Clinical Epidemiology

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ORIGINAL RESEARCH

Self-Selection Bias in Randomized and Observational Studies on Screening Mammography: A Quantitative Assessment

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Background: Observational studies aimed at evaluating the effectiveness of screening mammography are prone to self-selection due to differences in personal characteristics between women attending and those not attending screening. A method based on a quantity *Dr* has been promoted to correct for this bias, *Dr* being the risk of breast cancer death in a group of women not attending screening compared to the risk of breast cancer death in a population without screening.

Objective: To estimate the amount of self-selection in observational studies aimed at evaluating screening mammography effectiveness and to estimate *Dr* quantities needed to correct for this bias.

Methods: A first step quantified self-selection and *Dr* quantities specific to Swedish randomized trials using the most recent publications. A second step estimated self-selection specific to cohort studies on screening mammography effectiveness using the relative risk of 0.54 for all-cause death from these studies and the relative risk of all-cause death of 0.98 reported in Swedish trials. Using self-selection estimated from cohort studies, the *Dr* quantity needed to correct observational studies on screening mammography effectiveness was estimated. In a last step, corrections for self-selection in observational studies on screening mammography were retrieved.

Results: The self-selection bias was 2.10 in Swedish trials. Self-selection in cohort studies was computed as (0.98/0.54) = 1.78. The *Dr* quantity required to correct results of observational studies was 1.53. In 19 case-control and cohort studies on screening mammography effectiveness, the median *Dr* quantity used for correction purposes was 1.16 (IQR: 1.11–1.28).

Conclusion: Compared to women attending screening, the risk of breast cancer death was approximately two times greater in women not attending screening. This increased risk was independent of screening effects. Most observational studies have overestimated the effectiveness of screening mammography because they used *Dr* quantities that were too small to correct for self-selection.

Plain Language Summary: Women attending and not attending mammography screening differ in several ways. Non-attending women have a higher risk of dying from breast cancer because they tend to be less health aware, more deprived, have more comorbidities, develop more aggressive breast cancer, and to be less compliant with therapies. This phenomenon is called self-selection. Consequently, observational studies (ie case-control and cohort studies) have nearly always found that women attending screening are at a lower risk of breast cancer death than women not attending screening. In a previous publication, we showed that methods used to date to control self-selection removed only a fraction of this bias. The objective of this study was to quantify how much of the changes in the risk of breast cancer death reported by observational studies on mammography screening was due to self-selection bias. To this end, we used a method allowing us to estimate the amount of self-selection in populations where women are invited to screening. The method was based on the fact that screening mammography cannot influence causes of death other than breast cancer. Self-selection was first quantified using most recent results of Swedish randomized trials on screening mammography, and then in cohort studies that estimated the reduction in the risk of breast cancer death associated with attendance to screening mammography. Our study found that compared to women who attended screening, women who did not attend screening had an approximately 2-fold increased risk of breast cancer death. This increased risk was independent of screening effects on the risk of breast cancer death. Hence, observational studies conducted to date have overestimated the health benefits of mammography screening.

Keywords: breast, cancer, screening, selection, bias

Received: 3 January 2025
Accepted: 24 April 2025
Published: 1 May 2025

Introduction

Observational studies have been conducted since the 1980s to evaluate the effectiveness of breast cancer screening programs. These studies compare the risk of breast cancer death between women attending and not attending screening mammography. Case-control studies retrospectively assess the attendance at screening mammography of case women who died from breast cancer and of control women who were still alive when case women died from breast cancer. Cohort studies prospectively compare the risk of breast cancer deaths of women attending screening to the risk of women who do not attend screening. However, these studies are prone to self-selection bias (or "healthy user bias"). Women not attending screening are generally less educated and less health-aware, are more deprived, and have more comorbidities or disabilities, all of which are associated with increased risks of developing more aggressive cancers, as well as increased risk of breast cancer mortality and all-cause mortality. These increased risks are independent of the effect of screening.[1–3] Because of this bias, observational studies tend to overestimate the benefits of screening.[4]

To address the issue of self-selection, a correction of relative risk estimates was proposed in 2002.[5] The correction is based on the quantity *Dr* which is the ratio of breast cancer mortality rates in women invited but not attending screening to rates in a similar population of women not (yet) invited to screening. Authors willing to correct their relative risk estimates have to select a *Dr* quantity from another study, which included a group of women invited to screening but who did not participate and a group a women not (yet) invited to screening. Correction for self-selection has most often led to corrected relative risk estimates closer to the 25% reduction of breast cancer death associated with invitation to screening reported by Swedish randomized trials.[6,7]

