].

study design

We analyzed data from two widely cited reports [9, 12] on breast cancer mortality before and after introduction of screening in Denmark and Norway. Both studies used incidence-based mortality as the primary outcome and compared four groups; areas where screening was and was not undertaken in the study period, each divided into prescreening period and screening period (‘current’ and ‘historical screening groups’ and ‘current’ and ‘historical nonscreening groups’) (Figure 1). We used the same inclusion period as in the published papers [9, 12]; in Denmark, the historical (prescreening) period was from 1 April 1981 to 31 March 1991, and the current period was from 1 April 1991 to 31 March 2001 [12]. In Norway, the historical period was from 1 January 1986 to 31 December 1995, and the current period was from 1 January 1996 to 31 December 2005 (Figure 1) [9].

statistical analysis

Using data from the published reports [9, 12], we calculated breast cancer mortality rate ratios (MRR) in different age groups in the current and historical screening and nonscreening groups. Incidence-based mortality includes only deaths from breast cancers diagnosed after invitation to mammography screening. We used the Mantel-Haenszel method to test for homogeneity of mortality rate ratios comparing the screening and nonscreening groups.

Age at death (or the end of follow-up) was analyzed in the Danish study [12], while the Norwegian study analyzed both age at diagnosis and age at death [9]. Data on age groups not eligible to screening allowed us to elucidate trends in breast cancer mortality that was not attributable to screening. Such data were not included in the original paper from Denmark [12], but later provided in a letter to the editor [20].

To validate the findings in the studies, we obtained breast cancer incidence and mortality rates in Denmark and Norway. We used the NORDCAN database to compare trends in incidence for women aged 50–79 years and crude

![Figure 1. The different study groups in the two studies, according to the time period.](image-url)
mortality for women aged 55–74 between Denmark and Norway [21, 22]. We thus obtained rates standardized according to the world population from 1981 to 2008. Because NORDCAN does not distinguish between screening and nonscreening areas, we used these data to illustrate differences in nationwide breast cancer incidence and mortality trends in Denmark and Norway.

In our analyses, based on numbers from the published papers, we assumed the number of breast cancer deaths to follow a Poisson distribution. 95% confidence intervals (95% CIs) and P-values are estimated, and P-values <0.05 are considered to be statistically significant.

results

The two studies published incidence-based mortality with ten years of follow-up after the start of screening [9, 12]. In Denmark, the reported incidence-based mortality from breast cancer among women invited to screening was statistically significantly reduced by 25% [12]. In Norway, a nonsignificant 10% reduction was observed [9]. Table 1 shows the number of deaths, number of person-years, mortality rates and MRRs in the historical and current screening and nonscreening groups, respectively. Data are split into the same age groups as in the original publications.

comparison of current with historical nonscreening groups

In Denmark, comparison of current and historical nonscreening groups shows decreasing breast cancer mortality among women younger than 60 years (Table 1, Figure 2A and B). Among older women, mortality increased in the current compared with the historical nonscreening group. For women aged 70–79 years, this increase is 21% (MRR 1.21, 95% CI 1.08–1.35) (Table 1, Figure 2B). In contrast, in Norway, comparison of the current with historical nonscreening groups shows decreasing breast cancer mortality in all age groups (Table 1, Figure 2A and B).

comparison of current with historical screening groups

In both countries, comparison of current and historical screening groups shows decreasing breast cancer mortality (Table 1, Figure 2A and B). Among women below the age limit for screening has been offered to women between 50 and 69 years in the current screening group.

Table 1. Number of deaths from breast cancer, numbers of person-years, mortality rates (MR) and mortality rate ratios (MRR) with 95% confidence interval (CI) in the screening and the nonscreening groups in Denmark and Norway. Age-groups presented in bold text are offered mammography screening

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Non-screening</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Historical</td>
<td>Current</td>
</tr>
<tr>
<td><strong>Denmark study [12]</strong></td>
<td>50–59</td>
<td>No. of deaths</td>
<td>547</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>1 508 773</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>36.3</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>MRR (95% CI)</td>
<td>0.79 (0.70–0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of deaths</td>
<td>976</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>1 755 399</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>55.6</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>MRR (95% CI)</td>
<td>1.09 (1.00–1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of deaths</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>790 832</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>75.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRR (95% CI)</td>
<td>1.21 (1.08–1.35)</td>
</tr>
<tr>
<td><strong>Norway study [9]</strong></td>
<td>20–49</td>
<td>No. of deaths</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>3 842 740</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>MRR (95% CI)</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of deaths</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>884 889</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>22.4</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>MRR (95% CI)</td>
<td>0.91 (0.75–1.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of deaths</td>
<td>296</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>1 014 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>29.2</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>MRR (95% CI)</td>
<td>0.77 (0.63–0.93)</td>
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<tr>
<td></td>
<td></td>
<td>No. of deaths</td>
<td>296</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of person-years</td>
<td>841 326</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MR</td>
<td>35.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRR (95% CI)</td>
<td>0.83 (0.70–0.99)</td>
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Screening has been offered to women between 50 and 69 years in the current screening group.
Although the original study from screening (50 years), mortality decreased both in Denmark and Norway (Table 1) [11]. Although the original study from screening (50 years), mortality decreased both in Denmark and Norway (Figure 2A and B). In contrast, mortality increases in the current nonscreening groups in Denmark, especially among women older than 59 years (Figure 2B). For women older than 59 years, breast cancer mortality increases by 14% (MRR 1.14, 95% CI 1.07–1.22) in Denmark, whereas, in Norway, a 19% reduction is seen (MRR 0.81, 95% CI 0.72–0.92). This increase accounts for the different relative effect of the screening program in Denmark and Norway; 25% breast cancer mortality reduction in Denmark, and 10% in Norway (difference in mortality reduction between Denmark and Norway: 16%, P = 0.004), Figure 2A. In comparison of the MRRs in the screening and nonscreening groups, only the MRR for women aged 70–79 years (1.21 in the nonscreening groups and 0.74 for the screening groups) in Denmark were statistically significant (P = 0.0007). MRRs by age at death in Norway are similar to those presented in Figure 2A and B (data not shown).

