Research Article

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Mammographic Screening and Breast Cancer Mortality: A Case–Control Study and Meta-analysis

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Abstract

Background: Observational studies are necessary to assess the impact of population screening on breast cancer mortality. While some ecological studies have notably found little or no association, case–control studies consistently show strong inverse associations, but they are sometimes ignored, perhaps due to theoretical biases arising from the study design. We conducted a case–control study of breast cancer deaths in Western Australia to evaluate the effect of participation in the BreastScreen Australia program, paying particular attention to potential sources of bias, and undertook an updated meta-analysis of case–control studies.

Methods: Our study included 427 cases (women who died from breast cancer), each matched to up to 10 controls. We estimated the association between screening participation and breast cancer mortality, quantifying the effect of potential sources of bias on our findings, including selection bias, information bias, and confounding. We also conducted a meta-analysis of published case–control studies.

Results: The OR for participation in the Western Australian BreastScreen program in relation to death from breast cancer was 0.48 [95% confidence interval (CI), 0.38–0.59; $P < 0.001$]. We were unable to identify biases that could negate this finding: sensitivity analyses generated ORs from 0.45 to 0.52. Our meta-analysis yielded an OR of 0.51 (95% CI, 0.46–0.55).

Conclusions: Our findings suggest an average 49% reduction in breast cancer mortality for women who are screened. In practice, theoretical biases have little effect on estimates from case–control studies.

Impact: Case–control studies, such as ours, provide robust and consistent evidence that screening benefits women who choose to be screened. *Cancer Epidemiol Biomarkers Prev; 21(9); 1479–88. ©2012 AACR.*

Introduction

Trials of mammographic screening for breast cancer show that screening reduces breast cancer mortality by 25% (1). With population screening programs now established in at least 27 countries (2), observational study designs can be used to estimate the impact of population screening programs. These designs include case–control studies comparing prior screening participation by individual women who have died from breast cancer and living women, cohort studies comparing breast cancer mortality between screened and unscreened women, and ecological studies relating population levels of breast cancer mortality and screening activity without information on which individuals were screened and which were not (3). Assuming a benefit of screening, case–control and cohort studies would be expected to give stronger associations than ecological studies, except if participation rates are close to 100%.

The Australian population-based screening program BreastScreen Australia has provided free biennial mammographic screening since the mid-1990s. Since 1996, biennial participation in the target age group of 50 to 69 years has ranged from 52% to 57% (4). Four observational studies in Australia have yielded highly varied estimates of the association between screening and breast cancer mortality. A case–control study from South Australia reported an OR of 0.53 [95% confidence interval (CI), 0.40–0.70; ref. 5]. Two ecological studies comparing screening participation rates and breast cancer mortality for small areas within New South Wales (6) and the whole of Australia (7) found that higher participation was associated with lower breast cancer mortality after adjustment for several potential confounding variables. Another more recent ecological study found that the screening program has had little effect on mortality (8) and although an expert committee rejected this design as too crude (7), the study received considerable attention in the media as evidence that mammographic screening programs are ineffective or less effective than previously described (9, 10).

A recently published European ecological study that found no mortality benefit from screening (11) also received considerable attention and reignited the debate

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about the efficacy of screening (12–15). The study and the subsequent media coverage paid little heed to numerous contrary results from randomised trials and previous observational studies (including studies in the countries evaluated; ref. 16, 17), and a subsequent study by the same authors finding screening participation was associated with a 16% reduction in mortality in Sweden (18) maintained a low profile. Meanwhile, case-control studies have consistently demonstrated that participation in screening is associated with lower breast cancer mortality (19, 20) with a previous meta-analysis yielding a pooled odds ratio (OR) of 0.44 (95% CI 0.38–0.50; ref. 20).

