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Assessment of the impact of decision aids on breast cancer screening. A systematic review

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Assessment of the impact of decision aids on breast cancer screening: A systematic review

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ABSTRACT

Objective: The aim of this systematic review of randomised controlled trials (RCTs) and observational studies is to assess the effect of decision aids (DA) in women facing the decision to be screened for breast cancer.

Setting: Screening for breast cancer.

Intervention: DA aimed to help women make a deliberative choice regarding participation in mammography screening by providing information on the options and outcomes.

Primary and secondary outcomes: The main outcome measures were informed choice, decisional conflict, and knowledge. Secondary outcomes were values, attitudes, uncertainty, and the final participation intention in breast cancer screening.

Results: A total of 607 studies were identified, but only three randomized controlled studies and one before-after study were selected. DA increased the proportion of women taking an informed decision. Confidence in the decision was lower in the intervention group. The use of a DA provided a higher level of knowledge according to all studies and only one study noted a decrease in the intention of screening.

Conclusions: Tools to aid decision-making in screening for breast cancer improve knowledge and promote informed decision, although this benefit is not free of decisional conflict and loss of confidence. Under the current paradigm change, that values informed choice rather than maximising uptake, more research is necessary for the improvement of DA.

Keywords: breast cancer, decision aid, mammography, screening, shared decision making.

Strengths and limitations of this study

- This is the first systematic review focused in the impact of DA on breast cancer screening.

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- DA for breast cancer screening produce a significant improvement in knowledge and contribute to a significant increase of the frequency of women making an informed choice.

- Decision aids do not affect decision conflict, decision confidence and positive attitudes towards screening.

- The limitations of the study are related mainly with the generalization of the results.

- One of the limitations is that women included in the studies probably had a higher education level, greater health awareness, and were more actively involved in health care decisions, than women in the general population.

INTRODUCTION

In Western countries screening for breast cancer spread during the 1990s. There was a general consensus on the benefits of screening since several clinical trials in the US and Northern Europe estimated a statistically significant and clinically relevant reduction of mortality from breast cancer[1]. But, in the year 2000 the systematic review from Gotzsche et al. started a hot debate, still alive, on the relevance and magnitude of benefits and harms of breast cancer screening[2].

More than two decades after the introduction of breast cancer mass screening, the evidence on the harm-benefit balance remains inconclusive. On the one hand, advances in adjuvant treatments, a multidisciplinary approach for breast cancer treatment, and earlier identification of symptoms by women, have diminished the impact of screening on breast cancer mortality reduction[3]. On the other hand, the evidence on adverse effects of screening, characterized by a high consensus on the risk of false positive results and lack of agreement on the size of overdiagnosis and overtreatment, show that the potential harms of screening are not insignificant[4,5].

The current prevailing paradigm, which encourages participation, is changing. Two proposals are gaining strength. First, the need to inform women of potential benefits and harms of screening. Some propose not devoting more energy to increase participation but dedicating it to inform women to make the best decision based on their preferences and values[6–9]. Second, customizing the screening strategies to individual risk. Some recent studies[10–12] based on mathematical models suggest that risk-based screening may increase benefits and reduce harms. The literature shows that both proposals are gaining strength[13,14].

Decision aids (DA) are instruments that communicate evidence-based information on benefits and harms of different health-care options to help people make informed choices. According to Stacey et al.[15], DA can help patients to clarify the value they place on benefits, harms, and scientific uncertainties. The Stacey work[15], a recently updated Cochrane systematic review on DA for people facing treatment or screening decisions, included 115 published randomized controlled trials of DA, 26 of them

were about cancer screening (13 prostate, 10 colon, 2 breast, and 1 cervix) and 7 on breast cancer genetic testing. The authors concluded that here was high-quality evidence that DA compared to usual care improve people's knowledge regarding options, and reduce their decisional conflict related to feeling uninformed and unclear about their personal values. There was moderate-quality evidence that DA stimulate people to take a more active role in decision making, and improve accurate risk perceptions when probabilities are included in DA, compared to not being included. Finally, there was low-quality evidence that DA improve congruence between the chosen option and the patient's values.

Information on cancer screening is often biased, incomplete and persuasive[16]. Some leaflets mention the possibility of harms however do not quantify them. In Europe, some organizations are providing information on benefits and harms of breast cancer screening, in particular, estimates of mortality reduction, and frequency of false positive results of mammography and invasive tests (e.g. Cochrane collaboration, UK NHS Breast Screening Programme; German Institute for Quality and Efficiency in Health Care; Fundació Lliga per a la Investigació i Prevenció del Càncer and Agència de Salut Pública de Barcelona, in Catalonia (Spain)). Information on overdiagnosis appears in some of the information materials. Two recent studies[8,17] have compared the impact of adding information on overdiagnosis to support informed choice on breast cancer screening. Prior to the initiation of a randomized controlled study on the effect of a DA in mass screening in two regions of Spain, we aimed to identify and summarize all the studies reporting the description and assessment of a DA when applied to women facing the decision to be screened with mammography in a population-based screening or opportunistic case-finding framework. We expected to find that DA improve knowledge of options, benefits, and harms; create accurate perceptions of benefits and harms; reduce decisional conflict; and enhance informed choice.

METHODS

Eligibility criteria

Types of studies

We included all the published studies with randomized controlled trial (RCT) or before-after designs that compared DA to no intervention, usual care, or alternative interventions. The search date upper limit was December 31, 2016.

Types of participants

Participants were women facing decisions about screening in a population-based screening or opportunistic case-finding framework within the age interval of recommended mammography screening. We excluded studies aimed at elderly women only, and studies where participants were asked to make hypothetical choices.

Types of interventions

DA were defined as interventions aimed to help women make a deliberative choice regarding participation in mammography screening, by providing information on the options and outcomes. We excluded studies aimed at increasing participation or promoting adherence, and studies not carried out in a real context of women facing the decision.

Types of outcome measures

The primary outcomes were: informed choice based on values, decisional conflict and/or confidence, and knowledge. The secondary outcomes included: values and/or attitudes towards screening, proportion remaining undecided, and proportion reporting screening participation intention.

Language

We included articles reported in any language.

Information sources

Search methods for identification of studies

The search strategy was performed in MEDLINE and SCOPUS and adapted and replicated in EMBASE, CINAHL, PsycInfo, and Cochrane Library Plus. The search included the key words "breast cancer" and "decision" (or "choice") and "aid" (or "informed") and "mammography" (or "mammogram"), within the paper title or the abstract. It excluded the key word "protocol" from the paper titles and allowed synonyms and free suffixes and prefixes. The reviews identified by this search, as well as the references that they included, were exhaustively used to refine the search strategy to ensure that all the possible relevant references for our review were identified (see online supplementary appendix 1).

Study selection and synthesis of results

All the studies satisfying the inclusion and exclusion criteria referred to design, participants and interventions were included in this review. Their selection and risk of bias assessment was independently conducted in pairs by four reviewers (MC, MJP, MMA, and MR). In case of disagreement, studies were discussed by the whole team of reviewers till an agreement was reached.

Data extraction

The data extraction for the selected studies was independently conducted by two reviewers (MMA and MR) and a consensus version was obtained. In case of data needed, that was not shown in the articles, the corresponding authors were contacted.

Risk of bias of individual studies

For the risk of bias assessment of randomized comparative studies, the *Cochrane risk of bias* tool for randomized controlled trials was used. In case of non-randomized controlled trials, the selection, allocation and blinding assessment were not

applicable. The sampling bias (a problem for external validity) was assessed in all the included studies.

The risk of bias (*low, unclear,* or *high*) was assessed considering the study design and the methodological quality of the studies. Data consistency was rated as *no inconsistency*, *inconsistency present*, or *not applicable* if there was only one study available, considering each outcome's direction, magnitude, and statistical significance through the included studies. The assessment methods followed the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/) and were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist[18].

Analysis of results

For each endpoint of interest, the decision to combine the results of the selected studies in a meta-analysis was based on the heterogeneity of patient populations and interventions, as well as on methodological heterogeneity of study designs and reported outcomes.

If comparable measures were obtained, we pooled the data for the outcomes. To facilitate the data pooling, scores with different ranges (minimum and/or maximum values) were standardized to range from 0 to 100 points. We estimated a weighted effect intervention (with 95% confidence interval) as the difference between the intervention and control groups in experimental designs, and as changes in outcome measures post-intervention assessment from baseline in before-after studies. Mean differences or pooled relative risks (RR) were estimated for continuous or dichotomous outcomes, respectively.

RESULTS

Study selection

In total, we identified 607 unique citations from the electronic database searches. Of these, only 14 were selected for evaluation of the inclusion and exclusion criteria. Figure 1 presents the flowchart of the study selection process. Ten studies were excluded after full text assessment (see Table S2.1 in the supplementary appendix 2 for details). Finally, three randomized controlled studies (Mathieu 2010[19], Gummersbach 2015[17], and Hersch 2015[8], and one before-after study, Eden 2015,[20] were selected. These four studies involved a total of 1650 participants from four countries (Australia with two of them, Germany, and the United States of America).

Study characteristics

Table 1 presents the studies' characteristics. Gummersbach and Hersch compared two DAs with information about the benefits and harms of mammography screening, providing the intervention group with more complete information. Whereas Gummersbach added more critical information in the harms of screening mammography in the intervention group, the DA in Hersch only differed in providing thorough information of overdetection or not. In contrast, Mathieu compared a DA with receiving no information, and Eden assessed changes after providing a DA.

Participants' characteristics are shown in Table 2. Means of age were located in the 40-50 yrs interval. There are differences between studies in the prevalence of previous mammograms and in education level.

Table 1: Description of the studies' characteristics

Study	Design	Age group	Exclusion criteria	Decision aid (DA)
Mathieu 2010	Randomized controlled study, pragmatic[a]	38-45	Personal history of breast cancer (BC)	Web-based DA, information on possible screening outcomes and worksheet to help weigh up and clarify preferences. Intervention group: immediate access; control group: delayed access after completing the outcome measures.
Eden 2015	Before-after study, clinical	40-49	Personal history of BC, prior breast biopsy, high risk of BC[b], previous mammography within 1 year, non-English speaking	Web-based DA, within 3 rural clinical settings, including BC information and questions for risk and self-preferences assessment.
Gummersbach 2015	Randomized controlled study, primary care based	48-49	None	Mailed leaflet, more informative (specially on overdiagnosis) for the intervention group.
Hersch 2015	Randomized controlled study, community-based	48-50	Personal or strong family history of BC, BC risk higher than average, mammography in the past 2 years, non-English speaking	Mailed DA, outcomes assessed by phone interview. Evidence-based explanatory and quantitative information on overdiagnosis, BC mortality reduction, and false positives for the intervention group vs. information on BC mortality reduction and false positives for the control group.

[a] :The trial was advertised on the media. Women had free access to the site for eligibility assessment.
[b] : Breast cancer risk based on the Breast Cancer Genetics Referral Screening Tool (B-RST).

Table 2: Description of studies' participants

Study	Group	Participants	Age Mean (SD)	Previous mammography	University degree
Mathieu 2010	Intervention	172	41.9 (2.0)[a]	53 (30.8%)	76 (44.2%)[b]
	Control	212	41.8 (2.2)[a]	52 (24.5%)	126 (59.4%)[b]
Eden 2015	Before-After	75	45.0 (2.5)	51 (68.0%)	34 (45.3%)
Gummersbach 2015	Intervention	178	48.67 (0.79)	[c]	33 (18.5%)
	Control	175	48.76 (0.80)	[c]	23 (13.2%)
Hersch 2015	Intervention	419	49.67 (0.44)	[d]	119 (28.4%)
	Control	419	49.70 (0.44)	[d]	123 (29.4%)

SD: Standard deviation.

[a] Out of the assessed participants, 116 and 198 in intervention and control group, respectively.

[b] Out of the assessed participants, 114 and 199 in intervention and control group, respectively.

[c] 3 and 4 women with BC in intervention and control group, respectively. Participants were not asked about mammographic exams in the past.

[d] No women with previous mammogram in the previous two years but it is not stated how many women had mammograms more than two years before being included in the study.

Risk of bias in included studies

The evaluation of the risk of bias for each of the studies included the assessment of biases in selection, performance, detection, attrition, reporting, sampling or any other source of bias. Details on the authors' judgement and rationale for risk of bias can be found in Tables A2.2-A2.5 (online supplementary appendix 2,). The majority of assessed criteria were judged as low risk. Hersch 2015[8] was the only study free of high risk of bias in all the domains assessed. Eden 2015[20] was rated as high risk of sampling bias due to the inclusion of women with high school education or higher, whereas Gummersbach 2015[17] was rated as high risk of attrition bias due to a high level of non-response. Mathieu 2010[19] was rated as unclear risk of allocation concealment and also of selective reporting.

Main outcomes

Tables 3 and 4 present the risk differences for the dichotomous outcomes and the mean differences for the continuous outcomes, respectively. Figures 2 and 3 show the results of the meta-analyses for the dichotomous and continuous outcomes, respectively.

Informed choice

The DA increased the proportion of women taking an informed decision, 58.0% vs. 36.5% according to Mathieu ($p < 0.001$) and 24.2% vs. 15.4% according to Hersch ($p = 0.002$). The meta-analysis estimation of risk difference was 14%, with a 95% CI of [2% , 27%] (Table 3 and Figure 2).

Decisional conflict or confidence

Eden observed a significant post-intervention decrease in decisional conflict and a significant increase in decisional confidence (Table 4, Figure 3). In contrast, Hersch noted no significant effect of the intervention on decisional conflict and a significant decrease in decisional confidence, observed also by Gummersbach. These contradictory results introduced high heterogeneity that increased the uncertainty about the overall impact of a DA on decisional conflict or confidence (Figure 3).

Knowledge

The use of a DA increased knowledge according to all studies, although the positive difference was not statistically significant in the Gummersbach study (Tables 3 and 4). The overall results provided by the meta-analyses were statistically significant, either in the proportion of women with adequate knowledge, with a significant increase of 12%, 95% CI=[7%, 16%], or in the mean score (difference of 0.70 out of 10 points, 95% CI =[0.27, 1.13]) (Figures 2 and 3).

Table 3: Outcomes assessment: Risk differences in informed choice, knowledge, positive attitudes/values towards screening, undecided and screening intention.

Outcome	Study	Group	Assessed	n(%)	Difference, *p-value*[a]
Informed choice[b]	Mathieu 2010[c]	Intervention	112	65 (58.0%)	21.5%, *p*< 0.001
		Control	192	70 (36.5%)	
	Hersch 2015[d]	Intervention	409	99 (24.2%)	8.8%, = 0.0017
		Control	408	63 (15.4%)	
Knowledge	Mathieu 2010[e]	Intervention	113	106 (93.8%)	10.7%, = 0.01
		Control	189	157 (83.1%)	
	Hersch 2015[f]	Intervention	419	122 (29.1%)	13.0%, < 0.001
		Control	419	71 (16.9%)	
Positive attitudes[g]	Mathieu 2010	Intervention	111	88 (79.3%)	0.2%, = 0.89
		Control	182	144 (79.1%)	
	Hersch 2015	Intervention	409	282 (68.9%)	-14.4%, < 0.001
		Control	408	340 (83.3%)	
Undecided	Mathieu 2010	Intervention	117	21 (17.9%)	-21.3%, < 0.001
		Control	209	82 (39.2%)	
	Eden 2015	Before	75	55.0 (41.71)	-40[h], < 0.001
		After	75	15.0 (31.57)	
	Hersch 2015	Intervention	419	69 (16.5%)	9.3%, < 0.001
		Control	419	30 (7.2%)	
Screening intention	Mathieu 2010	Intervention	117	50 (42.7%)	3.0%[a], *p=0.64*
		Control	209	83 (39.7%)	
	Eden 2015	Before	75	54 (72.0%)	6.7%[h], = 0.123
		After	75	59 (78.7%)[h]	
	Gummersbach 2015	Intervention	178	145 (81.5%)	-7.1%, = 0.06
		Control	175	155 (88.6%)	
	Hersch 2015	Intervention	419	308 (73.5%)	-13.1%, < 0.001
		Control	419	363 (86.6%)	

[a] Fisher's exact test.

