PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Could screening participation bias symptom interpretation? An interview study on women's interpretations of and responses to cancer symptoms between mammography screening rounds.
AUTHORS	Solbjør, Marit; Skolbekken, John-Arne; Sætnan, Ann; Hagen, Anne; Forsmo, Siri

VERSION 1 - REVIEW

REVIEWER	Mette Kalager MD University of Oslo Institute of Health and Society Department of Health Management and Health Economics and Telemark Hospital and Harvard School of Public Health Department of Epidemiology
REVIEW RETURNED	29-Jun-2012

GENERAL COMMENTS	*Abstract* In your objective you use "diagnostic delay". I think it would be better if you defined what you meant by diagnostic delay. I assume you had a predefined level of time (two weeks, one day, three months?). Was it due to the patient, the medical system (including time from mammography to diagnosis, and time from diagnosis to treatment)? Please clarify. You state "Practical reasons, uncertainty about having a symptom and previous experiences with illness or with medical personnel were reasons for delaying". I had to read the whole manuscript before I understood what you meant by this sentence. However, some will only read the abstract, and I would recommend that you try to be more specific when explaining the reasons for the delay. Please try to rewrite. Last, you objective is "To explore whether participation in mammography screening may have contributed to diagnostic delay among women with interval breast cancer". In the conclusion you say "The participation in mammography screening does not necessarily increase awareness of breast cancer symptoms." I am not sure you have the data to support this, and this is not part of your objective.

	Introduction In the first paragraph of the introduction you state “but remain worse than for screening detected cancers. Such rates may be due to the aggressive nature of interval cancers, but may potentially also be caused by diagnostic delay”. Comparison of interval cancer with interval breast cancer is not a valid comparison mostly due to length- and lead time bias, and bias due to overdiagnosis in mammography screening. There are some studies that have compared interval breast cancer survival with “non-screen” detected breast cancers, with inconsistent findings. (Brekelmans CT, Peeters PH, Deurenberg JJ, Collette HJ. Survival in interval breast cancer in the DOM screening programme. *Eur J Cancer* 1995;**31**: 1830–35; Schröen AA, Wobbes T, van der Sluis RF. Interval carcinomas of the breast: A group with intermediate outcome. *J Surgical Oncol* 1996; **63**: 141–144; Collins S, Woodman CBJ, Threlfall A, Prior P. Survival rates from interval cancers in NHS breast screening program. *BMJ* 1998; **316**: 832–3; Bordás P, Jonsson H. Nyström L, Lenner P. Survival from invasive breast cancer among interval cases in the mammography screening programmes of northern Sweden. *The Breast* 2007; **16**: 47–54). Rather use the results of some of these studies. Please rewrite. In the second paragraph of the introduction you state “will concentrate on the patients’ interpretation of symptoms and help-seeking”. Did you ask the women what they though were symptoms of breast cancer? Please explore more other symptoms of breast cancer and how these were recognized by your participants (You touch this briefly in the second paragraph of the discussion, please expand your discussion). You refer to a study by Crispo et al. where mode of detection was associated with delayed breast cancer diagnosis (your ref 15). However, in this study not only patient delay was studies, but also delay between diagnosis and treatment (medical delay). I do not quiet understand why you have referred to this study, and why you have stated: “Mode of detection is associated with diagnostic delay, favouring mammography over self-detection.” Please clarify. Further, you state “The positive effect of mammography must be balanced against wider issues about whether patient delay could be induced by the reassurance given following a false negative screening”. There are other negative “issues” of mammography screening than “false reassurance” such as low benefit (mortality reduction) and disadvantages/harms (false positives and overdiagnosis). Please