The first *Dr* quantity estimate of 1.36 was derived from Swedish randomized trials.[5] However, the estimate could not take heed of most recent results of the Swedish Malmo and Goteborg trials. In addition, the *Dr* correction method has never been tested against robust methods like the use of an instrumental variable associated with screening mammography but not causally associated with breast cancer death,[8] or the use of an off-target outcome, ie, an outcome on which screening mammography has no influence.[9] Screening mammography does not affect the causes of death other than breast cancer, and deaths from causes other than breast cancer are 20–50 times more common than deaths from breast cancer. A systematic review of 18 cohort studies on screening mammography attendance and the risk of breast cancer used non-breast cancer death has an off-target outcome. The review found that women attending screening mammography had a 45% reduction in the risk of breast cancer death as well as in their risk of death from any cause.[10] Hence, the reduced risk of breast cancer death associated with screening attendance found in cohort studies could be due to self-selection. It also prompted the hypothesis that *Dr* quantities used to date, including *Dr* quantities derived from Swedish trials, cannot fully correct for the effect of self-selection on reductions in the risk of breast cancer reported by observational studies.

Although they have been conducted some twenty to forty years ago, the Swedish randomized trials remain the principal justification for breast screening activities. The objective of this study was to estimate the amount of self-selection present in Swedish randomized trials and in observational studies aimed to evaluate screening mammography effectiveness and to estimate *Dr* quantities that may correct for this bias.

Methods

The parameters, including self-selection and *Dr* quantities, derived from randomized trials and cohort studies were first described, after which the study unfolded in four successive steps: (1) the computation of a *Dr* quantity based on most recent results of Swedish trials, (2) the quantification of self-selection in cohort studies on screening mammography effectiveness, (3) the determination of a *Dr* quantity able to remove self-selection in these cohort studies, and (4) a systematic review of *Dr* quantities used in observational studies.

Self-Selection and *Dr* Quantities

A typical randomized trial for the evaluation of the reduction in the risk of cancer-related death associated with invitation to screening is displayed in Figure 1.

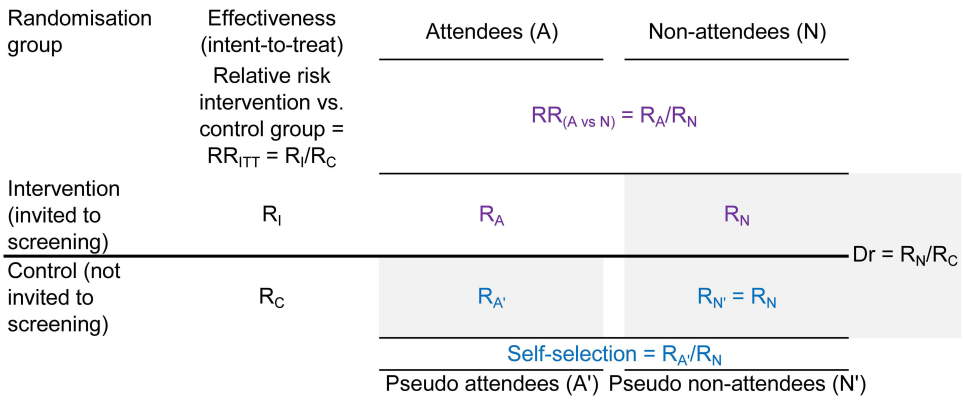

Figure 1 Randomised trials on screening mammography considered as two prospective cohorts with same follow-up (Keys: R stands for rates of No. of breast cancer deaths/ No. women in a group or subgroup; RR stands for relative risk).

The effectiveness of screening mammography is the relative risk RR_{ITT} equal to R_I/R_C, where ITT stands for intent-to -treat, R_I is the breast cancer death rate in the intervention group, and R_C is the breast cancer death rate in the control group.

The intervention group can be considered a cohort study of women invited to screening, with a subgroup A electing to attend screening and a subgroup N electing to not attend screening. The relative risk $RR_{(A\ vs\ N)} = R_A/R_N$ is the risk of breast cancer death in women attending screening compared with women not attending screening. $RR_{(A\ vs\ N)}$ could be the main outcome if the study was a cohort study that included only the intervention group.