[b] Eden provided only a post-intervention mean of the preparation for decision making scale of 73.2 (18.1).

[c] Out of the women assessed, including undecided women in the denominator.

[d] Informed choice defined as adequate knowledge and intentions consistent with attitudes.

[e] Knowledge (according to Mathieu): score higher than 5 out of 10.

[f] Knowledge (according to Hersch): Adequate knowledge when scoring at least 50% of the total available marks, including at least 1 numerical mark, on all three screening outcome subscales (breast cancer mortality benefit, false-positive screening result and overdiagnosis).

[g] Positive attitudes/values >50 out of 100 according to Mathieu and >=24 out of 30 according to Hersch.

[h] Difference as post minus pre-intervention values.

Table 4: Outcomes assessment: Mean difference in knowledge and in decisional conflict or confidence.

Outcome	Study	Group	N	mean (SD)	Difference p-value
Knowledge	Mathieu 2010[a]	Intervention	113	7.35(1.84)	1.1, < 0.001
		Control	189	6.27(1.85)	
	Gummersbach 2015[a]	Intervention	161	5.49 (1.99)	0.26, = 0.26
		Control	168	5.23 (2.06)	
	Hersch 2015[b]	Intervention	419	13.49[c](4.36)	1.65, < 0.001
		Control	419	11.84[c](3.74)	
Decisional conflict	Eden 2015[c]	Before	75	46.33 (27.04)	-38.0, < 0.001
		After	75	8.33 (15.58)	
	Hersch 2015	Intervention	419	12.55 (17.60)	0.35, = 0.78
		Control	419	12.20 (18.90)	
Decisional confidence	Eden 2015[d]	Before	75	79.67 (18.62)	16.16, < 0.001
		After	75	95.73 (6.86)	
	Gummersbach 2015[e]	Intervention	178	5.15 (1.36)	-0.37, = 0.017
		Control	182	5.52 (0.93)	
	Hersch 2015[f]	Intervention	419	4.35 (0.74)	-0.18, = 0.0003
		Control	419	4.53 (0.67)	

[a] Knowledge scored out of 10.

[b] Knowledge scored out of 22.

[c] Change in total decision conflict as post-intervention minus pre-intervention values, out of 100.

[d] Change in self-efficacy scale as post-intervention minus pre-intervention values, out of 100.

[e] Change in confidence scale in comparison with the control group, out of 6.

[f] Change in confidence scale in comparison with the control group, out of 5 (mean of 3 subscales).

Secondary outcomes

The high heterogeneity of the results did not allow concluding significant post-intervention changes or differences on secondary outcomes such as positive attitudes

and values towards screening, decision about screening, and screening intention (Table 3, Figure 2).

Positive attitudes/values towards screening

Mathieu did not showed any significant difference, but Hersch obtained a significant lower frequency of women with positive attitudes towards screening in women receiving the DA with overdiagnosis information.

Undecided about BC screening

Mathieu reported a significant decrease in the amount of undecided about BC screening after DA administration. In contrast, Hersch obtained a significant increase for the intervention group, with the DA including thorough overdiagnosis information.

Choice of BC screening

Only Hersch noted a decrease in the intention of screening, being the only one that reported the observed value instead of the intention reported by the other three studies.

DISCUSSION

Summary of main results

This systematic review includes three randomized controlled studies and one before-after study assessing DA given to women facing the decision to be screened with mammography. There was variability in the type and amount of information included in the DA, and also in the information given to the control group. This variability may explain in part, the significant heterogeneity in all the outcomes evaluated. Despite this heterogeneity, the meta-analysis revealed that DA produce a statistically significant improvement in knowledge of screening outcomes as well as a significant

increase of the frequency of women making an informed choice. However, no significant effects were observed for decision conflict, decision confidence and positive attitudes towards screening. Therefore, the overall conclusion from our review is that DA increase significantly the knowledge and therefore the proportion of women taking an informed choice, but do not significantly modify attitudes or intentions towards screening.

Similarly, no significant effects were observed for the secondary outcomes that measured the frequency of participants remaining undecided or choosing to be screened. More specifically, Eden detected a significant decrease in intra-individual post-intervention decision conflict which was not observed by Hersch, when comparing women receiving a DA with overdiagnosis information vs. those without it. Indeed, Eden also obtained a significant improvement in intra-individual post-intervention decision confidence, while Gummersbach and Hersch obtained a significant decrease in decision confidence when comparing women receiving a DA with exhaustive information on screening side effects vs. those without it. Positive attitudes towards screening significantly decreased when overdiagnosis information was added to the DA, as observed by Hersch, in contrast with the absence of change observed by Mathieu. The frequency of women remaining undecided after DA showed completely opposite results. While Mathieu observed a very significant decrease, Hersch obtained a significant increase. The frequency of women decided to be screened showed a significant difference only in the Hersch study, where a decrease was observed for the group provided with overdiagnosis information, while Gummersbach, the other study incorporating throrough information on mammography side effects, showed a decrease nearly significant.

Quality of the evidence

Risk of bias ratings show that the included studies had low risk of bias in most of the assessed domains. There may have been publication bias due to failure to report negative findings. Several of the outcomes showed a high level of heterogeneity that limits the interpretation of the pooled effect size.

Strengths and limitations

Studies differed in design, especially in terms of the control group. In the Mathieu study[19], the control group did not receive the DA until the outcome measures had been completed. In the Eden study[20], the post-intervention intra-individual changes after the DA were assessed. In the Gummersbach study[21], a more informative leaflet was compared to a less informative one. Finally, in the Hersch study[8], the intervention DA had evidence-based explanatory and quantitative information on overdiagnosis, breast cancer mortality reduction, and false positives, whereas the control DA included information on breast cancer mortality reduction and false positives. Previous knowledge was not measured in the randomized controlled studies, although one expects that both groups have similar knowledge about mammography screening at baseline. In the Eden study, which assessed the intra-individual change, DA were particularly useful for the least informed and least confident women. On the other hand, Gummersbach[21] noted that education level was positively associated with acquired knowledge and that the less educated women had less decisional relevant knowledge after reading the leaflet, but they were more willing to undergo mammography than more educated women. Only the Hersch study included a follow-up for final screening participation.

The limitations of the study are related mainly with the generalization of the results. Women included in the studies probably had a higher education level, greater health awareness, and were more actively involved in health care decisions, than women in the general population. Besides, the DA were designed using specific data from Australia (Mathieu and Hersch), United States (Eden) and Germany (Gummersbach), providing results which could be not generalizable to other countries. All studies evaluated brochures only from the women's perspective, and in the context of research, where participants may have a higher level of commitment than women invited to participate in a breast screening program.

Unanswered questions and future research

Women should use DA to be informed and support their decisions on breast cancer screening given their preferences and attitudes. It is important to ensure that the information provided is well understood by all women, including those with low educational level.

Internet is an inexpensive tool for the dissemination of DA or to search for additional information, if necessary, in order to present to the women all the options available and the harms and benefits of them. But there are women that are not familiarised or do not have access to Internet and therefore other ways to disseminate information are also necessary.

According to Gummersbach the doctor's advice was the most important factor to help in the decision of being screened for almost half of the women. This result indicates the importance of shared decision-making, where DA are essential tools. Shared decision-making also can help to reduce decisional conflict and improve confidence when information on screening harms is provided.

As highlighted by Hersch et al., establishing what constitutes an informed choice and what knowledge is needed to be informed, is an important issue and currently, no consensus exists on what knowledge constitutes being objectively informed for an informed or shared decision. When Hersch et al. used an expert-led approach based on medical guidelines and underpinned by decision theory, that required numerical and conceptual knowledge, only 24% in the intervention group and 15% in the control group were assessed as informed. When only conceptual knowledge was required these proportions increased to 50% and 19%, respectively. Difficulties understanding quantitative information or the widespread positive value on cancer screening can cause certain resistance to information on possible harms. Their study was the only one obtaining a significant increase in the amount of women remaining undecided about being screened in the group receiving information on overdiagnosis.

The DA of the included studies lacked detailed information on the outcomes of screening, detection, treatment, or financial strain and opportunity costs from the perspective of the society, what could be considered important to be included in future DA.

Conclusions

DA in screening for breast cancer improve knowledge and promote informed decision making, in accordance with their preferences, for women who face the decision of screening, although this benefit is not free of decisional conflict and loss of confidence. Under the current paradigm change that values informed choice rather than maximising uptake, more research is necessary for the improvement of DA.

Figure legends

Figure 1: Study flow diagram

Figure 2: Meta-analysis of risk differences (REML method)

Figure 3: Meta-analysis of mean differences in scores (REML method)

The InforMa Group

The members of the InforMa Study Group are (alphabetical order): *ÀreaQ, Evaluation and Qualitative Research, Barcelona*: Àngels Cardona, Núria Codern. *Canary Islands Health Service (SESCS)*: Lilisbeth Perestelo, Ana Toledo. *Universitat Auntònoma de Barcelona (UAB)*: Maria Feijoo. *Cancer Prevention and Control Program, Catalan Institute of Oncology, L'Hospitalet de Llobregat, Barcelona*: Montse García, Carmen Vidal. *IRBLLEIDA-Universitat de Lleida*: Sara Buil, Clara Vinyals, Laia Vinyals, Montserrat Martínez-Alonso, Marta Ortega, Sandra Pla, Anna Pons-Rodríguez, Montserrat Rué, Jorge Soler. *URV (University Rovira i Virgili), Reus*: Misericòrdia Carles,

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: funding from the Spanish Ministry of Health and the Biomedical Research Institute of Lleida (IRBLLEIDA) as described below; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Informed consent

Since the work does not involve direct research in human subjects, informed consent was not obtained. Nevertheless, the study was approved by the Ethics Committee of the Hospital Universitari Arnau de Vilanova in the city of Lleida (Spain).

Contributors and authorship

MMA, MC and MR designed the study. All authors contributed towards the execution of the study. MMA provided methodological expertise in systematic reviews and searching strategies. The selection and risk of bias assessment of each study was independently conducted in pairs by four reviewers (MC, MJP, MMA, and MR). AP contributed to extracting the information of the identified studies and assessing the inclusion criteria. MMA and MR wrote the first draft with guidance and contributions from MC, MJP, and MG. All authors read, provided critical feedback and approved the final manuscript.

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Funding

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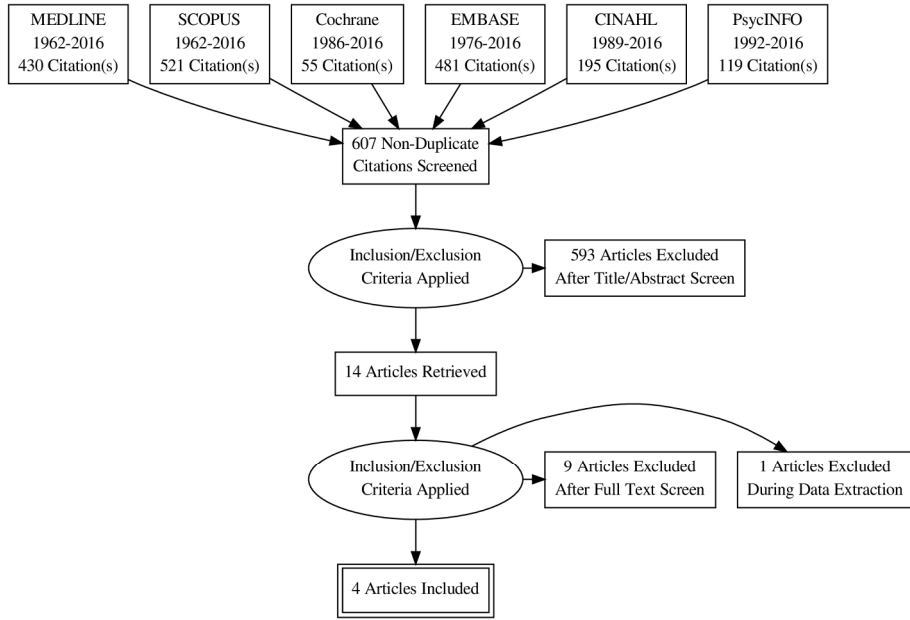
Figure 1: Study flow diagram

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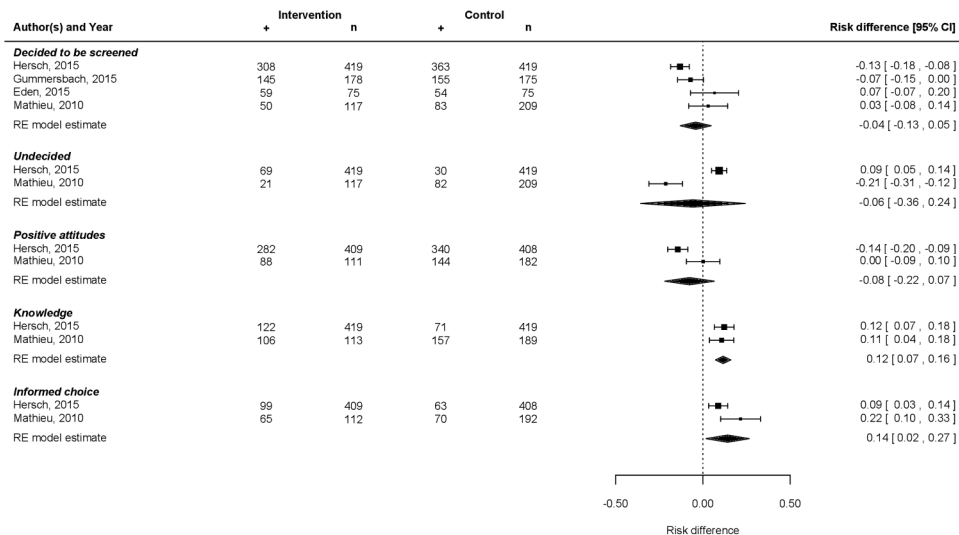
Figure 2: Meta-analysis of risk differences (REML method)

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Figure 3: Meta-analysis of mean differences in scores (REML method)

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APPENDIX 1

Search criteria for Decision Aids on breast cancer screening

1. In MEDLINE:

   "breast cancer"[tiab] (decision[tiab] OR choice[tiab]) AND (aid[tiab] OR informed[tiab]) AND (mammography[tiab] OR mammogram[tiab]) NOT protocol[ti]

2. Adapting it to SCOPUS:

   (TITLE-ABS-KEY ("breast cancer") AND (TITLE-ABS-KEY (decision) OR TITLE-ABS-KEY (choice)) AND(TITLE-ABS-KEY (aid) OR TITLE-ABS-KEY (informed)) AND (TITLE-ABS-KEY (mammography) OR TITLE-ABS-KEY (mammogram)) AND NOT TITLE (protocol)