To evaluate the effect of participation in the BreastScreen Australia program, we conducted a case–control study of deaths from breast cancer in Western Australia. To evaluate the potential effect of biases discussed in the literature on case–control studies of screening, we conducted several sensitivity analyses. We also conducted a meta-analysis of case–control studies evaluating mammographic screening.

Materials and Methods

Primary analysis

Participants. In the BreastScreen Australia program, women aged 50 to 69 are directly invited to attend for screening from their registration on the Electoral Roll and then reinvited to their next screen [ref. 21; registration to vote is compulsory in Australia, and in 2005, an estimated 98.9% of the eligible population in Western Australia was registered (22)]. Women aged 40 to 49 years are also eligible to attend but are not directly invited.

For consistency with the program's target age range, the source population comprised all women on the Western Australia Electoral Roll between 1995 and 2006 who were 50 years of age or older at some time during that period.

To identify cases and potential controls, the Data Linkage Branch of the Department of Health Western Australia used standard protocols (23) to link data from the Electoral Roll to BreastScreen Western Australia screening records and the population-based Western Australia Cancer Registry (which routinely links cancer diagnoses to the national death registry). Cases were women in the source population who died from breast cancer between 1995 and 2006. For each case, incidence density sampling was used to randomly select 10 controls from women in the source population who were alive on the date the case died, resident in Western Australia at the time of the case's diagnosis, and born in the same month and year as the case (incidence density sampling involves matching each case to a sample of those who are at risk of becoming a case at the time of case occurrence; refs. 24, 25). Controls were not excluded if they had a breast cancer diagnosis. Women were assumed to be alive if the Western Australia Electoral Roll had no record of their death.

For each woman, we collected information on date of birth, screening history, date of any cancer diagnosis and, for cases, date of death. On the basis of place of residence, we assigned to each woman indicators of relative socioeconomic disadvantage (as a proxy for individual socioeconomic status) and remoteness from health services. Each case–control set was assigned a reference date that was the date of the earliest breast cancer diagnosis for that set.

Definition of exposure to screening with BreastScreen. Women were defined as exposed to screening if they received screening mammograms from BreastScreen at any time between their 50th birthday and their case–control set's reference date. Mammograms after the reference date were ignored to ensure equal opportunity for screening within the case–control set (26, 27). Because BreastScreen is intended for asymptomatic women and to avoid misclassifying diagnostic tests as screening (28), the small number of mammograms for which women presented with symptoms (specifically nipple discharge and/or breast lumps) were ignored.

Statistical analyses. Case–control sets were excluded if their reference date was before 1995 (thus excluding from the analysis women with a cancer diagnosis before potential screening exposure) or if the women were younger than 50 or older than 69 years at the reference date. Women were excluded from the primary analysis if they first attended BreastScreen for screening before 50 years of age. If a case was excluded, so were her matched controls.

All analyses were undertaken using Stata 11.0 (StataCorp). We used conditional logistic regression analysis to estimate the OR for participation in screening in relation to breast cancer mortality. Analyses were adjusted for confounding by socioeconomic status and remoteness from health services using proxy measures based on place of residence of each woman. The data linkage service determined each woman's place of residence at the small-area level of Census Collector District (CCD; ref. 29) and on the basis of this assigned women a score indicating relative socioeconomic disadvantage (based on the Socio-Economic Index For Areas (SEIFA); ref. 30) and remoteness (based on the Accessibility/Remoteness Index of Australia (ARIA); ref. 31). These scores were categorized into quintiles and used to infer individual socioeconomic status and geographical access to health services (recognizing that the use of proxy measures will result in some misclassification) in the closest Census year before the reference date. For the small number of women (18 cases and 195 controls) for whom data were unavailable at the CCD level, SEIFA and ARIA values were specified using larger spatial units (Statistical Local Areas (SLA) or, in the absence of SLA data, Local Government Areas).

Because we used incidence density sampling, the OR estimates the mortality rate ratio. Two-sided P values are reported.

