PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effects of awareness of breast cancer overdiagnosis among women with screen-detected or incidentally found breast cancer: A qualitative interview study
AUTHORS	Pickles, Kristen; Hersch, Jolyn; Nickel, Brooke; Vaidya, Jayant; McCaffery, Kirsten; Barratt, Alexandra

VERSION 1 – REVIEW

REVIEWER	Francesca De Nard Agency for the Protection of Health of the Metropolitan Area of Milan, Screening Unit
REVIEW RETURNED	14-Feb-2022

GENERAL COMMENTS	Dear Authors, this is a very interesting and informative study, conducted with a solid qualitative methodology, and well reported. The paper covers a novel topic (how women diagnosed with breast cancer, and aware about the possible overdiagnosis, experience living with the perceived risk of overdiagnosis and overtreatment, and how they react to the experience), through the recruitment of a unique sample of women. However, in my opinion the paper could benefit from some minor clarification regarding the methods and the interpretation of results. Below, I have provided some suggestions. Eligibility: The title of the study refers only to screen-detected breast cancer. The Recruitment section (P9, L43) clarifies that women were eligible if screen-detected OR incidentally-detected. The results (P13, L43) report that 5 women were deemed ineligible because their cancer was not screen-detected. Among participants, not all women had screen-detected breast cancer: one of them was diagnosed incidentally after breast reduction surgery (P14, L13). The inclusion of an incidentally-detected breast cancer could provide additional diversity within the sample, but it should be motivated, and the reporting should be coherent through different sections of the paper, including the title. Identification of patients and recruitment, interviews procedures and content, data analysis: This study was conducted with a grounded theory methodology. The iterative methodology used for data analysis was fully described in the 'data analysis' section, but the grounded theory methodology usually covers the whole study process, starting from study design. There are some typical elements of this methodology, which I think should be more detailed: was theoretical sampling applied (seeking for variation, confirming and disconfirming cases)? During the interviews, were the results of

	preliminary findings presented to subsequent interviewees for elaboration? Was the interview topic guide updated during the iterative process and, if so, how? Did the interviewer collect field notes and/or case-based memos? Consumer advisory panel: The Consumer Advisory Panel was involved in the development of the interview topic guide (P10, L57). The guide was then piloted with 7 people including 2 consumers (did these two belong to the panel as well?) (P11, L3). Two members of the panel also participated in the study as interviewees (P13, L18). The possible influence of these two participants in the data collection process should be cited in the limitations section. P20, L43: it would be interesting to know how many British women became aware about the risk of overdiagnosis after the diagnosis, despite having received, and possibly read and understood (and if not, why?), the NHS updated leaflet including information on overdiagnosis. Did they discuss this topic? Did they provide an explanation that could be useful for the developers of patient information materials? Resisting perceived overtreatment paragraph: regarding perceived overtreatment, I think that participant 12 (case study 4, P52 L6) belief that cancer would have developed more slowly without the biopsies deserved to be reported in the main text as well, since it is an important element of diversity within the spectrum of perceived overtreatment. Finally, one of the core concepts underlying the described narratives is overdiagnosis communication. Most of the interviewees were unaware of overdiagnosis at the time of breast cancer diagnosis; at that time clinicians were the key interlocutors for overdiagnosis communication. It would be interesting to analyse with the same methodology clinicians' experiences: barriers to an effective communication (on both sides) might have played a role, and could be addressed in training programs, and this point could be mentioned among unanswered questions/future research.

REVIEWER	Charlotte Kelley-Jones King's College London, Cancer Prevention Group
REVIEW RETURNED	16-Feb-2022

GENERAL COMMENTS	This is a well-conceived and nicely assembled expose of women's experience of coping with the uncertain realm that is overdiagnosis. Given the high-level of educational and professional attainment of this sample, it is shocking that only 10/12 participants were aware of overdiagnosis prior to screening. Consequently, this paper supports the pressing need for a concerted effort to communicate the benefits and harms of breast cancer screening, in equal measure, to promote informed consent. A few minor comments and suggestions: p.6: It may be worth citing the evidence women's tolerance of breast screening harms relative to perceived benefits alongside high-level's of enthusiasm for cancer screening (e.g., Mathioukadasis, et al., 2020) as this will serve to highlight the distinction between the concept of overdiagnosis and the reality of living with this complex downside of screening.

