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TITLE

How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

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ABSTRACT

Objectives: In a randomised controlled trial, we found that informing women about overdetection changed their breast screening decisions. We now present a mediation analysis aimed at exploring the pathways through which study participants who received the intervention processed information about overdetection and integrated it into their decision making. We examined a series of potential mediators of the relationship between exposure to this information and subsequent breast screening intentions.

Design: Serial multiple mediation analysis within a randomised controlled trial

Setting: New South Wales, Australia

Participants: 811 women aged 48–50 years with no personal history of breast cancer

Interventions: Two versions of a decision aid giving women information about breast cancer deaths averted and false positives from screening, either with (intervention) or without (control) information on overdetection.

Main outcome: Intentions to undergo breast screening in the next 2–3 years

Mediators: Knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret

Results: The effect of information about overdetection on women's breast screening intentions was mediated through multiple cognitive and affective pathways. In particular, the information led to substantial improvements in women's understanding of overdetection, and it influenced – both directly and indirectly via its effect on knowledge – their attitudes towards having screening. Mediation analysis showed that the mechanisms involving knowledge and attitudes were particularly important in determining intentions about screening participation.

Conclusions: Even in this emotive context, new information influenced women's decision making by changing their understanding of possible consequences of screening and their attitudes towards undergoing it. These findings emphasise the need to provide good-quality information on screening outcomes, and to communicate this information effectively, so that women can make well-informed decisions.

Trial registration: This study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613001035718) on 17 September 2013.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Random allocation between two decision aids, differing only in the presence or absence of information about overdetection, enabled a rigorous test of the specific effects of this information when described in the context of other screening outcomes.
- Participants were women entering the target age range for breast screening, who were sampled randomly from the general community and were facing real decisions.
- Our serial mediation model controlled for a comprehensive set of baseline variables and examined plausible, theory-driven cause-effect relationships between exposure to the intervention and subsequently measured variables.
- Nonetheless, given the cross-sectional nature of the outcome and mediator data, we cannot definitively establish the causal ordering of these variables.

KEYWORDS

Breast imaging
Overdiagnosis
Decision aid
Informed decision making
Cancer screening
Mediation

Breast cancer screening is a complex and emotionally charged issue,[1] a topic surrounded by what has been described as a perfect storm of politics and science.[2] While screening can reduce deaths from breast cancer, it can also cause harm through the counterintuitive phenomenon of overdetection. An overdetected breast cancer is one found by screening, and consequently treated, that would not have caused any health problems had it been left undetected and untreated.[3] Without screening, such a cancer would never have been diagnosed. Overdetected cancers are 'real' cancers in the sense that they meet current pathological criteria for cancer diagnosis, but finding and treating them does not improve health outcomes. Such a diagnosis and the resulting treatment can cause serious lifelong harm, and overdetection is therefore considered the major downside to breast screening.

Mounting evidence of the extent of overdetection (estimated as 19% of breast cancers diagnosed in women invited to screen [4] and 30% for those who attend screening [5]) has led to recognition that the benefits and harms of breast screening are finely balanced for women at population-level risk of breast cancer. The risk of overdetection and its consequences must be weighed against the benefit of reducing breast cancer mortality (relative risk reduction estimated as 20% for women invited to screen [4] and 30% for those screened [5]). Experts familiar with the evidence now acknowledge that individual women may perceive the harm-benefit trade-off differently depending on their personal context and preferences – some will opt for screening while others decline, and either choice may be appropriate if it represents an informed decision.[6-8] Throughout the history of breast screening, however, women invited to participate have not been given all the relevant information.[9-11] Consensus is growing that information on screening benefits and harms, including overdetection, must be communicated clearly and transparently to women offered screening so that they can make informed decisions about whether to be screened.[4, 12, 13] This is all the more important because of evidence that women hold misconceptions about breast screening and its effects.[14, 15]

Against the background of this recommended shift in communication, the issue of how information about overdetection affects women and their screening decisions is critical. In a randomised trial we addressed this question in women approaching the recommended age for mammography screening.[16] We sent women one of two versions of a decision aid (evidence-based information booklet) giving information about breast cancer deaths averted and false positives from screening (abnormal mammograms in women without cancer), either with or without information on overdetection.[17] The intervention produced several significant effects on decision making.[16] The additional overdetection information improved knowledge, increased the number of women making

an informed choice about screening, and reduced positive attitudes to screening and the number of women intending to be screened.[16]

From our study design – chosen to identify the specific impact of information about overdetection – it appears that communicating this information influenced women's assessment of the value of screening to them, leading to lower intentions to be screened within the intervention group. This finding has never been observed before, and raises important questions. In this paper we explore the psychological pathways through which study participants processed overdetection information and integrated it into their decision making. We provide an explanatory account incorporating cognitive and affective pathways, using psychological theories [18] and mediation analysis.[19]

METHODS

We did a parallel-group randomised controlled trial with women aged 48-50 years, recruited from the general community in New South Wales, Australia. The trial is described in detail elsewhere.[16, 20] Trained interviewers from an independent non-profit company recruited participants via telephone. Women were eligible if they had not undergone mammography in the past 2 years and did not have a personal or strong family history of breast cancer. Participants knew they would receive one of two versions of a breast screening information booklet but did not know how these differed or which was the intervention.

We collected sociodemographics and baseline data on women's stage of decision making (how far along they were with their decision about breast screening), basic conceptual knowledge, attitudes, and intentions.[16, 20] We randomly assigned 879 women to the intervention (n=440) or control group (n=439), then sent their allocated decision aid by post. A programmer who had no contact with participants generated the randomisation sequence, which was inaccessible until after recruitment, ensuring allocation concealment.

The intervention decision aid contained evidence-based explanatory and quantitative information about important outcomes of undergoing screening biennially from age 50 to 69 years (breast cancer mortality reduction, overdetection, and false positives) compared with not screening over this period. The control decision aid omitted all overdetection content but was otherwise identical to the intervention. The decision aids were short booklets combining text and visual formats, and are published.[16, 17]

We collected follow-up data using standardised questions in a structured telephone interview, 1-4 weeks after randomisation. The participant's group assignment was unclear to the interviewer until the final question.

Our knowledge scale assessed conceptual understanding of three key screening outcomes (breast cancer mortality reduction, overdetection, and false positives) and awareness of the approximate numbers affected.[16] For the mediation analysis we used the overdetection knowledge subscale (scored 0 to 10, including conceptual and numeric components) as conveying this new information was the main aim of the intervention. We assessed attitudes to breast screening via a widely used 6-item instrument (possible range 6 to 30), intentions to undergo screening in the next 2-3 years (1 item, 5-point response scale), and worry about developing breast cancer (1 item, 4-point scale).[16, 20, 21] Higher scores on these measures reflect better knowledge, more positive attitudes and intentions, and greater worry, respectively. We collected anticipated regret both for screening (action) and *not* screening (inaction),[22] and calculated a differential anticipated regret score [23] by subtracting the action from the inaction score. Higher scores on the resulting measure (possible range -4 to 4) reflect greater anticipated regret for *not* screening, adjusted for the woman's anticipated regret for screening.

Our purpose in the analysis reported here was to explore causal pathways between exposure to information about overdetection in a decision aid (intervention) and subsequent breast screening intentions (outcome). We examined a series of potential mediators of this relationship: knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret. We tested whether these variables functioned in a chain with a specified direction of causal flow (serial mediation).[19] Based on health psychology theories (e.g., theory of planned behaviour [24, 25]) we tested the following causal chain: intervention (group allocation) -> overdetection knowledge -> worry -> attitudes -> anticipated regret -> intentions.

Mediation models were tested using the PROCESS macro (Version 2.16) for SPSS (Version 24).[19] Baseline variables in Table 1 were statistically controlled by including them as covariates during mediation analyses. Outcome and mediator variables were standardised (expressed in units of standard deviations from the sample mean) for the mediation analysis. We used 50,000 bootstrap samples to create 95% bias-corrected confidence intervals (95% CIs) for the indirect effects (IEs), which we considered significant if the CI did not include zero.

RESULTS

Of 879 participants randomised, 838 completed the follow-up interview. Among these, 27 did not answer all relevant questions and were excluded from the mediation analysis. Sociodemographic characteristics were similar for randomised participants who were and were not included in the mediation analysis. Table 1 shows baseline characteristics of the 811 included participants.

Table 1. Baseline sample characteristics (n=811)

Variable	Intervention group (n=406)		Control group (n=405)	
Sociodemographics	**n**	**(%)**	**n**	**(%)**
Family history of breast cancer				
No close blood relative ever diagnosed	389	(96%)	386	(95%)
One close blood relative diagnosed aged ≥50 years	17	(4%)	19	(5%)
Country of birth				
Australia or New Zealand	327	(81%)	335	(83%)
Other	79	(19%)	70	(17%)
Main language spoken at home				
English	390	(96%)	396	(98%)
Other	16	(4%)	9	(2%)
Education				
School only or trade certificate	226	(56%)	225	(56%)
Diploma or university degree or higher	180	(44%)	180	(44%)
Marital status				
Married or living with a partner	317	(78%)	333	(82%)
Not currently living with a partner	89	(22%)	72	(18%)
Parent status				
Has one or more children	361	(89%)	363	(90%)
No children	45	(11%)	42	(10%)
Work status				
Working full time or part time	333	(82%)	341	(84%)
No paid job currently	73	(18%)	64	(16%)
Age				
48-49 years old	289	(71%)	294	(73%)
50 years old	117	(29%)	111	(27%)
Decision-making variables	**Mean**	**(SD)**	**Mean**	**(SD)**
Stage of decision making about screening	3.4	(1.0)	3.4	(0.9)
Knowledge (basic concepts of screening)	4.4	(0.8)	4.4	(0.8)
Attitudes towards having breast screening	26.5	(3.6)	26.8	(3.6)
Intentions about having breast screening	4.5	(0.8)	4.6	(0.8)

Note. Baseline variables were included as covariates in the mediation analysis. Sociodemographic factors were dichotomised as shown. Possible ranges for decision-making variables: Stage of decision making 1 (not yet thought about the options) to 4 (already made a choice), Knowledge 0 to 5, Attitudes 6 to 30, Intentions 1 to 5.

Table 2 presents mean post-intervention scores for intervention and control groups on the variables included in the mediation model. Compared with controls, the intervention group showed greater knowledge about overdetection, lower worry about breast cancer, less positive attitudes towards breast screening, lower anticipated regret for not screening (versus for screening), and lower intentions to undergo screening.

Table 2. Means and standard deviations for study groups on screening intentions and mediator variables

Variable	Intervention group (n=406)	Control group (n=405)	p value
Overdetection knowledge	6.2 (2.2)	4.0 (1.6)	<.001
Breast cancer worry	1.7 (0.7)	1.8 (0.7)	<.001
Screening attitudes	24.5 (4.4)	26.1 (4.1)	<.001
Anticipated regret	1.9 (1.7)	2.5 (1.6)	<.001
Screening intentions	4.1 (1.1)	4.5 (0.9)	<.001

Note. Possible score ranges were as follows: Overdetection knowledge 0 to 10, Breast cancer worry 1 to 4, Attitudes 6 to 30, Anticipated regret -4 to 4, Intentions 1 to 5. Groups were compared using t tests.

Serial mediation analysis found that the total indirect effect of the intervention on intentions was statistically significant, indicating that the intervention influenced intentions indirectly through its effects on the combined set of mediators. Reading the intervention rather than the control decision aid was associated with a decrease in screening intentions as a result of all specific indirect causal sequences in the model (Table 3). As the direct effect was not significant, there was no evidence that the intervention affected intentions independently of its influence on the mediators modelled.

Table 3 presents effect estimates and 95% CIs for the 15 specific indirect effects representing causal pathways through the various mediator sequences. The specific path coefficients are shown in Figure 1.

The main significant indirect effects of the intervention on intentions were those involving knowledge and attitudes as mediators, both separately (IE1, IE13 in Table 3) and together in sequence (IE3). The first specific indirect effect (IE1) tested whether overdetection knowledge mediated the relationship between the decision aid received and subsequent breast screening intentions; this effect was significant. Relative to those assigned to the control decision aid, participants receiving the intervention demonstrated better knowledge about overdetection and consequently expressed lower intentions to have screening. Another significant effect, IE13 showed

that the intervention resulted in less positive attitudes, which also led to lower screening intentions. IE3 tested the causal chain: intervention -> knowledge -> attitudes -> intentions. This was also significant and demonstrated that participants exposed to the intervention gained better overdetection knowledge, those with better knowledge had less positive attitudes, and these attitudes were in turn associated with reduced intentions to screen. Pair-wise contrasts revealed that the three largest specific indirect effects (IE1, IE3, and IE13) did not significantly differ in size.

