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Review

Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review



Nadine Zielonke ^{a,*}, Andrea Gini ^a, Erik E.L. Jansen ^a, Ahti Anttila ^b, Nereo Segnan ^c, Antonio Ponti ^c, Piret Veerus ^d, Harry J. de Koning ^a, Nicolien T. van Ravesteyn ^a, Eveline A.M. Heijnsdijk ^a on behalf of the EU-TOPIA consortium¹

^a Erasmus MC, University Medical Center Rotterdam, Department of Public Health, Rotterdam, the Netherlands

^b Finnish Cancer Registry, Helsinki, Finland

^c Epidemiology and Screening Unit – CPO, University Hospital Città della Salute e della Scienza, Turin, Italy

^d National Institute for Health Development, Tallinn, Estonia

Received 11 November 2019; accepted 2 December 2019

Available online 10 January 2020

KEYWORDS

Breast cancer screening;
Systematic review;
Breast cancer mortality

Abstract Background: The aim of this study was to quantify the impact of organised mammography screening on breast cancer mortality across European regions. Therefore, a systematic review was performed including different types of studies from all European regions and stringently used clearly defined quality appraisal to summarise the best evidence.

Methods: Six databases were searched including Embase, Medline and Web of Science from inception to March 2018. To identify all eligible studies which assessed the effect of organised screening on breast cancer mortality, two reviewers independently applied predefined inclusion and exclusion criteria. Original studies in English with a minimum follow-up of five years that were randomised controlled trials (RCTs) or observational studies were included. The Cochrane risk of bias instrument and the Newcastle–Ottawa Scale were used to assess the risk of bias.

Results: Of the 5015 references initially retrieved, 60 were included in the final analysis. Those comprised 36 cohort studies, 17 case–control studies and 7 RCTs. None were from Eastern Europe. The quality of the included studies varied: Nineteen of these studies were of very good or good quality. Of those, the reduction in breast cancer mortality in attenders versus non-

* Corresponding author: Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Dr. Molewaterplein 40, Rotterdam, 3015 GD, the Netherlands.

E-mail address: n.zielonke@erasmusmc.nl (N. Zielonke).

¹ The members of the collaborative group are listed in the supplementary material.

attenders ranged between 33% and 43% (Northern Europe), 43%–45% (Southern Europe) and 12%–58% (Western Europe). The estimates ranged between 4% and 31% in invited versus non-invited.

Conclusion: This systematic review provides evidence that organised screening reduces breast cancer mortality in all European regions where screening was implemented and monitored, while quantification is still lacking for Eastern Europe. The wide range of estimates indicates large differences in the evaluation designs between studies, rather than in the effectiveness of screening.

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1. Introduction

Breast cancer (BC) has become the most common cancer in women worldwide in both developed and developing countries [1,2]. Through early detection in asymptomatic women, screening aims to reduce morbidity associated with advanced stages of the disease, as well as cancer-specific mortality. However, the benefits and harms of mammography screening have been debated heatedly in the last decades [3].

It is 35 years since randomised controlled trials (RCT) showed that mammography screening leads to a reduction in BC mortality [4], which resulted in various policy recommendations [5]. More recently, the effect of running mammography screening outside the experimental setting has been assessed. Several observational studies have demonstrated that BC screening reduces BC mortality [6–12]. However, screening has also harms. After careful evaluation of the balance between the benefits and adverse effects of mammography screening, the most recent review by the International Agency for Research on Cancer (IARC) concluded that there is a net benefit from inviting women 50–69 years of age as well as sufficient evidence for women up to 74 years of age to receive screening [3].

At present, population-based BC screening programmes are ongoing, piloted or planned in 25 out of 28 European Union (EU) member states for nearly 95% of women in the age group of 50–69 years [13]. BC screening is delivered mainly by organised programmes encouraged by the European Commission, which has published quality assurance guidelines [14], which are currently being updated [15]. There is wide agreement on different aspects of the screening policy, such as the screening test (mammography), the minimum target age range (50–69 years) and the screening interval (two years). On the other hand, there are substantial differences within the European Union (EU) in the extent to which target populations are actually exposed to screening [16]. Currently there is nearly a two-fold difference among the EU-countries in the coverage by invitations and a more than five-fold difference in the participation rate reported [17].

A considerable number of systematic reviews have estimated the effectiveness of mammography screening in terms of a reduction in BC mortality. Some of these

reviews included only RCTs [18–21], whereas others focused exclusively on observational studies [8,11,12]. Several reviews did not follow a standardised quality appraisal protocol [8,19,22,23]. These reviews demonstrated high variability in estimates which led to different conclusions and recommendations on the most appropriate screening strategy. Probably, the most extensive and recent review was done for the IARC handbook. Their average estimate was 40% reduction in the risk of death from BC for women attending mammographic screening [1]. However, to our knowledge, no review has summarised the current evidence for all European regions, including different types of studies, using a methodologically sound quality appraisal. The aim of this systematic review, therefore was to systematically evaluate and quantify the impact of organised screening on BC-specific mortality across Europe.

The objective of this review is to answer the following questions:

1. What is the impact of organised BC cancer screening on BC mortality across Europe?
2. What are the differences between regions in Europe with regards to BC mortality reduction due to screening?

2. Methods

This systematic review was done in accordance with a peer-reviewed protocol that is published and registered with PROSPERO (CRD42016042433) [24]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist when reporting our findings [25].

All methodological steps were performed by two independent reviewers (N.Z. and A.G.). Disagreement between the two investigators were solved by consensus or by consulting a third independent reviewer (E.E.L.J.).

2.1. Data sources and search

Based on our research questions, the Population, Intervention, Control, Outcome, and Study design (PICOS components), Table 1) served to define specific keywords used in our comprehensive bibliographic

Table 1
PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Exclusion criteria
Population	People invited to/participating in organised ^a mass screening for breast cancer in a European country ^b	People from non-European countries.
Intervention	Organised screening for breast cancer.	Other screening interventions (e.g. breast self-examination)
Control	People not invited to/not attending organised screening or people participating in opportunistic screening only.	No control group (everybody is screened)
Outcome	Change in breast cancer mortality due to screening.	No direct estimation of breast cancer mortality reduction due to screening ^c
Study design	Randomised controlled trials, retrospective and prospective observational (cohort or case–control) studies	Non-original research studies (e.g. editorials, letters, and conference abstracts), modelling/simulation studies, ecological studies ^d .