To assess whether the ORs varied by time since the program was implemented, we tested for interaction between screening participation and the year of the case's death (1995–1997, 1998–2001, 2002–2006). In the early years of the program (1995–1997), many participants were attending BreastScreen for the first time (32). It is possible

that women who died soon after the introduction of screening had reduced opportunity for screening before their cancers became clinically detectable, and therefore, less opportunity to benefit from screening compared with women who died later, reducing the effect of screening on mortality during this period. By 2002, the program had been in existence for 7 years—the time period required before mortality benefits were observed in trials (32). We also tested for interaction between screening participation and 10-year age group to assess whether the ORs varied by age.

Sensitivity analyses

Our primary analysis was considered the approach least sensitive to theoretical biases, given the information available. To quantify the impact of potential sources of bias not addressed in our primary analysis or addressed differently by other authors, we executed a series of alternative analytic models in which we varied our treatment of sources of potential selection bias, information bias, and confounding.

Selection bias. For the primary analysis, we excluded women screened before the age of 50 years to limit the exposure of interest to screening provided within the BreastScreen target age range and to reduce confounding. Women in our sample who participated in screening before 50 years of age are more likely to be disease-free, because they had had a previous negative screen and, as prior screening behavior predicts future behavior, they are more likely to participate in screening. However, this approach may have introduced selection bias by excluding women at higher long-term risk of breast cancer (because women who chose to participate in the screening program before receiving a direct invitation may have had a higher underlying risk of disease) and excluding women at lower long-term risk of breast cancer (the "worried well"). To quantify this bias, in sensitivity analysis A, we allowed women to have been screened from the age of 40 years.

For our primary analysis, we excluded women diagnosed before the age of 50 years and this may have introduced another form of selection bias that can occur if the sample is restricted according to a minimum age at diagnosis (33) because screened cases are typically diagnosed at a younger age than unscreened cases and are therefore more likely to be excluded. In sensitivity analysis B, we allowed women to have been diagnosed from the age of 40 years (and therefore we allowed women to have been screened from age 40 so that they were eligible for exposure until the reference date).

Information bias. In our primary analysis, the reference date was set by the first diagnosis in the case–control set. Others have allowed only the case's diagnosis date to set the reference date (5, 34–36). This potentially introduces information bias because if a control has a breast cancer diagnosis before the date of their matched case, cases in the matched set can still accumulate screens while the control cannot, resulting in potential underestimation of screening benefit (26, 27). To quantify the impact of this potential bias, in sensitivity analysis C, we allowed only cases to set the reference dates.

Confounding. Our primary analysis might have been biased because it did not have information on potential confounders other than socioeconomic status and remoteness from health services. As a sensitivity analysis, we used the method of Greenland and Lash (37) to externally adjust for 2 potential sources of confounding: use of hormone replacement therapy and family history of breast cancer (sensitivity analysis D and E). For each confounder, this method requires the estimated prevalence for screened and unscreened women and the breast cancer mortality rate ratio. We used published population estimates of the prevalence of family history of breast cancer and hormone therapy use in the source population and in screened women and observed screening participation rates to derive estimates for prevalence in unscreened women. We estimated maximal plausible values for the mortality rate ratios from the literature. Specifically, for hormone therapy use, from observed data we assumed that 34.6% of BreastScreen participants aged 50 to 69 years used hormone therapy at the time of screening (38) and that 32.9% of all Australian women were current users of hormone therapy (39). We assumed screening participation in this age group was 53% (based on 2000–2001 data for Western Australia; ref. 38). We then inferred that hormone therapy use in unscreened women was 31.0%. The estimated breast cancer mortality rate ratio for hormone therapy users compared with nonusers was 1.48 (40). For family history of breast cancer, we assumed 16.1% of attendees aged 50–69 years had a strong family history of breast cancer (a first degree relative with breast cancer; ref. 38), and 12.0% of all women had a family history (41). Assuming screening participation of 53% as above, we then inferred that the prevalence of family history of breast cancer in unscreened women was 7.4%. The estimated breast cancer mortality rate ratio for women with a family history of breast cancer compared with other women was 2.32 (42).