3. And, equivalently for EMBASE, CINAHL, PsycInfo, and the Cochrane Library Plus.

APPENDIX 2

Table A2. 1: Excluded studies after full text assessment

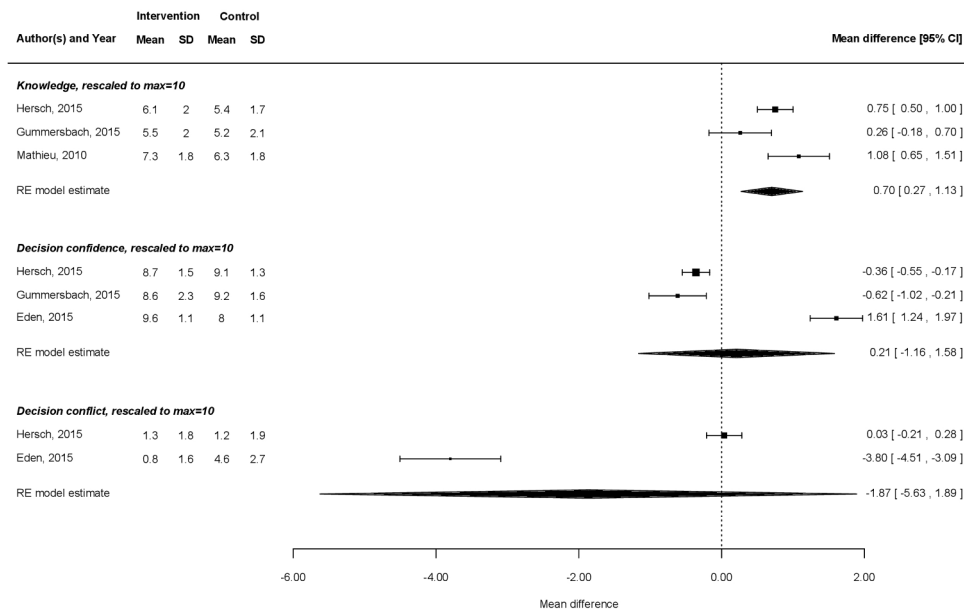| Study	Reason of exclusion
Lawrence 2000	No adequate evaluation of the decision aid (DA), only acceptability is assessed.
Webster 2007	No adequate evaluation of the DA, no DA but a leaflet is assessed.
Bodurtha 2009	No adequate evaluation of the DA, no decision is assessed.
Pasternack 2011	No adequate evaluation of the DA, only acceptability is assessed.
Waller 2013	No adequate evaluation of the DA, only the design is described, no assessment is reported.
Hersch 2014	Pilot study of a main study already included.
Waller 2014	No adequate evaluation of the DA, three formats of reporting information are compared.
Berens 2015	No adequate evaluation of the DA, no DA but a leaflet is assessed.
Petrova 2015	The DA is not assessed in a real context.
Bourmaud 2016	No adequate evaluation of the DA. Informed choice is assessed only by participation rate. The overdiagnosis harm is not mentioned.

Characteristics of the included studies

Table A2.2. Study Characteristics

Mathieu 2010	
Methods	Randomised to decision aid (DA) vs usual care (UC).
Participants	189 + 223 women, aged 38-45 years, considering mammography screening.
Interventions	DA: explained the benefits and harms, included a values clarification exercise and a worksheet to support decision making. UC: delayed intervention
Outcomes	Primary outcome: knowledge of benefits and harms of screening. Secondary outcomes: informed choice (composite of knowledge, values and intention), anxiety, acceptability of the DA, and intention regarding screening.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 66 (randomization and baseline questions section): "computer generated simple randomization schedule".
Allocation concealment (Selection bias)	Unclear risk	Pg. 66 "randomization was conducted in a concealed manner." The method of allocation concealment was not stated.
Blinding of participants and personnel (Performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (Detection bias)	Low risk	Unclear blinding but outcomes were not subjective to interpretation.
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Table 2: all outcomes mentioned in the paper were reported in the Results section. Table 3: outcomes of anxiety and acceptability can be found. Page 69 explains missing data. Figures 1 and 2 provide the reasons for the exclusions in each group.
Selective reporting (Reporting bias)	Unclear risk	No mention of protocol.
Other bias (Sampling and other)	Low risk	Pg. 65: "To proceed, women were required to click in a box on the computer screen to indicate they had read the study information and were eligible to participate." The trial was advertised on various websites and in a radio program.

Table A2.3. Study Characteristics

Eden 2015	
Methods	Observational study. Women were assessed before and after the decision aid (DA).
Participants	75 women aged 40-49 years.
Interventions	The decision aid (Mammopad) included modules on breast cancer, mammography, risk assessment, and priority setting about screening.
Outcomes	Primary outcome: decisional conflict measured before and after using DA. Secondary outcomes: decision self-efficacy and intention to begin or continue mammography screening.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	NA	
Allocation concealment (Selection bias)	NA	
Blinding of participants and personnel (Performance bias)	NA	
Blinding of outcome assessment (Detection bias)	NA	
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Study enrolment flow diagram is included in the publication. Information on procedures and results for the outcomes is detailed on pg. 1015 and on the publication appendices.
Selective reporting (Reporting bias)	Low risk	Results reported adhere to the protocol.
Other bias (sampling bias)	High risk	Pg. 1018 "We recruited fewer women with only high school education and also fewer Latinas".

Table A2.4. Study Characteristics

Gummersbach 2015	
Methods	Randomised to two decision aids (DA) with different information.
Participants	353 women, aged 48-49 years, about to receive the first invitation to screening.
Interventions	Intervention: DA with detailed information on screening harms. Control: standard DA.
Outcomes	Primary outcome: willingness to participate in screening. Secondary outcomes: knowledge, decisional confidence, determinants of the screening decision.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 62: "The 24 participants from each practice were selected by a computer-assisted random procedure."
Allocation concealment (Selection bias)	Low risk	Pg. 62: the group allotment process was also random.
Blinding of participants and personnel (Performance bias)	Low risk	Pg. 62: "The participants and their family physicians were blinded with respect to group allotment, but the study team was not".
Blinding of outcome assessment (Detection bias)	Low risk	Pg. 62: "The participants were asked by letter to fill out the questionnaire after reading the leaflet and to send it back in an envelope that was also enclosed in the mailing".
Incomplete outcomes' data. All outcomes (Attrition bias)	High risk	46.7% non-response.
Selective reporting (Reporting bias)	Low risk	The response rate was the same in both groups.
Other bias (sampling bias)	Low risk	Participants recruited from family practices.

Table A2.5. Study Characteristics

Hersch 2015	
Methods	Randomised to two decision aids (DA) with different information.
Participants	879 women, aged 48-50 years, about to receive the first invitation to screening.
Interventions	Intervention: comprising evidence-based explanatory and quantitative information on overdetection, breast cancer mortality reduction, and false positives. Control: decision aid including information on breast cancer mortality reduction and false positives.
Outcomes	Primary outcome: informed choice defined as adequate knowledge and consistency between attitudes and screening intentions. Secondary outcomes: screening attitudes, decisional conflict, worry about breast cancer, intention about undergoing screening, and opinions about the decision aid.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 1644: "A programmer who had no contact with participants generated the randomisation sequence using a computer system that was inaccessible until after recruitment... We assigned participants to either the intervention or control group in a 1:1 ratio with permuted block sizes of four and eight."
Allocation concealment (Selection bias)	Low risk	Pg. 1645: "Interviewers were unaware of the materials that women would receive (ensuring allocation concealment)."
Blinding of participants and personnel (Performance bias)	Low risk	Pg. 1645: "Double blinded. Women knew they would receive one of two versions of an information booklet but did not know how these differed or which one was the intervention. We designed the follow-up interview to ensure the group assignment was unclear to the interviewer until the final question."
Blinding of outcome assessment (Detection bias)	Low risk	Pg. 1645: "Researchers who analysed data were unaware of the random allocation."
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Both groups have similar dropout rates.
Selective reporting (Reporting bias)	Low risk	The response rate was the same in both groups.
Other bias	Low risk	It seems free of other biases.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

For more information, visit: **www.prisma-statement.org**.

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Assessment of the effects of decision aids about breast cancer screening: a systematic review and meta-analysis

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Assessment of the effects of decision aids about breast cancer screening: a systematic review and meta-analysis

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Word count: 4,130 words

ABSTRACT

Objective: The aim of this systematic review and meta-analysis of randomised controlled trials (RCTs) and observational studies is to assess the effect of decision aids (DAs) in women aged 50 and under facing the decision to be screened for breast cancer.

Setting: Screening for breast cancer.

Intervention: DAs aimed to help women make a deliberative choice regarding participation in mammography screening by providing information on the options and outcomes.

Eligible studies: We included published original, non-pilot, studies that assess the effect of DAs for breast cancer screening. We excluded the studies that evaluated only participation intention or actual uptake. The studies' risk of bias was assessed with the Cochrane Collaboration's tool for RCTs and the National Institutes of Heath Quality Assessment Tool for non-RCTs.

Primary and secondary outcomes: The main outcome measures were informed choice, decisional conflict and/or confidence, and knowledge. Secondary outcomes were values, attitudes, uncertainty, and intention to be screened.

Results: A total of 607 studies were identified, but only three RCTs and one before-after study were selected. The use of DAs increased the proportion of women making an informed decision by 14%, 95% CI=[2%, 27%] and the proportion of women with adequate knowledge by 12%, 95% CI=[7%, 16%]. We observed heterogeneity among the studies in confidence in the decision. The meta-analysis of the RCTs showed a significant decrease in confidence in the decision and in intention to be screened .

Conclusions: Tools to aid decision-making in screening for breast cancer improve knowledge and promote informed decision; however we found divergent results on decisional conflict and confidence in the decision. Under the current paradigm change, which favours informed choice rather than maximising uptake, more research is necessary for the improvement of DAs.

Keywords: breast cancer, decision aid, mammography, screening, shared decision making.

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Strengths and limitations of this study

- This is the first systematic review focused in the impact of DAs about breast cancer screening on informed choice, decisional conflict, knowledge, values, attitudes, and intention to be screened.

- The review focused on studies that assess DAs designed to inform and help women to decide, not on those aimed at encouraging participation and adherence.

- A limitation of the review is the reduced number of studies included, which can be explained by the recent development of DAs for breast cancer screening.

- There was variability in the type and amount of information included in the DAs and also in the information given to the control group, this variability may explain part of the significant heterogeneity in all the outcomes evaluated.

- The DAs were designed in Australia, the USA and Germany, and women included had higher education levels than women in the general population, limiting the generalisability of the results.

INTRODUCTION

In Western countries, screening for breast cancer spread during the 1990s. There was a general consensus on the benefits of screening since several clinical trials in the US and Northern Europe estimated a statistically significant and clinically relevant reduction in mortality from breast cancer.[1] But, in the year 2000 the systematic review from Gotzsche et al. started a hot debate, still alive, on the relevance and magnitude of benefits and harms of breast cancer screening.[2]

More than two decades after the introduction of breast cancer mass screening, the evidence on the harm-benefit balance remains inconclusive. On the one hand, advances in adjuvant treatments, a multidisciplinary approach for breast cancer treatment, and earlier identification of symptoms by women, have diminished the impact of screening on breast cancer mortality reduction.[3-5] On the other hand, the evidence on adverse effects of screening, charactesized by a high consensus on the risk of false positive results and lack of agreement on the size of overdiagnosis and overtreatment, show that the potential harms of screening are not insignificant.[6-8]

The current prevailing paradigm, which encourages participation, is changing. Two proposals are gaining strength. First, the need to inform women of potential benefits and harms of screening. Some propose not devoting more energy to increasing participation, but dedicating it to informing women to help them make the best decision based on their preferences and values. [9-12] Second, customising the screening strategies to individual risk. Some recent studies[13-15] based on mathematical models suggest that risk-based screening may increase benefits and reduce harms. The literature shows that both proposals are gaining strength.[16,17]

Decision aids (DA) are instruments that communicate evidence-based information on the benefits and harms of different health-care options to help people make informed choices. The Stacey et al. work,[18] a recently updated Cochrane systematic review on DAs for people facing treatment or screening decisions, included 105 published randomised controlled trials (RCTs) of DAs, 26 of which dealt with cancer screening (13 prostate, 10 colon, two breast, and one cervix) and four on breast cancer genetic

testing. The authors concluded that, compared with usual care, people exposed to DAs feel more knowledgeable, better informed, and clearer about their values, and they probably have a more active role in decision making and more accurate risk perceptions. In addition, Stacey et al.[18] think that more research is needed on their effects on adherence to the chosen option, cost-effectiveness, and use with lower literacy populations.

Information on cancer screening is often biased, incomplete and persuasive.[19] Some leaflets mention the possibility of harms, however they do not quantify them. In Europe, some organisations are providing information on benefits and harms of breast cancer screening, in particular, estimates of mortality reduction, and the frequency of false positive results of mammography and invasive tests (e.g. Cochrane collaboration, UK NHS Breast Screening Programme; German Institute for Quality and Efficiency in Health Care; Fundació Lliga per a la Investigació i Prevenció del Càncer and Agència de Salut Pública de Barcelona, in Catalonia (Spain)). Information on overdiagnosis appears in some of the information materials. Two recent studies[11,20] have compared the impact of adding information on overdiagnosis to support informed choice on breast cancer screening. In preparation for an PRCT on the effect of a DA in mass screening in two regions of Spain, we aimed to identify and summarise all the studies reporting the description and assessment of a DA when applied to women aged 50 and under facing the decision to be screened with mammography in a population-based screening or opportunistic case-finding framework. We expected to find that DAs improve knowledge of options, benefits, and harms; create accurate perceptions of benefits and harms; reduce decisional conflict; and enhance informed choice.

METHODS

Eligibility criteria

Types of studies

We included all the published studies with RCT or before-after designs that compared a DA to no intervention, usual care, or alternative interventions. The search date upper limit was December 31, 2016. Pilot studies were excluded.

Types of participants

Participants were women facing decisions about screening in a population-based screening or opportunistic case-finding framework within the age interval of recommended mammography screening. We excluded studies aimed at elderly women only, and studies where participants were asked to make hypothetical choices.

Types of interventions

DAs were defined as interventions aimed to help women make a deliberative choice regarding participation in mammography screening, by providing information on the options and outcomes. We excluded studies aimed at increasing participation or promoting adherence, and studies not carried out in the context of women facing a real decision.

Types of outcome measures

The primary outcomes were: informed choice based on values, decisional conflict and/or confidence, and knowledge. The secondary outcomes included: values and/or attitudes towards screening, proportion remaining undecided, and proportion reporting intention to be screened.

Language

We included articles reported in any language.

Information sources

Search methods for identification of studies

The search strategy was performed in MEDLINE and SCOPUS and adapted and replicated in EMBASE, CINAHL, PsycInfo, and the Cochrane Library Plus. The search included the key words "breast cancer" and "decision" (or "choice") and "aid" (or "informed") and "mammography" (or "mammogram"), within the paper title or the abstract. It excluded the key word "protocol" from the paper titles and allowed synonyms and free suffixes and prefixes. The reviews identified by this search, as well as the references that they included, were exhaustively used to refine the search strategy to ensure that all the possible relevant references for our review were identified (see online supplementary Appendix 1).

Study selection and synthesis of results

All the studies satisfying the inclusion criteria regarding design, participants and interventions were included in this review. Selection and the assessment of risk of bias was independently conducted in pairs by four reviewers (MC, MJP, MMA, and MR). In the case of disagreement, studies were discussed by the whole team of reviewers until an agreement was reached.

Data extraction

The data extraction for the selected studies was independently conducted by two reviewers (MMA and MR) and a consensus version was obtained. In the case that the necessary data was not provided in the articles, the corresponding authors were contacted.

Risk of bias of individual studies

For the risk of bias assessment we used the *Cochrane risk of bias* tool for RCTs and the *National Institutes of Heath quality assessment tool* for non-RCTs.[21] In case of non-RCTs, the selection, allocation and blinding assessments were not applicable.