Table 3. Direct and indirect effects of the intervention on screening intentions via four sequential mediators

Path	Effect	SE	95% CI	
Total effect	**-.2768**	**.0540**	**-.3828**	**-.1708**
Direct effect	-.0192	.0501	-.1175	.0791
Total indirect effect	**-.2576**	**.0449**	**-.3488**	**-.1734**
Specific indirect effects (IEs)				
1. Knowledge	**-.0731**	**.0267**	**-.1281**	**-.0230**
2. Knowledge, worry	-.0010	.0017	-.0073	.0007
3. Knowledge, attitudes	**-.0700**	**.0171**	**-.1071**	**-.0396**
4. Knowledge, anticipated regret	**-.0201**	**.0072**	**-.0375**	**-.0088**
5. Knowledge, worry, attitudes	-.0001	.0007	-.0023	.0011
6. Knowledge, worry, anticipated regret	-.0004	.0005	-.0021	.0002
7. Knowledge, attitudes, anticipated regret	**-.0121**	**.0040**	**-.0220**	**-.0059**
8. Knowledge, worry, attitudes, anticipated regret	-.0000	.0001	-.0004	.0021
9. Worry	-.0047	.0050	-.0191	.0021
10. Worry, attitudes	-.0003	.0027	-.0063	.0046
11. Worry, anticipated regret	**-.0020**	**.0014**	**-.0063**	**-.0003**
12. Worry, attitudes, anticipated regret	-.0001	.0005	-.0012	.0008
13. Attitudes	**-.0618**	**.0285**	**-.1178**	**-.0065**
14. Attitudes, anticipated regret	**-.0106**	**.0056**	**-.0241**	**-.0016**
15. Anticipated regret	-.0012	.0104	-.0216	.0200

Note. n = 811; 50,000 bootstrap samples; bias-corrected confidence intervals. The four sequential mediators are overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret. Bold effects are significant (p<.05).

The anticipated regret variable was also involved in several significant mediation pathways, influenced by knowledge and attitudes separately (IE4, IE14) and together (IE7). The most complex

of the significant indirect effects was IE7 leading from the intervention -> overdetection knowledge -> screening attitude -> anticipated regret -> screening intention. Compared with the control group, women receiving the intervention had greater overdetection knowledge, which led to less positive attitudes (as above); these were in turn associated with lower anticipated regret for not screening (versus screening), which translated into reduced intentions to screen.

The specific indirect effect for the pathway through the complete causal chain involving all four mediators in sequence (IE8) – that is, adding breast cancer worry to the mediators discussed above – was not significant. Worry was part of only one significant indirect effect (IE11). The intervention reduced breast cancer worry; women with lower worry had lower anticipated regret for not screening, which again reduced screening intentions.

DISCUSSION

This study showed that the relationship between exposure to information on overdetection and women's subsequent breast screening intentions was mediated by multiple cognitive and affective pathways. The intervention decision aid substantially improved understanding of overdetection, and it influenced – both directly and indirectly via its effect on knowledge – women's attitudes towards having screening. The mediation analysis revealed that these mechanisms involving knowledge and attitudes were particularly important in determining intentions about screening participation. Anticipated regret played a role in several additional pathways linking knowledge, attitudes and intentions. As women became more knowledgeable about overdetection and their screening attitudes became less positive, this lessened their expectation that *not* screening would cause regret and increased the realisation that *screening* might cause regret, which in turn influenced intentions.

The randomised controlled trial design is a key strength of this study. Random allocation between two decision aids, differing only in the presence or absence of information about overdetection, enabled a rigorous test of the specific effects of this information when described in the context of other screening outcomes. Our serial mediation model controlled for a comprehensive set of baseline variables and examined plausible, theory-driven cause-effect relationships between exposure to the intervention and subsequently measured variables. Nonetheless, given the cross-sectional nature of the outcome and mediator data, we cannot definitively establish the causal ordering of these variables.

Although previous literature has reported on screening decisions aided by decision support techniques,[26, 27] little work to date has examined mechanisms for *how* information provided in such resources translates into decisions. Our mediation findings are in line with the explanatory

account of health decisions offered by the theory of planned behaviour.[24, 25] Under this theory, attitudes towards a behaviour are determined by salient beliefs about its consequences (in this case, the understanding conveyed by the decision aid that overdetection is a possible consequence of screening); these attitudes in turn determine intentions. Our observed mediation effects involving anticipated regret accord with other empirical evidence supporting its usefulness as an extension to the theory of planned behaviour.[28] Worry about the threat of breast cancer, though emphasised by other health psychology theories, did not appear to play a major role in determining screening intentions among our study participants. Utilising a theoretical basis in behavioural psychology or decision making theory is often overlooked but may strengthen the design and evaluation of decision support materials, although operationalizing such theories can be challenging.[29]

CONCLUSIONS

We have previously shown that giving women evidence-based written information about overdetection in breast screening can change women's screening intentions. Importantly, for the first time we now provide evidence, using mediation analysis, of how this cognitive and affective process works: the decision aid intervention achieved substantial knowledge gains, and thereby influenced attitudes and intentions towards screening. Our findings underline the importance of providing good-quality information to women when they are invited to consider screening, using materials with the capacity to successfully impart new and relevant knowledge. Effective communication tools and decision support resources are especially needed against a background of widely documented unrealistic public expectations of screening.[30] Our findings are a reminder that information can be a powerful intervention, and that the development of information resources must be done properly with rigour and care.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by The University of Sydney human research ethics committee (2012/1429). Participants gave informed consent to take part in the study.

Patient consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: financial support from the National Health and Medical Research Council of Australia for the submitted work; 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.

Authors' contributions

All authors contributed to study design. KMcC, AB, JJ, NH, HD, and KMcG obtained funding. JH, KMcC, and JJ led development of the intervention and implementation of the trial. KMcG advised on the statistical analysis. JH performed the statistical analysis, produced the tables and figure, and drafted the manuscript. All authors contributed to data interpretation and critically reviewed the manuscript.

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REFERENCES

1 Harvey S. The charge and the challenges of breast cancer screening. *J Womens Health (Larchmt)* 2014;23(Suppl 1):S1-2. doi: 10.1089/jwh.2014.1509

2 Elmore J. Breast cancer screening: balancing evidence with culture, politics, money, and media. In: Houssami N, Miglioretti D, eds. Breast Cancer Screening: An Examination of Scientific Evidence. Amsterdam: Elsevier 2016:1-27.

3 Welch HG, Black W. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;102:605-13. doi: 10.1093/jnci/djq099

4 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380:1778-86. doi: 10.1016/S0140-6736(12)61611-0

5 Jacklyn G, Glasziou P, Macaskill P, et al. Meta-analysis of breast cancer mortality benefit and overdiagnosis adjusted for adherence: improving information on the effects of attending screening mammography. *Br J Cancer* 2016;114:1269-76. doi: 10.1038/bjc.2016.90

6 Heath I. It is not wrong to say no. *BMJ* 2009;338:b2529. doi: 10.1136/bmj.b2529

7 Kirwan C. Breast cancer screening: what does the future hold? *BMJ* 2013;346:f87. doi: 10.1136/bmj.f87

8 Stefanek M. Uninformed compliance or informed choice? A needed shift in our approach to cancer screening. *J Natl Cancer Inst* 2011;103:1821-26. doi: 10.1093/jnci/djr474

9 Gummersbach E, Piccoliori G, Oriol Zerbe C, et al. Are women getting relevant information about mammography screening for an informed consent: a critical appraisal of information brochures used for screening invitation in Germany, Italy, Spain and France. *Eur J Public Health* 2010;20:409-14. doi: 10.1093/eurpub/ckp174

10 Jorgensen K, Gotzsche P. Content of invitations for publicly funded screening mammography. *BMJ* 2006;332:538-41. doi: 10.1136/bmj.332.7540.538

11 Zapka J, Geller B, Bulliard J, et al. Print information to inform decisions about mammography screening participation in 16 countries with population-based programs. *Patient Educ Couns* 2006;63:126-37. doi: 10.1016/j.pec.2005.09.012

12 Welch HG, Passow H. Quantifying the benefits and harms of screening mammography. *JAMA Intern Med* 2014;174:448-54. doi: 10.1001/jamainternmed.2013.13635

13 Loberg M, Lousdal ML, Bretthauer M, et al. Benefits and harms of mammography screening. *Breast Cancer Res* 2015;17:63. doi: 10.1186/s13058-015-0525-z

14 Biller-Andorno N, Juni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. *N Engl J Med* 2014;370:1965-67. doi: 10.1056/NEJMp1401875

15 Schwartz L, Woloshin S, Sox H, et al. US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey. *BMJ* 2000;320:1635-40. doi: 10.1136/bmj.320.7250.1635

16 Hersch J, Barratt A, Jansen J, et al. Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial. *Lancet* 2015;385:1642-52. doi: 10.1016/S0140-6736(15)60123-4

17 Hersch J, Jansen J, Barratt A, et al. Overdetection in breast cancer screening: development and preliminary evaluation of a decision aid. *BMJ Open* 2014;4:e006016. doi: 10.1136/bmjopen-2014-006016

18 Armitage C, Conner M. Social cognition models and health behaviour: a structured review. *Psychol Health* 2000;15:173-89. doi: 10.1080/08870440008400299

19 Hayes A. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-based Approach. New York: Guilford 2013.

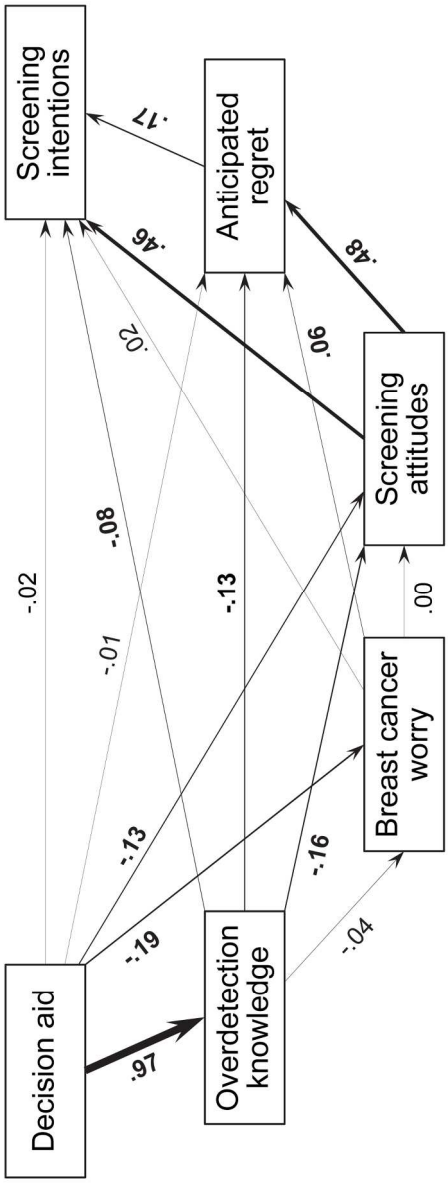
20 Hersch J, Barratt A, Jansen J, et al. The effect of information about overdetection of breast cancer on women's decision-making about mammography screening: study protocol for a randomised controlled trial. *BMJ Open* 2014;4:e004990. doi: 10.1136/bmjopen-2014-004990

21 Dormandy E, Michie S, Hooper R, et al. Informed choice in antenatal Down syndrome screening: a cluster-randomised trial of combined versus separate visit testing. *Patient Educ Couns* 2006;61:56-64. doi: 10.1016/j.pec.2005.02.006
22 Sandberg T, Hutter R, Richetin J, et al. Testing the role of action and inaction anticipated regret on intentions and behaviour. *Br J Soc Psychol* 2016;55:407-25. doi: 10.1111/bjso.12141
23 Sivell S, Elwyn G, Edwards A, et al. Factors influencing the surgery intentions and choices of women with early breast cancer: the predictive utility of an extended theory of planned behaviour. *BMC Med Inform Decis Mak* 2013;13:92. doi: 10.1186/1472-6947-13-92
24 Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991;50:179-211. doi: 10.1016/0749-5978%2891%2990020-T
25 Ajzen I. Martin Fishbein's legacy: the reasoned action approach. *Ann Am Acad Pol Soc Sci* 2012;640:11-27. doi: 10.1177/0002716211423363
26 Biesecker B, Schwartz M, Marteau T. Enhancing informed choice to undergo health screening: a systematic review. *Am J Health Behav* 2013;37:351-59. doi: 10.5993/AJHB.37.3.8
27 van Agt H, Korfage I, Essink-Bot M. Interventions to enhance informed choices among invitees of screening programmes – a systematic review. *Eur J Public Health* 2014;24:789-801. doi: 10.1093/eurpub/ckt205
28 Sandberg T, Conner M. Anticipated regret as an additional predictor in the theory of planned behaviour: a meta-analysis. *Br J Soc Psychol* 2008;47:589-606. doi: 10.1348/014466607X258704
29 Elwyn G, Stiel M, Durand MA, et al. The design of patient decision support interventions: addressing the theory-practice gap. *J Eval Clin Pract* 2011;17:565-74. doi: 10.1111/j.1365-2753.2010.01517.x
30 Hoffmann T, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med* 2015;175:274-86. doi: 10.1001/jamainternmed.2014.6016

FIGURES

Fig. 1. Title: Multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators

Fig. 1. Legend: Graphic representation of the serial multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators (overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret). The intervention was hypothesised to exert an effect on screening intentions through the four mediators in sequence. Outcome and mediator variables were standardised prior to analysis. Bold coefficients are significant (p<.05). Analyses controlled for baseline measures including screening intentions and attitudes, basic screening knowledge, stage of decision making, breast cancer family history, birthplace, main language spoken, education, marital status, parent status, work status, and age.



Multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators

Graphic representation of the serial multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators (overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret). The intervention was hypothesised to exert an effect on screening intentions through the four mediators in sequence. Outcome and mediator variables were standardised prior to analysis. Bold coefficients are significant (p<.05). Analyses controlled for baseline measures including screening intentions and attitudes, basic screening knowledge, stage of decision making, breast cancer family history, birthplace, main language spoken, education, marital status, parent status, work status, and age.

87x225mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5 + protocol[1]
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5 + protocol[1]
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5 + published protocol[1]
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5-6 + protocol[1]
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	Protocol[1]

	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Lancet[2]
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol[1]
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5 + protocol[1]
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Lancet[2]
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, 7, Lancet[2]
	13b	For each group, losses and exclusions after randomisation, together with reasons	6-7 + Lancet[2]
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Lancet[2]
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	7

Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6-7 + Lancet[2]
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	3
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12 + Lancet[2]

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

1 Hersch J, Barratt A, Jansen J, et al. The effect of information about overdetection of breast cancer on women's decision-making about mammography screening: study protocol for a randomised controlled trial. *BMJ Open* 2014;4:e004990. doi: 10.1136/bmjopen-2014-004990
2 Hersch J, Barratt A, Jansen J, et al. Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial. *Lancet* 2015;385:1642-52. doi: 10.1016/S0140-6736(15)60123-4

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How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

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TITLE

How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

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ABSTRACT

Objectives: In a randomised controlled trial, we found that informing women about overdetection changed their breast screening decisions. We now present a mediation analysis aimed at exploring the pathways through which study participants who received the intervention processed information about overdetection and integrated it into their decision making. We examined a series of potential mediators of the relationship between exposure to this information and subsequent breast screening intentions.

Design: Serial multiple mediation analysis within a randomised controlled trial

Setting: New South Wales, Australia

Participants: 811 women aged 48–50 years with no personal history of breast cancer

Interventions: Two versions of a decision aid giving women information about breast cancer deaths averted and false positives from screening, either with (intervention) or without (control) information on overdetection.

Main outcome: Intentions to undergo breast screening in the next 2–3 years

Mediators: Knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret

Results: The effect of information about overdetection on women's breast screening intentions was mediated through multiple cognitive and affective pathways. In particular, the information led to substantial improvements in women's understanding of overdetection, and it influenced – both directly and indirectly via its effect on knowledge – their attitudes towards having screening. Mediation analysis showed that the mechanisms involving knowledge and attitudes were particularly important in determining intentions about screening participation.

Conclusions: Even in this emotive context, new information influenced women's decision making by changing their understanding of possible consequences of screening and their attitudes towards undergoing it. These findings emphasise the need to provide good-quality information on screening outcomes, and to communicate this information effectively, so that women can make well-informed decisions.

Trial registration: This study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613001035718) on 17 September 2013.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Random allocation between two decision aids, differing only in the presence or absence of information about overdetection, enabled a rigorous test of the specific effects of this information when described in the context of other screening outcomes.
- Participants were women entering the target age range for breast screening, who were sampled randomly from the general community and were facing real decisions.
- Our serial mediation model controlled for a comprehensive set of baseline variables and examined plausible, theory-driven cause–effect relationships between exposure to the intervention and subsequently measured variables.
- Nonetheless, given the cross-sectional nature of the outcome and mediator data, we cannot definitively establish the causal ordering of these variables.

KEYWORDS

Breast imaging
Overdiagnosis
Decision aid
Informed decision making
Cancer screening
Mediation

Breast cancer screening is a complex and emotionally charged issue,[1] a topic surrounded by what has been described as a perfect storm of politics and science.[2] While screening can reduce deaths from breast cancer, it can also cause harm through the counterintuitive phenomenon of overdetection or overdiagnosis. The term overdetection is increasingly accepted in the specific context of screening to distinguish it from overdiagnosis that occurs via other mechanisms, such as broadening disease definitions. An overdetected breast cancer is one found by screening, and consequently treated, that would not have caused any health problems had it been left undetected and untreated.[3] Without screening, such a cancer would never have been diagnosed. Overdetected cancers are 'real' cancers in the sense that they meet current pathological criteria for cancer diagnosis, but finding and treating them does not improve health outcomes. Such a diagnosis and the resulting treatment can cause serious lifelong harm, and overdetection is therefore considered the major downside to breast screening.

Mounting evidence of the extent of overdetection (estimated as 19% of breast cancers diagnosed in women invited to screen from age 50 to 69 [4] and 30% for those who attend screening [5]) has led to recognition that the benefits and harms of breast screening are finely balanced for women at population-level risk of breast cancer. The risk of overdetection and its consequences must be weighed against the benefit of reducing breast cancer mortality (relative risk reduction estimated as 20% for women invited to screen from age 50 to 69 [4] and 30% for those screened [5]). Experts familiar with the evidence now acknowledge that individual women may perceive the harm-benefit trade-off differently depending on their personal context and preferences – some will opt for screening while others decline, and either choice may be appropriate if it represents an informed decision.[6-8] Throughout the history of breast screening, however, women invited to participate have not been given all the relevant information.[9-11] Consensus is growing that information on screening benefits and harms, including overdetection, must be communicated clearly and transparently to women offered screening so that they can make informed decisions about whether to be screened.[4, 12, 13] This is all the more important because of evidence that women hold misconceptions about breast screening and its effects.[14, 15]

Against the background of this recommended shift in communication, the issue of how information about overdetection affects women and their screening decisions is critical. In a randomised trial we addressed this question in women approaching the recommended age for starting mammography screening (age 50, when women are invited for screening in many countries including Australia).[16] We sent women one of two versions of a decision aid (evidence-based information booklet) giving information about breast cancer deaths averted and false positives from screening (abnormal

mammograms in women without cancer), either with or without information on overdetection.[17] The intervention produced several significant effects on decision making.[16] The additional overdetection information improved knowledge, increased the number of women making an informed choice about screening (primary outcome of the trial), and also reduced positive attitudes to screening and the number of women intending to be screened.[16]

From our study design – chosen to identify the specific impact of information about overdetection – it appears that communicating this information influenced women's assessment of the value of screening to them, leading to lower intentions to be screened within the intervention group. This finding has never been observed before, and raises important questions. To facilitate the translation of intervention research findings into other contexts, it is recommended to test hypothesised causal mechanisms.[18] However, causal processes leading from the use of decision aids to the decisions subsequently made are not well understood, as few studies have addressed questions about how these interventions achieve their effects.[19] Only recently have decision aid developers started to critically examine in detail how behavioural, cognitive and social theories of decision making could inform the design and evaluation of decision support interventions.[20] In this paper we explore the psychological pathways through which study participants processed overdetection information and integrated it into their decision making. We provide an explanatory account incorporating cognitive and affective pathways, using psychological theories [21] and mediation analysis.[22]

METHODS

We did a parallel-group randomised controlled trial with women aged 48-50 years, recruited from the general community in New South Wales, Australia. The trial is described in detail elsewhere.[16, 23] Trained interviewers from an independent non-profit company recruited participants via telephone. Women were eligible if they had not undergone mammography in the past 2 years and did not have a personal or strong family history of breast cancer. Participants knew they would receive one of two versions of a breast screening information booklet but did not know how these differed or which was the intervention.

We collected sociodemographics and baseline data on women's stage of decision making (how far along they were with their decision about breast screening), basic conceptual knowledge, attitudes, and intentions (Table 1).[16, 23] We then randomly assigned 879 women to the intervention (n=440) or control group (n=439) and sent their allocated decision aid by post. A programmer who had no contact with participants generated the randomisation sequence, which was inaccessible until after recruitment, ensuring allocation concealment.

The intervention decision aid contained evidence-based explanatory and quantitative information about important outcomes of undergoing screening biennially from age 50 to 69 years (breast cancer mortality reduction, overdetection, and false positives) compared with not screening over this period. The control decision aid omitted all overdetection content but was otherwise identical to the intervention. The decision aids were short booklets combining text and visual formats, and are published.[16, 17]

Our purpose in the analysis reported here was to explore causal pathways between exposure to information about overdetection in a decision aid (intervention) and subsequent breast screening intentions (outcome). We examined a series of potential mediators of this relationship: knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret. We collected follow-up data for these variables using standardised questions in a structured post-intervention telephone interview, 1-4 weeks after randomisation. The participant's group assignment was unknown to the interviewer until the end of the interview.

Our post-intervention knowledge scale assessed conceptual understanding of three key screening outcomes (breast cancer mortality reduction, overdetection, and false positives) and awareness of the approximate numbers affected.[16] For the mediation analysis we used the overdetection knowledge subscale (scored 0 to 10, including conceptual and numeric components) as conveying this new information was the main aim of the intervention. We assessed attitudes to breast screening via a widely used 6-item instrument (possible range 6 to 30), intentions to undergo screening in the next 2-3 years (1 item, 5-point response scale from *definitely* to *definitely not*), and worry about developing breast cancer (1 item, 4-point scale).[16, 23, 24] Higher scores on these measures reflect better knowledge, more positive attitudes and intentions, and greater worry, respectively. We collected women's anticipated regret both for screening (anticipating that if she undergoes screening (action) she may later wish she had not) and *not* screening (anticipating that if she does not undergo screening (inaction) she may later wish she had).[25] We then calculated a differential anticipated regret score [26] by subtracting the action from the inaction score. Higher scores on the resulting measure (possible range –4 to 4) reflect greater anticipated regret for *not* screening, adjusted for the woman's anticipated regret for screening. See the Appendix for further details about these measures.

We tested whether these variables functioned in a chain with a specified direction of causal flow (serial mediation).[22] Based on health psychology theories (e.g., theory of planned behaviour [27, 28]) we tested the following causal chain: intervention (group allocation) -> overdetection knowledge -> worry -> attitudes -> anticipated regret -> intentions. One could hypothesise, for

example, that exposure to information (if communicated effectively) should increase knowledge about overdetection. Understanding that some breast cancers would not cause harm even if untreated might reduce worry about breast cancer, which may affect attitudes towards screening. Anticipation of feeling regret if one does not (vs does) undergo screening might depend on attitudes and in turn influence intentions.

Mediation models were tested using model 6 in the PROCESS macro (Version 2.16) for SPSS (Version 24).[22] This procedure applies an ordinary least squares path analytic framework to estimate both direct and indirect effects of the intervention on screening intentions. To derive these effects, PROCESS fits a series of linear regression models with each variable treated as the outcome in turn. The regression coefficients estimate how each variable affects other variables later in the sequence. Baseline variables in Table 1 (all measured pre-intervention, including baseline screening intentions) were statistically controlled by including them as covariates during mediation analyses. Outcome and mediator variables were standardised (expressed in units of standard deviations from the sample mean) for the mediation analysis. We used a bootstrapping procedure in order to conduct inference tests for the indirect effects. This involved repeatedly drawing samples (with replacement) of size n (where n equals the original sample size) from the existing data, and then estimating the indirect effect in each resampled dataset. By repeating this process thousands of times, PROCESS generated an empirical approximation of the underlying sampling distribution of the indirect effect which was then used to construct a confidence interval for the effect. In this study, 50,000 bootstrap samples were used to create 95% bias-corrected confidence intervals (95% CIs) for the indirect effects (IEs), which we considered significant if the CI did not include zero.

RESULTS

Of 879 participants randomised, 838 completed the follow-up interview. Among these, 27 did not answer all relevant questions and were excluded from the mediation analysis. Sociodemographic characteristics were similar for randomised participants who were and were not included in the mediation analysis. Table 1 shows baseline characteristics of the 811 included participants, which were well balanced between the intervention and control groups.

Table 2 presents mean post-intervention scores for intervention and control groups on the variables included in the mediation model. Compared with controls, the intervention group showed greater knowledge about overdetection, lower worry about breast cancer, less positive attitudes towards breast screening, lower anticipated regret for not screening (versus for screening), and lower intentions to undergo screening. Correlations between these variables were significant ($p<.001$).