Replication of a previous Australian case–control study. Finally, for comparison with the only other Australian case–control study, we replicated as closely as possible the primary analysis of Roder and colleagues (5) by defining the reference date to be the date of diagnosis of the case, including women screened before the age of 50 years, including women with symptoms at screening and excluding matched sets where cases died before 2002 (sensitivity analysis F).

Meta-analysis

We conducted a meta-analysis to test the hypothesis that participation in mammographic service screening programs is associated with a reduction in breast cancer mortality. We included studies that met these criteria: case–control study of mammographic screening with breast cancer death as outcome; evaluation of population mammographic screening programs (not trials); exposure defined as ever versus never screened; exposure

measured over at least 4 years up to the reference date (to allow reasonable opportunity for exposure to screening for cases and controls); controls matched to cases on age or analysis adjusted for age; and study population age range encompassing or overlapping substantially with our age group of interest (50 to 69 years).

Two investigators (C. Nickson and K. Mason) searched the MEDLINE database through the Thomson Reuters (ISI) Web of Knowledge portal on May 30, 2012, using the search term "breast cancer AND screening AND (mortality OR death) AND (case–control OR case-referent)," with no restrictions on the year published. Studies published in languages other than English were excluded. We searched reference lists of included studies and review articles identified during the search. Search strategies and interim findings are detailed the Supplementary Data.

Nine studies remained for inclusion in the meta-analysis (refs. 5, 34–36, 43–47; Table 1). Where studies reported multiple estimates derived from different approaches to minimizing bias, C. Nickson and K. Mason jointly identified the analysis most similar to the primary analysis in our own case–control study—an approach we considered least prone to bias. We used ORs not adjusted for "self-selection bias" (confounding due to higher participation by women at increased risk of breast cancer; refs. 34–36, 45), as the need for such adjustment is uncertain (5, 35) and adjustment methods varied. We pooled study ORs using a random effects meta-analysis in Stata ("metan"); heterogeneity was quantified using I^2 (48).

To assess whether country differences biased the pooled estimate, we conducted a meta-regression of ORs by country. We examined publication bias using Egger's regression asymmetry test for publication bias (49). As a sensitivity analysis, we determined the minimum OR required in an additional study to change the pooled OR CI to include the null effect; we assumed the SE for the additional study's OR was half that of the smallest SE in the 10 studies included in the meta-analysis.

Ethics. Ethical approval for this study was granted by the University of Melbourne Health Sciences Ethics Sub-Committee (#0830631) and the Department of Health Western Australia Human Research Ethics Committee (#2009/06).

Results

Primary analysis

We identified 501 breast cancer deaths (cases) from 1995 to 2006. We excluded 66 of these cases because they had participated in screening before the age of 50 years and a further 7 cases with no data to determine relative disadvantage or remoteness, leaving 428. Each of these had 10 controls, but we excluded an additional 958 controls because they met one or both of the above exclusion criteria or their matched case was excluded. After excluding the controls, one case had no remaining controls and was thus also excluded.

The remaining 427 case–control sets in the primary analysis included an average of 8.5 controls per case (range 2–10) and for 382 (89%) sets, the reference date was the case's date of diagnosis. Key study variables for cases and controls are summarized in Table 2.

Screening was more common for controls (2,051 of 3,650; 56%) than cases (167 of 427; 39%). The adjusted OR from the primary analysis was 0.48 (95% CI, 0.38–0.59; $P < 0.001$; Table 3). The ORs varied little by reference age group or year of death and neither interaction was significant (Table 3).

Sensitivity analyses

The sample size varied from 123 to 248 case–control sets between sensitivity analyses according to the various inclusion and exclusion criteria. No sensitivity analyses made any material difference to the ORs, which were all between 0.45 and 0.53 (Table 4).