Sampling bias (a problem for external validity) was assessed in all the included studies.

The risk of bias (*low, unclear,* or *high*) was assessed considering the study design and the methodological quality of the studies. Data consistency was rated as *no inconsistency*, *inconsistency present*, or *not applicable* if there was only one study available, considering each outcome's direction, magnitude, and statistical significance over the set of included studies. The assessment methods followed the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/) and were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[22]

Analysis of results

For each endpoint of interest, the decision to combine the results of the selected studies in a meta-analysis was based on the heterogeneity of patient populations and interventions, as well as on the methodological heterogeneity of study designs and reported outcomes. Consistency and heterogeneity of the studies' results were assessed with the I^2 index and the Q test, respectively.

If comparable measures were obtained, we pooled the data for the outcomes. To facilitate the data pooling, scores with different ranges (minimum and/or maximum values) were standardised to range from 0 to 100 points. We estimated a weighted effect intervention (with 95% confidence interval) as the difference between the intervention and control groups in experimental designs, and as changes from baseline assessed in outcome measures post-intervention in before-after studies. Mean differences or pooled relative risks (RR) were estimated for continuous or dichotomous outcomes, respectively. The summary effects of the intervention were obtained using random effects meta-analysis. An additional meta-analysis of the RCTs was performed. We used the library `metafor` of the R package.[23]

RESULTS

Study selection

In total, we identified 607 unique citations from the electronic database searches. Of these, only 14 were selected for evaluation of the inclusion and exclusion criteria. Figure 1 presents the flowchart of the study selection process. Ten studies were excluded after full text assessment (see Table A2.1 in Appendix 2 for details). Finally, three randomised controlled studies (Mathieu 2010,[24] Gummersbach 2015,[20] and Hersch 2015,[11] and one before-after study, Eden 2015,[25] were selected. These four studies involved a total of 1650 participants from four countries (two from Australia, one each from Germany and the United States of America).

Study characteristics

Table 1 presents the studies' characteristics. Gummersbach and Hersch compared two DAs with information about the benefits and harms of mammography screening, providing the intervention group with more complete information. Whereas Gummersbach added more critical information on the harms of screening mammography in the intervention group, the DA in Hersch only differed in providing thorough information of overdetection or not. In contrast, Mathieu compared a DA with receiving no information, and Eden assessed changes after providing a DA. It is important to notice that whereas Hersch and Gummersbach targeted women who were approaching 50 and deciding whether to screen as per their national program, Mathieu included younger women considering whether to start screening in their 40s, before the recommended age of 50 in Australia. Participants' characteristics are shown in Table 2. Means of age were located in the 40-50 yrs interval. There are differences between studies in the prevalence of previous mammograms and in education level.

Table 1: Description of the studies' characteristics

Study	Design	Age group	Exclusion criteria	Decision aid (DA)
Mathieu 2010	Randomised controlled study, pragmatic[a]	38-45	Personal history of breast cancer (BC)	Web-based DA, information on possible screening outcomes and worksheet to help weigh up and clarify preferences. Intervention group: immediate access; control group: delayed access after completing the outcome measures.
Eden 2015	Before-after study, clinical	40-49	Personal history of BC, prior breast biopsy, high risk of BC[b], previous mammography within 1 year, non-English speaking	Web-based DA, in 3 rural clinical settings, including BC information and questions for risk and self-preferences assessment.
Gummersbach 2015	Randomised controlled study, primary care based	48-49	None	Mailed leaflet, more informative(especially on overdiagnosis) for the intervention group. The leaflet was not created in accordance with published criteria for evidence-based patient information, but it contained much more information relevant to decision-making than the leaflet of the control group.
Hersch 2015	Randomised controlled study, community-based	48-50	Personal or strong family history of BC, BC risk higher than average, mammography in the past 2 years, non-English speaking	Mailed DA, outcomes assessed by phone interview. Evidence-based explanatory and quantitative information on overdiagnosis, BC mortality reduction, and false positives for the intervention group vs. information on BC mortality reduction and false positives for the control group.

[a] :The trial was advertised on the media. Women had free access to the site for eligibility assessment.

[b] : Breast cancer risk based on the Breast Cancer Genetics Referral Screening Tool (B-RST).

Table 2: Description of studies' participants

Study	Group	Participants	Age Mean (SD)	Previous mammography	University degree
Mathieu 2010	Intervention	172	41.9 (2.0)[a]	53 (30.8%)	76 (44.2%)[b]
	Control	212	41.8 (2.2)[a]	52 (24.5%)	126 (59.4%)[b]
Eden 2015	Before-After	75	45.0 (2.5)	51 (68.0%)	34 (45.3%)
Gummersbach 2015	Intervention	178	48.67 (0.79)	[c]	33 (18.5%)
	Control	175	48.76 (0.80)	[c]	23 (13.2%)
Hersch 2015	Intervention	419	49.67 (0.44)	[d]	119 (28.4%)
	Control	419	49.70 (0.44)	[d]	123 (29.4%)

SD: Standard deviation.

[a] Out of the assessed participants, 116 and 198 in intervention and control group, respectively.

[b] Out of the assessed participants, 114 and 199 in intervention and control group, respectively.

[c] 3 and 4 women with BC in intervention and control group, respectively. Participants were not asked about mammographic exams in the past.

[d] No women with previous mammogram in the previous two years but it is not stated how many women had mammograms more than two years before being included in the study.

Risk of bias in the included studies

The evaluation of the risk of bias for the RCTs included the assessment of bias in selection, performance, detection, attrition, reporting, sampling or any other source of bias. Details on the authors' judgement and rationale for risk of bias can be found in Tables A2.2-A2.5 (Appendix 2). The majority of assessed criteria were judged as low risk. Hersch 2015[11] was the only study free of a high risk of bias in all the domains assessed. Gummersbach 2015[20] was rated as having a high risk of attrition bias due to a high level of non-response. Mathieu 2010[24] was rated as having an unclear risk of allocation concealment and also of selective reporting. Eden 2015[25] included a small sample of women with greater than a high school education, in a single rural geographical area. Therefore, the sample representativeness was limited.

Main outcomes

Tables 3 and 4 present the risk differences for the dichotomous outcomes and the mean differences for the continuous outcomes, respectively. Figures 2 and 3 show the results of the meta-analyses for the dichotomous and continuous outcomes, respectively. The results of the meta-analysis performed exclusively on the RCTs are presented in Table A3.1, Appendix 3.

Informed choice

The DAs increased the proportion of women making an informed decision, 58.0% vs. 36.5% according to Mathieu (p < 0.001) and 24.2% vs. 15.4% according to Hersch (p = 0.002). The meta-analysis estimation of risk difference was 14%, 95% CI=[2%, 27%] (Table 3 and Figure 2).

Decisional conflict and/or decisional confidence

Eden observed a significant post-intervention decrease in decisional conflict and a significant increase in decisional confidence (Table 4, Figure 3). In contrast, Hersch noted no significant effect of the intervention on decisional conflict and a significant decrease in decisional confidence, observed also by Gummersbach. These contradictory results introduced high heterogeneity that increased the uncertainty about the overall impact of a DA on decisional conflict and/or confidence (Figure 3). The meta-analysis of the RCTs showed a significant decrease in the confidence scale (Table A3.1, Appendix 3).

Knowledge

The use of a DA increased knowledge according to all studies, although the positive difference was not statistically significant in the Gummersbach study (Tables 3 and 4). The overall results provided by the meta-analyses were statistically significant, either in the proportion of women with adequate knowledge, with a significant increase of 12%, 95% CI=[7%, 16%], or in the mean score, with a difference of 0.70 out of 10 points, 95% CI =[0.27, 1.13] (Figures 2 and 3).

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Table 3: Risk differences for the dichotomous outcomes: informed choice, knowledge, positive attitudes/values towards screening, undecided and intention to be screened.

Outcome	Study	Group	Assessed	n(%)	Difference, *p-value*[a]
Informed choice[b]	Mathieu 2010[c]	Intervention	112	65 (58.0%)	21.5%, p<0.001
		Control	192	70 (36.5%)	
	Hersch 2015[d]	Intervention	409	99 (24.2%)	8.8%, p=0.0017
		Control	408	63 (15.4%)	
Knowledge	Mathieu 2010[e]	Intervention	113	106 (93.8%)	10.7%, p=0.01
		Control	189	157 (83.1%)	
	Hersch 2015[f]	Intervention	419	122 (29.1%)	13.0%, p<0.001
		Control	419	71 (16.9%)	
Positive attitudes[g]	Mathieu 2010	Intervention	111	88 (79.3%)	0.2%, p=0.89
		Control	182	144 (79.1%)	
	Hersch 2015	Intervention	409	282 (68.9%)	-14.4%, p<0.001
		Control	408	340 (83.3%)	
Undecided	Mathieu 2010	Intervention	117	21 (17.9%)	-21.3%, p<0.001
		Control	209	82 (39.2%)	
	Hersch 2015	Intervention	419	69 (16.5%)	9.3%, p<0.001
		Control	419	30 (7.2%)	
Intention to be screened	Mathieu 2010	Intervention	117	50 (42.7%)	3.0%, p=0.64
		Control	209	83 (39.7%)	
	Eden 2015	Before	75	54 (72.0%)	6.7%[h], p=0.123
		After	75	59 (78.7%)[h]	
	Gummersbach 2015	Intervention	178	145 (81.5%)	-7.1%, p=0.06
		Control	175	155 (88.6%)	
	Hersch 2015	Intervention	419	308 (73.5%)	-13.1%, p<0.001
		Control	419	363 (86.6%)	

[a] Fisher's exact test.

[b] Eden provided only a post-intervention mean of the preparation for decision making scale of 73.2 (18.1).

[c] Out of the women assessed, including undecided women in the denominator.

[d] Informed choice defined as adequate knowledge and intentions consistent with attitudes.

[e] Knowledge (according to Mathieu): score higher than 5 out of 10.

[f] Knowledge (according to Hersch): Adequate knowledge when scoring at least 50% of the total available marks, including at least 1 numerical mark, on all three screening outcome subscales (breast cancer mortality benefit, false-positive screening result and overdiagnosis).

[g] Positive attitudes/values >50 out of 100 according to Mathieu and >=24 out of 30 according to Hersch.

[h] Difference as post minus pre-intervention values.

Table 4:Mean differences for the continuous outcomes: knowledge, decisional conflict, and decisional confidence.

Outcome	Study	Group	N	mean (SD)	Difference p-value
Knowledge	Mathieu 2010[a]	Intervention	113	7.35(1.84)	1.1, p<0.001
		Control	189	6.27(1.85)	
	Gummersbach 2015[a]	Intervention	161	5.49 (1.99)	0.26, p=0.26
		Control	168	5.23 (2.06)	
	Hersch 2015[b]	Intervention	419	13.49(4.36)	1.65, p<0.001
		Control	419	11.84(3.74)	
Decisional conflict	Eden 2015[c]	Before	75	46.33 (27.04)	-38.0, p<0.001
		After	75	8.33 (15.58)	
	Hersch 2015	Intervention	419	12.55 (17.60)	0.35, p=0.78
		Control	419	12.20 (18.90)	
Decisional confidence	Eden 2015[d]	Before	75	79.67 (18.62)	16.16, p<0.001
		After	75	95.73 (6.86)	
	Gummersbach 2015[e]	Intervention	178	5.15 (1.36)	-0.37, p=0.017
		Control	182	5.52 (0.93)	
	Hersch 2015[f]	Intervention	419	4.35 (0.74)	-0.18, p=0.0003
		Control	419	4.53 (0.67)	

[a] Knowledge scored, range 0-10.
[b] Knowledge scored, range 0-22.
[c] Decision conflict scale, range 0-100.
[d] Self-efficacy scale, range 0-100.
[e] Confidence scale, range 0-6.
[f] Confidence scale, range 0-5 (mean of 3 subscales).

Secondary outcomes

The high heterogeneity of the results did not make it possible to reach conclusions about significant post-intervention changes or differences in secondary outcomes, such as positive attitudes and values towards screening, decisions about screening,

and intention to be screened (Table 3, Figure 2). The results of the meta-analysis performed exclusively on the RCTs are presented in Table A3.2, Appendix 3.

Positive attitudes/values towards screening

Mathieu did not show any significant difference in attitudes, but Hersch obtained a significantly lower frequency of women with positive attitudes towards screening among women receiving the DA with overdiagnosis information.

Undecided about BC screening

Mathieu reported a significant decrease in the frequency of women undecided about BC screening after the DA administration. In contrast, Hersch obtained a significant increase for the intervention group, with the DA including thorough overdiagnosis information.

Intention to be screened

Hersch noted a statistically significant decrease in the intention to be screened and Gummersbach a nearly significant decrease. The meta-analysis of the RCTs showed a significant decrease in the intention to be screened, 7%, 95% CI=[2%, 15%] (Table A3.2, Appendix 3). The lower proportions intending to screen in the Mathieu study with respect to the other studies (Table 3) can be attributed to the fact that women were younger than 50, the recommended age for starting screening in Australia.

DISCUSSION

Summary of main results

This systematic review includes three RCTs and one before-after study assessing DAs given to women facing the decision to be screened with mammography. There was variability in the type and amount of information included in the DAs, and also in the information given to the control group. This variability may explain in part, the significant heterogeneity in all the outcomes evaluated. Despite this heterogeneity, the

meta-analysis revealed that DAs produce a statistically significant improvement in knowledge of screening outcomes as well as a significant increase in the frequency of women making an informed choice. However, no significant effects were observed for decision conflict, decision confidence and positive attitudes towards screening. Therefore, the overall conclusion from our review is that DAs significantly increase women's knowledge and therefore the proportion of women making an informed choice, but do not significantly modify attitudes or intentions towards screening. It is important to mention that when the meta-analysis was performed on the RCT subgroup we found a significant decrease in confidence in the decision and intention to be screened. This decrease in screening intention is consistent with the findings of Ivlev et al[26] in a recently published systematic review of the effect of DAs on women's intentions to undergo screening mammography in age groups where shared decision making is recommended.

Similarly, no significant effects were observed for the secondary outcomes that measured the frequency of participants remaining undecided or choosing to be screened. More specifically, Eden detected a significant decrease in intra-individual post-intervention decision conflict, which was not observed by Hersch, when comparing women receiving a DA with overdiagnosis information vs. those without it. Indeed, Eden also obtained a significant improvement in intra-individual post-intervention decision confidence, while Gummersbach and Hersch obtained a significant decrease in decision confidence when comparing women receiving a DA with exhaustive information on screening side effects vs. those without it. This result can be explained by the impact of the information on adverse events of screening. Positive attitudes towards screening significantly decreased when overdiagnosis information was added to the DA, as observed by Hersch, in contrast with the absence of change observed by Mathieu. The frequency of women remaining undecided after DAs showed completely contradictory results. While Mathieu observed a very significant decrease, Hersch obtained a significant increase. The frequency of women decided to be screened showed a significant difference in the Hersch study, where a decrease was observed for the group provided with overdiagnosis information, while

Gummersbach, the other study incorporating thorough information on mammography side effects, showed a nearly significant decrease.

Quality of the evidence

Risk of bias ratings show that the included studies had a low risk of bias in most of the assessed domains. There may have been publication bias due to failure to report negative findings. Several of the outcomes showed a high level of heterogeneity that limits the interpretation of the pooled effect size.

Strengths and limitations

This is the first systematic review focused on the impact of DAs about breast cancer screening on informed choice and other relevant outcomes from the women's perspective. Our review focused on studies that assess DAs designed to inform and help women to decide, not on studies aimed at encouraging participation and adherence.