Table 1. Baseline sample characteristics (n=811)

Variable	Intervention group (n=406)		Control group (n=405)	
Sociodemographics	**n**	**(%)**	**n**	**(%)**
Family history of breast cancer				
No close blood relative ever diagnosed	389	(96%)	386	(95%)
One close blood relative diagnosed aged ≥50 years	17	(4%)	19	(5%)
Country of birth				
Australia or New Zealand	327	(81%)	335	(83%)
Other	79	(19%)	70	(17%)
Main language spoken at home				
English	390	(96%)	396	(98%)
Other	16	(4%)	9	(2%)
Education				
School only or trade certificate	226	(56%)	225	(56%)
Diploma or university degree or higher	180	(44%)	180	(44%)
Marital status				
Married or living with a partner	317	(78%)	333	(82%)
Not currently living with a partner	89	(22%)	72	(18%)
Parent status				
Has one or more children	361	(89%)	363	(90%)
No children	45	(11%)	42	(10%)
Work status				
Working full time or part time	333	(82%)	341	(84%)
No paid job currently	73	(18%)	64	(16%)
Age				
48-49 years old	289	(71%)	294	(73%)
50 years old	117	(29%)	111	(27%)
Pre-intervention measures	**Mean**	**(SD)**	**Mean**	**(SD)**
Stage of decision making about screening	3.4	(1.0)	3.4	(0.9)
Knowledge (basic concepts of screening)	4.4	(0.8)	4.4	(0.8)
Baseline attitudes to breast screening	26.5	(3.6)	26.8	(3.6)
Baseline intentions about screening	4.5	(0.8)	4.6	(0.8)

Note. All baseline variables appearing above were included as covariates in the mediation analysis (sociodemographic factors were dichotomised as shown). Possible ranges: Stage of decision making 1 (not yet thought about the options) to 4 (already made a choice), Knowledge 0 (none correct) to 5 (all correct), Attitudes 6 (least positive) to 30 (most positive), Intentions 1 (definitely not) to 5 (definitely).

Table 2. Means and standard deviations for study groups on screening intentions and mediator variables

Variable	Intervention group (n=406)	Control group (n=405)	p value
Overdetection knowledge	6.2 (2.2)	4.0 (1.6)	<.001
Breast cancer worry	1.7 (0.7)	1.8 (0.7)	<.001
Screening attitudes	24.5 (4.4)	26.1 (4.1)	<.001
Anticipated regret	1.9 (1.7)	2.5 (1.6)	<.001
Screening intentions	4.1 (1.1)	4.5 (0.9)	<.001

Note. Possible score ranges were as follows: Overdetection knowledge 0 to 10, Breast cancer worry 1 to 4, Attitudes 6 to 30, Anticipated regret -4 to 4, Intentions 1 to 5. See Appendix for further details on measures. Groups were compared here using t tests.

Serial mediation analysis found that the total indirect effect of the intervention on intentions was statistically significant, indicating that the intervention influenced intentions indirectly through its effects on the combined set of mediators. Reading the intervention rather than the control decision aid was associated with a decrease in screening intentions as a result of all specific indirect causal sequences in the model (Table 3). As the direct effect was not significant, there was no evidence that the intervention affected intentions independently of its influence on the mediators modelled. The specific path coefficients are shown in Figure 1. The figure illustrates, for example, that participants who received the intervention decision aid demonstrated greater knowledge than controls, participants with greater knowledge expressed less positive attitudes, and participants with less positive attitudes also had less positive intentions.

Table 3 presents effect estimates and 95% CIs for the 15 specific indirect effects representing causal pathways through the various mediator sequences. The main significant indirect effects of the intervention on intentions were those involving knowledge and attitudes as mediators, both separately (IE1, IE13 in Table 3) and together in sequence (IE3). The first specific indirect effect (IE1) tested whether overdetection knowledge mediated the relationship between the decision aid received and subsequent breast screening intentions; this effect was significant. Relative to those assigned to the control decision aid, participants receiving the intervention demonstrated better knowledge about overdetection and consequently expressed lower intentions to have screening. Another significant effect, IE13 showed that the intervention resulted in less positive attitudes, which also led to lower screening intentions. IE3 tested the causal chain: intervention -> knowledge -> attitudes -> intentions. This was also significant and demonstrated that participants exposed to the intervention gained better overdetection knowledge, those with better knowledge had less positive

attitudes, and these attitudes were in turn associated with reduced intentions to screen. Pair-wise contrasts revealed that the three largest specific indirect effects (IE1, IE3, and IE13) did not significantly differ in size.

Table 3. Direct and indirect effects of the intervention on intentions via four sequential mediators

Path	Effect	SE	95% CI	
Total effect	**-.2768**	**.0540**	**-.3828**	**-.1708**
Direct effect	-.0192	.0501	-.1175	.0791
Total indirect effect	**-.2576**	**.0449**	**-.3488**	**-.1734**
Specific indirect effects (IEs)				
1. Knowledge	**-.0731**	**.0267**	**-.1281**	**-.0230**
2. Knowledge, worry	-.0010	.0017	-.0073	.0007
3. Knowledge, attitudes	**-.0700**	**.0171**	**-.1071**	**-.0396**
4. Knowledge, anticipated regret	**-.0201**	**.0072**	**-.0375**	**-.0088**
5. Knowledge, worry, attitudes	-.0001	.0007	-.0023	.0011
6. Knowledge, worry, anticipated regret	-.0004	.0005	-.0021	.0002
7. Knowledge, attitudes, anticipated regret	**-.0121**	**.0040**	**-.0220**	**-.0059**
8. Knowledge, worry, attitudes, anticipated regret	-.0000	.0001	-.0004	.0021
9. Worry	-.0047	.0050	-.0191	.0021
10. Worry, attitudes	-.0003	.0027	-.0063	.0046
11. Worry, anticipated regret	**-.0020**	**.0014**	**-.0063**	**-.0003**
12. Worry, attitudes, anticipated regret	-.0001	.0005	-.0012	.0008
13. Attitudes	**-.0618**	**.0285**	**-.1178**	**-.0065**
14. Attitudes, anticipated regret	**-.0106**	**.0056**	**-.0241**	**-.0016**
15. Anticipated regret	-.0012	.0104	-.0216	.0200

Note. n = 811; 50,000 bootstrap samples; bias-corrected confidence intervals. The sequential mediators are: overdetection knowledge, breast cancer worry, attitudes, anticipated regret. Bold effects are significant (p<.05).

The anticipated regret variable was also involved in several significant mediation pathways, influenced by knowledge and attitudes separately (IE4, IE14) and together (IE7). The most complex of the significant indirect effects was IE7 leading from the intervention -> overdetection knowledge -> screening attitude -> anticipated regret -> screening intention. Compared with the control group, women receiving the intervention had greater overdetection knowledge, which led to less positive attitudes (as above); these were in turn associated with lower anticipated regret for not screening (versus screening), which translated into reduced intentions to screen.

The specific indirect effect for the pathway through the complete causal chain involving all four mediators in sequence (IE8) – that is, adding breast cancer worry to the mediators discussed above – was not significant. Worry was part of only one significant indirect effect (IE11). The intervention reduced breast cancer worry; women with lower worry had lower anticipated regret for not screening, which again reduced screening intentions.

DISCUSSION

This study showed that the relationship between exposure to information on overdetection and women's subsequent breast screening intentions was mediated by multiple cognitive and affective pathways. The intervention decision aid substantially improved understanding of overdetection, and it influenced – both directly and indirectly via its effect on knowledge – women's attitudes towards having screening. The mediation analysis revealed that these mechanisms involving knowledge and attitudes were particularly important in determining intentions about screening participation. Anticipated regret played a role in several additional pathways linking knowledge, attitudes and intentions. As women became more knowledgeable about overdetection and their screening attitudes became less positive, this lessened their expectation that *not* screening would cause regret and increased the realisation that *screening* might cause regret, which in turn influenced intentions. The non-significance of the direct effect (i.e., relationship between study group and intentions after adjusting for all mediators) confirms that our model captured the key relevant constructs, suggesting little of the observed total effect was due to other differences between the intervention and control decision aids (e.g., length, newness of information, and time spent reading).

The randomised controlled trial design is a key strength of this study. Random allocation between two decision aids, differing only in the presence or absence of information about overdetection, enabled a rigorous test of the specific effects of this information when described in the context of other screening outcomes. Our serial mediation model controlled for a comprehensive set of baseline variables and examined plausible, theory-driven cause-effect relationships between exposure to the intervention and subsequently measured variables. Nonetheless, a limitation is that given the cross-sectional nature of the outcome and mediator data, we cannot definitively establish the causal ordering of these variables. While some of the group differences shown in Table 2 are small, our purpose in this article was not to establish the clinical significance of such differences (see elsewhere for more detailed analysis [16]) but rather to explore possible causal mechanisms involved. Whether the outcome variables in the serial mediation model are normally distributed or not, the inferences are likely to remain valid due to the large sample size of the study.[22, 29] Participants had not been screened in the 2 years prior to the study and were close to the age (50) at

which women are invited into the Australian national breast screening program. Intervention effects could vary in other populations depending on age and cultural context. For example, providing information about overdetection to women who already have more personal experience with screening (e.g., women in their sixties) might produce less of an effect on attitudes and intentions, as suggested by our previous qualitative research.[30]

Although previous literature has reported on screening decisions aided by decision support techniques,[31, 32] little work to date has examined mechanisms for *how* information provided in such resources translates into decisions. Our mediation findings are in line with the explanatory account of health decisions offered by the theory of planned behaviour.[27, 28] Under this theory, attitudes towards a behaviour are determined by salient beliefs about its consequences (in this case, the understanding conveyed by the decision aid that overdetection is a possible consequence of screening); these attitudes in turn determine intentions. Our observed mediation effects involving anticipated regret accord with other empirical evidence supporting its usefulness as an extension to the theory of planned behaviour.[33] Worry about the threat of breast cancer, though emphasised by other health psychology theories, did not appear to play a major role in determining screening intentions among our study participants. While the power of emotion has been cited as a challenge for communicating harms of mammography,[34] our findings reinforce the vital role of good educational materials by demonstrating how evidence-based information influenced women's cognitions about screening and showing that cognitions, rather than emotions, were instrumental in decision making. Utilising a theoretical basis in behavioural psychology or decision making theory is often overlooked but may strengthen the design and evaluation of decision support materials, although operationalizing such theories can be challenging.[20] There is a need to develop and employ comprehensive theoretical frameworks that help us better understand the role of comprehension of benefits and harms in shaping informed screening decisions, as well as how external factors – such as conflicting information from different sources – may influence both information processing and decision making in this sometimes controversial area.[2, 35-37]

CONCLUSIONS

We have previously shown that giving women evidence-based written information about overdetection in breast screening can change women's screening intentions. Importantly, for the first time we now provide evidence, using mediation analysis, of how this cognitive and affective process works: the decision aid intervention achieved substantial knowledge gains, and thereby influenced attitudes and intentions towards screening. Our findings underline the importance of providing good-quality information to women when they are invited to consider screening, using

materials with the capacity to successfully impart new and relevant knowledge. Effective communication tools and decision support resources are especially needed against a background of widely documented unrealistic public expectations of screening.[38] Our findings are a reminder that information can be a powerful intervention, and that the development of information resources must be done properly with rigour and care.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by The University of Sydney human research ethics committee (2012/1429). Participants gave informed consent to take part in the study.

Patient consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: financial support from the National Health and Medical Research Council of Australia for the submitted work; 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.

Authors' contributions

All authors contributed to study design. KMcC, AB, JJ, NH, HD, and KMcG obtained funding. JH, KMcC, and JJ led development of the intervention and implementation of the trial. KMcG advised on the statistical analysis. JH performed the statistical analysis, produced the tables and figure, and drafted the manuscript. All authors contributed to data interpretation and critically reviewed the manuscript.

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REFERENCES

1 Harvey S. The charge and the challenges of breast cancer screening. *J Womens Health (Larchmt)* 2014;23(Suppl 1):S1-2. doi: 10.1089/jwh.2014.1509

2 Elmore JG. Breast cancer screening: balancing evidence with culture, politics, money, and media. In: Houssami N, Miglioretti D, eds. Breast Cancer Screening: An Examination of Scientific Evidence. Amsterdam: Elsevier 2016:1-27.