	[p.6:52-53] May be helpful to include some references to specific de-escalation trials for low-risk cancers, e.g., BC-Predict (French et al., 2020). p.9: Was the international nature of the sample always going to be on-line interviews with one researcher, or did Covid-19 disrupt plans for a combination of face-to-face/online &/interviewers? Given the national differences in breast screening protocols and information, it would be helpful if participants' nationalities were provided in parathesis alongside their study id. Please ignore if there are concerns around information governance in doing so. [p.32-39] 'Suggestions for other women': Although not a theme, stylistically this is an abrupt end to the fluid narrative of the reported qualitative results. May be worth thinking about a bite-size summary of suggestions. [p.43:28-32] Re. future opportunities to communicate overdiagnosis, it may be worth mentioning risk-stratified breast screening approaches whereby a good understanding of the benefit-to-harm ratios of cancer screening will be key especially with the deintensification of screening intervention for individuals at low-risk.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a very interesting and informative study, conducted with a solid qualitative methodology, and well reported. The paper covers a novel topic (how women diagnosed with breast cancer, and aware about the possible overdiagnosis, experience living with the perceived risk of overdiagnosis and overtreatment, and how they react to the experience), through the recruitment of a unique sample of women.

However, in my opinion the paper could benefit from some minor clarification regarding the methods and the interpretation of results. Below, I have provided some suggestions.

1. Eligibility: The title of the study refers only to screen-detected breast cancer. The Recruitment section (P9, L43) clarifies that women were eligible if screen-detected OR incidentally-detected. The results (P13, L43) report that 5 women were deemed ineligible because their cancer was not screen-detected. Among participants, not all women had screen-detected breast cancer: one of them was diagnosed incidentally after breast reduction surgery (P14, L13). The inclusion of an incidentally-detected breast cancer could provide additional diversity within the sample, but it should be motivated, and the reporting should be coherent through different sections of the paper, including the title.

Response: Indeed, one participant's cancer was not diagnosed through the traditional method of screening, i.e., screening mammography. One could argue that it was detected by opportunistic "screening" of the tissue taken from her breast for a non-cancer reason; she had no symptoms at the time and was not seeking investigation for cancer. The participant had breast reduction surgery and unbeknownst to her the removed tissue was examined leading to DCIS detection. She reported having no symptoms. Conceptually, this method of detection could be called "screened". We have added text to the methods to define screening as used in the study, and to the results to clarify the circumstances of participants' diagnoses. We have modified the title to: '*The effects of awareness of*

breast cancer overdiagnosis among women with screen-detected or incidentally found breast cancer: A qualitative interview study'.

> P7: Women were eligible if they had been diagnosed with screen-detected breast cancer (defined as a cancer detected in an asymptomatic woman) at least 6 months previously, were already aware of the idea of overdiagnosis or overdetection in relation to screen-detected breast cancer,
>
> P12: Age at diagnosis was between 44 and 74 years (mean age 58 years), and their diagnoses occurred between 2004 and 2019. 11 out of 12 women were diagnosed as a result of participating in mammography screening, and one participant was diagnosed with DCIS as an incidental finding on routine histopathological examination of breast tissue following breast reduction surgery.

2. Identification of patients and recruitment, interviews procedures and content, data analysis: This study was conducted with a grounded theory methodology. The iterative methodology used for data analysis was fully described in the 'data analysis' section, but the grounded theory methodology usually covers the whole study process, starting from study design. There are some typical elements of this methodology, which I think should be more detailed: was theoretical sampling applied (seeking for variation, confirming and disconfirming cases)? During the interviews, were the results of preliminary findings presented to subsequent interviewees for elaboration? Was the interview topic guide updated during the iterative process and, if so, how? Did the interviewer collect field notes and/or case-based memos?