Studies differed in design, especially in terms of the control group. In the Mathieu study,[24] the control group did not receive the DA until the outcome measures had been completed. The Eden study, [25] assessed the post-intervention intra-individual changes after the DA was provided. In the Gummersbach study,[27] a more informative leaflet was compared to a less informative one. Finally, in the Hersch study,[11] the intervention DA had evidence-based explanatory and quantitative information on overdiagnosis, breast cancer mortality reduction, and false positives, whereas the control DA included information on breast cancer mortality reduction and false positives. Previous knowledge was not measured in the Mathieu and Gummersbach RCTs, although one expects that both groups had similar knowledge about mammography screening at baseline. Hersch et al.[11] measured some basic knowledge at baseline using a subset of items and showed similar results between groups. In the Eden study, which assessed intra-individual changes, the DA was particularly useful for the least informed and least confident women. On the other hand, Gummersbach[20] noted that education level was positively associated with acquired knowledge and

that the less educated women had less relevant decisional knowledge after reading the leaflet, but they were more willing to undergo mammography than more educated women. Only the Hersch study included a follow-up for final screening participation, but the results are not published yet.

The limitations of the study are principally related with the generalisation of the results. Women included in the studies probably had a higher education level, greater health awareness, and were more actively involved in health care decisions, than women in the general population. In addition, the DAs were designed using specific data from Australia (Mathieu and Hersch), the United States (Eden) and Germany (Gummersbach), providing results which may not be generalisable to other countries. All studies evaluated the DAs only from the women's perspective, and in the context of research, where participants may have a higher level of commitment than women invited to participate in a breast screening program.

Unanswered questions and future research

Women should use DAs to be informed and support their decisions about breast cancer screening given their preferences and attitudes. It is important to ensure that the information provided is well understood by all women, including those with lower level of education.

The Internet is an inexpensive tool for the dissemination of DAs or to provide additional information, if necessary, in order to present women with all the options available and the harms and benefits of each of them. But there are women that are not familiarised with or do not have access to the Internet and therefore other ways to disseminate information are also needed.

According to Gummersbach the doctor's advice was the most important factor helping with the decision to be screened for almost half of the women. This result indicates the importance of shared decision-making, where DAs are essential tools. Shared decision-making can also help reduce decisional conflict and improve confidence when information on screening harms is provided.

As highlighted by Hersch et al., establishing what constitutes an informed choice, and what knowledge is needed in order to be informed, is an important issue and no consensus currently exists on what knowledge constitutes being objectively informed enough for an informed or shared decision. When Hersch et al. used an expert-led approach based on medical guidelines and underpinned by decision theory, which required numerical and conceptual knowledge, only 24% in the intervention group and 15% in the control group were assessed as informed. When only conceptual knowledge was required these proportions increased to 50% and 19%, respectively. Difficulties understanding quantitative information or the widespread positive value placed on cancer screening can produce a certain resistance to information on possible harms. Their study was the only one obtaining a significant increase in the amount of women remaining undecided about being screened in the group receiving information on overdiagnosis.

The DAs of the included studies lacked detailed information on the outcomes of screening, detection, treatment, or financial strain and opportunity costs from the perspective of the society, which could be considered important for inclusion in future DAs.

Conclusions

DAs for breast cancer screening can improve knowledge and promote informed decision making, in accordance with their preferences, for women who face the decision of screening. However we found divergent results on decisional conflict and decision confidence. Under the new paradigm, which favours informed choice rather than maximising uptake, more research is necessary for the improvement of DA.

Figure legends

Figure 1: Study flow diagram

Figure 2: Meta-analysis of risk differences for the dichotomous outcomes (random effects model)

Figure 2 footnote

Heterogeneity measures: Informed choice: I^2=74.7%, Q test p-value=0.047; Knowledge: I^2=0%, Q test p-value=0.75; Positive attitudes: I^2=84.6%, Q test p-value=0.011; Undecided: I^2=96.9%, Q test p-value<0.001; Intention to be screened: I^2=75.9%, Q test p-value=0.008.

Figure 3: Meta-analysis of mean differences in scores for the quantitative outcomes (random effects model)

Figure 3 footnote

Heterogeneity measures: Decision conflict: I^2=99.0%, Q test p<0.001; Decision confidence: I^2=98.3%, Q test p<0.001; Knowledge: I^2=75.7%, Q test p=0.030.

The InforMa Group

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: funding from the Spanish Ministry of Health and the Biomedical Research Institute of Lleida (IRBLLEIDA) as described below; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Informed consent

Since the work does not involve direct research in human subjects, informed consent was not obtained. Nevertheless, the study was approved by the Ethics Committee of the Hospital Universitari Arnau de Vilanova in the city of Lleida (Spain).

Contributors and authorship

MMA, MC and MR designed the study. All authors contributed towards the execution of the study. MMA provided methodological expertise in systematic reviews and searching strategies. The selection and risk of bias assessment of each study was independently conducted in pairs by four reviewers (MC, MJP, MMA, and MR). AP contributed to extracting the information of the identified studies and assessing the inclusion criteria. MMA and MR wrote the first draft with guidance and contributions from MC, MJP, and MG. All authors read, provided critical feedback and approved the final manuscript.

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Data Sharing Statement

No additional data available.

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Author(s) and Year	Intervention +	n	Control +	n	Risk difference [95% CI]
Decided to be screened					
Hersch, 2015	308	419	363	419	-0.13 [-0.18, -0.08]
Gummersbach, 2015	145	178	155	175	-0.07 [-0.15, 0.00]
Eden, 2015	59	75	54	75	0.07 [-0.07, 0.20]
Mathieu, 2010	50	117	83	209	0.03 [-0.08, 0.14]
RE model estimate					-0.04 [-0.13, 0.05]
Undecided					
Hersch, 2015	69	419	30	419	0.09 [0.05, 0.14]
Mathieu, 2010	21	117	82	209	-0.21 [-0.31, -0.12]
RE model estimate					-0.06 [-0.36, 0.24]
Positive attitudes					
Hersch, 2015	282	409	340	408	-0.14 [-0.20, -0.09]
Mathieu, 2010	88	111	144	182	0.00 [-0.09, 0.10]
RE model estimate					-0.08 [-0.22, 0.07]
Knowledge					
Hersch, 2015	122	419	71	419	0.12 [0.07, 0.18]
Mathieu, 2010	106	113	157	189	0.11 [0.04, 0.18]
RE model estimate					0.12 [0.07, 0.16]
Informed choice					
Hersch, 2015	99	409	63	408	0.09 [0.03, 0.14]
Mathieu, 2010	65	112	70	192	0.22 [0.10, 0.33]
RE model estimate					0.14 [0.02, 0.27]

-0.5   0   0.5
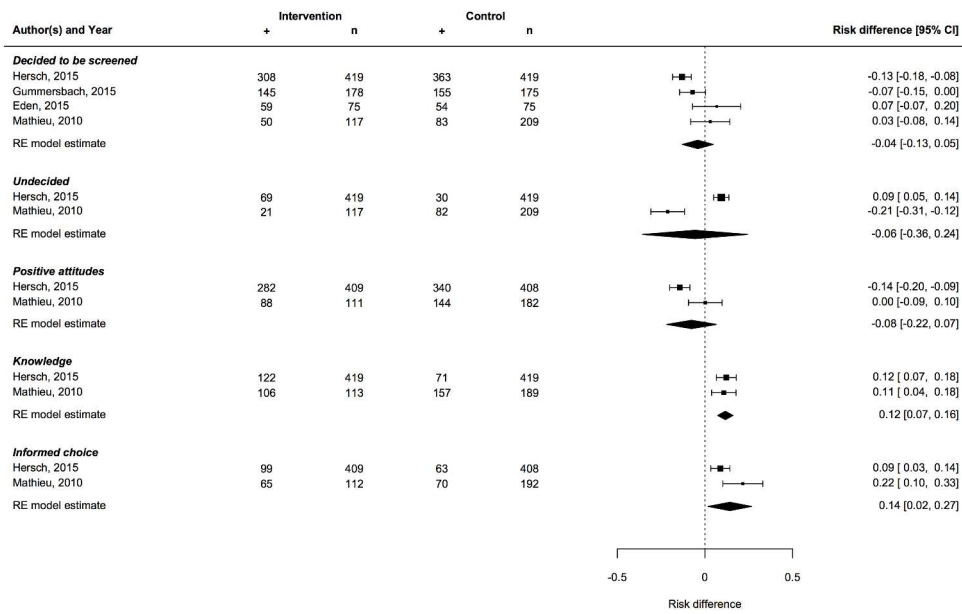
Risk difference

Figure 2: Meta-analysis of risk differences for the dichotomous outcomes (random effects model)

286x178mm (300 x 300 DPI)
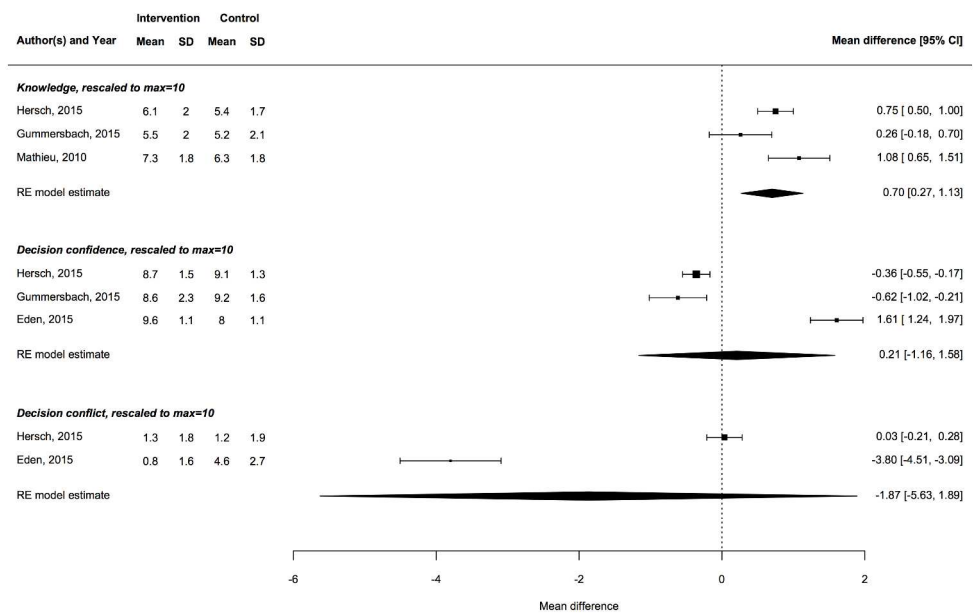
Figure 3: Meta-analysis of mean differences in scores for the quantitative outcomes (random effects model)

286x178mm (300 x 300 DPI)

APPENDIX 1

Search criteria for Decision Aids on breast cancer screening

1. In MEDLINE:

    "breast cancer"[tiab] (decision[tiab] OR choice[tiab]) AND (aid[tiab] OR informed[tiab]) AND (mammography[tiab] OR mammogram[tiab]) NOT protocol[ti]

2. Adapting it to SCOPUS:

    (TITLE-ABS-KEY ("breast cancer") AND (TITLE-ABS-KEY (decision) OR TITLE-ABS-KEY (choice)) AND(TITLE-ABS-KEY (aid) OR TITLE-ABS-KEY (informed)) AND (TITLE-ABS-KEY (mammography) OR TITLE-ABS-KEY (mammogram)) AND NOT TITLE (protocol)

3. And, equivalently for EMBASE, CINAHL, PsycInfo, and the Cochrane Library Plus.

APPENDIX 2

Table A2. 1: Excluded studies after full text assessment

Study	Reason of exclusion
Lawrence 2000	No adequate evaluation of the decision aid (DA), only acceptability is assessed.
Webster 2007	No adequate evaluation of the DA, no DA but a leaflet is assessed.
Bodurtha 2009	No adequate evaluation of the DA, no decision is assessed.
Pasternack 2011	No adequate evaluation of the DA, only acceptability is assessed.
Waller 2013	No adequate evaluation of the DA, only the design is described, no assessment is reported.
Hersch 2014	Pilot study of a main study already included.
Waller 2014	No adequate evaluation of the DA, three formats of reporting information are compared.
Berens 2015	No adequate evaluation of the DA, no DA but a leaflet is assessed.
Petrova 2015	The DA is not assessed in a real context.
Bourmaud 2016	No adequate evaluation of the DA. Informed choice is assessed only by participation rate. The overdiagnosis harm is not mentioned.

Characteristics of the included studies

Table A2.2. Study Characteristics

Mathieu 2010	
Methods	Online randomised controlled study of decision aid (DA) vs usual care (UC).
Setting	Australia, where biennial mammography screening is offered free of charge for all women over the age of 40, through a national population screening program. Women aged 50–69 years are invited by personal letter, and, women turning 40 are eligible for screening if they wish to start earlier.
Participants	189 + 223 women, aged 38-45 years, who accessed the web site. Eligible if they were considering whether to (a) start screening in their 40s (ie before the recommended age of 50) or (b) wait until they were 50.
Interventions	DA: explained the benefits and harms, included a values clarification exercise and a worksheet to support decision making. UC: delayed intervention
Outcomes	Primary outcome: knowledge of benefits and harms of screening. Secondary outcomes: informed choice (composite of knowledge, values and intention), anxiety, acceptability of the DA, and intention regarding screening.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 66 (randomization and baseline questions section): "computer generated simple randomization schedule".
Allocation concealment (Selection bias)	Unclear risk	Pg. 66 "randomization was conducted in a concealed manner." The method of allocation concealment was not stated.
Blinding of participants and personnel (Performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (Detection bias)	Low risk	Unclear blinding but outcomes were not subjective to interpretation.
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Table 2: all outcomes mentioned in the paper were reported in the Results section. Table 3: outcomes of anxiety and acceptability can be found. Page 69 explains missing data. Figures 1 and 2 provide the reasons for the exclusions in each group.
Selective reporting (Reporting bias)	Unclear risk	No mention of protocol.
Other bias (Sampling and other)	Low risk	Pg. 65: "To proceed, women were required to click in a box on the computer screen to indicate they had read the study information and were eligible to participate." The trial was advertised on various websites and in a radio program.

Table A2.3. Study Characteristics

Eden 2015	
Methods	Observational study. Women were assessed before and after the decision aid (DA).
Setting	Three clinics in the Oregon Rural Practice-Based Research Network (ORPRN), USA.
Participants	75 women aged 40-49 years with no known risk factors associated with high or moderate risks for breast cancer and no mammography during the previous year.
Interventions	The decision aid (Mammopad) included modules on breast cancer, mammography, risk assessment, and priority setting about screening.
Outcomes	Primary outcome: decisional conflict measured before and after using DA. Secondary outcomes: decision self-efficacy and intention to begin or continue mammography screening.

Criteria	**Yes/No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	Yes	
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	
4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?		NA

*CD, cannot determine; NA, not applicable; NR, not reported

National Institutes of Health. Quality Assessment Tool for before-after (pre-post) studies with no control group. Study Quality Assessment Tools. https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after. Accessed 11 May 2017.