By virtue of randomization, the control group includes a subgroup of pseudo attenders (A') who would attend screening if they were invited to do so as well as a subgroup of pseudo non-attenders N' who would not attend screening if they were invited to do so. Because of randomization, the rate of breast cancer death $R_{N'}$ in the subgroup of pseudo non-attendees is the same as that in the subgroup of non-attendees, ie, $R_{N'} = R_N$. In contrast, the rate of breast cancer in the subgroup of pseudo-attendees $R_{A'}$ should be equal to or lower than the rate of breast cancer death in subgroup of attendees R_A.

From Figure 1, one can compute an estimate of self-selection bias, which is the relative risk $R_{A'}/R_N$. This relative risk is an unbiased estimate of the risk of breast cancer death of women who would attend screening if invited to do so, to the risk of breast cancer death of women who would not attend screening if invited to do so. One can also compute the *Dr* quantity, which is the relative risk R_N/R_C.

RR_{ITT} is not biased by self-selection, whereas $RR_{(A\ vs\ N)}$ is biased. Using data from the intervention group only, RR_{ITT} can be estimated from $RR_{(A\ vs\ N)}$ after correction for self-selection using the *Dr* quantity and formulas of Duffy et al (2002). The *Dr* quantity and self-selection bias are algebraically related, and the estimated RR_{ITT} can be computed using the self-selection quantity, participation rate, and crude risk estimate but with equations somewhat different from those published by Duffy et al (2002)[5] (not shown).

Step 1

The first step consisted of computing self-selection and *Dr* quantities using the most recent data from four Swedish randomized trials.[11–14] After data extraction and adjustment for unequal sizes in the intervention and control groups, the rates of breast cancer death were calculated for each group and subgroup. In the publication of 1995, the Malmö trial did not report women attending or not attending screening.[12] We assumed that the proportion of breast cancer deaths in attendees and non-attendees was the same as in Andersson et al 1988.[15] The weighted average attendance rate for the four Swedish trials was 85%.

We corrected the number of breast cancer deaths in the control groups by multiplying the reported number of breast cancer deaths by 0.90, because 10% of breast cancer deaths in the two-county trial were due to cancers found during the first screening of control women.[6] The Stockholm and Goteborg trials did not report the percentage of breast cancer

https://doi.org/10.2147/CLEP.S515464

deaths linked to breast cancer diagnosis during the first screening round in the control group. For the Malmö trial, the correction was 0.955 because the first screening of the control group was approximately 45% of the total number of control women included in the trial.[16]

Step 2

The second step involved quantifying self-selection in the cohort studies that evaluated screening effectiveness. In the aforementioned review, the random-effect summary relative risks $RR_{(A\ vs\ N)}$ attenders vs nonattenders were 0.55 (95% CI: 0.50–0.60) for breast cancer mortality in 13 cohort studies, and 0.54 (0.50–0.58) for all-cause mortality in 10 cohort studies.[10] The summary relative risk of RR_{ITT} for all-cause deaths reported by Swedish trials was 0.98 (0.96–1.00).[7] Because screening mammography has no effect on all-cause death, the RR_{ITT} of all-cause death is the benchmark of $RR_{(A\ vs\ N)}$ in the absence of self-selection. The formulae proposed in Refs.[9,17] provided an estimate of the amount of self-selection, ie,

RR_{ITT}/ $RR_{(A\ vs\ N)}$, Where

RR_{ITT} is the relative risk of all-cause death of 0.98 associated with invitation to screening reported by Swedish randomized trials,[7] and $RR_{(A\ vs\ N)}$ is the relative risk of all-cause death of 0.54 associated with screening attendance reported by cohort studies.[10]

Step 3

The third step was to determine which *Dr* quantity would be adequate for observational studies that evaluated the effectiveness of screening mammography. Using the linear relationship between self-selection and *Dr* quantities found in Swedish trials (step 1), and the self-selection from cohort studies (step 2), we computed the *Dr* quantity specific to observational studies.

Step 4

The fourth step was a systematic search of observational studies recorded in PubMed that were corrected for self-selection, following the method of Duffy et al.[5] The literature search has been described elsewhere.[10] In brief, case-control and cohort studies had to be published after 2001 and conducted in women invited to screening or where screening was widely available and recommended. Studies with cross-sectional or unclear designs were excluded.