^a Based on the IARC Handbook of Cancer Prevention (2015) we defined organised screening as screening programmes organised at national or regional level, with an explicit policy.

^b Western Europe: Austria, Belgium, France, Germany, Ireland, Luxembourg, the Netherlands, United Kingdom and Switzerland. Northern Europe: Denmark, Estonia, Faroe Islands, Finland, Iceland, Latvia, Lithuania, Norway and Sweden. Southern Europe: Cyprus, Gibraltar, Greece, Italy, Malta, Portugal, Spain. Eastern Europe: Bulgaria, Czech Republic, Croatia, Hungary, Poland, Romania, Slovakia, Slovenia.

^c Studies that only provide estimates on changes of survival rates, were excluded.

^d Ecological studies that simply compare trends between unmatched regions or single regions over time without statistical adjustments for e.g. baseline risk, excluded.

searches. Systematic bibliographic searches were conducted on the Embase, Medline Ovid, Web of Science, PubMed publisher, Google Scholar, and Cochrane Library. All databases were searched from inception to March 2018. The computer-assisted searches were designed and performed by a research librarian using controlled keywords to assess the concepts related to mammographic screening, BC and mortality among European countries. In [Appendix 1](#), the detailed search strategies performed for every source are listed. To augment the search and to improve the likelihood of identifying studies that are only indexed in local journals, experts were asked to suggest additional articles that were not retrieved through the above-mentioned search strategy. Additional potentially eligible articles were identified by hand searching the reference lists of all included studies. The search was limited to articles written in English conducted in any European country and the authors only considered studies that included data from RCTs or observational studies such as prospective and retrospective controlled cohort or case–control studies. All references were managed in Thomson Reuters Endnote X7.1, and duplicates were removed.

2.2. Study selection

Two investigators independently reviewed the titles and abstracts of all references identified by the literature search by using the PICOS criteria displayed in [Table 1](#). Then all potentially suitable articles were reviewed in depth and additional exclusions have been made applying eligibility criteria proposed by Elmunzer and colleagues [26]: (1) Studies in which data or patients were duplicated in other manuscripts; (2) Studies in which data were not reported for at least 5 years of follow-up; (3) Studies in which the total number of

events and participants were not reported for each study group. If multiple studies compared the same region, period or population, or reported on the same trial, the study with the longest follow-up was retained. The full texts of all included publications were screened for eligibility. Relevant outcome data and study details such as first author; year of publication; country where the study was conducted; study design; screening target population; follow-up information; sample size of the study; assessment of confounding factors (such as adjustment for self-selection bias), and the reported estimates (with corresponding 95% confidence intervals [95%CI]) of the screening effect on BC mortality, were extracted. Furthermore, eligible articles were grouped according to European regions (Northern, Western, Southern and Eastern Europe) following the classification provided by the EUROVOC Multilingual Thesaurus of the European Union [27].

2.3. Quality appraisal

We used the Cochrane risk of bias instrument [28] to assess the quality of the included RCTs. This tool helps to indicate the validity of the studies' results and the presence of any systematic error leading to an overestimation or underestimation of the true intervention effect. The tool considers the risk of bias within five domains, including randomised sequence generation, allocation concealment, masking outcome assessors, incomplete outcome data reporting and selective outcome reporting. However, the sixth domain from the original tool, masking of participants and personnel, was not applied in this systematic review as it was deemed not applicable to screening. The reviewers judged each of the five domains and agreed in an overall judgement for each study as low, moderate, or high risk of bias.

To judge the quality of observational studies we used the Newcastle–Ottawa Scale (NOS) [29]. Using the tool with its specific questions for cohort studies and case–control studies respectively, each study is judged on several items, categorised into three areas: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest. Originally, the NOS does not award a point if the case definition of case–control studies was exclusively based on record linkage. However, many studies on cancer screening are based on data from cancer registries. As advocated in Anttila [30] cancer registries can be held co-responsible for the quality and impact assessment of screening programmes when mandated and resourced adequately. Thus, when the percentage of histologically verified cases of the respective cancer register was known to be above 95% according to the IARC [31,32], we qualified the case definition as independent validation and award a point on this question. The highest quality studies are awarded with a score of nine.

The risk of bias of studies included in this review has been categorised as follows:

- (I) Low risk RCTs,
- (II) Moderate risk RCTs or score of 8 or 9 in observational studies,
- (III) High risk RCTs or score 5 to 7 in observational studies and
- (IV) Observational studies with a score from 0 to 4.

3. Results

The PRISMA flowchart (Fig. 1) presents the number of articles found and excluded in each stage. The initial search retrieved a total of 6691 citations. The augmenting bibliographic search provided 153 additional references. After removing duplicates, 5015 citations were identified of which 150 potentially eligible articles were selected for detailed full-text evaluation. After the preliminary full-text analysis using the eligibility criteria mentioned above, 89 references were excluded from our review. A detailed overview of the reasons for exclusion are presented in Appendix 3.