Table A2.4. Study Characteristics

Gummersbach 2015	
Methods	Randomised to two decision aids (DA) with different information.
Setting	Family practices in the German federal state of North Rhine–Westphalia. In Germany, screening is recommended biennially for all women aged 50 to 69.
Participants	353 women, aged 48-49 years, about to receive the first invitation to screening.
Interventions	Intervention: DA with detailed information on screening harms. Control: standard DA.
Outcomes	Primary outcome: willingness to participate in screening. Secondary outcomes: knowledge, decisional confidence, determinants of the screening decision.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 62: "The 24 participants from each practice were selected by a computer-assisted random procedure."
Allocation concealment (Selection bias)	Low risk	Pg. 62: the group allotment process was also random.
Blinding of participants and personnel (Performance bias)	Low risk	Pg. 62: "The participants and their family physicians were blinded with respect to group allotment, but the study team was not".
Blinding of outcome assessment (Detection bias)	Low risk	Pg. 62: "The participants were asked by letter to fill out the questionnaire after reading the leaflet and to send it back in an envelope that was also enclosed in the mailing".
Incomplete outcomes' data. All outcomes (Attrition bias)	High risk	46.7% non-response.
Selective reporting (Reporting bias)	Low risk	Pg. 63. Primary outcome was assessed in accordance with the protocol.
Other bias (sampling bias)	Low risk	Participants recruited from family practices.

Table A2.5. Study Characteristics

Hersch 2015	
Methods	Randomised to two decision aids (DA) with different information.
Setting	Community-based sample of women around the target age for starting breast screening, in New South Wales, Australia.
Participants	879 women, aged 48-50 years, about to receive the first invitation to screening.
Interventions	Intervention: comprising evidence-based explanatory and quantitative information on overdetection, breast cancer mortality reduction, and false positives. Control: decision aid including information on breast cancer mortality reduction and false positives.
Outcomes	Primary outcome: informed choice defined as adequate knowledge and consistency between attitudes and screening intentions. Secondary outcomes: screening attitudes, decisional conflict, worry about breast cancer, intention about undergoing screening, and opinions about the decision aid.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 1644: "A programmer who had no contact with participants generated the randomisation sequence using a computer system that was inaccessible until after recruitment... We assigned participants to either the intervention or control group in a 1:1 ratio with permuted block sizes of four and eight."
Allocation concealment (Selection bias)	Low risk	Pg. 1645: "Interviewers were unaware of the materials that women would receive (ensuring allocation concealment)."
Blinding of participants and personnel (Performance bias)	Low risk	Pg. 1645: "Double blinded. Women knew they would receive one of two versions of an information booklet but did not know how these differed or which one was the intervention. We designed the follow-up interview to ensure the group assignment was unclear to the interviewer until the final question."
Blinding of outcome assessment (Detection bias)	Low risk	Pg. 1645: "Researchers who analysed data were unaware of the random allocation."
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Both groups have similar dropout rates.
Selective reporting (Reporting bias)	Low risk	Pg. 5. Primary outcome was assessed in accordance with the protocol.
Other bias	Low risk	It seems free of other biases.

APPENDIX 3

Table A3.1. Mean differences for the quantitative outcome decisional confidence. Meta-analysis of the RCTs

Outcome	Study	Group	N	Mean (SD)	Difference, p-value
Decisional confidence	Gummersbach 2015[a]	Intervention	178	5.15 (1.36)	-0.37, p=0.017
		Control	182	5.52 (0.93)	
	Hersch 2015[b]	Intervention	419	4.35 (0.74)	-0.18, p=0.0003
		Control	419	4.53 (0.67)	
Summary					-0.42 [-0.64, -0.21][c]

Heterogeneity measures: I^2=21.7%, Q test p=0.26.
[a] Confidence scale, range 0- 6.
[b] Confidence scale, range 0- 5 (mean of 3 subscales).
[c] Once re-scaled to a maximum score of 10.

Table A3.2. Risk differences for the dichotomous outcome informed choice. Meta-analysis of the RCTs

Outcome	Study	Group	Assessed	n (%)	Difference, p-value[a]
Decided to be screened	Mathieu 2010	Intervention	117	50 (42.7%)	3.0%[a], p=0.64
		Control	209	83 (39.7%)	
	Gummersbach 2015	Intervention	178	145 (81.5%)	-7.1%, p=0.06
		Control	175	155 (88.6%)	
	Hersch 2015	Intervention	419	308 (73.5%)	-13.1%, p<0.001
		Control	419	363 (86.6%)	
Summary					-7% [-15%, -2%]

[a] Fisher's exact test. Heterogeneity measures: I^2=73.7%, Q test p=0.030.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

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Assessment of the effects of decision aids about breast cancer screening: a systematic review and meta-analysis

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Assessment of the effects of decision aids about breast cancer screening: a systematic review and meta-analysis

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Word count: 4,130 words

ABSTRACT

Objective: The aim of this systematic review and meta-analysis of randomised controlled trials (RCTs) and observational studies is to assess the effect of decision aids (DAs) in women aged 50 and under facing the decision to be screened for breast cancer.

Setting: Screening for breast cancer.

Intervention: DAs aimed to help women make a deliberative choice regarding participation in mammography screening by providing information on the options and outcomes.

Eligible studies: We included published original, non-pilot, studies that assess the effect of DAs for breast cancer screening. We excluded the studies that evaluated only participation intention or actual uptake. The studies' risk of bias was assessed with the Cochrane Collaboration's tool for RCTs and the National Institutes of Heath Quality Assessment Tool for non-RCTs.

Primary and secondary outcomes: The main outcome measures were informed choice, decisional conflict and/or confidence, and knowledge. Secondary outcomes were values, attitudes, uncertainty, and intention to be screened.

Results: A total of 607 studies were identified, but only three RCTs and one before-after study were selected. The use of DAs increased the proportion of women making an informed decision by 14%, 95% CI=[2%, 27%] and the proportion of women with adequate knowledge by 12%, 95% CI=[7%, 16%]. We observed heterogeneity among the studies in confidence in the decision. The meta-analysis of the RCTs showed a significant decrease in confidence in the decision and in intention to be screened.

Conclusions: Tools to aid decision-making in screening for breast cancer improve knowledge and promote informed decision; however we found divergent results on decisional conflict and confidence in the decision. Under the current paradigm change, which favours informed choice rather than maximising uptake, more research is necessary for the improvement of DAs.

Keywords: breast cancer, decision aid, mammography, screening, shared decision making.

Strengths and limitations of this study

- This is the first systematic review focused in the impact of DAs about breast cancer screening on informed choice, decisional conflict, knowledge, values, attitudes, and intention to be screened.

- The review focused on studies that assess DAs designed to inform and help women to decide, not on those aimed at encouraging participation and adherence.

- A limitation of the review is the reduced number of studies included, which can be explained by the recent development of DAs for breast cancer screening.

- There was variability in the type and amount of information included in the DAs and also in the information given to the control group, this variability may explain part of the significant heterogeneity in all the outcomes evaluated.

- The DAs were designed in Australia, the USA and Germany, and women included had higher education levels than women in the general population, limiting the generalisability of the results.

INTRODUCTION

In Western countries, screening for breast cancer spread during the 1990s. There was a general consensus on the benefits of screening since several clinical trials in the US and Northern Europe estimated a statistically significant and clinically relevant reduction in mortality from breast cancer.[1] But, in the year 2000 the systematic review from Gotzsche et al. started a hot debate, still alive, on the relevance and magnitude of benefits and harms of breast cancer screening.[2]

More than two decades after the introduction of breast cancer mass screening, the evidence on the harm-benefit balance remains inconclusive. On the one hand, advances in adjuvant treatments, a multidisciplinary approach for breast cancer treatment, and earlier identification of symptoms by women, have diminished the impact of screening on breast cancer mortality reduction.[3-5] On the other hand, the evidence on adverse effects of screening, characterized by a high consensus on the risk of false positive results and lack of agreement on the size of overdiagnosis and overtreatment, show that the potential harms of screening are not insignificant.[6-8]

The current prevailing paradigm, which encourages participation, is changing. Two proposals are gaining strength. First, the need to inform women of potential benefits and harms of screening. Some propose not devoting more energy to increasing participation, but dedicating it to informing women to help them make the best decision based on their preferences and values. [9-12] Second, customising the screening strategies to individual risk. Some recent studies[13-15] based on mathematical models suggest that risk-based screening may increase benefits and reduce harms. The literature shows that both proposals are gaining strength.[16,17]

Decision aids (DA) are instruments that communicate evidence-based information on the benefits and harms of different health-care options to help people make informed choices. The Stacey et al. work,[18] a recently updated Cochrane systematic review on DAs for people facing treatment or screening decisions, included 105 published randomised controlled trials (RCTs) of DAs, 26 of which dealt with cancer screening (13 prostate, 10 colon, two breast, and one cervix) and four on breast cancer genetic

testing. The authors concluded that, compared with usual care, DAs increase participants' knowledge, objectively measured. In addition, people exposed to DAs feel more knowledgeable, better informed, and clearer about their values, and they probably have a more active role in decision making and more accurate risk perceptions. In addition, Stacey et al.[18] think that more research is needed on their effects on adherence to the chosen option, cost-effectiveness, and use with lower literacy populations.

Information on cancer screening is often biased, incomplete and persuasive.[19] Some leaflets mention the possibility of harms, however they do not quantify them. In Europe, some organisations are providing information on benefits and harms of breast cancer screening, in particular, estimates of mortality reduction, and the frequency of false positive results of mammography and invasive tests (e.g. Cochrane collaboration, UK NHS Breast Screening Programme; German Institute for Quality and Efficiency in Health Care; Fundació Lliga per a la Investigació i Prevenció del Càncer and Agència de Salut Pública de Barcelona, in Catalonia (Spain)). Information on overdiagnosis appears in some of the information materials. Two recent studies[11,20] have compared the impact of adding information on overdiagnosis to support informed choice on breast cancer screening. In preparation for an PRCT on the effect of a DA in mass screening in two regions of Spain, we aimed to identify and summarise all the studies reporting the description and assessment of a DA when applied to women aged 50 and under facing the decision to be screened with mammography in a population-based screening or opportunistic case-finding framework. We expected to find that DAs improve knowledge of options, benefits, and harms; create accurate perceptions of benefits and harms; reduce decisional conflict; and enhance informed choice.

METHODS

Eligibility criteria

Types of studies

We included all the published studies with RCT or before-after designs that compared a DA to no intervention, usual care, or alternative interventions. The search date upper limit was December 31, 2016. Pilot studies were excluded.

Types of participants

Participants were women facing decisions about screening in a population-based screening or opportunistic case-finding framework within the age interval of recommended mammography screening. We excluded studies aimed at elderly women only, and studies where participants were asked to make hypothetical choices.

Types of interventions

DAs were defined as interventions aimed to help women make a deliberative choice regarding participation in mammography screening, by providing information on the options and outcomes. We excluded studies aimed at increasing participation or promoting adherence, and studies not carried out in the context of women facing a real decision.

Types of outcome measures

The primary outcomes were: informed choice based on values, decisional conflict and/or confidence, and knowledge. The secondary outcomes included: values and/or attitudes towards screening, proportion remaining undecided, and proportion reporting intention to be screened.

Language

We included articles reported in any language.

Information sources

Search methods for identification of studies

The search strategy was performed in MEDLINE and SCOPUS and adapted and replicated in EMBASE, CINAHL, PsycInfo, and the Cochrane Library Plus. The search included the key words "breast cancer" and "decision" (or "choice") and "aid" (or "informed") and "mammography" (or "mammogram"), within the paper title or the abstract. It excluded the key word "protocol" from the paper titles and allowed synonyms and free suffixes and prefixes. The reviews identified by this search, as well as the references that they included, were exhaustively used to refine the search strategy to ensure that all the possible relevant references for our review were identified (see online supplementary Appendix 1).

Study selection and synthesis of results

All the studies satisfying the inclusion criteria regarding design, participants and interventions were included in this review. Selection and the assessment of risk of bias was independently conducted in pairs by four reviewers (MC, MJP, MMA, and MR). In the case of disagreement, studies were discussed by the whole team of reviewers until an agreement was reached.

Data extraction

The data extraction for the selected studies was independently conducted by two reviewers (MMA and MR) and a consensus version was obtained. In the case that the necessary data was not provided in the articles, the corresponding authors were contacted.

Risk of bias of individual studies

For the risk of bias assessment we used the *Cochrane risk of bias* tool for RCTs and the *National Institutes of Heath quality assessment tool* for non-RCTs.[21] In case of non-RCTs, the selection, allocation and blinding assessments were not applicable.

Sampling bias (a problem for external validity) was assessed in all the included studies.

The risk of bias (*low, unclear,* or *high*) was assessed considering the study design and the methodological quality of the studies. Data consistency was rated as *no inconsistency*, *inconsistency present*, or *not applicable* if there was only one study available, considering each outcome's direction, magnitude, and statistical significance over the set of included studies. The assessment methods followed the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/) and were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[22]

Analysis of results

For each endpoint of interest, the decision to combine the results of the selected studies in a meta-analysis was based on the heterogeneity of patient populations and interventions, as well as on the methodological heterogeneity of study designs and reported outcomes. Consistency and heterogeneity of the studies' results were assessed with the I^2 index and the Q test, respectively.

If comparable measures were obtained, we pooled the data for the outcomes. To facilitate the data pooling, scores with different ranges (minimum and/or maximum values) were standardised to range from 0 to 100 points. We estimated a weighted effect intervention (with 95% confidence interval) as the difference between the intervention and control groups in experimental designs, and as changes from baseline assessed in outcome measures post-intervention in before-after studies. Mean differences or pooled relative risks (RR) were estimated for continuous or dichotomous outcomes, respectively. The summary effects of the intervention were obtained using random effects meta-analysis. An additional meta-analysis of the RCTs was performed. We used the library `metafor` of the R package.[23]

RESULTS

Study selection

In total, we identified 607 unique citations from the electronic database searches. Of these, only 14 were selected for evaluation of the inclusion and exclusion criteria. Figure 1 presents the flowchart of the study selection process. Ten studies were excluded after full text assessment (see Table A2.1 in Appendix 2 for details). Finally, three randomised controlled studies (Mathieu 2010,[24] Gummersbach 2015,[20] and Hersch 2015,[11] and one before-after study, Eden 2015,[25] were selected. These four studies involved a total of 1650 participants from four countries (two from Australia, one each from Germany and the United States of America).

Study characteristics

Table 1 presents the studies' characteristics. Gummersbach and Hersch compared two DAs with information about the benefits and harms of mammography screening, providing the intervention group with more complete information. Whereas Gummersbach added more critical information on the harms of screening mammography in the intervention group, the DA in Hersch only differed in providing thorough information of overdetection or not. In contrast, Mathieu compared a DA with receiving no information, and Eden assessed changes after providing a DA. It is important to notice that whereas Hersch and Gummersbach targeted women who were approaching 50 and deciding whether to screen as per their national program, Mathieu included younger women considering whether to start screening in their 40s, before the recommended age of 50 in Australia. Participants' characteristics are shown in Table 2. Means of age were located in the 40-50 yrs interval. There are differences between studies in the prevalence of previous mammograms and in education level.

Table 1: Description of the studies' characteristics

Study	Design	Age group	Exclusion criteria	Decision aid (DA)
Mathieu 2010	Randomised controlled study, pragmatic[a]	38-45	Personal history of breast cancer (BC)	Web-based DA, information on possible screening outcomes and worksheet to help weigh up and clarify preferences. Intervention group: immediate access; control group: delayed access after completing the outcome measures.
Eden 2015	Before-after study, clinical	40-49	Personal history of BC, prior breast biopsy, high risk of BC[b], previous mammography within 1 year, non-English speaking	Web-based DA, in 3 rural clinical settings, including BC information and questions for risk and self-preferences assessment.
Gummersbach 2015	Randomised controlled study, primary care based	48-49	None	Mailed leaflet, more informative(especially on overdiagnosis) for the intervention group. The leaflet was not created in accordance with published criteria for evidence-based patient information, but it contained much more information relevant to decision-making than the leaflet of the control group.
Hersch 2015	Randomised controlled study, community-based	48-50	Personal or strong family history of BC, BC risk higher than average, mammography in the past 2 years, non-English speaking	Mailed DA, outcomes assessed by phone interview. Evidence-based explanatory and quantitative information on overdiagnosis, BC mortality reduction, and false positives for the intervention group vs. information on BC mortality reduction and false positives for the control group.