Corrections for self-selection could follow the potential attendance approach (RR2 of Duffy et al, 2002), that is, the relative risk estimate for women willing to attend screening if invited. It could also follow the intent-to-treat approach (RR1 of Duffy et al, 2002), which is the relative risk estimate for all women invited to screening. Roder et al (2008)[18] and Dunn et al (2021)[19] reported a corrected odds ratio of 0.71 but not *Dr* quantities or attendance rates. We worked out the correction assuming that the potential participants method had been used, using attendance rates in the control groups and a *Dr* quantity of 1.11. Algood et al (2008) reported a corrected odds ratio of 0.65 but did not report the *Dr* quantity used or the attendance rate.[20] We used an attendance rate of 75% as reported by Otten et al, 2008.[21] Working out the correction, we estimated that Algood et al (2008) most likely used a *Dr* quantity of 1.36, as suggested by Duffy et al (2002).[5]

Statistical Analysis

Data handling was mentioned in step 4, and meta-analysis computations followed the methods described in ref.[10]

Results

Step 1

Table 1 shows the numbers of randomized women and breast cancer deaths in Swedish randomized trials after subtraction of cancer deaths due to cancers diagnosed at the first invitation to screen for control women. The distributions of women and breast cancer deaths in the subgroups of attendees/non-attendees and pseudo-attendees/pseudo-non-attendees are detailed in Tables 2 and 3. The key parameters in Table 4 were derived from Tables 2 and 3. The summary effectiveness RR_{ITT} of 0.82 (0.72–0.93) was computed from the rates of breast cancer deaths in the intervention and

Table 1 Swedish Randomized Trials on Screening Mammography: Results Corrected for Differences in Group Sizes and for Extra Breast Cancer Deaths in Control Groups

Trial	Intervention Group (Women Invited to Screening)			Control Group (Women Not Invited to Screening), Adjusted for Differences in Group Size			Control Group, Corrected No. Breast Cancer Deaths*	
	No. Women	No. Breast Cancer Deaths	Rate (R_I)	No. Women	No. Breast Cancer Deaths	Rate	Corrected No. Breast Cancer Deaths	Corrected Rate (R_C)
Two-County[11]	77,080	232	3.01	77,080	322	4.18	290	3.76
Malmö[12]	21,088	87	4.13	21,088	108	5.12	103	4.89
Göteborg[13]	21,650	63	2.91	21,650	81	3.74	73	3.36
Stockholm[14]	40,846	67	1.64	40,846	92	2.26	83	2.03

Notes: Rates are per 1,000 women. *Correction is (1–0.045) for Malmö and (1–0.1) for other trials.

Table 2 Subgroups of Intervention Groups

Trial	Attendance to Screening (%)*	Invited Women Who Attended Screening			Invited Women Who Did Not Attend Screening		
		No. Women	No. Breast Cancer Deaths	Rate (R_A)	No. Women	No. Breast Cancer Deaths	Rate (R_N)
Two-County[11]	89	68,601	170	2.48	8479	62	7.31
Malmö[12§]	74	15,605	44	2.82	5483	43	7.84
Göteborg[13]	84	18,210	41	2.25	3440	22	6.39
Stockholm[14]	82	33,494	44	1.31	7352	23	3.13

Notes: Rates are per 1,000 women. §Assuming that proportions of breast cancer deaths in participants and non-participants were the same than in Andersson et al, 1989. *From Nyström et al, 2002; weighted average attendance of 85% for the 4 trials.

Table 3 Subgroups of Control Groups

Trial	Pseudo Attendees			Pseudo Non-Attendees		
	No. Women	No. Breast Cancer Deaths*	Rate ($R_{A'}$)	No. Women	No. Breast Cancer Deaths	Rate ($R_N = R_{N'}$)
Two-County[11]	68,601	228	3.32	8479	62	7.31
Malmö[12]	15,605	60	3.85	5483	43	7.84
Göteborg[13]	18,210	51	2.79	3440	22	6.39
Stockholm[14]	33,494	60	1.79	7352	23	3.13

Notes: Rates are per 1,000 women. *Equal corrected No. breast cancer deaths minus No. breast cancer deaths in pseudo non-attendees.

control groups. The estimated summary relative risk $RR_{(A\ vs\ N)}$ of 0.36 (0.29–0.44) was computed using intervention groups as cohort studies. Hence, in the absence of control groups, intervention groups of Swedish trials taken as cohort studies would obtain results suggesting breast cancer mortality reductions of the order of 64% among women attending screening. The summary self-selection quantity of 2.10 indicates that in these four randomized trials, the risk of breast cancer death in the intervention groups was approximately two times higher in non-attendees than in attendees, and this increased risk was independent of the effects of screening.

