Un key article per un epidemiologo

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Effect of population breast screening on breast cancer mortality up to 2005 in England and Wales: an individual-level cohort study

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Population breast screening was introduced in a number of countries from the late 1980s after randomised controlled trials reported that mammographic screening could reduce breast cancer mortality by an average of 23% in invited women aged 50–69 years (Lauby-Secretan et al, 2015).

Debate, however, continues about the relative benefits and disadvantages of such screening programmes (Paci et al, 2014; Bleyer et al, 2016; Jorgensen and Gotzsche, 2016).

This, coupled with ongoing improvements in breast cancer treatment, has led to questions about the value of population screening in reducing breast cancer mortality, and highlighted the need to evaluate the effectiveness of existing population breast screening programmes

Population-based breast screening has been introduced without intrinsic provision for evaluation, making identification of an uninvited comparison population difficult

The use of individual-level data to take into account the screening history of each woman and to identify breast cancers diagnosed before invitation has been strongly recommended

(Broeders et al, 2012; Weedon-Fekjaer et al, 2014).

However, such data are not readily available and relatively few evaluation studies have used individual screening and outcome data

The UK NHS Breast Screening Programme (NHSBSP) is one of the largest nationally organised programmes in the world, currently inviting nearly three million women each year (Health and Social Care Information Centre, 2016).

The NHSBSP was introduced in 1988 inviting women aged 50–64 years every 3 years.

Implementation of the NHSBSP was gradual, with the first screening round not completed until 1995

To evaluate the impact of the NHSBSP in England and Wales on breast cancer mortality a retrospective cohort analysis was conducted using individual-level screening exposure and mortality outcome data.

The staggered implementation period of the programme was used to provide an uninvited control group.

This paper presents an analysis of the **impact of NHSBSP activity on breast cancer mortality between 1991 and 2005**.

MATERIALS AND METHODS

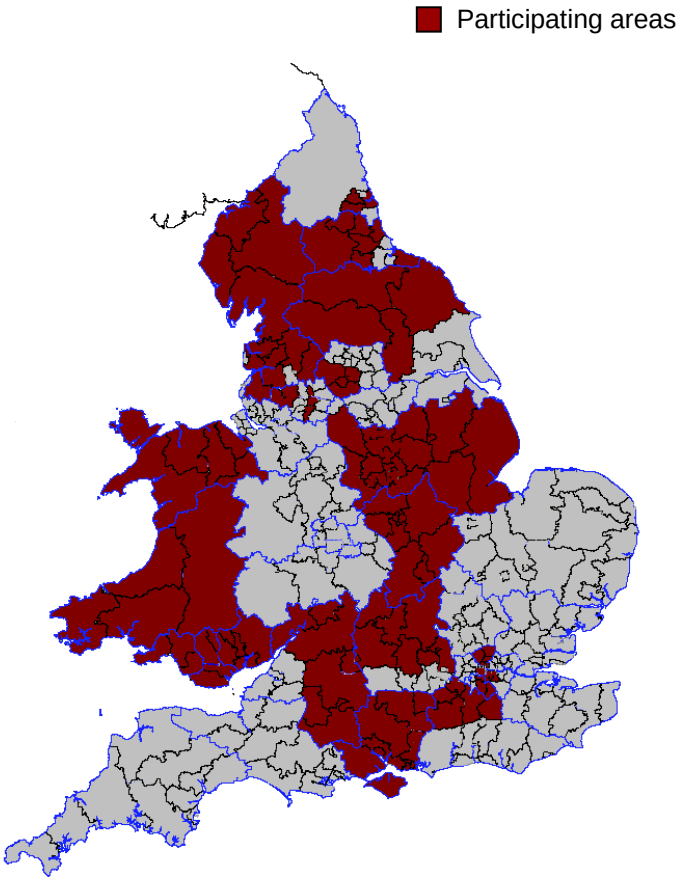
Subjects and data acquisition

The study area covered round

one third of England and the whole of Wales,

designed to include the earliest and latest areas to begin NHS screening.