Meta-analysis

The ORs from the 10 studies ranged from 0.35 to 0.65 (Fig. 1). The meta-analysis including our own study gave a pooled OR of 0.51 (95% CI, 0.46–0.55) with no significant heterogeneity between studies ($I^2 = 0.0\%$, $\chi^2 = 8.62$, $P = 0.473$).

Excluding our study from the meta-analysis yielded an OR of 0.51 (95% CI, 0.46–0.56).

Meta-regression showed that the pooled OR did not vary significantly by country. There was no evidence of publication bias due to study size (Egger test $P = 0.970$). The minimum OR required in an additional study to produce a pooled estimate with a CI including the null would be 2.4 (95% CI, 2.2–2.6), which would result in a pooled OR = 0.59 (95% CI, 0.34–1.01).

Discussion

Participation in the Western Australia BreastScreen program in the target age range of 50 to 69 years was associated with an estimated 52% lower breast cancer mortality. The meta-analysis of results from this and 9 other studies in various settings indicates that, on average, screening participation was associated with a 49% lower mortality from breast cancer.

In practice, potential sources of bias appeared to have had little influence on the results as the ORs were similar in all the sensitivity analyses. Our results were strikingly similar to those of the previous case–control evaluation of the BreastScreen Australia program (OR, 0.52; 95% CI, 0.39–0.69). We found no evidence that the OR varied by year of death, despite recommendations that case–control studies should exclude early years of screening and/or be confined to long-term outcomes since the introduction of screening (32, 35).

The strengths of our study include rigorous linkage of good quality population data from a well-organized population screening program and cancer registry, careful minimization of bias in our primary analysis, and a range

Table 1. Overview of studies included in the meta-analysis

Study	Screening program location	Screening program details	Case selection	Controls	Exposure period in each case–control set	Period for diagnoses
Allgood 2008 (56)	United Kingdom (East Anglia)	3-yearly invitations to screening for women aged 50–70; est. 1989	Aged 50–70 years at diagnosis; died 1995–2004	Age-matched and alive when case died	Screened before case diagnosis	1995–2004
Fielder 2004 (57)	United Kingdom (Wales)	3-yearly invitations to screening for women aged 50–64; est. 1989 (fully underway 1991)	Aged 50–75 years at diagnosis; died 1998–2001	Age- and area-matched and alive when case died	Screened before case diagnosis	1995–2001
Gabe 2007 (58)	Iceland	2-yearly invitations to screening for women aged 40–69; initiated 1987, fully underway Dec 1989	Aged $\geq$ 40 years at diagnosis; died 1990–2002.	Age-matched and alive when case died	Screened between age 40 and the date of the first diagnosis in the case-control set	1987–2002
Miltenburg 1998 (59)	Netherlands (Utrecht)	Screening intervals varied in early years, originally annual then 2-yearly from 1985; screening invitations to women aged 50–69 (50–64 before 1985); est. 1974	Born 1911–1925; died 1975–1992	Age- and area-matched and alive when case died	Screened before case diagnosis	1975–1992
Palli 1989 (60)	Italy (Florence district)	Approx. 30-month intervals, screening invitations to women aged 40–70; est. 1970	Aged $\geq$ 40 at diagnosis; died 1977–1987.	Age- and area-matched and alive when case died	Screened before case diagnosis	1977–1987
Puliti 2008 (61)	Italy (various regions)	2-yearly invitations to screening for women aged 50–69; est. 1990–1999 (multiple regions; most by 1995)	Aged 50–74 years between program commencement and 2001; died 1990–2002	Age-matched and alive when case died; cancer-free when case diagnosed	Case screened before diagnosis; controls screened up to one year after case diagnosis	1990–2001
Roder 2008 (62)	Australia (South Australia)	2-yearly invitations to screening for women aged 50–69 (but available for women 40–49 and 70+); est. 1994	Aged 45–80 years at death; diagnosed from 1994; died 2002–2005	Age- and area-matched and alive when case died	Screened before case diagnosis	1994–2005
van Schoor 2011 (63)	Netherlands (Nijmegen)	2-yearly invitations to screening, initially for women aged 35+, then later 50–69 then 50–74; est. 1975	Aged 50–69 years at screening invitation; died 1975–2008	Age- and area-matched and alive when case died; aged 50–69 years at screening invitation	Screened in the 4-year period before the invitation that preceded case diagnosis	1975–2008
Otto 2012 (64)	Netherlands (Southwest region)	2-yearly invitations to screening for women aged 50–75 (50–69 only in early years); initiated 1990, fully underway 1998	Aged 50–77 at diagnosis; died 1995–2003	Age-matched and alive when case died; cancer free when case diagnosed	Screened up to a maximum of two invitations prior to the screen preceding case diagnosis	1990–2003