A *Dr* quantity of 1.78 denotes the risk of breast cancer death among invited women not attending screening compared to women in the control group. The linear correlation between self-selection (SS) and *Dr* quantities is

$$Dr = (0.77^{*}\mathrm{SS}) + 0.16$$

https://doi.org/10.2147/CLEP.S515464

Table 4 Quantities Derived from the Four Swedish Randomized Trials On Screening Mammography

Trial	Effectiveness (ITT)	Effectiveness, Observational*	Self-Selection	Dr
	$RR_{ITT} = R_I/R_C$	$(RR_{(A\ vs\ N)}) = R_A/R_N$	$=R_{A'}/R_N$	$=R_N/R_C$
Two-County[11]	0.80	0.34	2.20	1.94
Malmö[12]	0.84	0.36	2.03	1.60
Göteborg[13]	0.86	0.35	2.29	1.90
Stockholm[14]	0.81	0.42	1.75	1.54
Summary relative risks §	0.82	0.36	2.10	1.78
95% confidence interval	0.72–0.93	0.29–0.44	1.73–2.53	1.48–2.13

Notes: ITT: intent-to-treat analysis of randomized trials. * Intervention groups of trials taken as cohort studies. §Random-effect meta-analysis.

Cohort studies evaluating screening effectiveness typically assess the relative risk of cancer death among women attending screening compared to women not attending screening ($RR_{(A\ vs\ N)}$). Using *Dr* quantities in Table 4, attendance rates specific to each trial or for all trials (Table 2), and Duffy et al (2002) equations, one can find back the screening mammography effectiveness. For instance, for all four trials,

$$\text{corrected summary } RR_{(A\ vs\ N)} = 1.78 * ((0.36 * 0.85) - 0.85 + 1) = 0.82$$

a result identical to the summary relative risk RR_{ITT} of 0.82 reported in Nyström et al.[7]

Step 2

This step used summary relative risks from cohort studies on screening mammography effectiveness,[10] which were 0.55 (0.50–0.60) for breast cancer death and 0.54 (0.50–0.58) for all-cause death.

Considering all-cause mortality as an off-target outcome for screening mammography, the self-selection bias was (0.98/0.54) = 1.78, which means that in cohort studies, the risk of breast cancer death was 1.78 higher in non-attendees than in attendees, and this increased risk was independent of the effects of screening.

Step 3

Using the linear relationship found in step 1 and the self-selection quantity from step 2, the average *Dr* quantity for cohort studies can be estimated as:

$$Dr = (0.77 * 1.78) + 0.16 = 1.53.$$

Step 4

Fourteen case-control and five cohort studies reported corrected relative risk estimates using the Duffy et al method (Table 5).[18,19,22–38] The median attendance rate to screening mammography was 74% and the relative risk estimates of the 19 studies ranged from 0.35 to 0.65, with a summary risk estimate of 0.51 (95% CI: 0.47–0.55).

The corrected relative risk estimates ranged from 0.50 to 0.96, but approaches (intent-to-treat vs potential participation approach[5]) for correction varied across studies. Occasionally, the approach or *Dr* quantities used have not been reported. When known, *Dr* quantities ranged from 0.87 to 1.56, with a median of 1.16 (IQR: 1.11–1.28). In three instances, *Dr* quantities were less than 1.0, suggesting that women attending screening would have a greater risk of cancer death than those who do not attend screening. An inverse correlation was found between *Dr* quantities selected by the authors and relative risk estimates (correlation coefficient r = 0.52, slope of the linear trend: −0.82; 95% CI: −1.58 to −0.06; p = 0.035), indicating that there was an inclination to select D_r quantities closer to 1.0, if the relative risk estimates for breast cancer mortality tended to be closer to 1.0.