	rewrite. Finally, the aim: “This study aims at exploring how women with negative mammography screening results react when they observe breast symptoms that could indicate malignancy in-between screening rounds.” This is not quiet what your objective is in the abstract (“To explore whether participation in mammography screening may have contributed to diagnostic delay among women with interval breast cancer”). Which of the two did you study? Further, in the first paragraph in the method section you say: “interview study with women who had experienced interval breast cancer”. Based on your aim in the end of the introduction, it seems as the selection of participants was women with negative screening results (also including women with symptoms that were not diagnosed with breast cancer). However, based on the methods, the selection seems to be women with negative screening results who had breast symptoms and who were diagnosed with breast cancer. Please clarify. *Methods* Mammography screening is offered biennial (every second year) in Norway not biannual (twice a year). Please correct (also stated in the discussion fourth paragraph). Please clarify what you mean by last in the following sentence: “They were the twenty last women diagnosed with interval breast cancer at each hospital”. Why did you select these women? I do miss a description (tumor characteristics and treatment) of the 14 women who chose not to participate in you study and if possible, all the interval cancers in the region you preformed you study. How many interval cancers were there all together in these counties (hospitals)? I believe it would be useful to add a table with the tumor characteristics and treatment variables (size, node involvement, metastasis, treatment) of all interval cancers and compare these to those that were delayed. Such information is available from the Cancer Registry of Norway. Since you are arguing that attendance in the screening program could lead to a diagnostic delay it would be useful to see if that is visible in tumor characteristics and treatment as well. (I would believe that diagnostic delay would increase tumor size, node involvement, and use of more aggressive treatment; even though I recognized that the sample would be too small to observe any statistically significant findings).

	Results and discussion In the first paragraph in the result section you say: “Few women knew whether their malignant tumor represented a false negative mammography scan or a true interval cancer.” Was this important information for the women or for you? How do you interpret this? Ten of 26 women (38%) delayed seeking medical advice more than two weeks. That is a substantial amount of women. I would like you to discuss further the significance of a delayed diagnosis. You do comment on this in the first paragraph in the discussion, but I would like to know more how this delay could influence survival (any studies? A table of tumor characteristics and treatment as suggested previously, would strengthen you paper). In the third paragraph in the discussion you say: “The present study indicates that participating in mammography screening may provide other explanations for bodily signs, since cancer had not been detected by mammography.” Do you have any knowledge about the delay in seeking medical advice among women who do not attend mammography screening? My impression is that women with symptoms could be stratified into two categories (very harsh categories!): those who seek advice immediately and those who are waiting for the symptoms to disappear (seek help late). This seems to be the case regardless of participation in screening or not. I do not understand this sentence: “The two arguments about mammography screening as reason for delaying seeking medical advice about potential breast cancer did suggest that having a public screening programme may lead to too much trust.” Please clarify. You use the term “pre-cancerous”, I do think this is confusing. Usually this term is used to describe ducal carcinoma in situ, and lobular carcinoma in situ among others. Please consider using an alternative term. “Despite their age and cancer diagnosis, only six of these women were fully retired, which indicates that participants could have been more resourceful than average.” What is the expected amount of retirement? You say:” Women with advanced cancer might not have participated in the study.” By adding a table as I suggested, you would get

	information on this. Please explore the symptoms of breast cancer a bit more (see my comments above). You say “Awareness of symptoms other than lumps must be improved.” Symptoms such as?

REVIEWER	Maria C. Katapodi, PhD, RN Assistant Professor University of Michigan School of Nursing, Ann Arbor, MI 48109
REVIEW RETURNED	16-Jul-2012

GENERAL COMMENTS	The authors examine an important topic, namely patient delay in seeking medical evaluation of a self-discovered breast lump. The manuscript is overall well written and well presented. Few recommendations for improvement: 1) Most participants were from urban or semi-urban settings. This is described in the limitations. It would be better mentioned under recruitment. 2) Give some examples of questions asked during the interviews. Was there an interview guide? 3) Was information about medical treatments based on self-report or extracted from medical records? 3) p. 6, ln. 55-57. The sentence "The women...mutually exclusive." is not clear. Please elaborate further. 4) p. 7. ln. 55-57. The sentence "This suggests that...their identity." is not clear. Please expand. 5) p. 9. ln. 13-15. The sentence "The two women....screening participants" is not clear. Please expand. 6) please expand on Clinical implications.