Table 2. Summary figures for cases and controls included in the analysis

	Cases	Controls
N in sample for analysis	427	3,650
Age information (y): mean (SD); range		
At first screen (if ever screened)	56.5 (4.7); 50–70	57.7 (5.2); 50–79
Age at reference date (first diagnosis in set)	59.6 (5.6); 50–69	60.4 (5.4); 50–69
Age at death	63.5 (6.0); 50–77	—
Calendar year information: mean (range)		
Year of first screen	1994 (1989–2004)	1996 (1989–2009)
Year of death	2002 (1995–2006)	
Relative socioeconomic disadvantage (SEIFA score): mean (SD)	1,004.5 (89.9)	1,009.1 (90.0)
Remoteness from services (ARIA): distribution		
Major city	73.3%	74.1%
Inner regional	11.2%	13.0%
Outer regional	10.1%	8.2%
Remote	3.0%	3.3%
Very remote	2.3%	1.4%

of sensitivity analyses which identified that, in practice, previously described potential biases in the case–control design might have negligible influence on results.

It was not possible for us to address all potential biases. We had limited information on confounders, although external adjustment for 2 possible confounding variables (family history and hormone therapy use) did not change the OR, as found by others (5, 50). This suggests that residual confounding is unlikely to arise from other, unmeasured determinants of screening and mortality (including "self-selection bias"; ref. 1), in keeping with evidence that the baseline risk of death does not differ according to participation (5, 50, 51).

Although we had no information on screening outside the BreastScreen program, rates are estimated to be low (1%–4%; ref. 21).

For the meta-analysis, our selection criteria ensured that each included study had comparable opportunity for exposure between cases and controls, and suitable matching for, or adjustment by, age. The pooled estimate is made more convincing by the lack of heterogeneity and confirmation that study size was not associated with the OR.

The meta-analysis may be subject to publication bias. Only 5 countries are represented, although at least 19 countries have population mammographic screening programs (52). Our shortlist included studies from the United States, but these were excluded because they did not evaluate whole population programs. Our restriction to papers published in English led to the exclusion of only 2 papers, (53, 54) both from the Netherlands, which is already well represented in the meta-analysis. While studies may have been conducted but not published due to a null finding, this is unlikely as this is a contested field and ecological studies that found no association have been published and received considerable attention (8, 11). Finally, it is possible that some studies were missed due to the search terms used. However, our assessment of 3 previous review papers revealed no additional studies for inclusion, and our sensitivity analysis showed only a study with an

Table 3. ORs for death from breast cancer according to history of participation in the BreastScreen Western Australia program, overall and according to year of death and age at reference date

Analysis	OR (95%CI)[a]	*P*	*P* for interaction term
Aged 50–69, cases died 1995–2006	0.48 (0.38–0.59)	<0.001	
Year of death			
Cases died 2002–2006	0.49 (0.37–0.66)	<0.001	0.841
Cased died 1998–2001	0.43 (0.29–0.64)	<0.001	
Cases died 1995–1997	0.51 (0.25–1.07)	0.077	
Age at reference date			
Age 50–59 at reference date	0.52 (0.37–0.72)	<0.001	0.507
Age 60–69 at reference date	0.44 (0.33–0.59)	<0.001	