3 Welch HG, Black W. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;102:605-13. doi: 10.1093/jnci/djq099

4 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380:1778-86. doi: 10.1016/S0140-6736(12)61611-0

5 Jacklyn G, Glasziou P, Macaskill P, et al. Meta-analysis of breast cancer mortality benefit and overdiagnosis adjusted for adherence: improving information on the effects of attending screening mammography. *Br J Cancer* 2016;114:1269-76. doi: 10.1038/bjc.2016.90

6 Heath I. It is not wrong to say no. *BMJ* 2009;338:b2529. doi: 10.1136/bmj.b2529

7 Kirwan C. Breast cancer screening: what does the future hold? *BMJ* 2013;346:f87. doi: 10.1136/bmj.f87

8 Stefanek M. Uninformed compliance or informed choice? A needed shift in our approach to cancer screening. *J Natl Cancer Inst* 2011;103:1821-26. doi: 10.1093/jnci/djr474

9 Gummersbach E, Piccoliori G, Oriol Zerbe C, et al. Are women getting relevant information about mammography screening for an informed consent: a critical appraisal of information brochures used for screening invitation in Germany, Italy, Spain and France. *Eur J Public Health* 2010;20:409-14. doi: 10.1093/eurpub/ckp174

10 Jorgensen K, Gotzsche P. Content of invitations for publicly funded screening mammography. *BMJ* 2006;332:538-41. doi: 10.1136/bmj.332.7540.538

11 Zapka J, Geller B, Bulliard J, et al. Print information to inform decisions about mammography screening participation in 16 countries with population-based programs. *Patient Educ Couns* 2006;63:126-37. doi: 10.1016/j.pec.2005.09.012

12 Welch HG, Passow H. Quantifying the benefits and harms of screening mammography. *JAMA Intern Med* 2014;174:448-54. doi: 10.1001/jamainternmed.2013.13635

13 Loberg M, Lousdal ML, Bretthauer M, et al. Benefits and harms of mammography screening. *Breast Cancer Res* 2015;17:63. doi: 10.1186/s13058-015-0525-z

14 Biller-Andorno N, Juni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. *N Engl J Med* 2014;370:1965-67. doi: 10.1056/NEJMp1401875

15 Schwartz L, Woloshin S, Sox H, et al. US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey. *BMJ* 2000;320:1635-40. doi: 10.1136/bmj.320.7250.1635

16 Hersch J, Barratt A, Jansen J, et al. Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial. *Lancet* 2015;385:1642-52. doi: 10.1016/S0140-6736(15)60123-4

17 Hersch J, Jansen J, Barratt A, et al. Overdetection in breast cancer screening: development and preliminary evaluation of a decision aid. *BMJ Open* 2014;4:e006016. doi: 10.1136/bmjopen-2014-006016

18 Riddle M, Science of Behavior Change Working Group. News from the NIH: using an experimental medicine approach to facilitate translational research. *Transl Behav Med* 2015;5(4):486-8. doi: 10.1007/s13142-015-0333-0

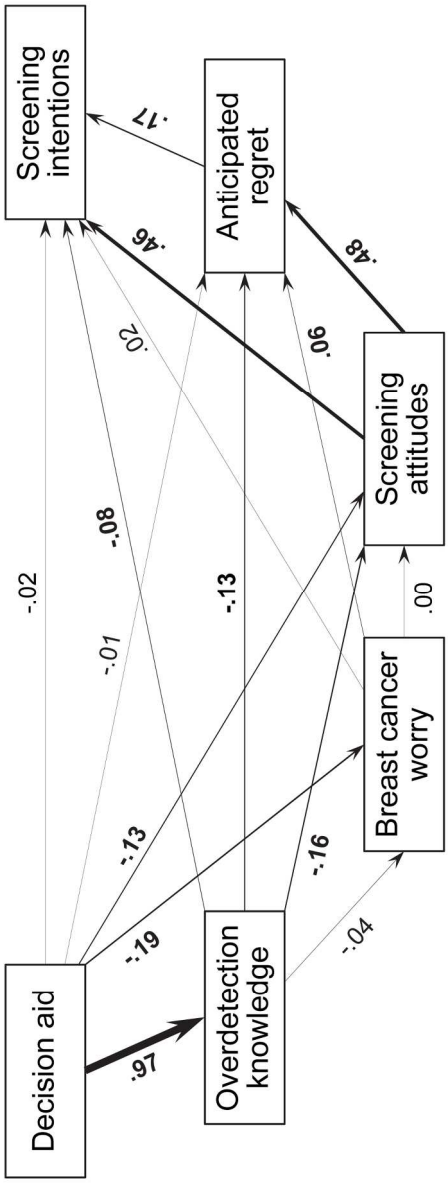
19 Krones T, Keller H, Becker A, et al. The theory of planned behaviour in a randomized trial of a decision aid on cardiovascular risk prevention. *Patient Educ Couns* 2010;78(2):169-76. doi: 10.1016/j.pec.2009.06.010

20 Elwyn G, Stiel M, Durand MA, et al. The design of patient decision support interventions: addressing the theory-practice gap. *J Eval Clin Pract* 2011;17:565-74. doi: 10.1111/j.1365-2753.2010.01517.x
21 Armitage CJ, Conner M. Social cognition models and health behaviour: a structured review. *Psychol Health* 2000;15:173-89. doi: 10.1080/08870440008400299
22 Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York: Guilford 2013:xvii, 507.
23 Hersch J, Barratt A, Jansen J, et al. The effect of information about overdetection of breast cancer on women's decision-making about mammography screening: study protocol for a randomised controlled trial. *BMJ Open* 2014;4:e004990. doi: 10.1136/bmjopen-2014-004990
24 Dormandy E, Michie S, Hooper R, et al. Informed choice in antenatal Down syndrome screening: a cluster-randomised trial of combined versus separate visit testing. *Patient Educ Couns* 2006;61:56-64. doi: 10.1016/j.pec.2005.02.006
25 Sandberg T, Hutter R, Richetin J, et al. Testing the role of action and inaction anticipated regret on intentions and behaviour. *Br J Soc Psychol* 2016;55:407-25. doi: 10.1111/bjso.12141
26 Sivell S, Elwyn G, Edwards A, et al. Factors influencing the surgery intentions and choices of women with early breast cancer: the predictive utility of an extended theory of planned behaviour. *BMC Med Inform Decis Mak* 2013;13:92. doi: 10.1186/1472-6947-13-92
27 Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991;50:179-211. doi: 10.1016/0749-5978%2891%2990020-T
28 Ajzen I. Martin Fishbein's legacy: the reasoned action approach. *Ann Am Acad Pol Soc Sci* 2012;640:11-27. doi: 10.1177/0002716211423363
29 Lumley T, Diehr P, Emerson S, et al. The importance of the normality assumption in large public health data sets. *Annu Rev Public Health* 2002;23:151-69. doi: 10.1146/annurev.publhealth.23.100901.140546
30 Hersch J, Jansen J, Barratt A, et al. Women's views on overdiagnosis in breast cancer screening: a qualitative study. *BMJ* 2013;346:f158. doi: 10.1136/bmj.f158
31 Biesecker B, Schwartz M, Marteau T. Enhancing informed choice to undergo health screening: a systematic review. *Am J Health Behav* 2013;37:351-59. doi: 10.5993/AJHB.37.3.8
32 van Agt H, Korfage I, Essink-Bot M. Interventions to enhance informed choices among invitees of screening programmes – a systematic review. *Eur J Public Health* 2014;24:789-801. doi: 10.1093/eurpub/ckt205
33 Sandberg T, Conner M. Anticipated regret as an additional predictor in the theory of planned behaviour: a meta-analysis. *Br J Soc Psychol* 2008;47:589-606. doi: 10.1348/014466607X258704
34 Rosenbaum L. Invisible risks, emotional choices – mammography and medical decision making. *N Engl J Med* 2014;371(16):1549-52. doi: 10.1056/NEJMms1409003
35 Steckelberg A, Kasper J, Mühlhauser I. Selective information seeking: can consumers' avoidance of evidence-based information on colorectal cancer screening be explained by the theory of cognitive dissonance? *German Medical Science* 2007;5:Doc05.
36 Baena-Canada JM, Rosado-Varela P, Exposito-Alvarez I, et al. Using an informed consent in mammography screening: a randomized trial. *Cancer Med* 2015;4:1923-32. doi: 10.1002/cam4.525
37 Petrova D, Garcia-Retamero R, Catena A, et al. To screen or not to screen: What factors influence complex screening decisions? *J Exp Psychol Appl* 2016;22:247-60. doi: 10.1037/xap0000086
38 Hoffmann T, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med* 2015;175:274-86. doi: 10.1001/jamainternmed.2014.6016

FIGURES

Fig. 1. Title: Multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators

Fig. 1. Legend: Graphic representation of the serial multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators (overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret). The intervention was hypothesised to exert an effect on screening intentions through the four mediators in sequence. Outcome and mediator variables were standardised prior to analysis. Bold coefficients are significant (p<.05). Analyses controlled for baseline measures including screening intentions and attitudes, basic screening knowledge, stage of decision making, breast cancer family history, birthplace, main language spoken, education, marital status, parent status, work status, and age.



Multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators

Graphic representation of the serial multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators (overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret). The intervention was hypothesised to exert an effect on screening intentions through the four mediators in sequence. Outcome and mediator variables were standardised prior to analysis. Bold coefficients are significant (p<.05). Analyses controlled for baseline measures including screening intentions and attitudes, basic screening knowledge, stage of decision making, breast cancer family history, birthplace, main language spoken, education, marital status, parent status, work status, and age.

87x225mm (300 x 300 DPI)

Measurement of outcome and mediator variables used in:

Hersch J et al. How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

This appendix contains the questions used for the measures included in the mediation analysis, including the range of available response options, and describes how each score was calculated.

The questions were administered during a structured, computer-assisted telephone interview that took place after the participant had read her allocated decision aid.

Knowledge about overdetection

OC1. Who do you think is more likely to be diagnosed with breast cancer?

- Women who have screening mammograms [1]
- Women who do not have screening mammograms [0]

OC2. All breast cancers will eventually cause illness and death if they are not found and treated.

- TRUE [0]
- FALSE [1]

OC3. When screening finds cancer, doctors can reliably predict whether it will ever cause harm.

- TRUE [0]
- FALSE [1]

OC4. Even breast cancers that may not cause any health problems are likely to be treated.

- TRUE [1]
- FALSE [0]

OC5. Screening leads some women with a harmless cancer to get treatment they do not need.

- TRUE [1]
- FALSE [0]

OC6. Screening finds harmless cancers more often than it prevents death from breast cancer.

- TRUE [1]
- FALSE [0]

OC7. Which of these 2 statements best describes over-detection?

- Screening finds a cancer that would never have caused trouble [1]
- Screening finds an abnormality but extra tests show it is not cancer [0]

I would like you to imagine 1000 ordinary women who are 50 years old.

BN1. If these 1,000 women have breast screening every 2 years for 20 years, in that time about how many women do you think will avoid dying from breast cancer because of screening?

____

ON1. If these 1,000 women have screening every 2 years for 20 years, in that time about how many will be diagnosed and treated for a breast cancer that is not harmful?

____

1 mark was awarded if the answer given for ON1 was greater than the answer given for BN1.

1 mark was awarded if the answer given for ON1 was between 6 and 57. An additional 1 mark was awarded if the answer given for ON1 was between 10 and 38.

Marks were allocated as indicated above, and summed for a total score ranging between 0 and 10. Higher scores reflect better knowledge.

Attitudes to breast screening

For you, having breast screening is: Beneficial

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: A good thing

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: Harmful

- Strongly agree [1]
- Agree [2]
- Neither agree nor disagree [3]
- Disagree [4]
- Strongly disagree [5]

For you, having breast screening is: Worthwhile

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: Important

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: A bad thing

- Strongly agree [1]
- Agree [2]
- Neither agree nor disagree [3]
- Disagree [4]
- Strongly disagree [5]

Scores were allocated as indicated above, and summed for a total score ranging between 6 and 30. Higher scores reflect more positive attitudes.

Anticipated regret

If you do NOT have breast screening in the next few years, you may later wish you DID.

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

Higher scores above indicate greater anticipated regret for *not* screening (inaction score).

If you DO have breast screening in the next few years, you may later wish you did NOT.

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

Higher scores above indicate greater anticipated regret for screening (action score).

The action score was subtracted from the inaction score to produce a differential anticipated regret score ranging between –4 and 4. Higher scores reflect greater anticipated regret for *not* screening, adjusted for anticipated regret for screening.

Worry about breast cancer

How worried are you about developing breast cancer?

- Not worried at all [0]
- A bit worried [1]
- Quite worried [2]
- Very worried [3]

Scores were allocated as indicated above. Higher scores reflect greater worry.

Intentions about breast screening

At the moment, which of the following best describes your intentions about having breast screening within the next 2-3 years?