Of the 153 additional references from experts, 31 were already identified by our initial literature search. The remaining 122 studies were excluded mostly because

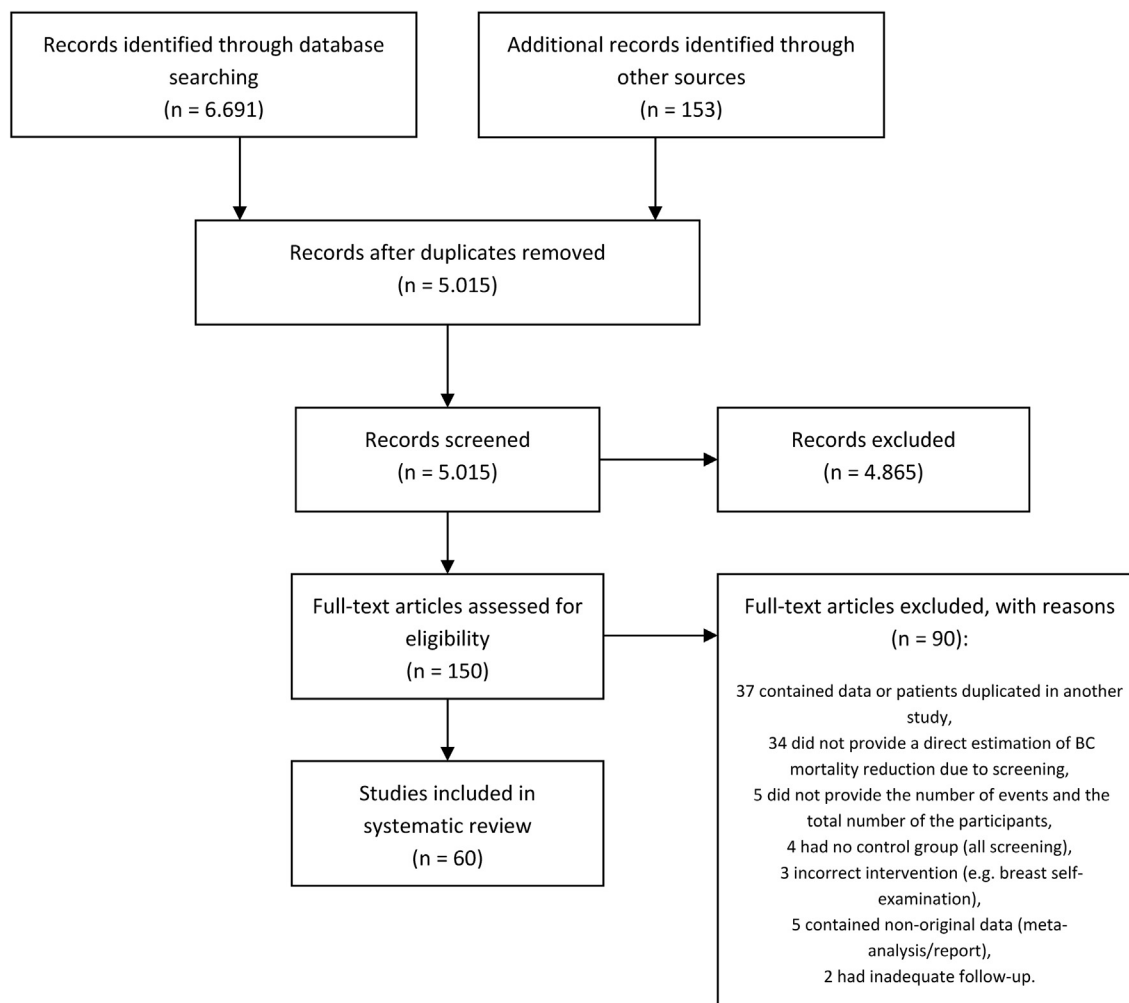


Fig. 1. PRISMA flow chart of records through the review searching and inclusion process.

they did not provide a direct estimation of the impact of BC screening on cancer-specific mortality.

In total, 60 studies were included in the final in-depth analysis. Those included 38 cohort studies [33–70], 17 case–control studies [71–87] and 7 randomised controlled trials [88–94]. Details of these studies and their main characteristics – sorted by European region – are reported in Table 2–4. Thirty studies were included for Northern Europe [33–55,68,74,75,89–92,94]; 9 for Southern Europe [56–61,81,82,86]; and 22 studies for Western Europe [62–67,69–73,76–80,83–85,87,88,93]. None of the included studies came from Eastern Europe. The majority of studies (51/60) covered the age group 50–69.

Considering the results of all 60 studies included in this review, BC mortality reduction estimates for invited versus non-invited women varied from 4% [89] to 36% [90] in Northern Europe, from 25% [59,82] to 35% [56] in Southern Europe and from 6% [66] to 47% [67] in Western Europe. When comparing BC mortality of screened versus non-screened women, estimates varied from 2% [50] to 89% [38] in Northern Europe, from 43% [86] to 67% [57] in Southern Europe and 12% [64] to 58% [80] in Western Europe. Of the 60 included studies, 40 had statistically significant results.

3.1. European regions

The quality of the included studies was miscellaneous. Among the 60 included reported results, 5% (3/60) fell into quality category I, 27% (17/60) were graded as quality category II, 60% (37/60) fell into category III and 8% (5/60) into category IV. Due to the numerousness of included studies, we will only highlight the results from those 19 studies from group I and II. The estimated effect of organised mammographic screening on BC-specific mortality from these studies, by European regions, is described in Fig. 2. The entirety of the risk of bias assessment of all included cohort studies, case–control studies, and RCTs is displayed in Appendix 4–6, respectively. Additionally, Appendix 7 is a summary of the risk of bias assessment for the RCTs used in this review.

3.2. North

A total of 30 studies were selected and reported for Northern European countries, including Denmark, Finland, Sweden, Norway and Iceland (Table 2). Five of these references were randomised controlled trials, all from Sweden, of which two were of low risk of bias and one of moderate risk of bias. Two of the (very) good studies establish the protective effect of being invited to mammographic screening. Tabar (2011) [94] reports the long-term effect of mammographic screening in the Swedish Two-County trial. They found a highly