Table 5 Observational Studies on Attendance to Screening Mammography and the Risk of Breast Cancer Death

First Author (Year Publication)	Setting, Country	Participation (%)	Risk Estimate of Breast Cancer Death Ever vs Never Attending Breast Screening	95% CI		Dr Selected by Studies	Author's Correction for Self-Selection*	95% CI
Case-control studies			Odds ratios	Lower bound	Upper bound		Corrected odds ratios	
Fielder (2004)[22]	Wales, United Kingdom	77%	0.62	0.47	0.82	1.36	0.75*	0.49–1.14
Gabe (2007)[23]	Iceland	68%	0.59	0.41	0.84	1.17	0.75*	0.52–1.09
Allgood (2008)[24]	East Anglia, England	75%	0.35	0.24	0.50	1.32	0.65 †	0.48–0.88
Roder (2008)[18]	South Australia	68%	0.59	0.47	0.74	1.11	0.70 †	NR
Puliti (2008)[25]	City of Florence, Italy	65%	0.46	0.38	0.56	1.11	0.55*	0.36–0.85
Van Schoor (2011)[26]	Nijmegen, The Netherlands	77%	0.65	0.49	0.87	0.87	NR	NR
Otto (2012)[27]	The Netherlands	75%	0.45	0.37	0.54	1.11	0.51*	0.40–0.66
Paap (2014)[28]	The Netherlands	81%	0.48	0.40	0.58	0.87	0.42*	0.33–0.53
VanderWaal (2015)[29]	UK Age trial	70%	1.05	0.63	1.75	NR	0.86*	0.40–1.89
Massat (2016)[30]	London, England	73%	0.65	0.53	0.80	0.95	0.61*	0.44–0.85
Heinävaara (2016)[31]	Finland	86%	0.39	0.34	0.44	1.56	0.67*	0.49–0.90
Johns (2018)[32]	England	75%	0.42	0.37	0.47	1.19	0.53*	0.46–0.62
Maroni (2020)[33]	England	73%	0.49	0.45	0.53	1.19	0.74§	0.68–0.81
De Troeyer (2023)[34]	Flanders, Belgium	54%	0.49	0.44	0.55	1.15	0.83§	0.76–0.91
Cohort studies			Relative risks				Corrected relative risk	
Hofvind (2013)[35]	Norway	84%	0.39	0.35	0.44	1.36	0.57*	0.51–0.64
Morrell (2017)[36]	New Zealand	71%	0.33	0.19	0.54	1.17	0.67*	0.55–0.82
Johns (2017)[37]	England	74%	0.54	0.51	0.57	1.19	0.68*	0.63–0.73
Duffy (2020)[38]	Sweden	80%	0.59	0.51	0.68	1.07	0.66*	0.55–0.79
Dunn (2020)[19]	Queensland, Australia	71%	0.61	0.55	0.68	1.11	0.77†	NR
Median participation		74%						
Summary risk estimate‡			0.51	0.47	0.55			

Notes: NR: not reported in the publication. *Correction according to the potential participation approach. §Correction according to the intent-to-treat approach. †Approach for correction not mentioned. ‡Random-effect model.

Discussion

Our study defined self-selection and *Dr* quantities in the context of randomized trials and cohort studies. Two types of cohorts were studied: intervention groups (ie women invited to screening) of Swedish randomized trials and cohort studies conducted in women who were invited to screening. The main results and consequences of our study are summarized in Figure 2.

Our study suggests that in populations where 80% or more of women attend screening, as in Swedish trials, women not attending screening have an approximately 2.1-fold increased risk of death from breast cancer. This increased risk is independent of screening effects. When attendance rates diminish, non-attendees are a less extreme subgroup than attendees, which accords with a smaller self-selection quantity of about 1.78 found in cohort studies where the median attendance rate was 74%.

The summary *Dr* quantity estimated from Swedish randomized trials was 1.78. In the same trials, Duffy et al found a summary *Dr* quantity of 1.36. This difference was mainly due to two factors. First, Duffy et al did not use the most recent results of the Goteborg and Malmö trials. Second, Duffy et al did not exclude breast cancer deaths associated with breast cancers diagnosed at first screening of control groups.[7,14,39] The high *Dr* quantity of 1.94 we estimated for the two-county trial indicates that compared to the control group, invited women who did not attend screening had a 2-fold