- You definitely will have breast screening [5]
- You are likely to have breast screening [4]
- You are unsure [3]
- You are not likely to have breast screening [2]
- You definitely will not have breast screening [1]

Scores were allocated as indicated above. Higher scores reflect more positive intentions.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5 + protocol[1]
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5 + protocol[1]
	4b	Settings and locations where the data were collected	5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6 + published protocol[1]
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6 + published protocol[1]
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	Protocol[1]

	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Lancet[2]
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Protocol[1]
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5 + protocol[1]
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5-6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Lancet[2]
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7 + Lancet[2]
	13b	For each group, losses and exclusions after randomisation, together with reasons	7 + Lancet[2]
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Lancet[2]
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7 + Lancet[2]

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	16
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14 + Lancet[2]

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

1 Hersch J, Barratt A, Jansen J, et al. The effect of information about overdetection of breast cancer on women's decision-making about mammography screening: study protocol for a randomised controlled trial. *BMJ Open* 2014;4:e004990. doi: 10.1136/bmjopen-2014-004990
2 Hersch J, Barratt A, Jansen J, et al. Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial. *Lancet* 2015;385:1642-52. doi: 10.1016/S0140-6736(15)60123-4

BMJ Open

How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

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Primary Subject Heading:	Communication
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Keywords:	Breast imaging < RADIOLOGY & IMAGING, Overdiagnosis, Decision aid, Informed decision making, Cancer screening, Mediation

TITLE

How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

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ABSTRACT

Objectives: In a randomised controlled trial, we found that informing women about overdetection changed their breast screening decisions. We now present a mediation analysis exploring the psychological pathways through which study participants who received the intervention processed information about overdetection and how this influenced their decision making. We examined a series of potential mediators in the causal chain between exposure to overdetection information and women's subsequently reported breast screening intentions.

Design: Serial multiple mediation analysis within a randomised controlled trial

Setting: New South Wales, Australia

Participants: 811 women aged 48–50 years with no personal history of breast cancer

Interventions: Two versions of a decision aid giving women information about breast cancer deaths averted and false positives from mammography screening, either with (intervention) or without (control) information on overdetection

Main outcome: Intentions to undergo breast cancer screening in the next 2–3 years

Mediators: Knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret

Results: The effect of information about overdetection on women's breast screening intentions was mediated through multiple cognitive and affective processes. In particular, the information led to substantial improvements in women's understanding of overdetection, and it influenced – both directly and indirectly via its effect on knowledge – their attitudes towards having screening. Mediation analysis showed that the mechanisms involving knowledge and attitudes were particularly important in determining women's intentions about screening participation.

Conclusions: Even in this emotive context, new information influenced women's decision making by changing their understanding of possible consequences of screening and their attitudes towards undergoing it. These findings emphasise the need to provide good-quality information on screening outcomes, and to communicate this information effectively, so that women can make well-informed decisions.

Trial registration: This study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613001035718) on 17 September 2013.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Random allocation between two decision aids, differing only in the presence or absence of information about overdetection, enabled a rigorous test of the specific effects of this information when described in the context of other screening outcomes.
- Participants were women entering the target age range for breast screening, who were sampled randomly from the general community and were facing real decisions.
- Our serial mediation model controlled for a comprehensive set of baseline variables and examined plausible, theory-driven cause–effect relationships between exposure to the intervention and subsequently measured variables.
- Nonetheless, given the cross-sectional nature of the outcome and mediator data, we cannot definitively establish the causal sequence of these variables.

KEYWORDS

Breast imaging
Overdiagnosis
Decision aid
Informed decision making
Cancer screening
Mediation

Breast cancer screening is a complex and emotionally charged issue,[1] a topic surrounded by what has been described as a perfect storm of politics and science.[2] While screening can reduce deaths from breast cancer, it can also cause harm through the counterintuitive phenomenon of overdetection or overdiagnosis. The term overdetection is increasingly accepted in the specific context of screening to distinguish it from overdiagnosis that occurs via other mechanisms, such as broadening disease definitions. An overdetected breast cancer is one found by screening, and consequently treated, that would not have caused any health problems had it been left undetected and untreated.[3] Without screening, such a cancer would never have been diagnosed. Overdetected cancers are 'real' cancers in the sense that they meet current pathological criteria for cancer diagnosis, but finding and treating them does not improve health outcomes. Such a diagnosis and the resulting treatment can cause serious lifelong harm, and overdetection is therefore considered the major downside to breast screening.

Mounting evidence of the extent of overdetection (estimated as 19% of breast cancers diagnosed in women invited to screen from age 50 to 69 [4] and 30% for those who attend screening [5]) has led to recognition that the benefits and harms of breast screening are finely balanced for women at population-level risk of breast cancer. The risk of overdetection and its consequences must be weighed against the benefit of reducing breast cancer mortality (relative risk reduction estimated as 20% for women invited to screen from age 50 to 69 [4] and 30% for those screened [5]). Experts familiar with the evidence now acknowledge that individual women may perceive the harm-benefit trade-off differently depending on their personal context and preferences – some will opt for screening while others decline, and either choice may be appropriate if it represents an informed decision.[6-8] Throughout the history of breast screening, however, women invited to participate have not been given all the relevant information.[9-11] Consensus is growing that information on screening benefits and harms, including overdetection, must be communicated clearly and transparently to women offered screening so that they can make informed decisions about whether to be screened.[4, 12, 13] This is all the more important because of evidence that women hold misconceptions about breast screening and its effects.[14, 15]

Against the background of this recommended shift in communication, the issue of how information about overdetection affects women and their screening decisions is critical. In a randomised trial we addressed this question in women approaching the recommended age for starting mammography screening (age 50, when women are invited for screening in many countries including Australia).[16] We sent women one of two versions of a decision aid (evidence-based information booklet) giving information about breast cancer deaths averted and false positives from screening (abnormal

mammograms in women without cancer), either with or without information on overdetection.[17] The intervention produced several significant effects on decision making.[16] The additional overdetection information improved knowledge, increased the number of women making an informed choice about screening (primary outcome of the trial), and also reduced positive attitudes to screening and the number of women intending to be screened.[16]

From our study design – chosen to identify the specific impact of information about overdetection – it appears that communicating this information influenced women's assessment of the value of screening to them, leading to lower intentions to be screened within the intervention group. This finding has never been observed before, and raises important questions. To facilitate the translation of intervention research findings into other contexts, it is recommended to test hypothesised causal mechanisms.[18] However, causal processes leading from the use of decision aids to the decisions subsequently made are not well understood, as few studies have addressed questions about how these interventions achieve their effects.[19] Only recently have decision aid developers started to critically examine in detail how behavioural, cognitive and social theories of decision making could inform the design and evaluation of decision support interventions.[20] In this paper we explore the psychological pathways through which study participants processed overdetection information and integrated it into their decision making. We provide an explanatory account incorporating cognitive and affective pathways, using psychological theories [21] and mediation analysis.[22]

METHODS

We did a parallel-group randomised controlled trial with women aged 48-50 years, recruited from the general community in New South Wales, Australia. The trial is described in detail elsewhere.[16, 23] Trained interviewers from an independent non-profit company recruited participants via telephone. Women were eligible if they had not undergone mammography in the past 2 years and did not have a personal or strong family history of breast cancer. Participants knew they would receive one of two versions of a breast screening information booklet but did not know how these differed or which was the intervention.

We collected sociodemographics and baseline data on women's stage of decision making (how far along they were with their decision about breast screening), basic conceptual knowledge, attitudes, and intentions (Table 1).[16, 23] We then randomly assigned 879 women to the intervention (n=440) or control group (n=439) and sent their allocated decision aid by post. A programmer who had no

contact with participants generated the randomisation sequence, which was inaccessible until after recruitment, ensuring allocation concealment.

The intervention decision aid contained evidence-based explanatory and quantitative information about important outcomes of undergoing screening biennially from age 50 to 69 years (breast cancer mortality reduction, overdetection, and false positives) compared with not screening over this period. The control decision aid omitted all overdetection content but was otherwise identical to the intervention. The decision aids were short booklets combining text and visual formats, and are published.[16, 17]

Our purpose in the analysis reported here was to explore causal pathways between exposure to information about overdetection in a decision aid (intervention) and subsequent breast screening intentions (outcome). We examined a series of potential mediators of this relationship: knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret. We collected follow-up data for these variables using standardised questions in a structured post-intervention telephone interview, 1-4 weeks after randomisation. The participant's group assignment was unknown to the interviewer until the end of the interview.

Our post-intervention knowledge scale assessed conceptual understanding of three key screening outcomes (breast cancer mortality reduction, overdetection, and false positives) and awareness of the approximate numbers affected.[16] For the mediation analysis we used the overdetection knowledge subscale (scored 0 to 10, including conceptual and numeric components) because conveying this new information was the main aim of the intervention. We assessed attitudes to breast screening via a widely used 6-item instrument (possible range 6 to 30), intentions to undergo screening in the next 2-3 years (1 item, 5-point response scale from *definitely* to *definitely not*), and worry about developing breast cancer (1 item, 4-point scale).[16, 23, 24] Higher scores on these measures reflect better knowledge, more positive attitudes and intentions, and greater worry, respectively. We collected women's anticipated regret both for screening (anticipating that if she undergoes screening (action) she may later wish she had not) and *not* screening (anticipating that if she does not undergo screening (inaction) she may later wish she had).[25] We then calculated a differential anticipated regret score [26] by subtracting the action from the inaction score. Higher scores on the resulting measure (possible range –4 to 4) reflect greater anticipated regret for *not* screening, adjusted for the woman's anticipated regret for screening. See the Appendix for further details about these measures.

We tested whether these variables functioned in a chain with a specified direction of causal flow (serial mediation).[22] Based on health psychology theories (e.g., theory of planned behaviour [27, 28]) we tested the following causal chain: intervention (group allocation) -> overdetection knowledge -> worry -> attitudes -> anticipated regret -> intentions. One could hypothesise, for example, that exposure to information (if communicated effectively) should increase knowledge about overdetection. Understanding that some breast cancers would not cause harm even if untreated might reduce worry about breast cancer, which may affect attitudes towards screening. Anticipation of feeling regret if one does not (vs does) undergo screening might depend on attitudes and in turn influence intentions.

Mediation models were tested using model 6 in the PROCESS macro (Version 2.16) for SPSS (Version 24).[22] This procedure applies an ordinary least squares path analytic framework to estimate both direct and indirect effects of the intervention on screening intentions. To derive these effects, PROCESS fits a series of linear regression models with each variable treated as the outcome in turn. The regression coefficients estimate how each variable affects other variables later in the sequence. Baseline variables in Table 1 (all measured pre-intervention, including baseline screening intentions) were statistically controlled by including them as covariates during mediation analyses. Outcome and mediator variables were standardised (expressed in units of standard deviations from the sample mean) for the mediation analysis. We used a bootstrapping procedure in order to conduct inference tests for the indirect effects. This involved repeatedly drawing samples (with replacement) of size n (where n equals the original sample size) from the existing data, and then estimating the indirect effect in each resampled dataset. By repeating this process thousands of times, PROCESS generated an empirical approximation of the underlying sampling distribution of the indirect effect which was then used to construct a confidence interval for the effect. In this study, 50,000 bootstrap samples were used to create 95% bias-corrected confidence intervals (95% CIs) for the indirect effects (IEs), which we considered significant if the CI did not include zero.

RESULTS

Of 879 participants randomised, 838 completed the follow-up interview. Among these, 27 did not answer all relevant questions and were excluded from the mediation analysis. Sociodemographic characteristics were similar for randomised participants who were and were not included in the mediation analysis. Table 1 shows baseline characteristics of the 811 included participants, which were well balanced between the intervention and control groups.

Table 1. Baseline sample characteristics (n=811)

Variable	Intervention group (n=406)		Control group (n=405)	
Sociodemographics	**n**	**(%)**	**n**	**(%)**
Family history of breast cancer				
No close blood relative ever diagnosed	389	(96%)	386	(95%)
One close blood relative diagnosed aged ≥50 years	17	(4%)	19	(5%)
Country of birth				
Australia or New Zealand	327	(81%)	335	(83%)
Other	79	(19%)	70	(17%)
Main language spoken at home				
English	390	(96%)	396	(98%)
Other	16	(4%)	9	(2%)
Education				
School only or trade certificate	226	(56%)	225	(56%)
Diploma or university degree or higher	180	(44%)	180	(44%)
Marital status				
Married or living with a partner	317	(78%)	333	(82%)
Not currently living with a partner	89	(22%)	72	(18%)
Parent status				
Has one or more children	361	(89%)	363	(90%)
No children	45	(11%)	42	(10%)
Work status				
Working full time or part time	333	(82%)	341	(84%)
No paid job currently	73	(18%)	64	(16%)
Age				
48-49 years old	289	(71%)	294	(73%)
50 years old	117	(29%)	111	(27%)
Pre-intervention measures	**Mean**	**(SD)**	**Mean**	**(SD)**
Stage of decision making about screening	3.4	(1.0)	3.4	(0.9)
Knowledge (basic concepts of screening)	4.4	(0.8)	4.4	(0.8)
Baseline attitudes to breast screening	26.5	(3.6)	26.8	(3.6)
Baseline intentions about screening	4.5	(0.8)	4.6	(0.8)

Note. All baseline variables appearing above were included as covariates in the mediation analysis (sociodemographic factors were dichotomised as shown). Possible ranges: Stage of decision making 1 (not yet thought about the options) to 4 (already made a choice), Knowledge 0 (none correct) to 5 (all correct), Attitudes 6 (least positive) to 30 (most positive), Intentions 1 (definitely not) to 5 (definitely).