Response: We specify in the manuscript that we used key components of a grounded theory approach in our analysis, namely an iterative thematic approach and constant comparative method, rather than a full grounded theory methodology. We are aware that a GT methodology requires theoretical sampling, revision of the interview schedule, and testing of theory in subsequent interviews. However, these techniques were not possible or appropriate for this study and our research question. Instead, purposive sampling was used as we expected that the pool of women identifying with this experience was likely to be small and recruitment might be challenging. The interview schedule remained the same for each interview, but probes and follow up questions were tailored to each participant's experience. Interviews were recorded and KP made notes to discuss each interview with AB at fortnightly meetings. All participants were given opportunity to read and comment on the manuscript prior to publication (p11).

3. Consumer advisory panel: The Consumer Advisory Panel was involved in the development of the interview topic guide (P10, L57). The guide was then piloted with 7 people including 2 consumers (did these two belong to the panel as well?) (P11, L3). Two members of the panel also participated in the study as interviewees (P13, L18). The possible influence of these two participants in the data collection process should be cited in the limitations section.

Response: Thank you for this comment, to clarify, two of our consumers did pilot the interview topic guide. In our experience it is usual practice for consumer advisors to be actively involved in the development and piloting of study materials, and in this study their contributions were extremely valuable given the sensitivity of this topic. Our consumers were well informed about the aims of the study and its true purpose was never concealed. The consumer panel were not involved in the data analysis and interpretation phase, so we have not made any change to the limitations section.

4. P20, L43: it would be interesting to know how many British women became aware about the risk of overdiagnosis after the diagnosis, despite having received, and possibly read and understood (and if not, why?), the NHS updated leaflet including information on overdiagnosis. Did they discuss this topic? Did they provide an explanation that could be useful for the developers of patient information materials?

Response: 2 of the 6 UK participants were diagnosed prior to information about overdiagnosis being included in the NHS breast screening leaflets. 3/4 of the remaining women found out about overdiagnosis after diagnosis and one knew about overdiagnosis before screening. None of the women said that they found out about it from the NHS leaflet and did not mention this in the context of describing how they came to be screened and diagnosed. While we agree this is an interesting point that could be pursued in future work, we are unable to shed further light on it as it was outside the scope of our study (which aimed to understand the lived experience of possible overdiagnosis rather than to evaluate any specific information intervention about it).

5. Resisting perceived overtreatment paragraph: regarding perceived overtreatment, I think that participant 12 (case study 4, P52 L6) belief that cancer would have developed more slowly without the biopsies deserved to be reported in the main text as well, since it is an important element of diversity within the spectrum of perceived overtreatment.

Response: Thank you for this suggestion, we have added a line to the manuscript:

> P21: Two of the women (P12 and P2) believed that having biopsies or surgery can stimulate the spread of cancer.

6. Finally, one of the core concepts underlying the described narratives is overdiagnosis communication. Most of the interviewees were unaware of overdiagnosis at the time of breast cancer diagnosis; at that time clinicians were the key interlocutors for overdiagnosis communication. It would be interesting to analyse with the same methodology clinicians' experiences: barriers to an effective communication (on both sides) might have played a role, and could be addressed in training programs, and this point could be mentioned among unanswered questions/future research.

Response: We agree with the reviewers that this is important to explore in future studies, we have done so qualitatively around communication about overdiagnosis of prostate cancer screening. We have added,

> P32: Future research could also repeat and improve this research in other jurisdictions and cultures with larger samples of women where breast cancer screening is offered. Investigating clinician-related barriers to effective communication may also be worthy of further investigation to inform communication training programs. It is important to consider how best to inform people about the risk of overdiagnosis when establishing screening programs.

Reviewer: 2

This is a well-conceived and nicely assembled expose of women's experience of coping with the uncertain realm that is overdiagnosis. Given the high-level of educational and professional attainment of this sample, it is shocking that only 10/12 participants were aware of overdiagnosis prior to screening. Consequently, this paper supports the pressing need for a concerted effort to communicate the benefits and harms of breast cancer screening, in equal measure, to promote informed consent.