The cohort were women aged 49–64 years, resident in the study area and free from breast cancer on 1 January 1991.



Breast screening histories were extracted from screening call/ recall databases in the study area.

Dates of death were obtained from screening call/recall databases, the NSTS, and the Office for National Statistics (ONS).

Data on underlying cause of death were collected from ONS and breast cancer deaths were those for which breast cancer was coded as the underlying cause.

Data on incidence of breast cancer, including in situ disease, were collected from the national cancer registration system.

Socioeconomic status (SES) was estimated based on postcode of residence at study entry using the Townsend Index

(Phillimore et al, 1994) based on data from the 1991 census

The NHSBSP in England and Wales started in 1988, but data on cause of death collected by linkage for 1988–1990 were incomplete and therefore analyses for this study started in 1991. Follow-up ended at 31st December 2005

Analyses.

Women entered the study on 1 January 1991 and exited at date of death, date lost to follow-up or 31 December 2005, whichever was earliest

Primary analysis was conducted on an 'intention-to-screen' basis (i.e., 'exposed' women were those invited for screening, not just those who attended).

In the NHSBSP, women were scheduled for invitation on the basis of demographic information and their further eligibility was checked by their GP practice before being invited.

Under these circumstances, use of invitation as the measure of exposure in an intention to screen analysis could have led to an estimate that was biased in favour of screening because of a healthy invitee effect.

To avoid healthy invitee bias, therefore scheduling for invitation was used as the measure of exposure in our intention-to-screen analyses (referred to below simply as ‘invitation’)

To reflect the potential for women to move between exposure groups over time, the intention-to-screen analysis of mortality used incidence-based mortality (IBM), in which deaths from breast cancer were assigned to the woman's exposure group at diagnosis (Njor et al, 2012).

This excludes deaths in breast cancer diagnosed before the start of the study period, and ensures that a woman who dies after invitation to breast screening from a breast cancer diagnosed before invitation is counted as a death in the unexposed group.

It is important to ensure that length of IBM follow-up is similar between exposure groups. For each exposure group, there was a period to accrue breast cancer cases ('accrual period') and a period to encompass IBM follow-up that started at entry to the group ('observation period').

The 15-year period 1991–2005 was partitioned into observation periods that were of equal length in both the invited and uninvited groups.

Lead-time bias consequent on screening advancing the date of diagnosis can bias results against a positive effect of screening in IBM analysis by including breast cancer deaths in women who would otherwise have been diagnosed beyond the accrual period (Njor et al, 2012).

Intention-to-screen analyses were adjusted for this bias assuming a lead-time of 3 years for screen-detected cases, based on published estimates of lead-time (Weedon-Fekjaer et al, 2005; Svendsen et al, 2006). Analyses were repeated using lead-time estimates of one, 5 and 7 years.

An analysis based on screening attendance was conducted, dividing women at entry according to whether or not they had attended within 6 months of their first screening invitation.

The limit of 6 months ensures that any attendance relates directly to the correct invitation.

In this analysis, only women who had been sent an invitation were included.

Estimates were adjusted to take account of the increased mortality risk in women who do not accept screening (self-selection bias; Duffy and Cuzick, 2002), using information on uninvited women from the cohort to derive a population-specific correction factor

Poisson regression, was used to calculate rate ratios and associated 95% confidence intervals and P-values.

Age and socioeconomic status were included as covariates in the model.

RESULTS

Data on a total of 1 426 379 women aged 49–64 years on 1 January 1991 were extracted from 28 screening call/recall databases.

Of these, we excluded from analyses women who were not traced at NSTS (14 157), women with breast cancer diagnosed before 1 January 1991 (28 870) and women invited before 1 January 1991 (395 262).

This resulted in an analysis population of **988 090 women**.

Between 1 January 1991 and 31 December 2005, there were 41 120 cases of breast cancer diagnosed and 146 539 deaths in the cohort, including 8002 deaths from breast cancer.

Linkage failed to produce an underlying cause of death for 2% of deaths (3032/146 539).