Table 2 presents mean post-intervention scores for intervention and control groups on the variables included in the mediation model. Compared with controls, the intervention group showed greater knowledge about overdetection, lower worry about breast cancer, less positive attitudes towards breast screening, lower anticipated regret for not screening (versus for screening), and lower intentions to undergo screening. Correlations between these variables were significant (p<.001) as shown in the Appendix.

Table 2. Means and standard deviations for study groups on screening intentions and mediator variables

Variable	**Intervention group (n=406)**		**Control group (n=405)**		
	Mean	(SD)	Mean	(SD)	**p value**
Overdetection knowledge	6.2	(2.2)	4.0	(1.6)	<.001
Breast cancer worry	1.7	(0.7)	1.8	(0.7)	<.001
Screening attitudes	24.5	(4.4)	26.1	(4.1)	<.001
Anticipated regret	1.9	(1.7)	2.5	(1.6)	<.001
Screening intentions	4.1	(1.1)	4.5	(0.9)	<.001

Note. Possible score ranges were as follows: Overdetection knowledge 0 to 10, Breast cancer worry 1 to 4, Attitudes 6 to 30, Anticipated regret -4 to 4, Intentions 1 to 5. See Appendix for further details on measures. Groups were compared here using t tests.

Serial mediation analysis found that the total indirect effect of the intervention on intentions was statistically significant, indicating that the intervention influenced intentions indirectly through its effects on the combined set of mediators. Reading the intervention rather than the control decision aid was associated with a decrease in screening intentions as a result of all specific indirect causal sequences in the model (Table 3). As the direct effect was not significant, there was no evidence that the intervention affected intentions independently of its influence on the mediators modelled. The specific path coefficients are shown in Figure 1. The figure illustrates, for example, that participants who received the intervention decision aid demonstrated greater knowledge than controls, participants with greater knowledge expressed less positive attitudes, and participants with less positive attitudes also had less positive intentions.

Table 3 presents effect estimates and 95% CIs for the 15 specific indirect effects representing causal pathways through the various mediator sequences. The main significant indirect effects of the intervention on intentions were those involving knowledge and attitudes as mediators, both separately (IE1, IE13 in Table 3) and together in sequence (IE3). The first specific indirect effect (IE1)

tested whether overdetection knowledge mediated the relationship between the decision aid received and subsequent breast screening intentions; this effect was significant. Relative to those assigned to the control decision aid, participants receiving the intervention demonstrated better knowledge about overdetection and consequently expressed lower intentions to have screening. Another significant effect, IE13 showed that the intervention resulted in less positive attitudes, which also led to lower screening intentions. IE3 tested the causal chain: intervention -> knowledge -> attitudes -> intentions. This was also significant and demonstrated that participants exposed to the intervention gained better overdetection knowledge, those with better knowledge had less positive attitudes, and these attitudes were in turn associated with reduced intentions to screen. Pair-wise contrasts revealed that the three largest specific indirect effects (IE1, IE3, and IE13) did not significantly differ in size.

Table 3. Direct and indirect effects of the intervention on intentions via four sequential mediators

Path	Effect	SE	95% CI	
Total effect	**-.2768**	**.0540**	**-.3828**	**-.1708**
Direct effect	-.0192	.0501	-.1175	.0791
Total indirect effect	**-.2576**	**.0449**	**-.3488**	**-.1734**
Specific indirect effects (IEs)				
1. Knowledge	**-.0731**	**.0267**	**-.1281**	**-.0230**
2. Knowledge, worry	-.0010	.0017	-.0073	.0007
3. Knowledge, attitudes	**-.0700**	**.0171**	**-.1071**	**-.0396**
4. Knowledge, anticipated regret	**-.0201**	**.0072**	**-.0375**	**-.0088**
5. Knowledge, worry, attitudes	-.0001	.0007	-.0023	.0011
6. Knowledge, worry, anticipated regret	-.0004	.0005	-.0021	.0002
7. Knowledge, attitudes, anticipated regret	**-.0121**	**.0040**	**-.0220**	**-.0059**
8. Knowledge, worry, attitudes, anticipated regret	-.0000	.0001	-.0004	.0021
9. Worry	-.0047	.0050	-.0191	.0021
10. Worry, attitudes	-.0003	.0027	-.0063	.0046
11. Worry, anticipated regret	**-.0020**	**.0014**	**-.0063**	**-.0003**
12. Worry, attitudes, anticipated regret	-.0001	.0005	-.0012	.0008
13. Attitudes	**-.0618**	**.0285**	**-.1178**	**-.0065**
14. Attitudes, anticipated regret	**-.0106**	**.0056**	**-.0241**	**-.0016**
15. Anticipated regret	-.0012	.0104	-.0216	.0200

Note. n=811; 50,000 bootstrap samples; bias-corrected confidence intervals. The sequential mediators are: overdetection knowledge, breast cancer worry, attitudes, anticipated regret. Bold effects are significant ($p<.05$).

The anticipated regret variable was also involved in several significant mediation pathways, influenced by knowledge and attitudes separately (IE4, IE14) and together (IE7). The most complex of the significant indirect effects was IE7 leading from the intervention -> overdetection knowledge -> screening attitude -> anticipated regret -> screening intention. Compared with the control group, women receiving the intervention had greater overdetection knowledge, which led to less positive attitudes (as above); these were in turn associated with lower anticipated regret for not screening (versus screening), which translated into reduced intentions to screen.

The specific indirect effect for the pathway through the complete causal chain involving all four mediators in sequence (IE8) – that is, adding breast cancer worry to the mediators discussed above – was not significant. Worry was part of only one significant indirect effect (IE11). The intervention reduced breast cancer worry; women with lower worry had lower anticipated regret for not screening, which again reduced screening intentions.

DISCUSSION

This study showed that the relationship between exposure to information on overdetection and women's subsequent breast screening intentions was mediated by multiple cognitive and affective pathways. The intervention decision aid substantially improved understanding of overdetection, and it influenced – both directly and indirectly via its effect on knowledge – women's attitudes towards having screening. The mediation analysis revealed that these mechanisms involving knowledge and attitudes were particularly important in determining intentions about screening participation. Anticipated regret played a role in several additional pathways linking knowledge, attitudes and intentions. As women became more knowledgeable about overdetection and their screening attitudes became less positive, this lessened their expectation that *not* screening would cause regret and increased the realisation that *screening* might cause regret, which in turn influenced intentions. The non-significance of the direct effect (i.e., relationship between study group and intentions after adjusting for all mediators) confirms that our model captured the key relevant constructs, suggesting little of the observed total effect was due to other differences between the intervention and control decision aids (e.g., length, newness of information, and time spent reading).

The randomised controlled trial design is a key strength of this study. Random allocation between two decision aids, differing only in the presence or absence of information about overdetection, enabled a rigorous test of the specific effects of this information when described in the context of other screening outcomes. Our serial mediation model controlled for a comprehensive set of

baseline variables and examined plausible, theory-driven cause-effect relationships between exposure to the intervention and subsequently measured variables. Nonetheless, a limitation is that given the cross-sectional nature of the outcome and mediator data, we cannot definitively establish the causal sequence of these variables. While some of the group differences shown in Table 2 are small, our purpose in this article was not to establish the clinical significance of such differences (see elsewhere for more detailed analysis [16]) but rather to explore possible causal mechanisms involved. Whether the outcome variables in the serial mediation model are normally distributed or not, the inferences are likely to remain valid due to the large sample size of the study.[22, 29] Participants had not been screened in the 2 years prior to the study and were close to the age (50) at which women are invited into the Australian national breast screening program. Intervention effects could vary in other populations depending on age and cultural context. For example, providing information about overdetection to women who already have more personal experience with screening (e.g., women in their sixties) might produce less of an effect on attitudes and intentions, as suggested by our previous qualitative research.[30]

Although previous literature has reported on screening decisions aided by decision support techniques,[31, 32] little work to date has examined mechanisms for *how* information provided in such resources translates into decisions. Our mediation findings are in line with the explanatory account of health decisions offered by the theory of planned behaviour.[27, 28] Under this theory, attitudes towards a behaviour are determined by salient beliefs about its consequences (in this case, the understanding conveyed by the decision aid that overdetection is a possible consequence of screening); these attitudes in turn determine intentions. Our observed mediation effects involving anticipated regret accord with other empirical evidence supporting its usefulness as an extension to the theory of planned behaviour.[33] Worry about the threat of breast cancer, though emphasised by other health psychology theories, did not appear to play a major role in determining screening intentions among our study participants. While the power of emotion has been cited as a challenge for communicating harms of mammography,[34] our findings reinforce the vital role of good educational materials by demonstrating how evidence-based information influenced women's cognitions about screening and showing that cognitions, rather than emotions, were instrumental in decision making. Utilising a theoretical basis in behavioural psychology or decision making theory is often overlooked but may strengthen the design and evaluation of decision support materials, although operationalizing such theories can be challenging.[20] There is a need to develop and employ comprehensive theoretical frameworks that help us better understand the role of comprehension of benefits and harms in shaping informed screening decisions, as well as how

external factors – such as conflicting information from different sources – may influence both information processing and decision making in this sometimes controversial area.[2, 35-37]

CONCLUSIONS

We have previously shown that giving women evidence-based written information about overdetection in breast screening can change women's screening intentions. Importantly, for the first time we now provide evidence, using mediation analysis, of how this cognitive and affective process works: the decision aid intervention achieved substantial knowledge gains, and thereby influenced attitudes and intentions towards screening. Our findings underline the importance of providing good-quality information to women when they are invited to consider screening, using materials with the capacity to successfully impart new and relevant knowledge. Effective communication tools and decision support resources are especially needed against a background of widely documented unrealistic public expectations of screening which may be driven by psychological factors in combination with sometimes misleading messages about benefits and lack of attention to harms.[38, 39] Our findings are a reminder that information can be a powerful intervention, and that the development of information resources must be done properly with rigour and care.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by The University of Sydney human research ethics committee (2012/1429). Participants gave informed consent to take part in the study.

Patient consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: financial support from the National Health and Medical Research Council of Australia for the submitted work; 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.

Authors' contributions

All authors contributed to study design. KMcC, AB, JJ, NH, HD, and KMcG obtained funding. JH, KMcC, and JJ led development of the intervention and implementation of the trial. KMcG advised on the statistical analysis. JH performed the statistical analysis, produced the tables and figure, and drafted the manuscript. All authors contributed to data interpretation and critically reviewed the manuscript.

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REFERENCES

1 Harvey S. The charge and the challenges of breast cancer screening. *J Womens Health (Larchmt)* 2014;23(Suppl 1):S1-2. doi: 10.1089/jwh.2014.1509

2 Elmore JG. Breast cancer screening: balancing evidence with culture, politics, money, and media. In: Houssami N, Miglioretti D, eds. Breast Cancer Screening: An Examination of Scientific Evidence. Amsterdam: Elsevier 2016:1-27.

