Mammography screening in three Finnish residential areas: comprehensive population-based study of breast cancer incidence and incidence-based mortality 1976–2009

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Background: The aim of this study was to evaluate the effectiveness of a large-scale screening programme for breast cancer (BC) in Turku, Finland. Incidence and incidence-based mortality (IBM) figures were compared with the areas applying different screening policies.

Methods: Deaths and person-time of women aged 40–84 were assessed for the period 1976–1986 (prescreening era) and the periods 1987–1997 and 1998–2009 (screening periods) using incidence and IBM by age at diagnosis and at death. There was a total of 40.7 million women-years, 83,497 invasive BCs obtained from the Finnish Cancer Registry; 17,508 BC deaths were linked with the data from Statistics Finland.

Results: In Turku, a significant (> 20%) reduction in IBM occurred during 1987–2009 among women aged 60–74 years at diagnosis compared with Helsinki (IBMRR: 0.75, 95% CI: 0.57–1.00), and in women aged 75–84 years at death compared with the rest of Finland (IBMRR: 0.72, 95% CI: 0.53–0.96).

Conclusions: The wide mammography screening programme in Turku was effective in decreasing BC mortality in the elderly age groups. These results support the implementation of BC screening from age 50 up to 74 years.
from the mortality analysis, but shown separately (Table 3). Most of the data on all invasive BCs (first primary BC) among women aged 40–84 years were included and, irregularly, women aged 65–69 years (Sarkeala, 2008; Sarkeala et al, 2008a).

During the early 1990s, the nationwide coverage of invitations (aged 50–59) was nearly 100% (Finnish Cancer Registry, 2014). In Helsinki and in most municipalities in RoF, women aged 60–74 were not invited before the year 2007. Since then the upper age of invitation has gradually been raised to 69 years in the national programme, and currently it covers the whole country. In the city of Turku and the two other residential areas, Turku, Helsinki, and the rest of Finland, for mammography screens aged 40–84 years. Effectiveness was evaluated by examining the results of the different invitation policies in the city of Turku and the two other residential areas.

MATERIALS AND METHODS

National BC mammography screening programmes by invitation began in 1987 in Finland. Since 1992, all women aged 50–59 years receive screening invitations every second year. The screening in Turku targeted female inhabitants aged 40–74 years. In the reference areas only women aged 50–59 (Helsinki) and in a few municipalities (in the rest of Finland) women aged 60–64 were included and, irregularly, women aged 65–69 years (Sarkeala, 2008; Sarkeala et al, 2008a).

The Finnish Cancer Registry (FCR) registers all incident cancer cases and all deaths from cancer since 1953 (Anttila et al, 2008; Sarkeala et al, 2008b; Finnish Cancer Registry, 2014). Coding of death from cancer is based on regular linkages between incidence records of the FCR and the death certificates registered by Statistics Finland. For the period 1976–2009, the study material consisted of the data on all invasive BCs (first primary BC) among women aged 40–84 years. There were 3890 in situ BCs, which were excluded from the mortality analysis, but shown separately (Table 3). Most of the in situ cancers (CIS) were of the ductal type (DCIS).

The material was divided into the following subcategories for analysis:

1. Residence: analyses were made for the city of Turku (TKU), Helsinki (HEL) and the rest of Finland (RoF), Helsinki is the most populated and urbanized residential area in Finland and has the most background factors contributing to BC risk: higher alcohol consumption (Addictionlink, 2014), higher use of hormonal replacement therapy (Salmi et al, 2004) and less favourable reproductive risk factors (Statistics Finland, 2014). The separation of Helsinki from the rest of Finland (covering all rural areas) was made to compare the city of Turku with these two different types of residential areas.

2. Age group at time of BC diagnosis and at BC death: analyses were made for the age groups 40–49, 50–59, 60–74 and 75–84 years. Analysis by age at incidence corresponded to the difference in the screening invitation programme in Turku and other residential areas and the postscreening age group. Owing to a long period of time between the incidence date and death, it was essential to describe the impact of mortality also by the age at death. This analysis produced additional information on the potential benefit of screening by age group with regard to the optimum age of screening and the risk of death from BC. It was also possible to avoid the bias caused by the lead-time. These long-term effects gave a strong cause for including a late screening age group (75–84 years) in the analyses.

