PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	How information about overdetection changes breast cancer screening decisions: a mediation analysis within a randomised controlled trial
AUTHORS	Hersch, Jolyn; McGeechan, Kevin; Barratt, Alexandra; Jansen, Jesse; Irwig, Les; Jacklyn, Gemma; Houssami, Nehmat; Dhillon, Haryana; McCaffery, Kirsten

VERSION 1 – REVIEW

REVIEWER	Ingrid Mühlhauser Health Sciences and Education, University Hamburg, Germany I have led several projects on evidence based patient information and public information on cancer screening including mammography screening. I fully support honest, evidence-based, complete and understandable patient information. I have a critical attitude towards cancer screening and I object public cancer screening campaigns.
REVIEW RETURNED	23-Feb-2017

GENERAL COMMENTS	This is a relevant and very interesting study which is appropriately performed and reported.

REVIEWER	J Elmore, MD, MPH University of WA School of Medicine
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	The title of this paper sounded important to me as a primary care physician, thus I agreed to review. Helping my patients to make informed decisions about medical care is challenging and the topic does not seem to have been as well studied as many other areas in medicine. While I have experience as a physician trying to provide support to my patients as they make informed decisions about cancer screening and also as an epidemiologist studying breast cancer screening, I do not have a background in cognitive psychology or the mediation analysis method used by these investigators. My review should therefore be considered with this caveat. These authors recently published the results of a very important randomized controlled trial in The Lancet that demonstrated that information on overdetection of breast cancer provided within a

	decision aid increased the number of women making an informed choice about breast screening. While this earlier RCT found that this decision aid changed the women's breast screening decisions, sadly 3 out of 4 women still did not make an "informed choice" even after using their intervention decision aid. The current paper under submission is a secondary analysis of the baseline and immediate ~4 week post-intervention survey data from the women in their RCT. The authors' state that they are seeking to identify the cognitive pathways in which the educational material was processed and applied when making decisions about whether they will engage in screening. The authors performed serial multiple mediation analysis with the main outcome self reported intention to undergo breast screening in the next 2-3 years. The following mediators were studied: knowledge about overdetection, worry about breast cancer, attitudes towards breast screening, and anticipated regret. The authors conclude that the mechanisms involving knowledge and attitudes towards screening were important in determining intentions about screening participation. The study's greatest strengths are that data are from a randomized control trial of a large number of women on an important clinical topic. Limitations are the inability to definitively draw conclusions based on inadequately defined outcome and predictor variables used in this analysis. The value of this study is not clear as the discussion lacks details in how the results might be used to guide the development of future decision aids. INTRODUCTION The introduction provides an excellent overview of the primary randomized control study, its findings, and the issue of overdiagnosis in breast cancer screening in general. However, more information about the theory that supports the mediation model used in this study and the value of this study in development of educational materials (i.e. why is this manuscript's analysis important?) is needed. METHODS The methods are clearly written, but perhaps a bit terse. The authors only very briefly describe the measurement instruments used for this analysis. More information is necessary to provide a clear understanding of how measures are being defined and at what time period. Please clarify when data are used from the pre-intervention and the immediate post (1-4 week) intervention survey to help the reader. I suggest including an appendix with the full survey instruments or at least key questions, as well as clear instructions for how the questions were then incorporated into each measurement construct. I had to read the BMJOpen protocol to make certain I understood the data collected and the timing of data collection. Please especially clarify the primary outcome of "screening intentions" and explain how this was defined. Many readers will not understand the description of the causal chain on page 6, lines 35-37. The authors do a good job describing their results in figure 1, but readers will benefit from additional description in the methods section to aid in understanding the methods. The addition of information to the introduction about the psychological theory their model is based on will also help the reader. RESULTS