A total of 39 134 women (4%) were lost to follow-up for reasons other than death before 31 December 2005, and a further 8014 who left the study area before being scheduled for NHSBSP invitation were lost to follow-up in the IBM analysis

Intention-to-screen analyses

A total of 790 946 women were invited to their first screen between ages 49 and 64 years,

Table 1. Breast cancer mortality in invited compared with uninvited women

					Rate ratio (95% CI, *P*-value)		
Exposure status	Number of women	Number of person-years	Number of breast cancer deaths	Crude breast cancer mortality rate per 1000 person-years	Crude	Adjusted for age and socioeconomic status[a]	Adjusted for age, socioeconomic status and lead-time[b]
Incidence-based mortality							
Not invited	988 090	1 675 356	1239	0.74	1.00	1.00	1.00
Invited		4 719 228	2912	0.62	0.83 (0.78–0.89, <0.001)	0.82 (0.76–0.88, <0.001)	0.79 (0.73–0.84, <0.001)
Late- and early-starting screening areas							
Late-starting	52 949	723 558	490	0.68	1.00	1.00	n/a[c]
Early-starting	49 713	685 758	373	0.54	0.80 (0.70–0.92, 0.001)	0.82 (0.71–0.94, 0.004)	n/a[c]

Abbreviation: CI = confidence interval.
[a] Adjusted for single year of age and socioeconomic status quintile.
[b] Adjusted for lead-time of 3 years.
[c] Lead-time does not affect this analysis.

The number needed to be invited to save one death from breast cancer was 1436 (based on inviting women for 2 years and 9 years of follow-up).

Intention-to-treat analyses

Breast cancer mortality in screening attenders compared with non-attenders.

A total of 790 946 women were invited to their first screen between ages 49 and 64 years, and 587 809 (74%) attended within 6 months

Table 2. Breast cancer mortality (conventional) in attenders and non-attenders in response to first round screening invitation: women aged 49–64 years at invitation

					Rate ratio (95% CI, *P*-value)		
Exposure status	Number of women	Number of person-years	Number of breast cancer deaths	Rate per 1000 person-years	Unadjusted	Adjusted for age and socioeconomic status[a]	Adjusted for age, socioeconomic status and selection bias[b]
Attenders	587 809	7 411 762	3120	0.42	0.54 (0.51–0.57, <0.001)	0.54 (0.51–0.57, <0.001)	0.68 (0.63–0.73, <0.001)
Non-attenders	203 137	2 347 909	1845	0.79	1.00	1·00	1.00

Abbreviation: CI = confidence interval.
[a] Adjusted for single year of age and socioeconomic status quintile.
[b] Adjusted for self-selection bias using non-attender to uninvited breast cancer mortality ratio.

The number needed to be screened in order to save one death from breast cancer was 1020 (where screened women attended a first screen within 6 months of invitation and attended on average 2.8 screens over a mean 12.3 years follow-up).

Analyses of overdiagnosis of breast cancer

0.3% overdiagnosis after one invitation and 12 years of follow-up as a percentage of the observed incidence in either invited or uninvited women

DISCUSSION

These results are similar to those from a recent review and metaanalysis of the impact of mammographic screening on breast cancer mortality in Europe published in 2012 for the EUROSCREEN Working Group (Broeders et al, 2012).

The reviewers identified seven eligible IBM studies, where mortality rates were calculated on the basis of breast cancer deaths occurring in women with breast cancer diagnosed after their first invitation to screening.

The reported pooled breast cancer mortality reduction was 25% (RR 0.75, 95% CI: 0.69–0.81) among invited women and 38% among those screened (RR 0.62, 95% CI: 0.56–0.69).

Two additional large IBM evaluations of organised breast screening in Norway and Finland have been published (Weedon-Fekjaer et al, 2014; Parvinen et al, 2015).

These studies reported reductions in death from breast cancer of between 25 and 28% associated with invitation to screening.