significant reduction in BC mortality in women invited to mammographic screening (RR = 0.69 [95% CI: 0.56–0.84]), whereas the Malmö mammographic screening trial [89] initially did not find a statistically significant effect of screening (RR = 0.96 [95% CI: 0.68–1.35]) after a little less than 9 years of follow-up. Andersson [90] provided additional follow-up data of the two cohorts from the Malmö Mammographic Screening Trial, particularly for women between 45 and 50 years of age who were followed for an average of 10 years. They conclude that being invited to screening lowers the BC mortality significantly (RR = 0.64 [95% CI: 0.45–0.89]). The reviewers appraised five of the 30 cohort studies from northern Europe to be of good quality. Three come from Norway. The Norwegian BC screening programme was initiated in 1996, when it began as a pilot study in four of the 19 Norwegian counties. The programme targets women aged 50 to 69 who are invited every 2 years. Olsen (2013) [48] observed the change in BC mortality due to screening comparing it to historical control groups in the four pilot study counties, using an incidence-based approach. The cohort study has a short follow-up of only 6 years and a reported relative risk (RR) of 0.93 (0.77–1.12). Two other reports included 15 years of follow-up. Weedon-Fekjaer's prospective cohort study estimated that invitation to mammographic screening was associated with a 28% reduced risk of death from BC compared with not being invited (RR = 0.72 [0.64–0.79]) [55]. Hofvind (2013) [40] compared BC mortality of women attending screening with that of a non-screened cohort, considering incidence-based mortality (IBM). Fifteen years after the start of the programme, the reduction was estimated to be 43% (RR = 0.57 [0.51–0.64]). For Copenhagen (Denmark), Olsen (2007) [49] analysed IBM of women invited to the routine mammography by linking screening registry, cancer registry, cause of death registry, and population registry data for individual women age 50–69. Using historical comparison groups, the effect of invitation to mammography screening every two years was as BC mortality reduction of 20% (RR = 0.80 [0.68–0.94]). Tabar *et al.* (2003) [54] assessed the long-term effects (20 years) of mammographic service screening on BC mortality in two Swedish counties for women aged 40–69 years. Taking potential biases (e.g. age and self-selection bias) into account, BC mortality of screened women was 41% lower than that of unscreened women (RR = 0.59 [0.53–0.66]).

Heinävaara (2016) [75] evaluated the long-term effect of organised mammography screening on IBM in Finland during 1992–2011 among 50–84-year-old women using a case–control design. The effect of screening, corrected for self-selection bias, was 33% (HR = 0.67 [0.49–0.90]).

Table 2
 Characteristics, risk of bias and results on breast cancer mortality of included studies, by quality score. Northern Europe.

Study	Country	Study type	Participants	Attendance	Target age (years)	Follow-up (years)	Correction for self-selection bias	Quality score ^a	Effect sizes for breast cancer mortality, RR/HR/OR (95%CI)	
									Invited versus not invited	Attenders versus not attenders
Andersson I, 1988	Sweden	RCT	I:21,088, C: 21,195	85%	45–79	9	n/a	A	RR = 0.96 (0.68–1.35)	
Tabar L., 2011	Sweden	RCT	I: 77,080, C: 55,985	85%	40–74	29	n/a	A	RR = 0.69 (0.56–0.84)	
Andersson I, 1997	Sweden	RCT	I: 13,528, C: 12,242	NA	<50	10	n/a	B	RR = 0.64 (0.45–0.89)	
Heinävaara S, 2016	Finland	Case-control	Cases: 1,907 Controls: 18,978	86%	50–69	7.4	yes	8/9		HR = 0.67 (0.49–0.90)
Olsen AH, 2007	Denmark	Cohort	Participants: 430,823 pyr, Non-participants: 634,224 pyr ^b	NA	50–69	10	n/a	8/9	RR = 0.80 (0.68–0.94)	
Olsen AH, 2013	Norway	Cohort	Participants: 1,182,747 pyr, Non-participants: 1,152,755 pyr ^b	NA	50–69	6	n/a	8/9	RR = 0.93 (0.77–1.12)	
Tabar L, 2003	Sweden	Cohort	Participants: 2,399,000 pyr, Non-participants: 2,416,000 pyr ^b	85%	40–69	20	yes	8/9		RR = 0.59 (0.53–0.66)
Weedon-Fekjaer H, 2014	Norway	Cohort	Participants: 2,407,709 pyr, Non-participants: 12,785,325 pyr ^b	76%	50–69	15	n/a	8/9	RR = 0.72 (0.64–0.79)	
Hofvind S, 2013	Norway	Cohort	Participants: 4,184,060 pyr, Non-participants: 988,641 pyr ^b	NA	50–69	15	yes	8/9		RR = 0.57 (0.51–0.64)
Bjurtsam N, 2016	Sweden	RCT	I: 21,904, C: 30,31830.318	84%	39–59	14	n/a	C	RR = 0.70 (0.53–0.93)	
Frisell J, 1997	Sweden	RCT	I: 40,318, C: 19,943	N/A	40–64	11.4	n/a	C	RR = 0.74 (0.50–1.10)	
Anttila A, 2008	Finland	Cohort	Participants: 89,893, Non-participants: 68,862 ^b	90%	50–59	15	n/a	7/9	Mortality rate –11.1% (–19.4–2.1)	
Anttinen A, 2006	Finland	Cohort	Participants: 552, Non-participants: 341 ^b	71%	50–69	8.0–12.5	n/a	7/9	HR = 0.82 (0.59–1.12)	
Njor SH, 2015	Denmark	Cohort	Participants: 870,465 pyr, Non-participants: 828,508 pyr ^b	NA	50–69	14	yes	7/9		RR = 0.72 (0.59–0.87)
Anttila A, 2002	Finland	Cohort	Participants: 161,400 Wy, Non-participants: 155,400 Wy ^b	81.8%	50–59	8.5–10.5	n/a	6/9	RR = 0.81 (0.62–1.05)	
Duffy SW, 2006	Sweden	Cohort	Participants: 566,423, Non-participants: 542,187 ^b	75%	40–69	>20	yes	6/9		RR = 0.57 (0.53–0.62)
Hakama M, 1995	Finland	Cohort	Participants: 3,708 Non-participants: 6,223 ^b	86%	40–47	9	no	6/9		RR = 0.11 (0.00–0.71)
Hakama M, 1997	Finland	Cohort	Participants: 89,893, Non-participants: 68,862 ^b	85%	45–69	6	n/a	6/9	RR = 0.76 (0.53–1.09)	
Jonsson H, 2001	Sweden	Cohort	Participants: 162,986 Non-participants: 98,608	NA	50–69	10.6	n/a	6/9	RR = 0.84 (0.67–1.05)	