1. p.6: It may be worth citing the evidence women's tolerance of breast screening harms relative to perceived benefits alongside high-level's of enthusiasm for cancer screening (e.g., Mathioukadasis, et al., 2020) as this will serve to highlight the distinction between the concept of overdiagnosis and the reality of living with this complex downside of screening.

Response: Thank you for providing this useful reference, we have added a line to the discussion,

> P31: This is consistent with other evidence showing that women value breast cancer screening and intend to participate in screening even when aware of the risk of overdiagnosis[19]. A systematic review on women's values and preferences around breast cancer screening showed that women are willing to tolerate the potential harms of screening for an early diagnosis, but highlighted concern that women may not understand the concept of overdiagnosis[20]. Even in our highly educated, health literate sample of women, most (10/12) women found out about overdiagnosis after diagnosis (rather than before screening).

2. [p.6:52-53] May be helpful to include some references to specific de-escalation trials for low-risk cancers, e.g., BC-Predict (French et al., 2020).

Response: Again thank you for the reference, we have added the French et al reference to P33 where we refer to de-escalation trials.

P33: Where appropriate, clinicians should consider participation in trials of active surveillance, de-escalated treatment of low-risk DCIS (ref French), newer less harmful treatments such as TARGIT-IORT[30-32], and using lumpectomy for invasive breast cancer.

3. p.9: Was the international nature of the sample always going to be on-line interviews with one researcher, or did Covid-19 disrupt plans for a combination of face-to-face/online &/interviewers?

Response: Yes, we intended for all interviews to be conducted by one interviewer and online from study inception to enable us to recruit women internationally and to ensure consistency across the interviews.

4. Given the national differences in breast screening protocols and information, it would be helpful if participants' nationalities were provided in parathesis alongside their study id. Please ignore if there are concerns around information governance in doing so.

Response: Please refer to our response to the Editor request above, we are unable to provide additional information so that we may protect the anonymity of our participants and their comments.

5. [p.32-39] 'Suggestions for other women': Although not a theme, stylistically this is an abrupt end to the fluid narrative of the reported qualitative results. May be worth thinking about a bite-size summary of suggestions.

Response: Thank you for this suggestion, we have now provided a brief summary of the suggestions.

P27: All participants were asked, when reflecting on their personal experience, for advice on how to improve the experience for other women considering breast screening. Their suggestions are summarised in Supplementary file 3. Responses focused on individual level factors such as clinician responsibility to elicit and prioritise patient preferences, health system factors including creating opportunity for proper discussion about the benefits and harms of screening prior to attending a screening appointment, and society level factors like influencing a societal shift in thinking about and labelling cancer.

6. [p.43:28-32] Re. future opportunities to communicate overdiagnosis, it may be worth mentioning risk-stratified breast screening approaches whereby a good understanding of the benefit-to-harm

ratios of cancer screening will be key especially with the deintensification of screening intervention for individuals at low-risk.

Response: We have added the following text to the manuscript,

P31: Research in the context of screening for cancer and in other settings (refs) has shown it is challenging to communicate about overdiagnosis. Overcoming this challenge will be essential however, as screening policy evolves in the light of emerging evidence and new risk assessment tools. A good understanding of the potential benefits and harms of screening will be key in successful implementation of these developments, including risk targeted screening with deintensification of screening for those at low risk (refs).

VERSION 2 – REVIEW

REVIEWER	Francesca De Nard Agency for the Protection of Health of the Metropolitan Area of Milan, Screening Unit
REVIEW RETURNED	12-Apr-2022

GENERAL COMMENTS	The authors have satisfactorily addressed all of my concerns. In particular, a definition of screen-detected breast cancers has been added in the text and the title, relevant details from the case studies have been addressed in the text; and clinician-related communicative barriers have been cited in the 'future research' section. My previous methodological concerns have been properly addressed by the authors' response. I recommend the manuscript for publication.