	Adding more detail to the methods section will help the reader. However, the footnotes in the tables are also important, as readers will likely not be familiar with the scales (e.g., is a 0 or a 5 better in the score of knowledge?) Table 2 presents differences in the means for each study group across the different mediator variables, all of which are shown to be significant at the P<.001 level. The authors mention “statistically significant” findings in Table 2, yet what about clinical significance? What does a difference of a “breast cancer worry” score of 1.7 in the intervention arm vs a score of 1.8 in the control group mean? I assume that there are significant correlations between all four variables but this is not stated. I found Figure 1 interesting and admit that this figure allowed me to quickly have a sense of what the authors were actually trying to study. I did wonder about how the authors can say that the intervention influenced screening intentions when I think that the authors defined screening intentions only using data from the immediate post-intervention survey (as noted above, please define this outcome variable clearly). It does not seem as if the authors are taking into consideration the woman’s intentions toward future screening from the baseline survey, which would be needed to assess any “change” in intention that might be due to the decision aid. Perhaps more importantly, as a primary care doctor, self reported “intention” doesn’t seem as important as actual screening behavior and actual screening behavior doesn’t seem as important as the quality of the decision and whether it fits with the woman’s own personal informed choice (e.g., where she might decide she doesn’t want to be screened). Given this, more explanation as to how screening “intentions” are defined and why they are important would be helpful in convincing me of this study’s utility. DISCUSSION Can the authors bring into the discussion any information on cultural differences between women in Australia vs other locations? I wonder how much the local culture in Australia impacts these findings. Can the authors describe comparison data on Australian women vs U.S. women in fear or anxiety about breast cancer perhaps? Can the authors also hypothesize how the psychological processes studied here may vary across age groups (e.g. would some facets of this model vary if the women were over 60?)? This information would be useful in understanding the generalizability of their model. The fact that this study is cross-sectional should be discussed as a potential limitation. The main finding that “knowledge and attitudes” are mediators of a woman’s self reported intent to be screened seems self-evident to me. More detail regarding their theory and explanation as to why this is important is needed. In the end, I am uncertain of the value of this study. The primary RCT study was very well designed and produced a major contribution to the literature demonstrating how comprehensive information about breast cancer screening can influence a woman’s informed decision about cancer screening. This secondary analysis attempts to identify the specific cognitive pathways that are engaged

	in going from point A to point B. It is possible that my concerns could be addressed if the authors clarify the variables used and provide more detail about the mediation analysis and the theory that it is based on, as well as how this work might affect future research and the development of educational materials. Is there anything that you've learned from this analysis that will influence how you might develop future decision making tools or update your existing tool?

REVIEWER	Cornelia Baines Dalla Lana School of Public Health University of Toronto Canada
REVIEW RETURNED	05-Apr-2017

GENERAL COMMENTS	General Comments It is important to stress that I believe this paper is methodologically sound and makes appropriate conclusions. However it is also important to make such papers accessible to a general reader. My concern is directed entirely at improving reader-accessibility. The text can be cryptic and obscure. Specific comments. 1. The title and text refer to overdetection. The keywords include overdiagnosis with no mention of overdetection. Perhaps I am not au courant with current nomenclature but my opinion is overdiagnosis is overdiagnosis and that is an issue in this paper. 2. Prevalence of overdiagnosis is presented in a confusing way. Not all women who are invited to be screened attend screening – I prefer talking about overdiagnosis in screen-detected cancers which leaves no uncertainty as to the population referred to. And it is also useful to give prevalence by age group. More references could be cited. 3. Similarly I find the reported mortality benefit from screening to be less than compelling. Again the absence of age data is unfortunate and I dispute the appropriateness of reporting an unspecified 30% reduction of mortality. Uninformed readers will happily apply a 30% reduction to women of all ages. Most unfortunate. More compelling references could be cited. 4. Somewhere before line 7 on page 5 it would be useful to inform the reader that the study participants, women age 48-50, will only face screening opportunities at age 50. 5. Line 56-7 on page 5 uses the word "unclear", a rather ambiguous term. Maybe yes and maybe no? This is unsatisfactory. The interviewer would usually not know the assignment? 6. I have a problem understanding what regret means in the context of this paper. It should be clearly explained the first time it is mentioned. Interestingly the regret I have most often encountered in reacting with patients, is fear of regretting choosing not to be screened in the event of subsequent diagnosis of breast cancer independently of screening. Clarification would be helpful. What do the women mean by "regretting"? 7. Lines 16 to 22 on page 6 defy my comprehension but perhaps they will be meaningful to others. 8. On page 6, lines 30 on, we are given a list of mediators of ultimate decisions. They are: knowledge of overdiagnosis, breast cancer worry, attitudes to breast screening and anticipated regret. In Table 2 on Page 7, we see a list of base-line decision-making variables: state of decision-making about screening, knowledge, attitudes and intentions. There seem to be two problems: a degree of overlap between the two lists and possibly inappropriate headings. If

	decision-making variables were entitled “participant attitudes to screening before and after intervention”, presented in an enlarged Table 2, more clarity would result. 9. Finally I would recommend that interpretation of Figure 1 be expanded in the text (Page 8 lines 44,45). So far it is descriptive, not explanatory. The reader deserves more. 10. An admirable and carefully executed study.