VERSION 1 – AUTHOR RESPONSE

The research question in this paper is highly important and the authors have produced a well-written and understandable manuscript. The use of qualitative interview is an important tool for medical research of this sort. However, I miss some quantitative measures in this manuscript.
Abstract: In your objective you use “diagnostic delay”. I think it would be better if you defined what you meant by diagnostic delay. I assume you had a predefined level of time (two weeks, one day, three months?). Was it due to the patient, the medical system (including time from mammography to diagnosis, and time from diagnosis to treatment)? Please clarify.
Answer: We have changed the aim in the abstract to: “To explore how women with negative mammography screening results, but who were later diagnosed with interval breast cancer, reacted when they observed breast symptoms that could indicate malignancy in-between screening rounds.”
You state “Practical reasons, uncertainty about having a symptom and previous experiences with illness or with medical personnel were reasons for delaying”. I had to read the whole manuscript before I understood what you meant by this sentence. However, some will only read the abstract, and

I would recommend that you try to be more specific when explaining the reasons for the delay. Please try to rewrite.
Answer: We have rewritten the sentence to: “Ten women delayed seeking medical advice, explaining their delay as a result of practical difficulties such as holidays, uncertainty about the symptom, and previous experiences of health care services’ ability to handle diffuse symptoms.”
Last, you objective is “To explore whether participation in mammography screening may have contributed to diagnostic delay among women with interval breast cancer”. In the conclusion you say “The participation in mammography screening does not necessarily increase awareness of breast cancer symptoms.” I am not sure you have the data to support this, and this is not part of your objective.
Answer: Objective has been changed, see answer to first comment by reviewer.

Introduction
In the first paragraph of the introduction you state “but remain worse than for screening detected cancers. Such rates may be due to the aggressive nature of interval cancers, but may potentially also be caused by diagnostic delay”. Comparison of interval cancer with interval breast cancer is not a valid comparison mostly due to length- and lead time bias, and bias due to overdiagnosis in mammography screening. There are some studies that have compared interval breast cancer survival with “non-screen” detected breast cancers, with inconsistent findings. (Brekelmans CT, Peeters PH, Deurenberg JJ, Collette HJ. Survival in interval breast cancer in the DOM screening programme. Eur J Cancer 1995;31: 1830–35; Schröen AA, Wobbes T, van der Sluis RF. Interval carcinomas of the breast: A group with intermediate outcome. J Surgical Oncol 1996; 63: 141–144; Collins S, Woodman CBJ, Threlfall A, Prior P. Survival rates from interval cancers in NHS breast screening program. BMJ 1998; 316: 832–3; Bordás P, Jonsson H. Nyström L, Lenner P. Survival from invasive breast cancer among interval cases in the mammography screening programmes of northern Sweden. The Breast 2007; 16: 47¬–54). Rather use the results of some of these studies. Please rewrite.
Answer: We have changed the paragraph to: “Survival rates for interval cancers have improved during recent decades 2, and it is controversial whether true interval cancers have less favourable prognosis than screening detected cancers or breast cancers diagnosed outside a screening programme.3-5 Rayson et al found poorer survival in true interval breast cancer compared to screen-detected cancers. The findings of adverse prognostic factors like higher grade and stage, receptor negativity and high mitotic index in true interval cancers might contribute to poorer survival outcome 6;7. Diagnostic delay may also be a factor. “

In the second paragraph of the introduction you state “will concentrate on the patients’ interpretation of symptoms and help-seeking”. Did you ask the women what they thought were symptoms of breast cancer? Please explore more other symptoms of breast cancer and how these were recognized by your participants (You touch this briefly in the second paragraph of the discussion, please expand your discussion).
Answer: We asked the women what kind of symptoms they had that led them to seek medical advice, but we did not present to them the different kinds of symptoms. The findings in the article presents what the women themselves had interpreted as breast cancer symptoms before having the diagnosis. All women in the present study had identified a breast lump as a symptom of breast cancer. Other symptoms had not been acknowledged until after having the cancer diagnosis.
We have changed the sentence to: ”We will here concentrate on screening participants interpretation of bodily changes, and their help-seeking.”
We have also added to the methods section: “Following a semi-structured interview guide, the women were invited to tell their breast cancer story, including what kind of breast cancer symptoms they had reacted to. Other questions were about their views on mammography screening and reactions upon having interval breast cancer.”
To the discussion, we have added: “Other symptoms known to represent breast cancer, such as retraction of the nipple or skin, nipple discharge, skin discolouring or change in texture, mastalgia, a

palpable lump in the axilla or a changed breast contour, had only been recognized as breast cancer symptoms after having the cancer diagnosis."