The UK evaluation is very similar in design to the study in Norway, where screening was implemented gradually between 1995 and 2005. The Norwegian study found a 28% reduction in breast cancer mortality among women invited (RR=0.72, 95% CI: 0.64–0.79) and a 37% reduction associated with screening attendance (Weedon-Fekjaer et al, 2014)

The greater magnitude of mortality reduction in Norway compared with our UK study might be accounted for by a more recent screening period employing contemporary screening practice, a shorter screening interval (2 years in Norway, 3 years in the UK) and the use of two-view mammography at all screens throughout the Norwegian evaluation period compared with two-views at the first screen only in most of the NHSBSP during the study period

Strengths and limitations of this analysis.

This study uses individual-level data for both screening and outcome data.

The IBM analyses were restricted to women free from breast cancer at entry to avoid dilution of the effect of screening; 57% of breast cancer deaths occurring between 1991 and 2000 were diagnosed before 1991, similar to proportions reported by others (Hakama et al, 1999; Duffy et al, 2002).

The study was potentially subject to a range of biases.

Healthy invitee bias was minimised by using scheduling for invitation rather than invitation for screening as the measure of exposure in intention-to-screen analyses.

Incidence based mortality analyses were adjusted for the form of lead-time bias that acts against screening in this type of analysis (Njor et al, 2012). Varying the lead-time estimate used in the adjustment to 1, 5 and 7 years resulted in estimated breast cancer mortality reductions of 17, 22 and 26%, respectively.

Findings from analyses comparing mortality in screening attenders with that in non-attenders are highly dependent on the magnitude of the correction factor used to adjust for self-selection bias.

In this study a population-specific correction factor of 1.19 was applied, derived from the UK cohort study data, that was similar in magnitude to the correction factors 1.11 and 1.17 derived from Italian and Icelandic evaluation study data, respectively (Gabe et al, 2007; Puliti et al, 2008).

An alternative analysis, using the correction factor of 1.36 derived from Swedish and Canadian trials (Duffy and Cuzick, 2002) resulted in a reduction of 17%.

However, uptake of screening in those trials was high compared with the UK and applying a trial-derived correction to UK population screening may overcorrect (Paap et al, 2011).

Application of a correction factor of 0.95, derived from a recent case–control evaluation of the NHSBSP (Massat et al, 2016) would increase estimated breast cancer mortality reduction amongst attenders for screening in our study to 50%.

Temporal differences between exposure groups in the intention to screen IBM analyses mean they are potentially confounded by changes in non-screening factors over time.

Falling UK breast cancer mortality rates since 1990 are likely to be due to a combination of factors, including improvements in treatment and the direct effect of screening through earlier detection and treatment.

In addition, there are likely to be indirect screening effects which include increased breast awareness associated with promotion of the NHSBSP (Stockton et al, 1997) and better access to multi-disciplinary breast care (Department of Health and Welsh Office, 1995; Kalager et al, 2010).

Not able to differentiate the contribution made by the direct and indirect effects of screening.

However, these temporal differences were relatively small, thus minimising the likelihood of confounding due to changes in non-screening factors. Furthermore, use of Tamoxifen and adjuvant therapy was widespread during the period covered by this evaluation (Alexander et al, 1994; Moritz et al, 1997; Swerdlow and Jones, 2005) so that changes in these factors are unlikely to have substantially affected the results.

CONCLUSIONS

Invitation to NHSBSP screening was associated with a reduction in breast cancer mortality in 1991–2005 of 21% after adjustment for age, socioeconomic status and lead-time

Breast cancer deaths among first invitation attenders were 46% lower than among non-attenders and 32% lower following adjustment for age, socioeconomic status and self-selection bias

There was little evidence of overdiagnosis associated with invitation to first screen

The wide variety of approaches that have been used to estimate the impact of population breast screening reflects the difficulty of evaluating programmes that were introduced without provision of a suitable comparison population.

Cohort studies using individual level data and observed mortality represent a robust approach to evaluation and this study is the first evaluation of the NHS breast screening programme to adopt such a strategy.

This cohort study adds considerably to the body of evidence indicating that population-based mammographic screening leads to a reduction in breast cancer mortality

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