[a]Adjusted for remoteness and relative socioeconomic disadvantage

Table 4. ORs for death from breast cancer according to history of participation in the BreastScreen Western Australia program, for primary analysis and a range of sensitivity analyses

Analysis	*n*	BreastScreen participation *n* screened/*n* total (%)		Mean (SD) age at reference date	OR (95%CI)[a]	*P*
		Cases (deaths)	Controls			
Primary analysis	4,077	167/427 (39.1)	2,051/3,650 (56.2)	60.3 (5.5)	0.48 (0.38–0.59)	<0.001
Sensitivity analysis A	5,273	230/490 (46.9)	2,957/4,783 (61.8)	58.8 (5.8)	0.51 (0.42–0.62)	<0.001
Sensitivity analysis B	6,271	248/582 (42.6)	3,176/5,689 (55.8)	56.9 (6.8)	0.53 (0.44–0.63)	<0.001
Sensitivity analysis C	4,024	165/424 (38.9)	2,064/3,600 (57.3)	60.4 (5.5)	0.45 (0.36–0.56)	<0.001
Sensitivity analysis D[b]	4,077				0.49	
Sensitivity analysis E[b]	4,077				0.45	
Sensitivity analysis F	2,499	123/232 (53.0)	1,532/2,267 (67.6)	58.9 (5.5)	0.52 (0.39–0.69)	<0.001

NOTE: The primary analysis includes case–control sets where the case died between 1995 and 2006 and the reference date (first breast cancer diagnosis in the case–control set) occurred at age 50–69 years and between 1995 and 2006. Women were defined as exposed to screening participation if they participated at least once between the age of 50 years and the reference date. Sensitivity analyses vary in sample size according to inclusions or exclusions for each analysis (see Methods).

[a]Adjusted for remoteness and relative socioeconomic disadvantage

[b]Method does not allow for meaningful values in other columns, or CIs for ORs.

extreme finding (OR = 2.4) could influence the pooled estimate CI to include the null effect.

Meta-regression according to country showed no evidence of any association between country and estimated mortality reductions associated with screening, although this result should be interpreted with caution due to low statistical power. If the finding does hold, it would be reasonable to generalize to other countries with screening programs similar to those in our evaluation (Table 1), with consideration of underlying population health profiles and the availability of treatment following diagnosis.

Unlike case–control studies of screening, inconsistent results have been reported from ecological studies. The inconsistency in results of ecological studies is partly due to differences in measuring screening activity (17). Ecological studies assess whether the level of screening activity in different populations or subgroups (either geographically or over time) is associated with breast cancer mortality in those populations or subgroups.