Figure 3 shows nationwide age-standardized breast cancer incidence and mortality rates in Denmark and Norway from 1981 to 2008 for women aged 50–79 years and 55–74 years, respectively. The incidence of breast cancer increases in the period from 1981 to 2008, with a marked increase when screening was introduced in 1991 in Denmark and 1996 in Norway. Breast cancer mortality was stable both in Denmark and Norway with a slight decrease from 1995/1996 in both countries.

**discussion**

Our analysis reveals that the reported differences in effectiveness of mammography screening in Denmark and Norway do not reflect different reductions in breast cancer mortality in the screening groups, but rather different country specific trends in mortality rates in the nonscreening groups. The reduction in breast cancer mortality after implementing screening is strikingly similar in Denmark and Norway. The apparent greater effect in Denmark may be due to an increase in breast cancer deaths among women older than 59 years in the nonscreening groups; changes in mortality in the nonscreening groups differ by 32% between the two countries. Nationwide trends in breast cancer incidence and mortality are similar in Denmark and Norway (Figure 3).

In Denmark, women older than 59 years in the nonscreening group experienced an increase in incidence-based mortality. Compared with the prescreening era, this increase was 21% in the 70–79 year age group, whereas in those invited to screening, a 25% reduction in mortality was found. In contrast, a significant reduction in mortality occurred both among screened and nonscreened women of all ages in Norway. This reduction was of similar magnitude in the screening and nonscreening groups, with an additional 8%–10% nonsignificant drop in mortality for women aged 50–84 in the screening groups [9]. Among women aged 55–74 years at death, mortality rates are declining from 1996 both in Denmark and in Norway. In Denmark, this decline may be associated with introduction of screening, unlike...
Norway where screening first started in 1996. In Denmark, overall breast cancer mortality was 115.4 (per 100,000 women-years) in 1996 and declined by 19% to 93.0 in 2006, 15 years after screening began in only 20% of the population. If screening was the sole explanation for this decline, and the 25% reduction attributable to screening is valid, we would expect a drop in a nationwide mortality by 5% (20% × 25%). As the observed drop was fourfold larger, mammography screening alone cannot explain the decreasing mortality rates in Denmark. Indeed, from 1982 to 2006, the mortality reduction was more pronounced in nonscreening than in screening areas (Figure 1 in [11]).

Of note, the randomized trials on mammography screening did not find any effect of screening after 3 years, which is when Olsen et al. claim to have found the full effect [12]. In the trials, an effect only began to appear after 5 years, with the full effect emerging after 10 years or more [23]. Further, the 25% effect estimate from Denmark was challenged in a paper published 5 years later in the same journal by the Nordic Cochrane Centre [11]. This study did not use incidence-based breast cancer mortality, but crude mortality with longer follow-up; and did not find any effect of screening in Denmark. Some have argued that breast cancer mortality trends cannot be used to evaluate screening [24]. However, if screening has a substantial effect on breast cancer mortality, this should be observed in crude breast cancer mortality trends. The result of the Norwegian study was later confirmed in another study that found a nonsignificant mortality reduction of 7%–11% [25]. Some have argued that these nonsignificant findings can be explained by nonprogram screening outside the program [25].

Denmark has not had opportunistic screening [26]; heighten awareness with earlier clinical detection might have contributed to the observed mortality reduction because tumor size and prevalence of lymph node-positive disease decreased during the time period 1977–2006 [27, 28]. In Norway, the stage distribution remained similar in the prescreening compared with the screening period among women not invited to mammography screening [29]. Although the amount of opportunistic mammography screening has not been recorded in Norway, there is reassuring evidence against this [9, 30–32]. The incidence of ductal carcinoma in situ (DCIS) (an indicator of the amount of screening) in Denmark (with no opportunistic screening [26]), before the start of the screening program, was 10–15 per 100,000 person-years in women aged 50–69 years [33]. Similarly, in Norway, the incidence of DCIS was 10–12 per 100,000 person-years in women aged 50–69 years before the start of the program [34]. Both in Denmark and in Norway, the rate of DCIS increased after screening was implemented in women aged 50–69 and was 40–50 per 100,000 person-years [33, 34]. Thus, differences in opportunistic screening are not likely to confound comparisons between Denmark and Norway. Breast cancer incidence trends are similar in the two countries, and the expected increase in incidence after start of the screening program is noticeable in both countries (Figure 3). Among women older than 69 years, breast cancer incidence increased in Denmark [33], but not so in Norway [9, 30]. The increase was larger in the screening areas than in the nonscreening areas, and the increasing mortality was only noted in the nonscreening areas in Denmark. Thus, the increasing incidence is not likely to explain the differences in mortality among older women in the two studies.