Jonsson H, 2003	Sweden	Cohort	Participants: 43,749 Non-participants: 618,342	NA	40–64	22	n/a	6/9	RR = 0.84 (0.67–1.05)	
Jonsson H, 2003	Sweden	Cohort	Participants: 83,830, Non-participants: 41,608	NA	70–74	10	n/a	6/9	RR = 0.82 (0.57–1.19)	
Kalager M, 2010	Norway	Cohort	Participants: 2,337,323 pyr, Non-participants: 1,866,741 pyr ^b	NA	50–69	8	n/a	6/9	RR = 0.90 (0.76–1.04) ^c	
Parvinen I, 2006	Finland	Cohort	Participants: 963,362 pyr, Non-participants: 1,016,664 pyr ^b	NA	55–69	15	n/a	6/9	Helsinki: RR = 1.11 (0.95–1.29), Tampere: RR = 0.86 (0.65–1.12), Turku: RR = 0.64 (0.47–0.88)	
Sarkeala T, 2008	Finland	Cohort	Participants: 1,439,753 pyr, Non-participants: 34,803,524 pyr	NA	50–69	10	yes	6/9		RR = 0.62 (0.43–0.85)
Tabar L, 2001	Sweden	Cohort	Participants: 1,100,931 pyr, Non-participants: 1,213,136 pyr ^b	85%	40–69	30	yes	6/9	RR = 0.50 (0.41–0.60)	RR = 0.52 (0.43–0.63)
Gabe R, 2007	Iceland	Case-control	Cases: 226, Controls: 902 ^b	61–68%	40–69	N/A	yes	5/9		OR = 0.65 (0.39–1.09)
Hellquist BN, 2011	Sweden	Cohort	Participants: 7,261,415, Non-participants: 8,843,852	80–90%	40–49	16	no	5/9	RR = 0.74 (0.66–0.83)	RR = 0.71 (0.62–0.80)
Jonsson H, 2000	Sweden	Cohort	Participants: 202,152 Non-participants: 237,279	NA	40–49	8	n/a	5/9	RR = 0.91 (0.72–1.15)	
Jonsson H, 2007	Sweden	Cohort	Participants: 109,000, Non-participants: 77,000	NA	40–74	11	yes	5/9	RR = 0.74 (0.62–0.88)	
Parvinen I, 2015	Finland	Cohort	Participants: 1,439,753 pyr, Non-participants: 34,803,524 pyr	86.7	40–84	>10	n/a	5/9	TKU versus RoF: RR = 0.85 (0.66–1.1) TKU versus HEL: RR = 0.75 (0.57–1.00)	

BC = Breast cancer, pyr = person years, Wy = Women years, OR = Odds ratio; RR = Relative risk; HR = Hazard ratio; I: Intervention group; C: Control group; NA: not available; n/a: not applicable; TKU: Turku, RoF: Rest of Finland, HEL: Helsinki, Target age: Ages targeted by the screening programme; Follow-up: Follow-up after initiation of the screening programme.

^a Quality assessment made according to the Newcastle–Ottawa scale and the Cochrane risk of bias instrument. Risk of bias for RCT was categorised as follow: A (Low risk), B (Moderate risk) and C (High risk).

^b Controls were drawn from the same population as the intervention group.

^c this value was recomputed as RR from the results provided in the original article.

Table 3
 Characteristics, risk of bias and results on breast cancer mortality of included studies, by quality score. Southern Europe.

Study	Country	Study type	Participants	Attendance	Target age (years)	Follow-up (years)	Correction for self-selection bias	Quality score ^a	Effect sizes for breast cancer mortality, RR/HR/OR (95%CI)	
									Invited versus not invited	Attenders versus not attenders
Palli D, 1986	Italy	Case-control	Cases: 57, Controls: 257 ^b	NA	40–70		yes	8/9		OR = 0.57 (0.35–0.89)
Puliti D, 2012	Italy	Cohort study	Participants: 32,544, Non-participants: 18,552 ^b	56%	50–69	16.5	yes	8/9		50-59: RR = 0.55 (0.41–0.75), 60–69: RR = 0.49 (0.38–0.64)
Barco I, 2015	Spain	Cohort study	Participants: 496, Non-participants: 1,325 ^b	NA	50–69	6	no	7/9		HR = 0.33 (0.18–0.63)
Puliti D, 2008	Italy	Case-control	Cases: 2,371 (Exp: 297), Controls: 9,484 (Exp: 1,718) ^b	n/a	50–74	n/a	yes	7/9	OR = 0.75 (0.62–0.92)	OR = 0.50 (0.42–0.60)
Paci E, 2002	Italy	Cohort study	Participants: 254,890 pyr, Non-participants: 164,742 pyr ^b	NA	50–69	8	n/a	6/9	RR = 0.75 (0.54–1.04)	
Palli D, 1989	Italy	Case-control	Cases: 103 (Exp: 55), Controls: 515 (Exp: 355) ^b	n/a	40-49, 50+	n/a		6/9		40-49: OR = 0.63 (0.24–1.64), 50+: OR = 0.51 (0.29–0.89)
Ascunce EN, 2007	Spain	Cohort study	Participants: 185, Non-participants: 123 ^b	85%	50–69	14	n/a	5/9	RR = 0.65 (0.51–0.82)	
Paci E, 2005	Italy	Cohort study	Participants: 2,105, Non-participants: 2,339 ^b	NA	50–69	5	n/a	5/9	RR = 0.73 (0.61–0.87)	

BC = Breast cancer, pyr = person years, Wy = Women years, OR = Odds ratio; RR = Relative risk; HR = Hazard ratio; I: Intervention group; C: Control group; NA: not available; n/a: not applicable; Target age: Ages targeted by the screening programme; Follow-up: Follow-up after initiation of the screening programme.

^a Quality assessment made according to the Newcastle–Ottawa scale and the Cochrane risk of bias instrument.

^b Controls were drawn from the same population as the intervention group.

Table 4

Characteristics, risk of bias and results on breast cancer mortality of included studies, by quality score. Western Europe.