3. Time of diagnosis: the data were analysed separately for diagnoses made 1976–1986, 1987–1997 and 1998–2009. The first period represents the period just before the start of screening (prescreening era), the two others the periods after the start of screening invitations (first and second screening periods). The second screening period represents the continuation of the screening programme, which allowed observation of long-term consequences of the screening invitation programme and changes in the most recent period due to factors other than the screening programme itself.

The total incidence and mortality (per 100 000) were calculated for each residential area by age (1-year intervals) and calendar year. All primary invasive BC cases and BC deaths were included until the end of follow-up (31 December, 2009). The aggregated dynamic cohort data covered thus the three residential areas by calendar period and age group. The data of all screening periods (1987–1997, 1998–2009) were combined for final analyses. Altogether, 40.7 million women-years were included in this study. During the three study periods, there were 83 497 invasive BCs and 17 508 BC deaths. The number of BCs and BC deaths in each residential area and for each time period is shown in Table 1.

Statistical methods. To maximise the precision of the estimates, differences in the incidence and IBM between the residential areas were analysed by age group and calendar period with Poisson’s regression. Appropriate adjustments were made for the underlying differences in the prescreening era (1976–1986) regarding the effectiveness of breast cancer screening policies, age-specific differences in the incidence and IBM among the residential areas during the screening period (1987–2009). The changes in IBM within each residential area were also analysed; for this, IBM was restricted to 10 years in each calendar period. The differences in IBM changes between the residential areas were tested with Wald’s test.

The cumulative incidence was calculated by summing the observed one-year age-specific incidence rates for ages 40–84 for the calendar periods 1976–1986 and 1998–2009. Stata release 12 (StataCorp, Brazos Valley, TX, USA) was used for running the statistical calculations.

Ethics. The Ethics Committee of the Hospital District of Southwest Finland approved the study and authorisation was obtained from the Finnish Ministry of Social Affairs and Health to use the hospital records for data retrieval.
were compared (Figure 1). The influence of the rapid screening start in Turku was evident during the period 1987–1997, but the incidence rose further between 1998 and 2009.

The rise occurred most prominently in the two younger age groups: the incidence in Helsinki was reached compared with Turku and temporally surpassed, whereas the increase in the age group 60–74 years was more stable. There was a decreasing trend in the oldest (postscreening) age group of 75–84 years, which deviated in Turku from Helsinki, and was similar to that found for the rest of the country (See Figure 1).

Figure 2 shows the cumulative BC incidence, until the age of 84, before the start of the screening (1976–86 dashed lines) and during the second screening period (1998–2009, solid lines). During both time periods, the incidence for RoF remained the lowest and for Helsinki the highest. In Turku, the cumulative incidence increased by 154% from 0.0826 in the prescreening era of 1976–1986 to 0.1269 in the second screening period, of 1998–2009. The corresponding values and percentages were 0.0673 and 0.1124 (increase 167%) for RoF and 0.0975 and 0.1466 (increase 50%) for Helsinki, respectively.

The relations in the rate ratios (RRs) for the crude results of the prescreening era (1976–86) and screening period (1987–2009) are shown in Table 2. It also shows that before the start of screening the BC incidence in all age groups was higher in Turku than in the RoF, and correspondingly in all the age groups the BC incidence was lower in Turku than in Helsinki.

After the start of screening, during 1987–2009, the relative decrease in breast cancer incidence in Turku’s oldest age group (75–84 years) was significantly larger, by 20%, compared with the RoF (Table 4). In the 60- to 74-year-age group, the differences remained unchanged, whereas, among the younger age groups, Turku reached the same level as Helsinki. In the 40– to 49-year and the 50–59-year-age groups, the increase in the incidence of BC was 12 and 26%, respectively.