REVIEWER	José M. Baena-Cañada Hospital Universitario Puerta del Mar, Cádiz, Spain
REVIEW RETURNED	07-Apr-2017

GENERAL COMMENTS	This is a study that presents the results of a mediation analysis within a controlled clinical trial on the efficacy of two decision aids: an intervention decision aid that included information about overdiagnosis, and a control decision aid that did not have this information. Title seems appropriate. Abstract is informative and well structured. The content of the introduction allows the subsequent development of the paper. In Methods, I have to admit that I do not have experience in serial multiple mediation analysis, so I cannot safely say about this technique. I recommend that editors consult with a trained reviewer. The authors find that there was no significant direct effect between the intervention and the decision to participate in the screening, but this effect was indirectly through its effects on the combined set of mediators. The intervention is performed, as the authors say, in an emotive context (women entering the target age range for screening). It is possible that the phenomenon of cognitive dissonance is generated between the truthful information provided about the damage caused by overdiagnosis in the study, and the information that mammography lacks damage that have previously been received by health institutions, health professionals and the media. The ignorance of issues that concern them and directly affect their bodies and their lives, such as overdiagnosis, places women in a position of powerlessness in the act of screening mammography. In this situation of asymmetry, power rests with the institution - legitimate power - and with health professionals - the power of the expert. Meanwhile, the position of subordination is occupied by women and is manifested, for example, in the ignorance of overdiagnosis. The calls for freedom of choice occur in a context where cultural hegemony around the screening mammography marks a discourse prone to such test. Thus, what is being considered a situation of freedom of choice is more a "myth of free choice". That is, the participants are not taking into account the contextual influences that are conditioning their positive attitude towards the screening test. Do the authors believe that the cognitive dissonance and subordination position of women has had any effect on outcomes? Could there have been a direct effect between the intervention and the decision to participate if these external factors did not exist? Could the differences between the scores obtained in the knowledge, attitude and screening intentions by the two trial groups have been greater If the cognitive dissonance and subordination of women to institutional and professional power had not influenced? If the authors believe in the importance of these external influences

	perhaps they would like to make some comment in the discussion section.

REVIEWER	Wei Wang Division of Biostatistics the Center for Devices and Radiological Health (CDRH) U S Food and Drug Administration
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	In this manuscript, the authors provided evidence, using mediation analysis, to assess how the cognitive and affective process works: the decision aid intervention achieved substantial knowledge gains, and thereby influenced attitudes and intentions towards screening. The mediation analysis method presented is acceptable and the final results presentation is clear. I have two comments that may need further clarification. 1) In the method section, the authors defined that the differential anticipated regret score by “subtracting the action from the inaction score”. Since the Control group has higher anticipated regret than the Intervention group (Table 2), I wonder whether the differential anticipated regret score should be defined by “subtracting the inaction from the action score” instead. Please double check and confirm 2) For the mediation analysis methods, the author only described that “mediation models were tested using the PROCESS macro for SPSS”. At least the authors need to describe the mediation analysis method used in this macro briefly (e.g. which model was used etc.). In addition, I believe the authors used the PROCESS macro by applying an ordinary least squares path analytic framework for estimating direct and indirect effects in single and multiple mediator models (parallel and serial), in that sense, the authors assumed that all outcomes are normally distributed which obviously does not hold in this paper, since all outcomes assessed are integers and bounded. The authors should clearly describe this point as a major limitation in the discussion.

REVIEWER	Marie-Abele Bind (jointly with Alice Sommer) Harvard University, USA
REVIEW RETURNED	25-May-2017

GENERAL COMMENTS	-Strengths: randomized assignment, blinded programmer, manuscript clear and well-written -Limitations: Mediation analysis not described in detail, timing of mediator and outcome measurements -Major comments: The mediation models should be clearly stated with adjusting covariates and the distributional assumptions, which should be checked. Were multi-mediator models fitted? Did SUTVA (stable unit treatment value assumption) hold in this context? Approaches using pre- vs. post-intervention scores have some limitations / assumptions. They could be stated. -Minor comments: The manuscript could discuss in more details whether the randomization was successful at balancing background covariates.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Ingrid Mühlhauser

1.1. This is a relevant and very interesting study which is appropriately performed and reported.
1.1. RESPONSE: We thank Reviewer 1 for this positive feedback.