Study	Country	Study type	Participants	Attendance	Target age (years)	Follow-up (years)	Correction for self-selection bias	Quality score ^a	Effect sizes for breast cancer mortality, RR/HR/OR (95%CI)	
									Invited versus not invited	Attendees versus not attendees
Moss S, 2015	UK	RCT	I: 53,883, C: 106,953	81%	39–41	17	yes	A		RR = 0.88 (0.74–1.04)
Johns LE, 2017	UK	Cohort study	Participants: 2,407,709 pyr, Non-participants: 12,785,325 pyr ^c	74%	49–64	15	yes	9/9	RR = 0.79 (0.73–0.84)	RR = 0.68 (0.63–0.73)
Johns LE, 2017	UK	Case-control ^b	Cases: 11,754 (Exp: 5,109) Controls: 37,601 (Exp: 20,545) ^c	n/a	49–64		yes	9/9	OR = 0.79 (0.71–0.88)	OR = 0.53 (0.46–0.62)
Allgood PC, 2008	United Kingdom	Case-control	Cases: 284 (Exp: 208), Controls: 568 (Exp: 505) ^c	n/a	50–70		yes	8/9		OR = 0.65 (0.48–0.88)
Massat NJ, 2015	UK	Case-control	Cases: 391, Controls: 417 ^c	61.7%	47–89		yes	8/9		OR = 0.69 (0.50–0.94)
Massat NJ, 2015	UK	Case-control	Cases: 869, Controls: 1,642 ^c	70.5–62.8%	47–89		yes	8/9		OR = 0.61 (0.44–0.85)
Otto S, 2012	Netherlands	Case-control	Cases: 755, Controls: 3,739 ^c	79%	50–75	n/a	yes	8/9		OR = 0.51 (0.40–0.66)
Paap E, 2014	Netherlands	Case-control	Cases: 1,233, Controls: 2,090	81.3%	50–75	n/a	yes	8/9		OR = 0.42 (0.33–0.53)
Alexander FE, 1999	United Kingdom	RCT	I: 28,628 C: 26,026	NA	45–65	14	no	C		RR = 0.79 (0.60–1.02)
Broeders MJM, 2002	Netherlands	Case-control	Cases: 157 (Exp: 157), Controls: 758 (Exp: 758) ^c	n/a	40–80		no	7/9		40-49: OR = 0.90 (0.38–2.14), 50-59: OR = 0.71 (0.35–1.46), 60-69: OR = 0.80 (0.42–1.54)
Ernst M, 2004	Netherlands	Cohort study	Participants: 419, Non-participants: 250 ^c	NA	50–69	8	n/a	6/9	HR = 0.75 (0.57–1.01)	
Fielder HM, 2004	UK	Case-control	Cases: 419 (Exp: 275), Controls: 717 (Exp: 535) ^c	n/a	50–75		yes	6/9		OR = 0.75 (0.49–1.14)
Mook S, 2011	Netherlands	Cohort study	Participants: 958, Non-participants: 1,634 ^c	70–80%	50–69	10	no	6/9		HR = 0.62 (0.50–0.86)
van Dijk JAAM, 1996	Netherlands	Case-control	Cases: 82 (Exp: 15), Controls: 410 (Exp: 101) ^c	n/a	65+	n/a	no	6/9		RR = 0.56 (0.28–1.13)
Miltenburg GAJ, 1998	Netherlands	Case-control	Cases: 177 (Exp: 51), Controls: 531 (Exp: 64) ^c	n/a	50–69		no	5/9		OR = 0.54 (0.37–0.79)
Moss S, 1999	UK	Cohort study	Participants: 45,607, Non-participants: 190,496	65–70%	45–64	16	no	5/9		RR = 0.74 (0.63–0.86)
Sankatsing V, 2017	Netherlands	Cohort study	Participants: NA, Non-participants: NA ^c	80%	50–74	13–20	n/a	5/9	% rate change 2010 compared with 1980: –30	
Otto SJ, 2003	Netherlands	Cohort study	Participants: 8,414, Non-participants: 14,971 ^c	NA	55–74	>10	n/a	4/9	% rate change 2001 compared with 1986–1988: –19.9 (–26.6 to –14.2)	

(continued on next page)

Table 4 (continued)

Study	Country	Study type	Participants	Attendance	Target age (years)	Follow-up (years)	Correction for self-selection bias	Quality score ^a	Effect sizes for breast cancer mortality, RR/HR/OR (95%CI)	
									Invited versus not invited	Attendees versus not attendees
Peer PM, 1995	Netherlands	Cohort study	Participants: 166,307 Wy, Non-participants: 154,103 Wy	87%	35–49	16	n/a	4/9	RR = 0.94 (0.68–1.29)	
van Dijk JAAM, 1997	Netherlands	Cohort study	Participants: 16,383 Wy, Non-participants: 17,487 Wy	46%	65+	8–13	n/a	4/9	RR = 0.53 (0.27–1.04)	
van Schoor G, 2010	Netherlands	Case-control	Cases: 76 (Exp: 50), Controls: 750 (Exp: 596) ^c	n/a	40–49	n/a	no	4/9		OR = 0.50 (0.30–0.82)
van Schoor G, 2011	Netherlands	Case-control	Cases: 282, Controls: 1,410 ^c	NA	50–69		no	4/9		OR = 0.65 (0.49–0.87)

BC = Breast cancer, pyr = person years, Wy = Women years, OR = Odds ratio; RR = Relative risk; HR = Hazard ratio; I: Intervention group; C: Control group; NA: not available; n/a: not applicable; Target age: Ages targeted by the screening programme; Follow-up: Follow-up after initiation of the screening programme.

^a Quality assessment made according to the Newcastle–Ottawa scale and the Cochrane risk of bias instrument. Risk of bias for RCT was categorised as follows: A (Low risk), B (Moderate risk) and C (High risk).

^b Nested case–control study

^c Controls were drawn from the same population as the intervention group.

3.3. South

The characteristics of the nine included articles from Southern European countries are reported in Table 3. All selected studies were performed in Italy and Spain. One case–control study and one cohort study, both from Florence/Italy, were judged to be of good quality (category II). In a rural area near Florence a population-based screening programme for BC was started in 1970. The case–control study by Palli (1986) [86] showed that women who have been screened at least once had a BC mortality reduction of 43% compared to women never screened (OR = 0.57 [0.35–0.89]). Puliti (2012) [61] followed up women invited to the Florentine screening programme every 2 years at age 50–69. Using an incidence-based approach, the estimated mortality reduction was 45% among 50- to 59-year-old women (RR = 0.55 [0.41–0.75]) and 51% among 60- to 69-year-old women (RR = 0.49 [0.38–0.64]) after 16 years of follow-up.