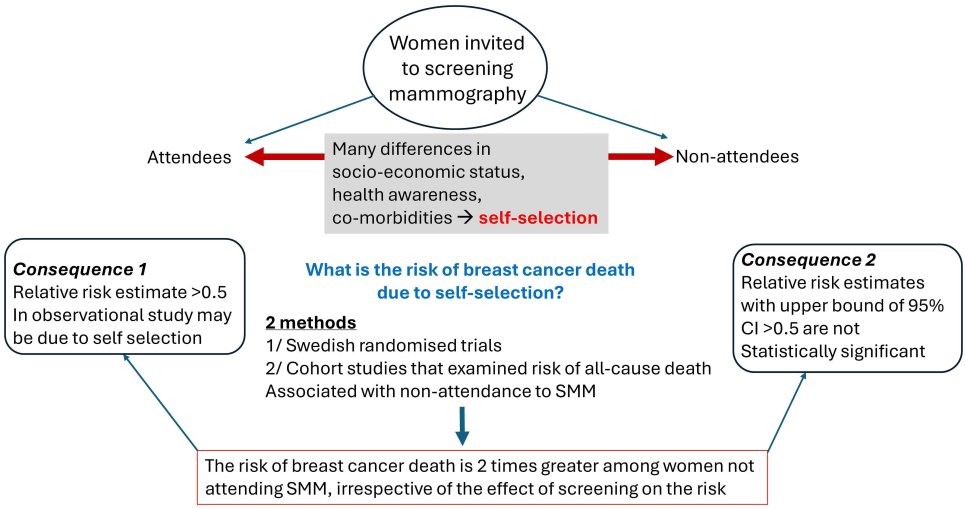

Figure 2 Summary of study and main conclusions.

increase in their risk of breast cancer death. In this trial, the hazard ratio of breast cancer-specific survival of non-attendees versus the control group was 1.97,[40] which supports the likelihood of our estimates.

Duffy's correction method is valid provided that the *Dr* quantity specific to each study is known. However, the 19 case-control and cohort studies that corrected for self-selection used *Dr* quantities usually less than 1.28, which was too small to achieve full correction of the bias. In real-world settings, knowledge of the *Dr* quantity appropriate for a specific observational study is rare. Because there is considerable uncertainty related to the extent of self-selection in any particular observational study,[33] *Dr* quantities have been highly variable between studies. Publications have provided few indications for reasons backing the selection of a particular *Dr* quantity. Moreover, the variation in the selected *Dr* quantities was correlated with the observed relative risk estimates, indicating that the authors may have chosen their correction factor post hoc.

An alternative to correcting for self-selection is to take the relative risk of all-cause death (0.54 (95% CI: 0.50–0.58)) as an unbiased benchmark result for observational studies (Figure 2).[9,17,41] Uncorrected relative risk estimates (odds ratios or relative risks) equal to or greater than 0.54 would be the consequence of self-selection and equivalent to corrected relative risk estimates of 1.00 or greater. Similarly, if the 95% confidence interval upper bound of an uncorrected relative risk estimate is less than 0.54, it could be considered statistically significant ($p < 0.05$). Therefore, only five or 19 observational studies would have a statistically significant result, suggesting a lower risk of breast cancer death associated with screening attendance. In addition, considering all 19 observational studies, the summary relative risk estimate of 0.51 (0.47–0.55) suggests a non-significant 6% (95% CI: 0.93–1.05; ie, 0.51/0.54; 0.55/0.54; 0.47/0.54) decrease in the risk of breast cancer death associated with screening attendance.

Another alternative is to have recourse to an instrumental variable, ie, an exposure variable that is correlated with the exposure of interest but not causality associated with the outcome, for instance general practitioner preference or dental care habits.[8]

In 2015, a viewpoint issued by a group that met the International Agency on Cancer Research (IARC) recommended observational studies to evaluate the effectiveness of screening mammography.[42] However, because of the intractability of biases affecting observational studies, an expert group on breast screening convened by the IARC in 2002 recommended against the use of observational studies to evaluate the effectiveness of mammography screening.[43] The IARC 2002 recommended to monitor decreases in incidence rates of advanced cancers, which should be seen after screening introduction. A key advantage of this indicator is its independence from the influence of improved treatment on cancer mortality. Based on our study, the 2002 IARC recommendations should be reinstated.

Ethics Statement

The study was entirely based on the published literature and did not require ethical approval.

Funding

The International Prevention Research Institute funded works required by this study. This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sector.

Disclosure

The author reports no conflicts of interest in this work.

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