Reviewer 2: Joann Elmore

2.1. [INTRODUCTION] The introduction provides an excellent overview of the primary randomized control study, its findings, and the issue of overdiagnosis in breast cancer screening in general. However, more information about the theory that supports the mediation model used in this study and the value of this study in development of educational materials (i.e. why is this manuscript's analysis important?) is needed.
2.1. RESPONSE: Since reporting our primary RCT findings, we have been asked questions about the causal pathway underlying our results (e.g., Did better knowledge change intentions?). In the current manuscript we tackle this. Theoretical underpinnings of our serial mediation analysis are discussed in the Methods and Discussion. We have added the following to the Introduction, last paragraph (p.5):
"To facilitate the translation of intervention research findings into other contexts, it is recommended to test hypothesised causal mechanisms (Riddle et al 2015). 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 (Krones et al 2010). 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 (Elwyn et al 2011)."

2.2. [METHODS] The methods are clearly written, but perhaps a bit terse. The authors only very briefly describe the measurement instruments used for this analysis. More information is necessary to provide a clear understanding of how measures are being defined and at what time period. Please clarify when data are used from the pre-intervention and the immediate post (1-4 week) intervention survey to help the reader. I suggest including an appendix with the full survey instruments or at least key questions, as well as clear instructions for how the questions were then incorporated into each measurement construct. I had to read the BMJ Open protocol to make certain I understood the data collected and the timing of data collection. Please especially clarify the primary outcome of "screening intentions" and explain how this was defined.
2.2. RESPONSE: We have now included an appendix containing the questions used for the measures included in the mediation analysis, together with a description of how each score was calculated. To further clarify the points raised by Reviewer 2 we have edited the Methods to now include this text:
"We collected follow-up data for these variables using standardised questions in a structured post-intervention telephone interview, 1-4 weeks after randomisation." (p.6);
"intentions to undergo screening in the next 2-3 years (1 item, 5-point response scale from definitely to definitely not)" (p.6);
"See the Appendix for further details about these measures." (p.6);
"variables in Table 1 (all measured pre-intervention, including baseline screening intentions)" (p.7).

2.3. Many readers will not understand the description of the causal chain on page 6, lines 35-37. The authors do a good job describing their results in figure 1, but readers will benefit from additional description in the methods section to aid in understanding the methods. The addition of information to the introduction about the psychological theory their model is based on will also help the reader.
2.3. RESPONSE: We have expanded the description of the causal chain by adding the following

(p.7):
“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.”

2.4. [RESULTS] Adding more detail to the methods section will help the reader. However, the footnotes in the tables are also important, as readers will likely not be familiar with the scales (e.g., is a 0 or a 5 better in the score of knowledge?)
2.4. RESPONSE: We have added detail to the footnote of Table 1 as follows (p.8):
“Knowledge 0 (none correct) to 5 (all correct), Attitudes 6 (least positive) to 30 (most positive), Intentions 1 (definitely not) to 5 (definitely)”.

2.5. Table 2 presents differences in the means for each study group across the different mediator variables, all of which are shown to be significant at the P<.001 level. The authors mention “statistically significant” findings in Table 2, yet what about clinical significance? What does a difference of a “breast cancer worry” score of 1.7 in the intervention arm vs a score of 1.8 in the control group mean?
2.5. RESPONSE: We have added the following sentence to the Discussion (p.12):
“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) (Hersch et al 2015) but rather to explore possible causal mechanisms involved.”

2.6. I assume that there are significant correlations between all four variables but this is not stated.
2.6. RESPONSE: We have added the following sentence confirming the significant correlations (p.9):
“Correlations between these variables were significant (p<.001).”