You refer to a study by Crispo et al. where mode of detection was associated with delayed breast cancer diagnosis (your ref 15). However, in this study not only patient delay was studies, but also delay between diagnosis and treatment (medical delay). I do not quite understand why you have referred to this study, and why you have stated: "Mode of detection is associated with diagnostic delay, favouring mammography over self-detection." Please clarify.
Answer: We have removed the reference to Crispo et al, and rephrased the sentence as follows: "An argument for mammography screening is that it could postpone breast cancer detection compared with self-detection."

Further, you state "The positive effect of mammography must be balanced against wider issues about whether patient delay could be induced by the reassurance given following a false negative screening". There are other negative "issues" of mammography screening than "false reassurance" such as low benefit (mortality reduction) and disadvantages/harms (false positives and overdiagnosis). Please rewrite.
Answer: This paragraph was not meant to summarize all negative effects from mammography screening. Rather, it was intended to show how mammography screening could potentially lead to delay as women feel too reassured after screening to act on a breast cancer symptom occurring between screening rounds. We have changed the sentence to: "The positive effect mammography may have on the time of detection must, however, be balanced against whether patient delay could be induced by the reassurance given following a false negative screening."

Finally, the aim: "This study aims at exploring how women with negative mammography screening results react when they observe breast symptoms that could indicate malignancy in-between screening rounds." This is not quiet what your objective is in the abstract ("To explore whether participation in mammography screening may have contributed to diagnostic delay among women with interval breast cancer"). Which of the two did you study?
Answer: We have changed the aim in the abstract to: "To explore how women with negative mammography screening results, who were later diagnosed with interval breast cancer, reacted when they observed breast symptoms that could indicate malignancy in-between screening rounds."
Further, in the first paragraph in the method section you say: "interview study with women who had experienced interval breast cancer". Based on your aim in the end of the introduction, it seems as the selection of participants was women with negative screening results (also including women with symptoms that were not diagnosed with breast cancer). However, based on the methods, the selection seems to be women with negative screening results who had breast symptoms and who were diagnosed with breast cancer. Please clarify.
Answer: The women participating in the present study had all been diagnosed with interval breast cancer. We have clarified the aim of the study as follows: "This study explores how women with negative mammography screening results who were later diagnosed with interval breast cancer, reacted when they observed breast symptoms that could indicate malignancy in-between screening rounds."

Methods
Mammography screening is offered biennial (every second year) in Norway not biannual (twice a year). Please correct (also stated in the discussion fourth paragraph).
Answer: We have changed biannual to biennial in the text.
Please clarify what you mean by last in the following sentence: "They were the twenty last women diagnosed with interval breast cancer at each hospital". Why did you select these women?
Answer: We have added a sentence in the methods section: "In order to have the women's stories as close to the event as possible, they were the twenty women last diagnosed with interval breast cancer