3.4. West

From Western European countries, the reviewers included 22 studies which exclusively came from the Netherlands and United Kingdom (Table 4). The UK Age Trial (Moss, 2015) [93] was the only RCT from this region that was judged to carry a low risk of bias. However, it only refers to the specific group of women aged 40–49 after 17 years of follow-up. Annual mammography screening below age 50 leads to a rate ratio (RR) for BC mortality of 0.88 (0.74–1.04). Six case–control studies reached a score of 8 or 9 (of 9), all with fairly similar results: Allgood (2008) [71] performed a study in the East Anglia region after the initiation of the breast screening programme in 1989. The odds ratio (OR) for death from BC in women who attend at least one routine screen compared to those who did not attend was 0.65 (0.48–0.88). Massat (2016) [76] assessed the impact of the UK National Health Service breast cancer Screening programme (NHS BSP) 20 years after the inception and showed a BC mortality reduction of 39% among attendees (OR = 0.61 [0.44–0.85]) In a companion case–control study, Massat (2016) [77] reported that breast screening attendance reduces the fatality risk by 31% (OR = 0.69 [0.50–0.94]). A 47% BC mortality reduction for attending women was found in a nested case–control study by Johns (2017) [87] (OR = 0.53 [0.46–0.62]), who evaluated the effectiveness of the NHS breast screening programme in England and Wales. All of the British observational study results were corrected for self-selection bias. For the Netherlands, Paap (2014) [80] estimated the benefit of the population-based screening programme to be as high as 58% (OR = 0.42 [0.33–0.53]) for screened compared to unscreened women. Otto's (2012) [79] assessment of the effectiveness of mammography screening of Dutch

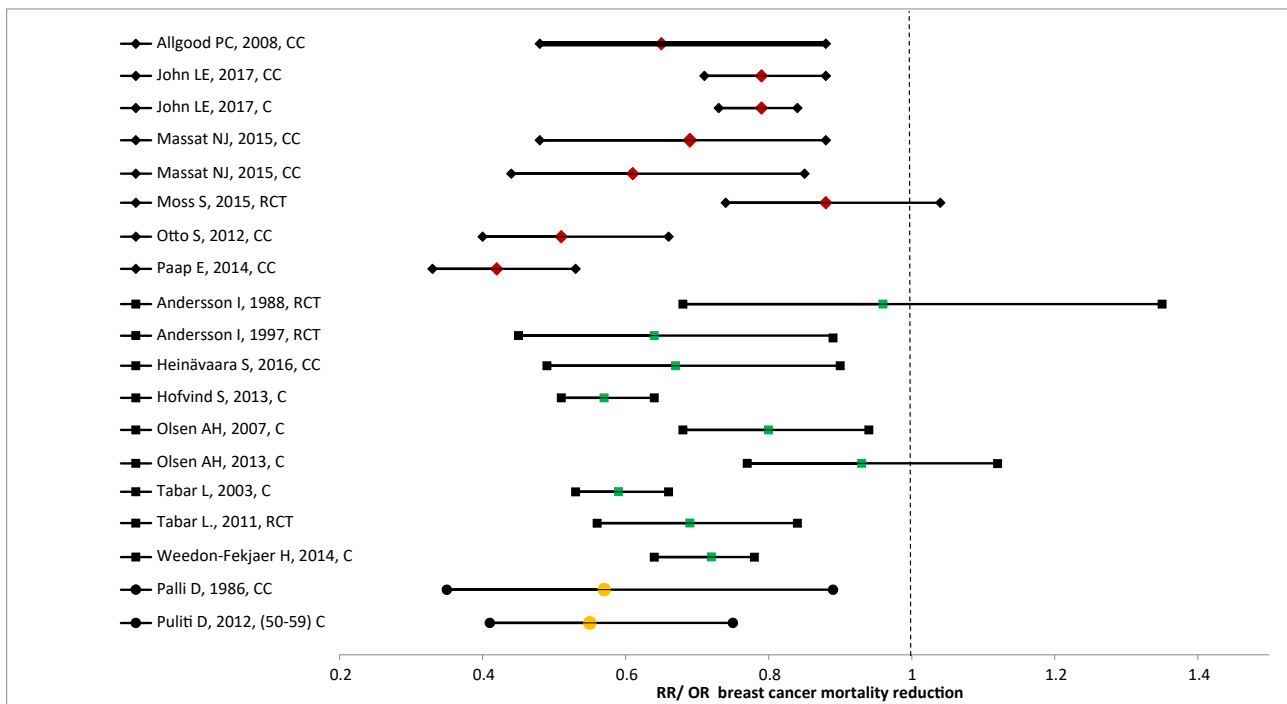


Fig. 2. Forest plot displaying the effectiveness of organised mammographic screening on breast cancer-specific mortality, of studies with (very) good quality (group I and II), by European regions (Western Europe: diamond, Northern Europe: square, Southern Europe: circle). The 95% confidence intervals for individual studies are represented by a horizontal line.

women indicated a significant association between attending mammography screening and risk of breast cancer death (OR = 0.51 [0.40–0.66]). Johns (2017) [70] conducted the first individual-based cohort evaluation of population breast screening in the UK, to estimate the impact of the NHS breast screening programme (NHS BSP) on BC mortality. After adjustment for self-selection bias, the mortality reduction was 32% (RR = 0.68 [0.63–0.73]).

3.5. East

No studies from Eastern Europe met the inclusion criteria.

4. Discussion

To the best of the authors’ knowledge, this review is the first that comprises evidence from RCTs as well as observational studies and stringently uses transparent grading tools to appraise the quality of each included reference and then highlights only those that provide the most valid information. The results fortify that mammography screening leads to reduced mortality from BC, and the evaluation studies conducted in the three European regions where screening was implemented are confirming this conclusion.