2.7. I found Figure 1 interesting and admit that this figure allowed me to quickly have a sense of what the authors were actually trying to study. I did wonder about how the authors can say that the intervention influenced screening intentions when I think that the authors defined screening intentions only using data from the immediate post-intervention survey (as noted above, please define this outcome variable clearly). It does not seem as if the authors are taking into consideration the woman’s intentions toward future screening from the baseline survey, which would be needed to assess any “change” in intention that might be due to the decision aid. Perhaps more importantly, as a primary care doctor, self-reported “intention” doesn’t seem as important as actual screening behavior and actual screening behavior doesn’t seem as important as the quality of the decision and whether it fits with the woman’s own personal informed choice (e.g., where she might decide she doesn’t want to be screened). Given this, more explanation as to how screening “intentions” are defined and why they are important would be helpful in convincing me of this study’s utility.
2.7. RESPONSE: By including baseline screening intentions as a covariate we were, effectively, assessing change in intention. We have edited the text as follows to make this clearer (p.7):
“Baseline variables in Table 1 (all measured pre-intervention, including baseline screening intentions) were statistically controlled by including them as covariates during mediation analyses.”
As for outcome variables, we agree that decision quality is most important, hence informed choice was our trial’s primary outcome (now noted on p.5). In the process of assessing informed choice, we measured intentions in order to capture each woman’s stated preference, in light of having read the decision aid, for being screened (definitely/likely) or not (definitely/likely) or being unsure at that time. The group differences in intentions post-intervention (in the RCT comparison reported previously) showed that the intervention had an immediate effect on women’s thinking, and we designed this mediation analysis to explore why. We agree that actual screening behaviour is also of interest (and will be reported for our study after 2 years of follow up), and we note that intention is recognised as

the strongest psychosocial predictor of behaviour (Cooke & French 2008, Krones et al 2010, Ajzen 2012). However, screening behaviour might not reflect people's informed decisions because of various external factors (Irwig et al 2006, Ajzen 2011, Johansson & Brodersen 2015). The effect of the intervention on behaviour is therefore a separate question that is beyond the scope of this paper.

2.8. [DISCUSSION] Can the authors bring into the discussion any information on cultural differences between women in Australia vs other locations? I wonder how much the local culture in Australia impacts these findings. Can the authors describe comparison data on Australian women vs U.S. women in fear or anxiety about breast cancer perhaps? Can the authors also hypothesize how the psychological processes studied here may vary across age groups (e.g. would some facets of this model vary if the women were over 60?)? This information would be useful in understanding the generalizability of their model.
2.8. RESPONSE: We do not know of any studies directly comparing US vs Australian women's fear or anxiety about breast cancer. We agree, though, that the findings could vary across age groups and different cultural contexts, and we have added the following text regarding this point (p.12):
"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 (Hersch et al 2013)."

2.9. The fact that this study is cross-sectional should be discussed as a potential limitation.
2.9. RESPONSE: The cross-sectional nature of the study is included in the Strengths and Limitations bullet points as well as the Discussion, where we have now explicitly labelled it as a limitation (p.12):
"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."

2.10. The main finding that "knowledge and attitudes" are mediators of a woman's self-reported intent to be screened seems self-evident to me. More detail regarding their theory and explanation as to why this is important is needed.
2.10. RESPONSE: We have added the following to try and clarify why the analysis is important (p.11):
"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)."

2.11. In the end, I am uncertain of the value of this study. The primary RCT study was very well designed and produced a major contribution to the literature demonstrating how comprehensive information about breast cancer screening can influence a woman's informed decision about cancer screening. This secondary analysis attempts to identify the specific cognitive pathways that are engaged in going from point A to point B. It is possible that my concerns could be addressed if the authors clarify the variables used and provide more detail about the mediation analysis and the theory that it is based on, as well as how this work might affect future research and the development of educational materials. Is there anything that you've learned from this analysis that will influence how you might develop future decision making tools or update your existing tool?
2.11. RESPONSE: To better address the value of this analysis and how it might inform future research, we have added the following sentences (p.12):
"While the power of emotion has been cited as a challenge for communicating harms of mammography (Rosenbaum 2014), 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. ... 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 influence both information processing and decision making (Steckelberg et al 2007, Baena-Canada et al 2015, Petrova et al 2016, Elmore 2016)."

Reviewer 3: Cornelia Baines

It is important to stress that I believe this paper is methodologically sound and makes appropriate conclusions. However it is also important to make such papers accessible to a general reader. My concern is directed entirely at improving reader-accessibility. The text can be cryptic and obscure.

3.1. The title and text refer to overdetection. The keywords include overdiagnosis with no mention of overdetection. Perhaps I am not au courant with current nomenclature but my opinion is overdiagnosis is overdiagnosis and that is an issue in this paper.
3.1. RESPONSE: Overdiagnosis is a broad term which encompasses multiple interrelated concepts (Carter et al 2015). We have added the following sentence to the Introduction, first paragraph (p.4): "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."
Our previously published papers about this RCT used overdetection (BMJ Open 2014, Lancet 2015), and we consider it important for the current paper to be consistent with them. For clarity, we have added the alternative term overdiagnosis to the 2nd sentence of the Introduction (p.4).