Data from several European countries consistently show a reduction in mortality from breast cancer among women aged 50–69 years after mammography screening, but also among women younger than 50 years not offered screening and partly among older women in the western part of Europe [10, 35]. These reductions started after reports on efficacy of adjuvant chemotherapy and hormone therapy [10]. Hence, the reduction in mortality from breast cancer after introduction of mammography screening in Denmark and Norway could also be explained by improvements in therapy.

Because common guidelines for breast cancer treatment were established in Denmark in 1977 [36], it has been argued that differences in therapy could not confound the mortality reduction after mammography screening was implemented [12]. However, county of residence seemed associated with breast cancer prognosis, with higher survival rates in counties with centralized surgical treatment [37]. The association between differences in management and prognosis in counties with and without screening in Denmark has not been published, but Copenhagen had a higher breast cancer survival rate than the rest of the country before guidelines were published in 1977 [38]. Improved therapy in the screened group in Denmark could explain the unexpected early

Figure 3. Age-standardized breast cancer incidence and mortality from 1981 to 2008, based on NORDCAN data [21, 22], in Denmark and Norway for women aged 50–79 and 55–74 years, respectively.
reduction in breast cancer mortality that was apparent already three years after the screening program started [12]. Despite common guidelines for breast cancer treatment, differences in breast cancer survival can be attributed to suboptimal management [19, 39]. The increased mortality among women in the nonscreening groups older than 59 years documented in the study from Denmark is of concern [12]. Particularly in a time period where there are substantial improvements in therapy that can be given to patients [40], and when crude mortality rates are declining [10].

Our study is observational and can therefore not quantify the different factors beyond screening which may or may not have contributed to the observed effects in breast cancer mortality. One may argue that we would have observed the same increase in breast cancer mortality in the screening group as in the nonscreening group in Denmark if the former had not been invited to screening. However, this would require that there is an underlying increase of breast cancer mortality in Denmark during the study period, due to factors not related to any known interventions or population and environment changes. As far as we know, there is no evidence of any such unknown factor.

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**disclosure**

The authors have declared no conflicts of interest.

**references**

Survival of women with inflammatory breast cancer: a large population-based study†

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Background: Our group has previously reported that women with inflammatory breast cancer (IBC) continue to have worse outcome compared with those with non-IBC. We undertook this population-based study to see if there have been improvements in survival among women with stage III IBC, over time.

Patient and methods: We searched the Surveillance, Epidemiology and End Results Registry to identify female patients diagnosed with stage III IBC between 1990 and 2010. Patients were divided into four groups according to year of diagnosis: 1990–1995, 1996–2000, 2001–2005, and 2006–2010. Breast cancer-specific survival (BCSS) was estimated using the Kaplan–Meier method and compared across groups using the log-rank test. Cox models were then fit to determine the association of year of diagnosis and BCSS after adjusting for patient and tumor characteristics.

Results: A total of 7679 patients with IBC were identified of whom 1084 patients (14.1%) were diagnosed between 1990 and 1995, 1614 patients (21.0%) between 1996 and 2000, 2683 patients (34.9%) between 2001 and 2005, and 2298 patients (29.9%) between 2006 and 2010. The 2-year BCSS for the whole cohort was 71%. Two-year BCSS were 62%, 67%, 72%, and 76% for patients diagnosed between 1990–1995, 1996–2000, 2001–2005, and 2006–2010, respectively (P < 0.0001). In the multivariable analysis, increasing year of diagnosis (modeled as a continuous variable) was associated with decreasing risks of death from breast cancer (HR = 0.98, 95% confidence interval 0.97–0.99, P < 0.0001).

Conclusion: There has been a significant improvement in survival of patients diagnosed with IBC over a two-decade time span in this large population-based study. This suggests that therapeutic strategies researched and evolved in the context of non-IBC have also had a positive impact in women with IBC.

Key words: inflammatory breast cancer, stage III, survival, time trends

introduction

Significant therapeutic advances have been made in the realm of early-stage breast cancer management that has led to an improvement in survival outcome over the decades. Aggregate data from large randomized clinical trials presented by the Early Breast Cancer Trials’ Collaborative group has shown that 6 months of an adjuvant anthracycline-based polychemotherapy regimen reduces the annual breast cancer death rate by 38% for women younger than 50 years and by 20% for those women aged 50–69 years [1]. The addition of a taxane has also been demonstrated to improve both disease-free and overall survival (OS) [2, 3]. Furthermore, the introduction of the monoclonal...