The large number of possibly eligible studies for this review as well as the number of other (systematic)

reviews on this topic reflect the long history of evaluations regarding the benefits of mammographic screening, including some contrasting views.

In 2012, the Independent UK Panel on BC screening relied mainly on findings from RCTs in order to provide estimates of the level of benefits and harms. Based on 11 trials with 13 years of follow-up they concluded that the relative risk reduction was 20% in women invited for screening [19]. Gøtzsche and Jørgensen [21], who included only RCTs in their review, found that the trials with adequate randomisation did not find a statistically significant effect of screening on BC mortality. Nevertheless, in the past decade concerns have been raised about the applicability of RCTs in times of growing availability of service screening and about the validity of these trials. More recently, the evaluation of screening benefits has shifted to population-based screening services, and observational studies became the main contributors of new information on the impact of BC screening on BC mortality reduction [8]. Prerequisites for methodologically sound results therefore are individual data on screening exposure that is sufficiently long (>5 years), reliable information on the vital status as well as cancer data which can be directly linked to a women’s screening history and to her cause of death. The susceptibility to bias can furthermore be limited when studies use incidence-based mortality (IBM) and adjust for self-selection bias. By using standardised tools to judge on the presence of all of

those methodological components, we were able to identify those observational studies that are qualitatively consistent with well conducted RCTs. Of the 38 cohort studies included in this systematic review, 24 considered IBM and therewith only observed BC deaths in women diagnosed after their first invitation to (or attendance in) mammographic screening. In that way, these studies only account for a risk of BC death at a time, when it could have been affected by service screening. BC mortality reductions were consistently greater when the analysis compared screened versus unscreened women rather than women who were invited versus not invited to screening. All of the 17 case–control studies included in this review compared women attending in screening to non-attending ones. The attractiveness of the case–control approach is that it uses observed mortality, and it requires fewer participants than cohort studies. Thus it is a very efficient tool to evaluate (new) organised screening programmes [6,95]. However, non-compliers, those women who did not accept the invitation to screening within organised programmes, can potentially have a different risk of death from BC than the general population. Therefore, one major disadvantage of this study design is the tendency to selection bias. Duffy *et al.* [9] provided a method of adjustment for potential confounders. The majority of the included case–control studies adjusted for self-selection bias. While most researchers agree that the combination of both screening and treatment leads to a reduction of BC mortality, some claim that the reduction of BC mortality observed in Europe since the 1990s is mostly due to changes in cancer treatment [96]. Changes in treatment over time – in Norway, for example, multidisciplinary breast care centres that have been introduced parallelly with the organised screening programme [40,46,97] - make the results difficult to interpret. Both, case–control or IBM studies implicitly imply a treatment effect though. In order to disentangle the synergistic effect of screening with better treatment modelling analysis under different assumptions are needed. In their simulation modelling study, Plevritis *et al.* (2018) [98] evaluated the contributions associated with screening and treatment to BC mortality reductions for US women. The estimated reduction in BC mortality rate between 2000 and 2012 was 49%, of which 37% were associated with screening and 63% with treatment, although the associations varied by BC molecular subtype.

We discovered a lack of eligible studies from Eastern Europe on mortality reduction due to screening. One main explanation could be serious (financial) barriers to organising and/or evaluating screening services [17]. Among the regions included in this study, some populations had long-established screening programmes running since the end of the 1980s (e.g. Finland) and since the beginning of the 1990s (the Netherlands,

Norway, Tuscany and Turin (Italy)) with complete coverage of populations at screening age, but potentially different age groups covered across these areas. Particularly for eastern European countries, opportunistic screening has been offered to women since the early 1990s [99] and still plays an important role in explaining low participation rates in the organised programmes [17]. In most eastern European countries breast screening programmes started more recently: Hungary in 2001, Estonia in 2005, Lithuania in 2006, Cracow (Poland) in 2007 and Slovenia in 2008. Hence a long running monitoring and evaluation system is either still missing or does not provide sound results yet.

This qualitative review is based on well-defined *a priori* criteria and a rigorous systematic methodology. Nonetheless, we note four potential limitations. First, non-English-language studies were excluded. Second, the large number of included studies and their methodological designs led to a wide range of estimates of mortality reduction due to screening. Therefore, we did not aim for a meta-analysis and to synthesise the results, but rather to highlight the reported evidence. Three, we used very strict PICOS criteria during the selection process following an in-depth quality assessment through the Cochrane and NOS tools to limit the risk of bias. While these choices may limit the number of references that will be included in this systematic review, it guarantees the best available evidence on which we base the conclusions. Last, this review did not include grey literature and thus solely relies on published studies. Therefore, it might be affected by publication bias, as published literature appears to be predominantly biased towards positive results [100].

The variation in the point estimates from individual studies indicates differences in evaluation designs, e.g. in ages of follow-up of breast cancer incidence or mortality, duration of follow-up since first invitation, comparison group and assessment methods of self-selection bias, rather than variability of the effectiveness of screening. It would have been very important to describe the patterns in more detail according to the above factors, but it was often not possible yet, due to lack of information provided in many studies. Recent studies suggest that the impact can be highly variable, depending upon, e.g. if breast cancers during screening age only, or also after the last invitation round would be included [75,101]. It would be very important to assess the screening impacts after the whole life span since the first invitation and describe the variable effects in the various follow-up windows of relevance.

We prove that there are several methodologically appropriate approaches that are able to capture the true beneficial effect of mammographic screening. However, in order to assess the validity of these results, future reviews would strongly profit from quality appraisal

tools which are specifically developed to judge the impact of screening, as well as the quality of European record linkage practice.

Funding

This systematic review is part of the EU-TOPIA project, funded by the European Union Framework Programme (Horizon 2020) of the European Commission project reference 634753. The authors alone are responsible for the views expressed in this manuscript.

Conflict of interest statement

The authors have declared no conflicts of interest.

Acknowledgements

We like to thank Wichor Bramer, biomedical information specialist at the medical library at Erasmus MC (Rotterdam, the Netherlands) for his valuable help, expert inputs and solutions in the making of this systematic review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2019.12.010>.

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