3.2. Prevalence of overdiagnosis is presented in a confusing way. Not all women who are invited to be screened attend screening – I prefer talking about overdiagnosis in screen-detected cancers which leaves no uncertainty as to the population referred to. And it is also useful to give prevalence by age group. More references could be cited.
3.2. RESPONSE: Our estimates were derived from the pooled estimates as calculated by the Independent UK Panel, as we wanted to use an authoritative and independent source for both mortality and overdiagnosis effects. We agree with Reviewer 3's point that not all women who are invited to be screened actually attend. Hence we present both the intention-to-treat estimate from the screening trials (applicable to women invited) and an estimate adjusted for adherence (relevant to those attending) as described by Jacklyn et al 2016. We consider it important to include both screen-detected and interval cancers in the denominator because excluding interval cancers provides an estimate that is dependent on the screening interval (Independent UK Panel 2012, Jacklyn et al 2016). Our decision aid presented the cumulated risk of overdetection for women attending a full 20-year 'package' of biennial screening, starting at age 50, as recommended in Australian policy. Therefore we believe it is appropriate, in the text of this manuscript, to cite this overall figure rather than attempting to break down prevalence of overdiagnosis by age group. A detailed discussion of overdiagnosis estimates is beyond the scope of this paper.

3.3. Similarly I find the reported mortality benefit from screening to be less than compelling. Again the absence of age data is unfortunate and I dispute the appropriateness of reporting an unspecified 30% reduction of mortality. Uninformed readers will happily apply a 30% reduction to women of all ages. Most unfortunate. More compelling references could be cited.
3.3. RESPONSE: We have now clarified in the 2nd paragraph of the Introduction that the figures cited are applicable to women invited and/or screened from age 50 to 69 (p.4).

3.4. Somewhere before line 7 on page 5 it would be useful to inform the reader that the study participants, women age 48-50, will only face screening opportunities at age 50.
3.4. RESPONSE: We have now clarified that women are targeted for screening from age 50 (p.4):

“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).”

3.5. Line 56-7 on page 5 uses the word “unclear”, a rather ambiguous term. Maybe yes and maybe no? This is unsatisfactory. The interviewer would usually not know the assignment?
3.5. RESPONSE: We have revised this sentence to now read as follows (p.6):
“The participant’s group assignment was unknown to the interviewer until the end of the interview.”

3.6. I have a problem understanding what regret means in the context of this paper. It should be clearly explained the first time it is mentioned. Interestingly the regret I have most often encountered in reacting with patients, is fear of regretting choosing not to be screened in the event of subsequent diagnosis of breast cancer independently of screening. Clarification would be helpful. What do the women mean by “regretting”?
3.6. RESPONSE: We have now included an Appendix containing the exact wording of the questions as well as a description of the scoring procedure.

3.7. Lines 16 to 22 on page 6 defy my comprehension but perhaps they will be meaningful to others.
3.7. RESPONSE: We have expanded the explanation of anticipated regret as follows (p.6):
“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).”

3.8. On page 6, lines 30 on, we are given a list of mediators of ultimate decisions. They are: knowledge of overdiagnosis, breast cancer worry, attitudes to breast screening and anticipated regret. In Table 2 on Page 7, we see a list of base-line decision-making variables: state of decision-making about screening, knowledge, attitudes and intentions.

There seem to be two problems: a degree of overlap between the two lists and possibly inappropriate headings. If decision-making variables were entitled “participant attitudes to screening before and after intervention”, presented in an enlarged Table 2, more clarity would result.
3.8. RESPONSE: We have edited the bottom part of Table 1 to clarify that the decision-making variables listed here are pre-intervention (baseline) measures. We have also edited the text describing the set of mediator variables to clarify that they were measured post-intervention (p.6).

3.9. Finally I would recommend that interpretation of Figure 1 be expanded in the text (Page 8 lines 44,45). So far it is descriptive, not explanatory. The reader deserves more.
3.9. RESPONSE: We have expanded the interpretation of Figure 1 in the text as follows (p.9):
“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.”

3.10. An admirable and carefully executed study.
3.10. RESPONSE: We thank Reviewer 3 for the positive feedback and helpful suggestions.