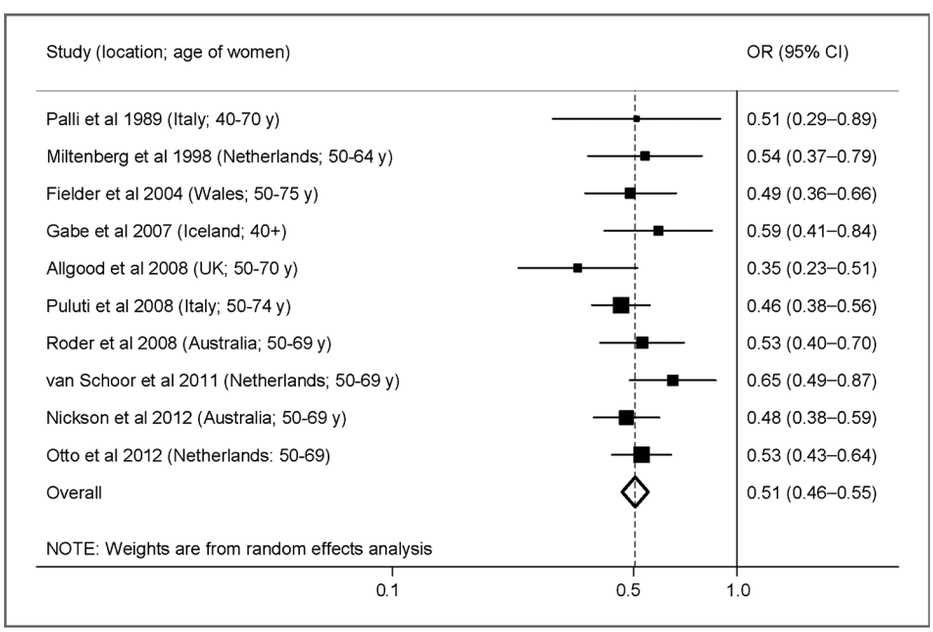

Figure 1. Meta-analysis of 10 case–control studies that have estimated the mortality benefit of screening for breast cancer, including the primary results from this study (5, 34–36, 43–47). Boxes show the estimate for each study, and horizontal lines show the confidence interval for each study estimate.

Geographic approaches include comparing rates of participation and mortality within and between municipalities (6), counties (16), or countries (8). The smaller and more homogenous the geographic area, the more likely it is that the participation rate is applicable to all women in the area and the less likely there is to be confounding due to regional differences in factors such as breast cancer treatment (e.g., adjuvant therapy).

For the two small-area Australian ecolgoical studies (6, 7), the first (restricted to New South Wales) estimated that a 60% participation rate in BreastScreen was associated with a 29% lower breast cancer mortality (relative risk 0.71; 95% CI, 0.60–0.85; ref. 6), while in the second, national, study, a 60% participation rate was associated with a 22% lower mortality (relative risk, 0.78; 95% CI, 0.69–0.88; ref. 7). In the second study in particular, several potential sources of confounding within small geographic areas were included in the analysis. In contrast, the European ecological study that drew substantial media attention compared mortality trends for 3 countries (11) and while the authors claimed the countries were similar with respect to health care and other determinants of breast cancer mortality, the analysis has been criticized by screening experts (55); indeed, interpretation of country-level time trends is prone to confounding by changes in treatment and other secular changes that are likely to vary by country.

Examining time trends by age within populations is another common but weak ecological design that is subject to confounding. For example, in the aforementioned Australian study the authors concluded that BreastScreen was ineffective because the decline in breast cancer mortality from 1991 to 2007 was greatest for women aged 40 to 49 at death rather than the target age groups for screening (8). The observed decline could be explained by other factors such as age differences in treatment access and efficacy, so it is inappropriate to infer that screening is ineffective for other age groups.

Our findings suggest that screening is of benefit to women who choose to be screened. We estimate a 52% reduction in breast cancer mortality for women who participate in screening in Australia, and an average 49% reduction from the studies included in our meta-analysis. Sensitivity analyses to address potential biases of case–control studies showed that none of the assumptions had any material effect, thus showing that these potential biases might be overstated. Our results were consistent with those of other case–control studies that have taken a range of approaches to minimizing bias. While ecological studies of large geographical areas may be sensational—particularly when they find no effect—interpreting trends in mortality is complex. Meanwhile, case–control studies offer a robust and consistent contribution to growing evidence that screening is of benefit to women who choose to be screened.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Nickson, D.R. English, A.M. Kavanagh
Development of methodology: C. Nickson, K.E. Mason, D.R. English, A.M. Kavanagh
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Nickson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Nickson, K.E. Mason, D.R. English
Writing, review, and/or revision of the manuscript: C. Nickson, K.E. Mason, D.R. English, A.M. Kavanagh
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Nickson, K.E. Mason
Study supervision: A.M. Kavanagh

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