CIS percentages are shown in Table 3. There were 3890 in situ breast carcinomas registered, which corresponded to 4.7% of all cancer cases. After the start period of screening, in situ carcinomas were diagnosed more frequently. In the 50- to 59-year-age group that was screened throughout the country, the CIS percentage was the highest in Helsinki (11.9%) and in RoF (9.4%) during 1998–2009. In the youngest (40–49) and oldest screened (60–74) age group 60–74 years was more stable. There was a decreasing trend in the oldest (postscreening) age group of 75–84 years, which deviated in Turku from Helsinki, and was similar to that found for the rest of the country (See Figure 1).
groups, Turku had the highest incidence of in situ carcinomas, 10.2% (1987–1997) and 9.5% (1998–2009), respectively.

**Mortality.** Before the start of screening (1976–1986), BC mortality in Turku was similar to the reference city, Helsinki, in the 40- to 49-year and 75- to 84-year age groups. Compared with the RoF, it was higher in all age groups (Figure 1). In the 50- to 59-year age group, mortality in Turku was intermediate between the two other residential areas. After screening start, mortality sank in the three age groups in Turku; in the 60- to 74-year age group, the already low mortality was nearly unchanged.

The incidence-based mortality was calculated taken into account the underlying IBM in the prescreening era for each age group at diagnosis and at death. In Turku, a statistically significant decrease of > 20% in the IBM took place between 1987 and 2009 in the 60- to 74-year age group at diagnosis compared with Helsinki (IBMRR: 0.75, 95% CI: 0.57–1.00, \( P < 0.05 \)) and in the 75- to 84-year age group at death compared with RoF (IBMRR: 0.72, 95% CI: 0.53–0.96) (Table 4).

We studied changes in the IBM over time and within each residential area for completeness also by 10-year IBM. These data showed that the 10-year IBM, based on age group at death, decreased during the first screening period (1987–1997) compared with the prescreening era and was different between the residential areas (\( P = 0.037 \)) in the 75- to 84-year age group. In Turku, this decline was 44% (IBMRR: 0.56, 95% CI: 0.38–0.83).

Because the 40- to 49-year age group was only screened in Turku, Turku was considered a unique study area. The largest decline in 10-year IBM occurred also in this age group between 1998 and 2009: 51% at diagnosis (IBMRR: 0.49, 95% CI: 0.27–0.83) and 59% at death (IBMRR: 0.41, 95% CI: 0.18–0.89). The estimated effect of screening in Turku in this age group varied from 0.73 (95% CI: 0.50–1.06) to 0.98 (0.64–1.47), depending on the region used for comparisons (Table 4).

### DISCUSSION

The effect of the early start and execution of the Turku mammography screening programme compared with other residential areas lead to an increase in the incidence of BC in the 40- to 74-year age group of women undergoing mammography screening from the first to the second time period, that is, from 1976–1986 to 1987–1997, after which it returned to starting level by 1998–2009 (Table 1).

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**Table 2.** Crude age-specific breast cancer (BC) incidence rate ratios (IRRs) and incidence-based mortality rate ratios (IBMRRs) with 95% confidence intervals in Turku (TKU) in comparison with the rest of Finland (RoF) and Helsinki (HEL)