Reviewer 4: José M. Baena-Cañada

4.1. The intervention is performed, as the authors say, in an emotive context (women entering the target age range for screening). It is possible that the phenomenon of cognitive dissonance is generated between the truthful information provided about the damage caused by overdiagnosis in the study, and the information that mammography lacks damage that have previously been received by health institutions, health professionals and the media. The ignorance of issues that concern them

and directly affect their bodies and their lives, such as overdiagnosis, places women in a position of powerlessness in the act of screening mammography. In this situation of asymmetry, power rests with the institution - legitimate power - and with health professionals - the power of the expert. Meanwhile, the position of subordination is occupied by women and is manifested, for example, in the ignorance of overdiagnosis. The calls for freedom of choice occur in a context where cultural hegemony around the screening mammography marks a discourse prone to such test. Thus, what is being considered a situation of freedom of choice is more a "myth of free choice". That is, the participants are not taking into account the contextual influences that are conditioning their positive attitude towards the screening test.
Do the authors believe that the cognitive dissonance and subordination position of women has had any effect on outcomes? Could there have been a direct effect between the intervention and the decision to participate if these external factors did not exist? Could the differences between the scores obtained in the knowledge, attitude and screening intentions by the two trial groups have been greater if the cognitive dissonance and subordination of women to institutional and professional power had not influenced? If the authors believe in the importance of these external influences perhaps they would like to make some comment in the discussion section.
4.1. RESPONSE: We have added the following to acknowledge important external influences (p.12): "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 (Steckelberg et al 2007, Baena-Canada et al 2015, Petrova et al 2016, Elmore 2016)."

Reviewer 5: Wei Wang

In this manuscript, the authors provided evidence, using mediation analysis, to assess how the cognitive and affective process works: the decision aid intervention achieved substantial knowledge gains, and thereby influenced attitudes and intentions towards screening. The mediation analysis method presented is acceptable and the final results presentation is clear. I have two comments that may need further clarification.

5.1. In the method section, the authors defined that the differential anticipated regret score by "subtracting the action from the inaction score". Since the Control group has higher anticipated regret than the Intervention group (Table 2), I wonder whether the differential anticipated regret score should be defined by "subtracting the inaction from the action score" instead. Please double check and confirm.
5.1. RESPONSE: We calculated the differential anticipated regret score for each participant by subtracting her action score from her inaction score, as stated. In the control group, the mean inaction score was 4.2 and the mean action score was 1.8. In the intervention group, the mean inaction score was 4.0 and the mean action score was 2.1. In both groups the differential score was therefore positive (as both groups anticipated regret more if they didn't screen than if they did) but the intervention group score was smaller as shown in Table 2. We have now added an Appendix to further explain the relevant scoring and calculations.

5.2. For the mediation analysis methods, the author only described that "mediation models were tested using the PROCESS macro for SPSS". At least the authors need to describe the mediation analysis method used in this macro briefly (e.g. which model was used etc.). In addition, I believe the authors used the PROCESS macro by applying an ordinary least squares path analytic framework for estimating direct and indirect effects in single and multiple mediator models (parallel and serial), in

that sense, the authors assumed that all outcomes are normally distributed which obviously does not hold in this paper, since all outcomes assessed are integers and bounded. The authors should clearly describe this point as a major limitation in the discussion.
5.2. RESPONSE: In the final paragraph of the Methods, we have now specified which model was used in PROCESS (model 6 as appropriate for serial multiple mediators) and have added the following (p.7):
"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. … 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."
The normality assumption relates to the distribution of the errors in estimation of outcome variable. We have added the following sentence to the Discussion to acknowledge this limitation (p.12):
"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 (Lumley et al 2002, Hayes 2013)."

Reviewer 6: Marie-Abele Bind (jointly with Alice Sommer)

Strengths: randomized assignment, blinded programmer, manuscript clear and well-written
Limitations: Mediation analysis not described in detail, timing of mediator and outcome measurements

6.1. Major comments: The mediation models should be clearly stated with adjusting covariates and the distributional assumptions, which should be checked. Were multi-mediator models fitted? Did SUTVA (stable unit treatment value assumption) hold in this context? Approaches using pre- vs. post-intervention scores have some limitations / assumptions. They could be stated.
6.1. RESPONSE: We fitted a serial mediation model including multiple mediators that were measured post-intervention, organised in a theoretically-informed sequence as described in the text and depicted in the Figure. We adjusted for covariates that were measured pre-intervention, as described in Table 1 and the Figure caption. We did not use any 'pre- vs. post-intervention' scores.
In the revised manuscript we have added detail and clarified several aspects of the timing of measurement and the analysis method used including further information about the serial mediation model (as described above in response to Reviewer 5). We also acknowledge the limitation relating to the normality assumption and have added the following sentence to the Discussion (p.12):
"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 (Lumley et al 2002, Hayes 2013)."
The stable unit treatment value assumption was met in this study. Participants were individually sampled at random from a large geographically diverse population, individually randomised and sent a pre-printed decision aid booklet that was identical for all members within each study group. Recruitment and data collection proceeded entirely by phone. Contamination is extremely unlikely. It is therefore reasonable to assume that participant outcomes were unaffected by the group allocation of other participants.