3 Welch HG, Black W. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;102:605-13. doi: 10.1093/jnci/djq099

4 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380:1778-86. doi: 10.1016/S0140-6736(12)61611-0

5 Jacklyn G, Glasziou P, Macaskill P, et al. Meta-analysis of breast cancer mortality benefit and overdiagnosis adjusted for adherence: improving information on the effects of attending screening mammography. *Br J Cancer* 2016;114:1269-76. doi: 10.1038/bjc.2016.90

6 Heath I. It is not wrong to say no. *BMJ* 2009;338:b2529. doi: 10.1136/bmj.b2529

7 Kirwan C. Breast cancer screening: what does the future hold? *BMJ* 2013;346:f87. doi: 10.1136/bmj.f87

8 Stefanek M. Uninformed compliance or informed choice? A needed shift in our approach to cancer screening. *J Natl Cancer Inst* 2011;103:1821-26. doi: 10.1093/jnci/djr474

9 Gummersbach E, Piccoliori G, Oriol Zerbe C, et al. Are women getting relevant information about mammography screening for an informed consent: a critical appraisal of information brochures used for screening invitation in Germany, Italy, Spain and France. *Eur J Public Health* 2010;20:409-14. doi: 10.1093/eurpub/ckp174

10 Jorgensen K, Gotzsche P. Content of invitations for publicly funded screening mammography. *BMJ* 2006;332:538-41. doi: 10.1136/bmj.332.7540.538

11 Zapka J, Geller B, Bulliard J, et al. Print information to inform decisions about mammography screening participation in 16 countries with population-based programs. *Patient Educ Couns* 2006;63:126-37. doi: 10.1016/j.pec.2005.09.012

12 Welch HG, Passow H. Quantifying the benefits and harms of screening mammography. *JAMA Intern Med* 2014;174:448-54. doi: 10.1001/jamainternmed.2013.13635

13 Loberg M, Lousdal ML, Bretthauer M, et al. Benefits and harms of mammography screening. *Breast Cancer Res* 2015;17:63. doi: 10.1186/s13058-015-0525-z

14 Biller-Andorno N, Juni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. *N Engl J Med* 2014;370:1965-67. doi: 10.1056/NEJMp1401875

15 Schwartz L, Woloshin S, Sox H, et al. US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey. *BMJ* 2000;320:1635-40. doi: 10.1136/bmj.320.7250.1635

16 Hersch J, Barratt A, Jansen J, et al. Use of a decision aid including information on overdetection to support informed choice about breast cancer screening: a randomised controlled trial. *Lancet* 2015;385:1642-52. doi: 10.1016/S0140-6736(15)60123-4

17 Hersch J, Jansen J, Barratt A, et al. Overdetection in breast cancer screening: development and preliminary evaluation of a decision aid. *BMJ Open* 2014;4:e006016. doi: 10.1136/bmjopen-2014-006016

18 Riddle M, Science of Behavior Change Working Group. News from the NIH: using an experimental medicine approach to facilitate translational research. *Transl Behav Med* 2015;5(4):486-8. doi: 10.1007/s13142-015-0333-0

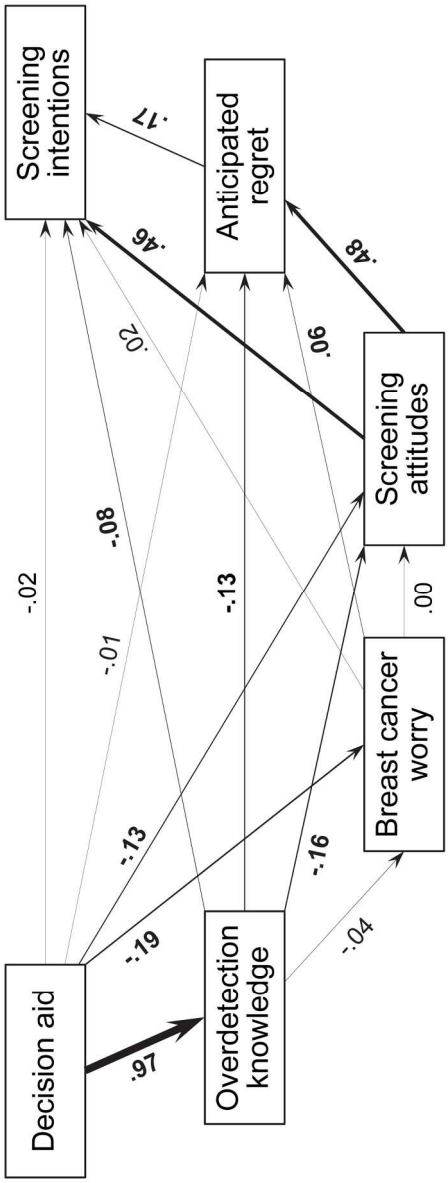
19 Krones T, Keller H, Becker A, et al. The theory of planned behaviour in a randomized trial of a decision aid on cardiovascular risk prevention. *Patient Educ Couns* 2010;78(2):169-76. doi: 10.1016/j.pec.2009.06.010

20 Elwyn G, Stiel M, Durand MA, et al. The design of patient decision support interventions: addressing the theory-practice gap. *J Eval Clin Pract* 2011;17:565-74. doi: 10.1111/j.1365-2753.2010.01517.x
21 Armitage CJ, Conner M. Social cognition models and health behaviour: a structured review. *Psychol Health* 2000;15:173-89. doi: 10.1080/08870440008400299
22 Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York: Guilford 2013:xvii, 507.
23 Hersch J, Barratt A, Jansen J, et al. The effect of information about overdetection of breast cancer on women's decision-making about mammography screening: study protocol for a randomised controlled trial. *BMJ Open* 2014;4:e004990. doi: 10.1136/bmjopen-2014-004990
24 Dormandy E, Michie S, Hooper R, et al. Informed choice in antenatal Down syndrome screening: a cluster-randomised trial of combined versus separate visit testing. *Patient Educ Couns* 2006;61:56-64. doi: 10.1016/j.pec.2005.02.006
25 Sandberg T, Hutter R, Richetin J, et al. Testing the role of action and inaction anticipated regret on intentions and behaviour. *Br J Soc Psychol* 2016;55:407-25. doi: 10.1111/bjso.12141
26 Sivell S, Elwyn G, Edwards A, et al. Factors influencing the surgery intentions and choices of women with early breast cancer: the predictive utility of an extended theory of planned behaviour. *BMC Med Inform Decis Mak* 2013;13:92. doi: 10.1186/1472-6947-13-92
27 Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991;50:179-211. doi: 10.1016/0749-5978%2891%2990020-T
28 Ajzen I. Martin Fishbein's legacy: the reasoned action approach. *Ann Am Acad Pol Soc Sci* 2012;640:11-27. doi: 10.1177/0002716211423363
29 Lumley T, Diehr P, Emerson S, et al. The importance of the normality assumption in large public health data sets. *Annu Rev Public Health* 2002;23:151-69. doi: 10.1146/annurev.publhealth.23.100901.140546
30 Hersch J, Jansen J, Barratt A, et al. Women's views on overdiagnosis in breast cancer screening: a qualitative study. *BMJ* 2013;346:f158. doi: 10.1136/bmj.f158
31 Biesecker B, Schwartz M, Marteau T. Enhancing informed choice to undergo health screening: a systematic review. *Am J Health Behav* 2013;37:351-59. doi: 10.5993/AJHB.37.3.8
32 van Agt H, Korfage I, Essink-Bot M. Interventions to enhance informed choices among invitees of screening programmes – a systematic review. *Eur J Public Health* 2014;24:789-801. doi: 10.1093/eurpub/ckt205
33 Sandberg T, Conner M. Anticipated regret as an additional predictor in the theory of planned behaviour: a meta-analysis. *Br J Soc Psychol* 2008;47:589-606. doi: 10.1348/014466607X258704
34 Rosenbaum L. Invisible risks, emotional choices – mammography and medical decision making. *N Engl J Med* 2014;371(16):1549-52. doi: 10.1056/NEJMms1409003
35 Steckelberg A, Kasper J, Mühlhauser I. Selective information seeking: can consumers' avoidance of evidence-based information on colorectal cancer screening be explained by the theory of cognitive dissonance? *German Medical Science* 2007;5:Doc05.
36 Baena-Canada JM, Rosado-Varela P, Exposito-Alvarez I, et al. Using an informed consent in mammography screening: a randomized trial. *Cancer Med* 2015;4:1923-32. doi: 10.1002/cam4.525
37 Petrova D, Garcia-Retamero R, Catena A, et al. To screen or not to screen: What factors influence complex screening decisions? *J Exp Psychol Appl* 2016;22:247-60. doi: 10.1037/xap0000086
38 Hoffmann T, Del Mar C. Patients' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med* 2015;175:274-86. doi: 10.1001/jamainternmed.2014.6016
39 Hersch JK, Nickel BL, Ghanouni A, et al. Improving communication about cancer screening: moving towards informed decision making. *Public Health Res Pract* 2017;27:e2731728. doi: 10.17061/phrp2731728

FIGURES

Fig. 1. Title: Multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators

Fig. 1. Legend: Graphic representation of the serial multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators (overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret). The intervention was hypothesised to exert an effect on screening intentions through the four mediators in sequence. Outcome and mediator variables were standardised prior to analysis. Bold coefficients are significant (p<.05). Analyses controlled for baseline measures including screening intentions and attitudes, basic screening knowledge, stage of decision making, breast cancer family history, birthplace, main language spoken, education, marital status, parent status, work status, and age.



Multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators

Graphic representation of the serial multiple mediation model of decision aid effects on breast screening intentions via four sequential mediators (overdetection knowledge, breast cancer worry, screening attitudes, and anticipated regret). The intervention was hypothesised to exert an effect on screening intentions through the four mediators in sequence. Outcome and mediator variables were standardised prior to analysis. Bold coefficients are significant (p<.05). Analyses controlled for baseline measures including screening intentions and attitudes, basic screening knowledge, stage of decision making, breast cancer family history, birthplace, main language spoken, education, marital status, parent status, work status, and age.

87x225mm (300 x 300 DPI)

SUPPLEMENTARY APPENDIX

Measurement of outcome and mediator variables used in:

Hersch J et al. How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial

This appendix contains the questions used for the measures included in the mediation analysis, including the range of available response options, and describes how each score was calculated. Correlations among the set of variables are also presented.

The questions were administered during a structured, computer-assisted telephone interview that took place after the participant had read her allocated decision aid.

Knowledge about overdetection

OC1. Who do you think is more likely to be diagnosed with breast cancer?

- Women who have screening mammograms [1]
- Women who do not have screening mammograms [0]

OC2. All breast cancers will eventually cause illness and death if they are not found and treated.

- TRUE [0]
- FALSE [1]

OC3. When screening finds cancer, doctors can reliably predict whether it will ever cause harm.

- TRUE [0]
- FALSE [1]

OC4. Even breast cancers that may not cause any health problems are likely to be treated.

- TRUE [1]
- FALSE [0]

OC5. Screening leads some women with a harmless cancer to get treatment they do not need.

- TRUE [1]
- FALSE [0]

OC6. Screening finds harmless cancers more often than it prevents death from breast cancer.

- TRUE [1]
- FALSE [0]

OC7. Which of these 2 statements best describes over-detection?

- Screening finds a cancer that would never have caused trouble [1]
- Screening finds an abnormality but extra tests show it is not cancer [0]

I would like you to imagine 1000 ordinary women who are 50 years old.

BN1. If these 1,000 women have breast screening every 2 years for 20 years, in that time about how many women do you think will avoid dying from breast cancer because of screening?

____

ON1. If these 1,000 women have screening every 2 years for 20 years, in that time about how many will be diagnosed and treated for a breast cancer that is not harmful?

____

1 mark was awarded if the answer given for ON1 was greater than the answer given for BN1.

1 mark was awarded if the answer given for ON1 was between 6 and 57. An additional
1 mark was awarded if the answer given for ON1 was between 10 and 38.

Marks were allocated as indicated above, and summed for a total score ranging between 0 and 10. Higher scores reflect better knowledge.

Attitudes to breast screening

For you, having breast screening is: Beneficial

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: A good thing

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: Harmful

- Strongly agree [1]
- Agree [2]
- Neither agree nor disagree [3]
- Disagree [4]
- Strongly disagree [5]

For you, having breast screening is: Worthwhile

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: Important

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

For you, having breast screening is: A bad thing

- Strongly agree [1]
- Agree [2]
- Neither agree nor disagree [3]
- Disagree [4]
- Strongly disagree [5]

Scores were allocated as indicated above, and summed for a total score ranging between 6 and 30. Higher scores reflect more positive attitudes.

Anticipated regret

If you do NOT have breast screening in the next few years, you may later wish you DID.

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

Higher scores above indicate greater anticipated regret for *not* screening (inaction score).

If you DO have breast screening in the next few years, you may later wish you did NOT.

- Strongly agree [5]
- Agree [4]
- Neither agree nor disagree [3]
- Disagree [2]
- Strongly disagree [1]

Higher scores above indicate greater anticipated regret for screening (action score).

The action score was subtracted from the inaction score to produce a differential anticipated regret score ranging between –4 and 4. Higher scores reflect greater anticipated regret for *not* screening, adjusted for anticipated regret for screening.

Worry about breast cancer

How worried are you about developing breast cancer?

- Not worried at all [0]
- A bit worried [1]
- Quite worried [2]
- Very worried [3]

Scores were allocated as indicated above. Higher scores reflect greater worry.

Intentions about breast screening

At the moment, which of the following best describes your intentions about having breast screening within the next 2-3 years?

- You definitely will have breast screening [5]
- You are likely to have breast screening [4]
- You are unsure [3]
- You are not likely to have breast screening [2]
- You definitely will not have breast screening [1]

Scores were allocated as indicated above. Higher scores reflect more positive intentions.

Correlation matrix

	Overdetection knowledge	Breast cancer worry	Screening attitudes	Anticipated regret	Screening intentions
Overdetection knowledge	1	-.137	-.216	-.251	-.239
Breast cancer worry	-.137	1	.139	.184	.181
Screening attitudes	-.216	.139	1	.634	.730
Anticipated regret	-.251	.184	.634	1	.609
Screening intentions	-.239	.181	.730	.609	1

Note. n=811. All correlations are significant (p<.001).