|                |TKU vs RoF|TKU vs HEL|
|----------------|----------|----------|
|                |Incidence|BC-related risk of mortality by year of diagnosis|BC-related risk of mortality by year of death|
|                |          |          |
|TKU vs RoF      |          |          |
|40–49           |          |          |
|1976–1986       |1.20* (1.01–1.44)|1.24 (0.93–1.65)|1.48 (0.97–2.25)|
|1987–2009       |1.16** (1.06–1.27)|0.90 (0.71–1.16)|1.08 (0.77–1.53)|
|50–59           |          |          |
|1976–1986       |1.18* (1.00–1.38)|1.08 (0.85–1.37)|1.13 (0.86–1.49)|
|1987–2009       |1.13*** (1.06–1.22)|1.06 (0.86–1.30)|0.89 (0.71–1.11)|
|60–74           |          |          |
|1976–1986       |1.26*** (1.12–1.41)|1.09 (0.90–1.32)|1.02 (0.84–1.24)|
|1987–2009       |1.29*** (1.22–1.38)|0.94 (0.79–1.11)|0.98 (0.83–1.16)|
|75–84           |          |          |
|1976–1986       |1.28* (1.08–1.51)|1.05 (0.79–1.40)|1.21 (0.97–1.50)|
|1987–2009       |1.03 (0.93–1.14)|0.77 (0.59–1.00)|0.86 (0.71–1.05)|
|TKU vs HEL      |          |          |
|40–49           |          |          |
|1976–1986       |0.88 (0.72–1.07)|0.85 (0.62–1.17)|1.04 (0.65–1.67)|
|1987–2009       |0.98 (0.89–1.09)|0.83 (0.63–1.09)|0.98 (0.66–1.44)|
|50–59           |          |          |
|1976–1986       |0.77** (0.65–0.91)|0.75* (0.58–0.98)|0.90 (0.66–1.22)|
|1987–2009       |0.97 (0.89–1.05)|0.82 (0.65–1.03)|0.83 (0.66–1.07)|
|60–74           |          |          |
|1976–1986       |0.87* (0.76–0.98)|0.84 (0.68–1.04)|0.68*** (0.55–0.85)|
|1987–2009       |0.92* (0.86–0.99)|0.64*** (0.53–0.77)|0.65*** (0.54–0.78)|
|75–84           |          |          |
|1976–1986       |0.87 (0.72–1.05)|0.89 (0.65–1.22)|0.89 (0.69–1.13)|
|1987–2009       |0.77*** (0.69–0.86)|0.64* (0.47–0.85)|0.67*** (0.54–0.84)|

*\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \). Data are shown for four age groups in the prescreening era (1976–1986) and the screening period (1987–2009).
Reproductive factors (early menarche and age at first full-term pregnancy), lifestyle (alcohol consumption and obesity), an urban environment and hormonal factors (especially hormone replacement therapy) affect the BC incidence. Changes in the impact of these risk factor changes in Finland, as in most developed countries, explain the continuous increase in BC incidence of BC during the last decades. This rising trend took place in all residential areas.

It is important to observe that the relatively high occurrence of invasive breast cancer in the Turku population was not due to overdiagnosis caused by screening (Figure 2, Table 1). Comparisons between Turku and the reference residential areas did not show any consistent excess of BC diagnoses in Turku. These results are in line with the European estimates of overdiagnosis due to screening in general.

The estimated effect of screening in Turku in the age group of 40 to 49 years varied from 3 to 27% in terms of adjusted IBM results depending on the region the results for Turku are compared (Table 4). Thus, we cannot rule out a small amount of overdiagnosis in breast cancer screening in general.

The numbers of CIS of the breast increased in all residential areas and age groups in parallel with mammography screening frequency. The increases in the number of CIS are probably partially a consequence of overdiagnosis, and our results corroborate this (Miller et al, 2002; Moss, 2005; Zackrisson et al, 2006). There are no reliable methods available to predict which patients with CIS will have invasive BC (Allen et al, 2014). At present, the increasing number of CIS due by mammography screening must be accepted. CIS poses, however, a real threat to the patient: if left untreated CIS may often progress into invasive cancer (Duffy et al, 2005), even despite complete local excision. Indeed, 30% of patients whose CIS has been excised will have a recurrence within 10 years (Cuzick et al, 2011).

The significant reduction in mortality due to BC of screened subjects compared with non-screened subjects has been confirmed in several studies (Fielder et al, 2004; Allgood et al, 2008; Roder et al, 2008; Nickson et al, 2012; Puliti and Zappa, 2012; Otto et al, 2012; Hofvind et al, 2013).