[a] :The trial was advertised on the media. Women had free access to the site for eligibility assessment.
[b] : Breast cancer risk based on the Breast Cancer Genetics Referral Screening Tool (B-RST).

Table 2: Description of studies' participants

Study	Group	Participants	Age Mean (SD)	Previous mammography	University degree
Mathieu 2010	Intervention	172	41.9 (2.0)[a]	53 (30.8%)	76 (44.2%)[b]
	Control	212	41.8 (2.2)[a]	52 (24.5%)	126 (59.4%)[b]
Eden 2015	Before-After	75	45.0 (2.5)	51 (68.0%)	34 (45.3%)
Gummersbach 2015	Intervention	178	48.67 (0.79)	[c]	33 (18.5%)
	Control	175	48.76 (0.80)	[c]	23 (13.2%)
Hersch 2015	Intervention	419	49.67 (0.44)	[d]	119 (28.4%)
	Control	419	49.70 (0.44)	[d]	123 (29.4%)

SD: Standard deviation.

[a] Out of the assessed participants, 116 and 198 in intervention and control group, respectively.

[b] Out of the assessed participants, 114 and 199 in intervention and control group, respectively.

[c] 3 and 4 women with BC in intervention and control group, respectively. Participants were not asked about mammographic exams in the past.

[d] No women with previous mammogram in the previous two years but it is not stated how many women had mammograms more than two years before being included in the study.

Risk of bias in the included studies

The evaluation of the risk of bias for the RCTs included the assessment of bias in selection, performance, detection, attrition, reporting, sampling or any other source of bias. Details on the authors' judgement and rationale for risk of bias can be found in Tables A2.2-A2.5 (Appendix 2). The majority of assessed criteria were judged as low risk. Hersch 2015[11] was the only study free of a high risk of bias in all the domains assessed. Gummersbach 2015[20] was rated as having a high risk of attrition bias due to a high level of non-response. Mathieu 2010[24] was rated as having an unclear risk of allocation concealment and also of selective reporting. Eden 2015[25] included a small sample of women with greater than a high school education, in a single rural geographical area. Therefore, the sample representativeness was limited.

Main outcomes

Tables 3 and 4 present the risk differences for the dichotomous outcomes and the mean differences for the continuous outcomes, respectively. Figures 2 and 3 show the results of the meta-analyses for the dichotomous and continuous outcomes, respectively. The results of the meta-analysis performed exclusively on the RCTs are presented in Table A3.1, Appendix 3.

Informed choice

The DAs increased the proportion of women making an informed decision, 58.0% vs. 36.5% according to Mathieu (p < 0.001) and 24.2% vs. 15.4% according to Hersch (p = 0.002). The meta-analysis estimation of risk difference was 14%, 95% CI=[2%, 27%] (Table 3 and Figure 2).

Decisional conflict and/or decisional confidence

Eden observed a significant post-intervention decrease in decisional conflict and a significant increase in decisional confidence (Table 4, Figure 3). In contrast, Hersch noted no significant effect of the intervention on decisional conflict and a significant decrease in decisional confidence, observed also by Gummersbach. These contradictory results introduced high heterogeneity that increased the uncertainty about the overall impact of a DA on decisional conflict and/or confidence (Figure 3). The meta-analysis of the RCTs showed a significant decrease in the confidence scale (Table A3.1, Appendix 3).

Knowledge

The use of a DA increased knowledge according to all studies, although the positive difference was not statistically significant in the Gummersbach study (Tables 3 and 4). The overall results provided by the meta-analyses were statistically significant, either in the proportion of women with adequate knowledge, with a significant increase of 12%, 95% CI=[7%, 16%], or in the mean score, with a difference of 0.70 out of 10 points, 95% CI =[0.27, 1.13] (Figures 2 and 3).

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Table 3: Risk differences for the dichotomous outcomes: informed choice, knowledge, positive attitudes/values towards screening, undecided and intention to be screened.

Outcome	Study	Group	Assessed	n(%)	Difference, *p-value*[a]
Informed choice[b]	Mathieu 2010[c]	Intervention	112	65 (58.0%)	21.5%, p<0.001
		Control	192	70 (36.5%)	
	Hersch 2015[d]	Intervention	409	99 (24.2%)	8.8%, p=0.0017
		Control	408	63 (15.4%)	
Knowledge	Mathieu 2010[e]	Intervention	113	106 (93.8%)	10.7%, p=0.01
		Control	189	157 (83.1%)	
	Hersch 2015[f]	Intervention	419	122 (29.1%)	13.0%, p<0.001
		Control	419	71 (16.9%)	
Positive attitudes[g]	Mathieu 2010	Intervention	111	88 (79.3%)	0.2%, p=0.89
		Control	182	144 (79.1%)	
	Hersch 2015	Intervention	409	282 (68.9%)	-14.4%, p<0.001
		Control	408	340 (83.3%)	
Undecided	Mathieu 2010	Intervention	117	21 (17.9%)	-21.3%, p<0.001
		Control	209	82 (39.2%)	
	Hersch 2015	Intervention	419	69 (16.5%)	9.3%, p<0.001
		Control	419	30 (7.2%)	
Intention to be screened	Mathieu 2010	Intervention	117	50 (42.7%)	3.0%, p=0.64
		Control	209	83 (39.7%)	
	Eden 2015	Before	75	54 (72.0%)	6.7%[h], p=0.123
		After	75	59 (78.7%)[h]	
	Gummersbach 2015	Intervention	178	145 (81.5%)	-7.1%, p=0.06
		Control	175	155 (88.6%)	
	Hersch 2015	Intervention	419	308 (73.5%)	-13.1%, p<0.001
		Control	419	363 (86.6%)	

[a] Fisher's exact test.

[b] Eden provided only a post-intervention mean of the preparation for decision making scale of 73.2 (18.1).

[c] Out of the women assessed, including undecided women in the denominator.

[d] Informed choice defined as adequate knowledge and intentions consistent with attitudes.

[e] Knowledge (according to Mathieu): score higher than 5 out of 10.

[f] Knowledge (according to Hersch): Adequate knowledge when scoring at least 50% of the total available marks, including at least 1 numerical mark, on all three screening outcome subscales (breast cancer mortality benefit, false-positive screening result and overdiagnosis).

[g] Positive attitudes/values >50 out of 100 according to Mathieu and >=24 out of 30 according to Hersch.

[h] Difference as post minus pre-intervention values.

Table 4:Mean differences for the continuous outcomes: knowledge, decisional conflict, and decisional confidence.

Outcome	Study	Group	N	mean (SD)	Difference p-value
Knowledge	Mathieu 2010[a]	Intervention	113	7.35(1.84)	1.1, p<0.001
		Control	189	6.27(1.85)	
	Gummersbach 2015[a]	Intervention	161	5.49 (1.99)	0.26, p=0.26
		Control	168	5.23 (2.06)	
	Hersch 2015[b]	Intervention	419	13.49(4.36)	1.65, p<0.001
		Control	419	11.84(3.74)	
Decisional conflict	Eden 2015[c]	Before	75	46.33 (27.04)	-38.0, p<0.001
		After	75	8.33 (15.58)	
	Hersch 2015	Intervention	419	12.55 (17.60)	0.35, p=0.78
		Control	419	12.20 (18.90)	
Decisional confidence	Eden 2015[d]	Before	75	79.67 (18.62)	16.16, p<0.001
		After	75	95.73 (6.86)	
	Gummersbach 2015[e]	Intervention	178	5.15 (1.36)	-0.37, p=0.017
		Control	182	5.52 (0.93)	
	Hersch 2015[f]	Intervention	419	4.35 (0.74)	-0.18, p=0.0003
		Control	419	4.53 (0.67)	

[a] Knowledge scored, range 0-10.
[b] Knowledge scored, range 0-22.
[c] Decision conflict scale, range 0-100.
[d] Self-efficacy scale, range 0-100.
[e] Confidence scale, range 0-6.
[f] Confidence scale, range 0-5 (mean of 3 subscales).

Secondary outcomes

The high heterogeneity of the results did not make it possible to reach conclusions about significant post-intervention changes or differences in secondary outcomes, such as positive attitudes and values towards screening, decisions about screening, and intention to be screened (Table 3, Figure 2). The results of the meta-analysis performed exclusively on the RCTs are presented in Table A3.2, Appendix 3.

Positive attitudes/values towards screening

Mathieu did not show any significant difference in attitudes, but Hersch obtained a significantly lower frequency of women with positive attitudes towards screening among women receiving the DA with overdiagnosis information.

Undecided about BC screening

Mathieu reported a significant decrease in the frequency of women undecided about BC screening after the DA administration. In contrast, Hersch obtained a significant increase for the intervention group, with the DA including thorough overdiagnosis information.

Intention to be screened

Hersch noted a statistically significant decrease in the intention to be screened and Gummersbach a nearly significant decrease. The meta-analysis of the RCTs showed a significant decrease in the intention to be screened, 7%, 95% CI=[2%, 15%] (Table A3.2, Appendix 3). The lower proportions intending to screen in the Mathieu study with respect to the other studies (Table 3) can be attributed to the fact that women were younger than 50, the recommended age for starting screening in Australia.

DISCUSSION

Summary of main results

This systematic review includes three RCTs and one before-after study assessing DAs given to women facing the decision to be screened with mammography. There was variability in the type and amount of information included in the DAs, and also in the information given to the control group. This variability may explain in part, the significant heterogeneity in all the outcomes evaluated. Despite this heterogeneity, the meta-analysis revealed that DAs produce a statistically significant improvement in knowledge of screening outcomes as well as a significant increase in the frequency of

women making an informed choice. However, no significant effects were observed for decision conflict, decision confidence and positive attitudes towards screening. Therefore, the overall conclusion from our review is that DAs significantly increase women's knowledge and therefore the proportion of women making an informed choice, but do not significantly modify attitudes or intentions towards screening. It is important to mention that when the meta-analysis was performed on the RCT subgroup we found a significant decrease in confidence in the decision and intention to be screened. This decrease in screening intention is consistent with the findings of Ivlev et al[26] in a recently published systematic review of the effect of DAs on women's intentions to undergo screening mammography in age groups where shared decision making is recommended.

Similarly, no significant effects were observed for the secondary outcomes that measured the frequency of participants remaining undecided or choosing to be screened. More specifically, Eden detected a significant decrease in intra-individual post-intervention decision conflict, which was not observed by Hersch, when comparing women receiving a DA with overdiagnosis information vs. those without it. Indeed, Eden also obtained a significant improvement in intra-individual post-intervention decision confidence, while Gummersbach and Hersch obtained a significant decrease in decision confidence when comparing women receiving a DA with exhaustive information on screening adverse effects vs. those without it. This result can be explained by the impact of the information on adverse events of screening. Positive attitudes towards screening significantly decreased when overdiagnosis information was added to the DA, as observed by Hersch, in contrast with the absence of change observed by Mathieu. The frequency of women remaining undecided after DAs showed completely contradictory results. While Mathieu observed a very significant decrease, Hersch obtained a significant increase. The frequency of women decided to be screened showed a significant difference in the Hersch study, where a decrease was observed for the group provided with overdiagnosis information, while Gummersbach, the other study incorporating

thorough information on mammography adverse effects, showed a nearly significant decrease.

Quality of the evidence

Risk of bias ratings show that the included studies had a low risk of bias in most of the assessed domains. There may have been publication bias due to failure to report negative findings. Several of the outcomes showed a high level of heterogeneity that limits the interpretation of the pooled effect size.

Strengths and limitations

This is the first systematic review focused on the impact of DAs about breast cancer screening on informed choice and other relevant outcomes from the women's perspective. Our review focused on studies that assess DAs designed to inform and help women to decide, not on studies aimed at encouraging participation and adherence.

Studies differed in design, especially in terms of the control group. In the Mathieu study,[24] the control group did not receive the DA until the outcome measures had been completed. The Eden study, [25] assessed the post-intervention intra-individual changes after the DA was provided. In the Gummersbach study,[27] a more informative leaflet was compared to a less informative one. Finally, in the Hersch study,[11] the intervention DA had evidence-based explanatory and quantitative information on overdiagnosis, breast cancer mortality reduction, and false positives, whereas the control DA included information on breast cancer mortality reduction and false positives. Previous knowledge was not measured in the Mathieu and Gummersbach RCTs, although one expects that both groups had similar knowledge about mammography screening at baseline. Hersch et al.[11] measured some basic knowledge at baseline using a subset of items and showed similar results between groups. In the Eden study, which assessed intra-individual changes, the DA was particularly useful for the least informed and least confident women. On the other hand, Gummersbach[20] noted that education level was positively associated with acquired knowledge and

that the less educated women had less relevant decisional knowledge after reading the leaflet, but they were more willing to undergo mammography than more educated women. Only the Hersch study included a follow-up for final screening participation, but the results are not published yet.

The limitations of the study are principally related with the generalisation of the results. Women included in the studies probably had a higher education level, greater health awareness, and were more actively involved in health care decisions, than women in the general population. In addition, the DAs were designed using specific data from Australia (Mathieu and Hersch), the United States (Eden) and Germany (Gummersbach), providing results which may not be generalisable to other countries. All studies evaluated the DAs only from the women's perspective, and in the context of research, where participants may have a higher level of commitment than women invited to participate in a breast screening program.

Unanswered questions and future research

Women should use DAs to be informed and support their decisions about breast cancer screening given their preferences and attitudes. It is important to ensure that the information provided is well understood by all women, including those with lower level of education.

The Internet is an inexpensive tool for the dissemination of DAs or to provide additional information, if necessary, in order to present women with all the options available and the harms and benefits of each of them. But there are women that are not familiarised with or do not have access to the Internet and therefore other ways to disseminate information are also needed.

According to Gummersbach the doctor's advice was the most important factor helping with the decision to be screened for almost half of the women. This result indicates the importance of shared decision-making, where DAs are essential tools. Shared decision-making can also help reduce decisional conflict and improve confidence when information on screening harms is provided. In our search we found 17 papers

that described interventions to increase uptake compared to four studies designed to increase knowledge about the benefits and harms of the intervention. Given that the search was not designed to identify studies with "increased uptake", this finding adds information to the important debate about medical ethics in relation to screening interventions - basically the old fashioned paternalistic attitude versus citizen involvement and shared decision-making.

As highlighted by Hersch et al., establishing what constitutes an informed choice, and what knowledge is needed in order to be informed, is an important issue and no consensus currently exists on what knowledge constitutes being objectively informed enough for an informed or shared decision. When Hersch et al. used an expert-led approach based on medical guidelines and underpinned by decision theory, which required numerical and conceptual knowledge, only 24% in the intervention group and 15% in the control group were assessed as informed. When only conceptual knowledge was required these proportions increased to 50% and 19%, respectively. Difficulties understanding quantitative information or the widespread positive value placed on cancer screening can produce a certain resistance to information on possible harms. Their study was the only one obtaining a significant increase in the amount of women remaining undecided about being screened in the group receiving information on overdiagnosis.

The DAs of the included studies lacked detailed information on the outcomes of screening, detection, treatment, or financial strain and opportunity costs from the perspective of the society, which could be considered important for inclusion in future DAs.