6.2. Minor comments: The manuscript could discuss in more details whether the randomization was successful at balancing background covariates.
6.2. RESPONSE: We have now stated that covariates were balanced across groups, as follows (p.7): "Table 1 shows baseline characteristics of the 811 included participants, which were well balanced between the intervention and control groups."

VERSION 2 – REVIEW

REVIEWER	Cornelia J. Baines Dalla Lana School of Public Health, University of Toronto, Canada
REVIEW RETURNED	27-Jun-2017

GENERAL COMMENTS	It is a pleasure to read this revised manuscript although it remains a challenging one to read; for this reason my sparse comments focus on enhancing access for the general reader. Line numbers refer to the text with highlighted changes. Abstract. Process, integration and mediation are the prominent themes. They should be clearly articulated when they are presented in the first paragraph, and there should be continuity of language in the results section. Strengths: does causal ordering mean causal sequence, chronological ordering?? (line 22) Methods Page 6 Line 31. "Because conveying this information was the main aim" Is preferable to "as". I should mention that the instruments used and the statistical analysis are not areas which I can comment on. Results page 9 line 10. Correlations should be specified. Table 2 lacks column heading SD. The authors may not consider it relevant to their paper but somehow it might be appropriate to acknowledge in the conclusion that it is more than information that influences screening uptake; fear-driven emotions fuelled by misleading if not false information are major factors.

REVIEWER	José M. Baena Cañada University Hospital Puerta del Mar, Cádiz. Spain
REVIEW RETURNED	24-Jun-2017

GENERAL COMMENTS	I think this version is suitable for publishing.

REVIEWER	Wei Wang Division of Biostatistics, CDRH, FDA, USA
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	The revised manuscript addressed my concerns in my comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3: Cornelia Baines

It is a pleasure to read this revised manuscript although it remains a challenging one to read; for this reason my sparse comments focus on enhancing access for the general reader. Line numbers refer to the text with highlighted changes.

(1) Abstract. Process, integration and mediation are the prominent themes. They should be clearly articulated when they are presented in the first paragraph, and there should be continuity of language in the results section.
(1) RESPONSE: We have slightly edited the wording throughout the Abstract to improve continuity of language and articulate the meaning as clearly as possible within the word limit.

(2) Strengths: does causal ordering mean causal sequence, chronological ordering?? (line 22)
(2) RESPONSE: We have changed 'ordering' to 'sequence', both in the Strengths and Limitations bullet points and in the manuscript's Discussion.

(3) Methods Page 6 Line 31. "Because conveying this information was the main aim" Is preferable to "as". I should mention that the instruments used and the statistical analysis are not areas which I can comment on.
(3) RESPONSE: We have changed 'as' to 'because'.

(4) Results page 9 line 10. Correlations should be specified.
(4) RESPONSE: We have added a table displaying the correlation matrix in the Appendix.

(5) Table 2 lacks column heading SD.
(5) RESPONSE: We have added a row for the column headings: Mean (SD).

(6) The authors may not consider it relevant to their paper but somehow it might be appropriate to acknowledge in the conclusion that it is more than information that influences screening uptake; fear-driven emotions fuelled by misleading if not false information are major factors.
(6) RESPONSE: We have extended the second-last sentence in the Conclusion to now read as follows:
"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 (Hoffmann & Del Mar, 2015; Hersch et al, 2017)." The second reference is a new publication that further discusses the issues around communication in cancer screening.
The last paragraph of the Discussion, prior to the Conclusion, also discusses the reviewer's points relating to the influence of emotions and conflicting information. This paragraph includes two sentences that were newly added during the previous round of revisions in response to comments from two of the other reviewers, including citations to several papers from the literature that provide further reading around these topics for readers who are interested.

VERSION 3 – REVIEW

REVIEWER	Cornelia Baines Dalla Lana School of Public Health, University of Toronto, Canada
REVIEW RETURNED	14-Aug-2017

GENERAL COMMENTS	No comments other that to say the revision has met all my previous concerns and I think the conclusions very important.