A mortality reduction of at least 20% among invited to screening vs non-invited has also been reported by Sarkeala et al (2008a) and Tabár et al (2011) and recently by Weedon-Fekjaer et al (2014). In the present study, a corresponding benefit for screened persons regarding BC mortality was documented for 25 to 28%. These results are also in line with our previous reports on the survival (Klemi et al, 2003; Immonen-Räihä et al, 2005) and mortality (Parvinen et al, 2006) of patients with BC.

The estimated effect of screening in Turku in the age group of 40 to 49 years varied from 3 to 27% in terms of adjusted IBM results depending on the region the results for Turku are compared (Table 4). Thus, we cannot rule out that there was a real decline in IBM in the youngest invited age group in Turku, but the limited population size and the low number of deaths from BC in this age group weaken the statistical power. Screening of the youngest age group started to decrease gradually in 2000 in Turku and levelled off by 2009. This may also dilute incidence and mortality results among the youngest screening participants.

In a previous study in this youngest age group in Turku, there were no differences in the incidence of BC or IBM between the women who were invited for screening annually or triennially. Because of the lack of a control group (no screening), it was not possible to determine whether this result was due to a reduction in effects of mammography screening of this age group or whether the effectiveness of triennial screening is similar to that of annual screening (Parvinen et al, 2011). However, in this study, among the youngest (premenopausal) group, a >50% decline in the IBM (10 years follow-up restriction) occurred both in the age group at diagnosis and at death in Turku. These results are in accordance with Italian (Gorini et al, 2004), Icelandic (Gabe et al, 2006) and Swedish (Hellquist et al, 2011) results and give further support to our previous results regarding survival (Klemi et al, 2003).

Table 3. In situ breast cancer (% of all BC cases in three residential areas, 1976–2009)

| HELSINKI | TURKU | Rest of Finland (RoF) |
|----------|-------|-----------------------|
| 1976–1986 | 1987–1997 | 1998–2009 | Total | 1976–1986 | 1987–1997 | 1998–2009 | Total | 1976–1986 | 1987–1997 | 1998–2009 | Total |
| 40–49 | 68 (1.3) | 37 (4.7) | 77 (9.0) | 120 (5.7) | 0 (0.0) | 23 (10.2) | 23 (9.7) | 46 (7.8) | 59 (2.2) | 180 (3.7) | 347 (5.8) | 586 (4.3) |
| 50–59 | 4 (0.6) | 37 (4.0) | 188 (11.9) | 229 (7.3) | 2 (1.2) | 15 (4.8) | 34 (7.9) | 51 (5.6) | 36 (1.1) | 296 (5.0) | 1022 (9.4) | 1354 (6.8) |
| 60–74 | 6 (0.6) | 20 (1.6) | 149 (7.6) | 175 (4.1) | 0 (0.0) | 22 (5.1) | 57 (9.5) | 79 (5.9) | 20 (0.4) | 156 (2.2) | 822 (9.9) | 998 (4.1) |
| 75–84 | 0 (0.0) | 12 (1.8) | 36 (4.5) | 49 (2.4) | 0 (0.0) | 2 (1.1) | 8 (3.4) | 10 (1.8) | 1 (0.0) | 40 (1.1) | 153 (3.1) | 194 (1.8) |
| Total | 16 (0.6) | 106 (3.9) | 450 (8.7) | 572 (5.0) | 2 (0.3) | 62 (5.4) | 122 (8.1) | 186 (5.5) | 116 (0.9) | 672 (3.1) | 2344 (6.9) | 3132 (4.6) |

Table 4. Adjusted age-specific BC RRs and IBMRRs with 95% confidence intervals in Turku (TKU) in comparison with the rest of Finland (RoF) and Helsinki (HEL)

| TKU vs RoF | INCIDENCE | BC-related risk of mortality by year of diagnosis | BC-related risk of mortality by year of death |
|-----------|-----------|-----------------------------------------------|-----------------------------------------------|
| 40–49 | 0.97 (0.79–1.17) | 0.73 (0.50–1.06) | 0.73 (0.42–1.27) |
| 50–59 | 0.96 (0.81–1.14) | 0.98 (0.71–1.33) | 0.78 (0.55–1.12) |
| 60–74 | 1.03 (0.90–1.17) | 0.85 (0.66–1.10) | 0.96 (0.74–1.25) |
| 75–84 | 0.80* (0.66–0.98) | 0.78 (0.54–1.12) | 0.72* (0.53–0.96) |