Conclusions

DAs for breast cancer screening can improve knowledge and promote informed decision making, in accordance with their preferences, for women who face the decision of screening. However we found divergent results on decisional conflict and decision confidence. Under the new paradigm, which favours informed choice rather than maximising uptake, more research is necessary for the improvement of DA.

Figure legends

Figure 1: Study flow diagram

Figure 2: Meta-analysis of risk differences for the dichotomous outcomes (random effects model)

Figure 2 footnote

Heterogeneity measures: Informed choice: I^2=74.7%, Q test p-value=0.047; Knowledge: I^2=0%, Q test p-value=0.75; Positive attitudes: I^2=84.6%, Q test p-value=0.011; Undecided: I^2=96.9%, Q test p-value<0.001; Intention to be screened: I^2=75.9%, Q test p-value=0.008.

Figure 3: Meta-analysis of mean differences in scores for the quantitative outcomes (random effects model)

Figure 3 footnote

Heterogeneity measures: Decision conflict: I^2=99.0%, Q test p<0.001; Decision confidence: I^2=98.3%, Q test p<0.001; Knowledge: I^2=75.7%, Q test p=0.030.

The InforMa Group

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Competing interests

Informed consent

Since the work does not involve direct research in human subjects, informed consent was not obtained. Nevertheless, the study was approved by the Ethics Committee of the Hospital Universitari Arnau de Vilanova in the city of Lleida (Spain).

Contributors and authorship

MMA, MC and MR designed the study. All authors contributed towards the execution of the study. MMA provided methodological expertise in systematic reviews and searching strategies. The selection and risk of bias assessment of each study was independently conducted in pairs by four reviewers (MC, MJP, MMA, and MR). AP contributed to extracting the information of the identified studies and assessing the inclusion criteria. MMA and MR wrote the first draft with guidance and contributions

from MC, MJP, and MG. All authors read, provided critical feedback and approved the final manuscript.

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Data Sharing Statement

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MEDLINE	SCOPUS	Cochrane	EMBASE	CINAHL	PsycINFO
1962-2016	1962-2016	1986-2016	1976-2016	1989-2016	1992-2016
430 Citation(s)	521 Citation(s)	55 Citation(s)	481 Citation(s)	195 Citation(s)	119 Citation(s)

607 Non-Duplicate
Citations Screened

Inclusion/Exclusion
Criteria Applied → 593 Articles Excluded
After Title/Abstract Screen

14 Articles Retrieved

Inclusion/Exclusion
Criteria Applied → 9 Articles Excluded
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Figure 2: Meta-analysis of risk differences for the dichotomous outcomes (random effects model)
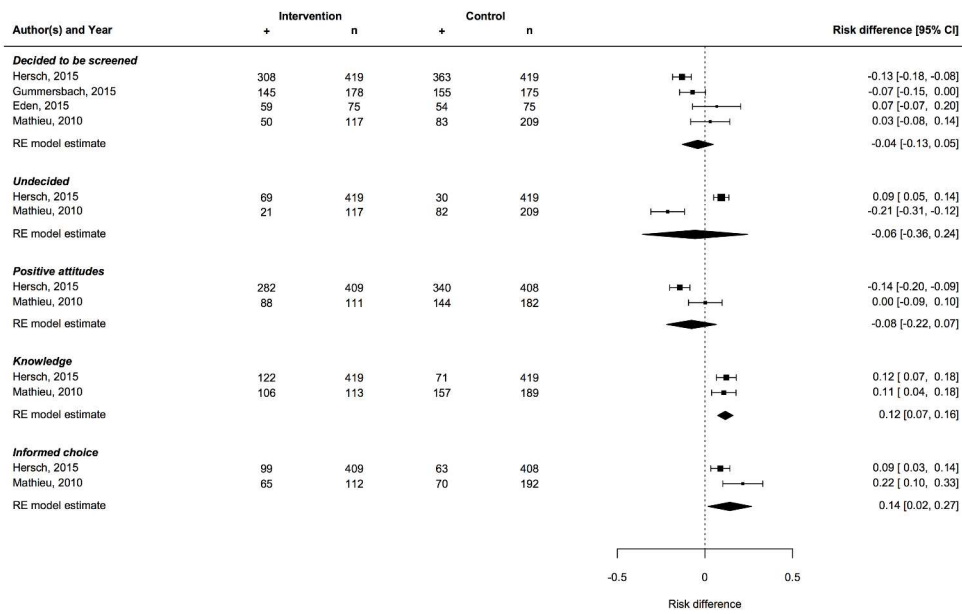
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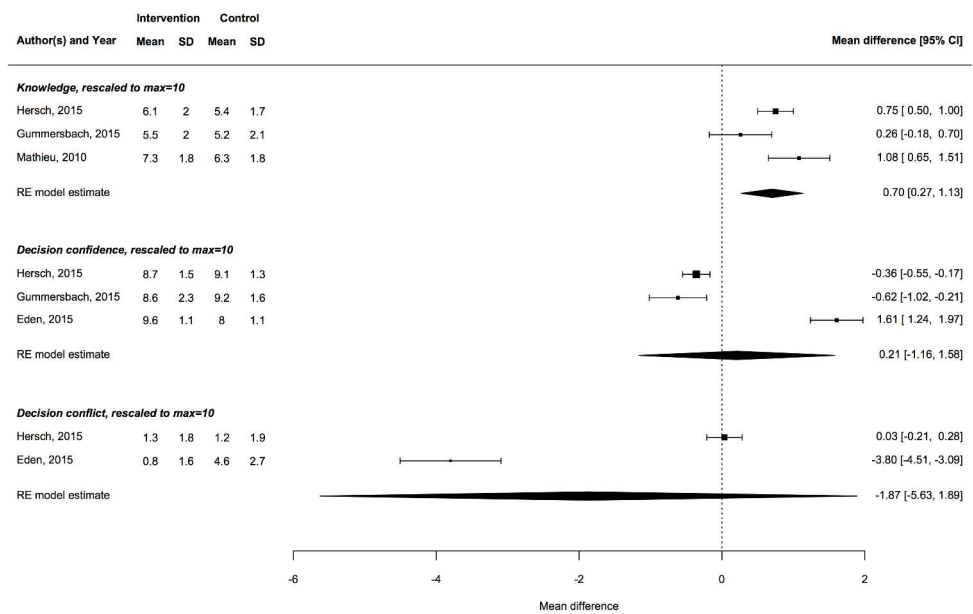
Figure 3: Meta-analysis of mean differences in scores for the quantitative outcomes (random effects model)

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APPENDIX 1

Search criteria for Decision Aids on breast cancer screening

1. In MEDLINE:

   "breast cancer"[tiab] (decision[tiab] OR choice[tiab]) AND (aid[tiab] OR informed[tiab]) AND (mammography[tiab] OR mammogram[tiab]) NOT protocol[ti]

2. Adapting it to SCOPUS:

   (TITLE-ABS-KEY ("breast cancer") AND (TITLE-ABS-KEY (decision) OR TITLE-ABS-KEY (choice)) AND(TITLE-ABS-KEY (aid) OR TITLE-ABS-KEY (informed)) AND (TITLE-ABS-KEY (mammography) OR TITLE-ABS-KEY (mammogram)) AND NOT TITLE (protocol)

3. And, equivalently for EMBASE, CINAHL, PsycInfo, and the Cochrane Library Plus.

APPENDIX 2

Table A2. 1: Excluded studies after full text assessment

Study	Reason of exclusion
Lawrence 2000	No adequate evaluation of the decision aid (DA), only acceptability is assessed.
Webster 2007	No adequate evaluation of the DA, no DA but a leaflet is assessed.
Bodurtha 2009	No adequate evaluation of the DA, no decision is assessed.
Pasternack 2011	No adequate evaluation of the DA, only acceptability is assessed.
Waller 2013	No adequate evaluation of the DA, only the design is described, no assessment is reported.
Hersch 2014	Pilot study of a main study already included.
Waller 2014	No adequate evaluation of the DA, three formats of reporting information are compared.
Berens 2015	No adequate evaluation of the DA, no DA but a leaflet is assessed.
Petrova 2015	The DA is not assessed in a real context.
Bourmaud 2016	No adequate evaluation of the DA. Informed choice is assessed only by participation rate. The overdiagnosis harm is not mentioned.

Characteristics of the included studies

Table A2.2. Study Characteristics

Mathieu 2010	
Methods	Online randomised controlled study of decision aid (DA) vs usual care (UC).
Setting	Australia, where biennial mammography screening is offered free of charge for all women over the age of 40, through a national population screening program. Women aged 50–69 years are invited by personal letter, and, women turning 40 are eligible for screening if they wish to start earlier.
Participants	189 + 223 women, aged 38-45 years, who accessed the web site. Eligible if they were considering whether to (a) start screening in their 40s (ie before the recommended age of 50) or (b) wait until they were 50.
Interventions	DA: explained the benefits and harms, included a values clarification exercise and a worksheet to support decision making. UC: delayed intervention
Outcomes	Primary outcome: knowledge of benefits and harms of screening. Secondary outcomes: informed choice (composite of knowledge, values and intention), anxiety, acceptability of the DA, and intention regarding screening.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 66 (randomization and baseline questions section): "computer generated simple randomization schedule".
Allocation concealment (Selection bias)	Unclear risk	Pg. 66 "randomization was conducted in a concealed manner." The method of allocation concealment was not stated.
Blinding of participants and personnel (Performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (Detection bias)	Low risk	Unclear blinding but outcomes were not subjective to interpretation.
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Table 2: all outcomes mentioned in the paper were reported in the Results section. Table 3: outcomes of anxiety and acceptability can be found. Page 69 explains missing data. Figures 1 and 2 provide the reasons for the exclusions in each group.
Selective reporting (Reporting bias)	Unclear risk	No mention of protocol.
Other bias (Sampling and other)	Low risk	Pg. 65: "To proceed, women were required to click in a box on the computer screen to indicate they had read the study information and were eligible to participate." The trial was advertised on various websites and in a radio program.

Table A2.3. Study Characteristics

Eden 2015	
Methods	Observational study. Women were assessed before and after the decision aid (DA).
Setting	Three clinics in the Oregon Rural Practice-Based Research Network (ORPRN), USA.
Participants	75 women aged 40-49 years with no known risk factors associated with high or moderate risks for breast cancer and no mammography during the previous year.
Interventions	The decision aid (Mammopad) included modules on breast cancer, mammography, risk assessment, and priority setting about screening.
Outcomes	Primary outcome: decisional conflict measured before and after using DA. Secondary outcomes: decision self-efficacy and intention to begin or continue mammography screening.

Criteria	Yes/No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Yes	
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	
4. Were all eligible participants that met the prespecified entry criteria enrolled?	No	
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?		NA

*CD, cannot determine; NA, not applicable; NR, not reported

National Institutes of Health. Quality Assessment Tool for before-after (pre-post) studies with no control group. Study Quality Assessment Tools. https://www.nhlbi.nih.gov/health-

pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after. Accessed 11 May 2017.

Table A2.4. Study Characteristics

Gummersbach 2015	
Methods	Randomised to two decision aids (DA) with different information.
Setting	Family practices in the German federal state of North Rhine–Westphalia. In Germany, screening is recommended biennially for all women aged 50 to 69.
Participants	353 women, aged 48-49 years, about to receive the first invitation to screening.
Interventions	Intervention: DA with detailed information on screening harms. Control: standard DA.
Outcomes	Primary outcome: willingness to participate in screening. Secondary outcomes: knowledge, decisional confidence, determinants of the screening decision.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 62: "The 24 participants from each practice were selected by a computer-assisted random procedure."
Allocation concealment (Selection bias)	Low risk	Pg. 62: the group allotment process was also random.
Blinding of participants and personnel (Performance bias)	Low risk	Pg. 62: "The participants and their family physicians were blinded with respect to group allotment, but the study team was not".
Blinding of outcome assessment (Detection bias)	Low risk	Pg. 62: "The participants were asked by letter to fill out the questionnaire after reading the leaflet and to send it back in an envelope that was also enclosed in the mailing".
Incomplete outcomes' data. All outcomes (Attrition bias)	High risk	46.7% non-response.
Selective reporting (Reporting bias)	Low risk	Pg. 63. Primary outcome was assessed in accordance with the protocol.
Other bias (sampling bias)	Low risk	Participants recruited from family practices.

Table A2.5. Study Characteristics

Hersch 2015	
Methods	Randomised to two decision aids (DA) with different information.
Setting	Community-based sample of women around the target age for starting breast screening, in New South Wales, Australia.
Participants	879 women, aged 48-50 years, about to receive the first invitation to screening.
Interventions	Intervention: comprising evidence-based explanatory and quantitative information on overdetection, breast cancer mortality reduction, and false positives. Control: decision aid including information on breast cancer mortality reduction and false positives.
Outcomes	Primary outcome: informed choice defined as adequate knowledge and consistency between attitudes and screening intentions. Secondary outcomes: screening attitudes, decisional conflict, worry about breast cancer, intention about undergoing screening, and opinions about the decision aid.

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (Selection bias)	Low risk	Pg. 1644: "A programmer who had no contact with participants generated the randomisation sequence using a computer system that was inaccessible until after recruitment... We assigned participants to either the intervention or control group in a 1:1 ratio with permuted block sizes of four and eight."
Allocation concealment (Selection bias)	Low risk	Pg. 1645: "Interviewers were unaware of the materials that women would receive (ensuring allocation concealment)."
Blinding of participants and personnel (Performance bias)	Low risk	Pg. 1645: "Double blinded. Women knew they would receive one of two versions of an information booklet but did not know how these differed or which one was the intervention. We designed the follow-up interview to ensure the group assignment was unclear to the interviewer until the final question."
Blinding of outcome assessment (Detection bias)	Low risk	Pg. 1645: "Researchers who analysed data were unaware of the random allocation."
Incomplete outcomes' data. All outcomes (Attrition bias)	Low risk	Both groups have similar dropout rates.
Selective reporting (Reporting bias)	Low risk	Pg. 5. Primary outcome was assessed in accordance with the protocol.
Other bias	Low risk	It seems free of other biases.

APPENDIX 3

Table A3.1. Mean differences for the quantitative outcome decisional confidence. Meta-analysis of the RCTs.

Outcome	Study	Group	N	Mean (SD)	Difference, p-value
Decisional confidence	Gummersbach 2015[a]	Intervention	178	5.15 (1.36)	-0.37, p=0.017
		Control	182	5.52 (0.93)	
	Hersch 2015[b]	Intervention	419	4.35 (0.74)	-0.18, p=0.0003
		Control	419	4.53 (0.67)	
Summary					-0.42 [-0.64, -0.21][c]

Heterogeneity measures: I^2=21.7%, Q test p=0.26.
[a] Confidence scale, range 0- 6.
[b] Confidence scale, range 0- 5 (mean of 3 subscales).
[c] Once re-scaled to a maximum score of 10.

Table A3.2. Risk differences for the dichotomous outcome screening intentions. Meta-analysis of the RCTs.

Outcome	Study	Group	Assessed	n (%)	Difference, p-value[a]
Decided to be screened	Mathieu 2010	Intervention	117	50 (42.7%)	3.0%[a], p=0.64
		Control	209	83 (39.7%)	
	Gummersbach 2015	Intervention	178	145 (81.5%)	-7.1%, p=0.06
		Control	175	155 (88.6%)	
	Hersch 2015	Intervention	419	308 (73.5%)	-13.1%, p<0.001
		Control	419	363 (86.6%)	
Summary					-7% [-15%, -2%]

[a] Fisher's exact test. Heterogeneity measures: I^2=73.7%, Q test p=0.030.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

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