| TKU vs HEL | INCIDENCE | BC-related risk of mortality by year of diagnosis | BC-related risk of mortality by year of death |
|-----------|-----------|-----------------------------------------------|-----------------------------------------------|
| 40–49 | 1.12 (0.89–1.39) | 0.97 (0.64–1.47) | 0.94 (0.51–1.72) |
| 50–59 | 1.26* (1.04–1.52) | 1.08 (0.76–1.54) | 0.93 (0.63–1.38) |
| 60–74 | 1.06 (0.92–1.23) | 0.75* (0.57–1.00) | 0.94 (0.71–1.25) |
| 75–84 | 0.89 (0.72–1.10) | 0.76 (0.51–1.13) | 0.76 (0.55–1.06) |

*P<0.05. Data are shown for four age groups in the screening period (1987–2009) after the adjustment of the underlying BC incidence in 1976–1986.
The decline in BC mortality in all age groups started in Finland in the late 1980s (NORDCAN database, 2014), as in many other developed countries (Siegel et al, 2012; GLOBOCAN 2012, 2014). In this study, this decline occurred among all age groups and in all residential areas. An obvious explanation for this beneficial trend is the global improvement in treating BC (Youlden et al, 2012). This effect seems to be evident, especially in the 40- to 49-year age group (Figure 1).

The effects of screening became less discrepant in terms of 1998–2009. First, the screening programmes became standardized during the last calendar period, and, second, the effect of improved therapy had an impact on all residential areas. Nevertheless, the follow-up of women diagnosed in the second screening period (1987–1997) was brief and this may affect the results.

Our database is huge and includes some 40 million women-over more than 20 years. The participation in mammography screening in Finland was excellent—the rate was 86.7% during 1992–2009 (Sarkeala et al, 2013). These factors increase the validity of the results. The results are drawn from homogenous, multi-residential areas and age groups with known prognostic background variables, but at the same time with similar treatments and participation rates. These types of results with urbanized (Helsinki) and unurbanized (RoF) references may also be considered more reliable than study results drawn from nonhomogeneous populations vulnerable to bias (Zahl et al, 2004; Autier et al, 2011; Bleyer and Welch, 2012; Gotzsche et al, 2012).

Owing to the multi-dimensional changes in the incidence and treatment of BC over the last decades, it is not straightforward to draw conclusions concerning the effectiveness of mammography screening programmes. These multi-dimensional changes interact strongly with mammography screening efficacy. Obviously, continuous long-term monitoring of the morbidity and mortality of patients with BC will be needed also in the future (Ursin, 2012).

The wide mammography screening programme in Turku was an effective and long-standing tool to decrease mortality in elderly age groups. The screening programme did not lead to any significant increase in the number of invasive breast cancers in any of the age groups (that is, overdiagnosis) compared with the other residential areas. On the basis of all available data, we have no other consistent explanation for the decrease in mortality among the elderly women in Turku than screening. While there was a clear decline in IBM in all residential areas. An obvious explanation for this beneficial trend is

Continuous and practical clinical study results such as the ones of this study are urgently needed in for example, the light of the ongoing discussion on epidemiological methodology (Signeurin et al, 2011; Ursin, 2012). The strength of this study was the long follow-up period, two different broad residential population comparison areas within the same country, as well as the opportunity to adjust the results with the 11-year period before the screening start. The results of this study provide evidence that unnecessary BC deaths in other parts of Finland could be avoided by using the Turku-based screening framework. The crucial elements in the Turku City were to invite both the younger and older age groups for mammography screening for getting the optimal life span BC mortality decline among women population. Taking into account the increasing life expectancy of women, these results support that mammography screening should be extended from age 50 to 74 years.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.
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