at each hospital, living in or nearby one of four cities (inhabitants 9,500-150,000), counting back from six months before the study invitation was sent."
I do miss a description (tumor characteristics and treatment) of the 14 women who chose not to participate in you study.
Answer: We have added the following to the methods section: "Due to confidentiality regulations, we have no access to information about the 14 women who did not respond to the invitation. "
We have added the following to the discussion: "It is a limitation to the study that we cannot compare those participating with the 14 non-respondents."
And if possible, all the interval cancers in the region you preformed you study. How many interval cancers were there all together in these counties (hospitals)?
Answer: We have added: "During the years 2006-2009, 178 interval breast cancers were diagnosed at these two hospitals."
I believe it would be useful to add a table with the tumor characteristics and treatment variables (size, node involvement, metastasis, treatment) of all interval cancers and compare these to those that were delayed. Such information is available from the Cancer Registry of Norway.
Answer: The research project does not have access to patient registers, and we are therefore unable to connect information about women's reactions to detecting a lump and information about tumor characteristics and treatment variables. We have, however, added a table (Now named Table 1) with information of treatment of the women who participated in the study, as reported by themselves in the qualitative interviews.
Since you are arguing that attendance in the screening program could lead to a diagnostic delay it would be useful to see if that is visible in tumor characteristics and treatment as well. (I would believe that diagnostic delay would increase tumor size, node involvement, and use of more aggressive treatment; even though I recognized that the sample would be too small to observe any statistically significant findings).
Answer: We agree with the reviewer that the sample is too small to observe any statistically significant findings. As pointed out above, we do not have information about tumor characteristics. Moreover, the qualitative data do not suggest any clear associations between tumor size and delay in help-seeking. We agree that these questions should be explored, but unfortunately it is not possible within the present study. We have added the following paragraph to the implications section: "In this qualitative study we have explored the women's own interpretation of help-seeking for interval breast cancer. Further studies are required as to whether their choice of actions have delayed diagnosis in medical terms, according to tumor characteristics and survival."

Results and discussion
In the first paragraph in the result section you say: "Few women knew whether their malignant tumor represented a false negative mammography scan or a true interval cancer." Was this important information for the women or for you? How do you interpret this?
Answer: This was important information to both researchers and the women. However, we were surprised that not more women talked about whether or not they had had a false negative screen. We have added to the results: "Some had asked for a review of previous images, but most did not associate with false negative screening when asked about their thoughts on having breast cancer between screening rounds. "
Ten of 26 women (38%) delayed seeking medical advice more than two weeks. That is a substantial amount of women. I would like you to discuss further the significance of a delayed diagnosis. You do comment on this in the first paragraph in the discussion, but I would like to know more how this delay could influence survival (any studies? A table of tumor characteristics and treatment as suggested previously, would strengthen your paper).
Answer: We added references on interval cancer and survival to the first paragraph, as outlined above. We do not have access to tumor characteristics, and our data cannot indicate how delay in diagnosis might have influenced these women's survival. We have added the following to the discussion: "True interval breast cancer could have poorer survival compared to screen-detected

cancers.6 Delaying acting on a breast cancer symptom between screening rounds could potentially decrease survival."

In the third paragraph in the discussion you say: "The present study indicates that participating in mammography screening may provide other explanations for bodily signs, since cancer had not been detected by mammography." Do you have any knowledge about the delay in seeking medical advice among women who do not attend mammography screening? My impression is that women with symptoms could be stratified into two categories (very harsh categories!): those who seek advice immediately and those who are waiting for the symptoms to disappear (seek help late). This seems to be the case regardless of participation in screening or not.
Answer: There are a number of published articles on women's practices of seeking medical advice when detecting a breast cancer symptom, such as references 12-14 in the manuscript, but we have not identified articles about women who have been offered screening but rejected participation and their help seeking practices.
I do not understand this sentence: "The two arguments about mammography screening as reason for delaying seeking medical advice about potential breast cancer did suggest that having a public screening programme may lead to too much trust." Please clarify.
Answer: We have changed the sentence to: "Seeing previous or upcoming mammography screening as reasons for delaying seeking medical advice about potential breast cancer suggest that too much trust in a public screening programme may cause delayed diagnostics."

You use the term "pre-cancerous", I do think this is confusing. Usually this term is used to describe ducal carcinoma in situ, and lobular carcinoma in situ among others. Please consider using an alternative term.
Answer: We have changed the sentence to: "Experiences before having cancer may not be the most important to remember after going through intensive cancer treatment, and could have been reinterpreted several times since experiencing them."

"Despite their age and cancer diagnosis, only six of these women were fully retired, which indicates that participants could have been more resourceful than average." What is the expected amount of retirement?
Answer: We have changed this paragraph to: "Despite their cancer diagnosis, only six of the 26 respondents were fully retired. In Norway, less than 50 per cent of the population aged 55-74 were employed in 200530, which indicates that participants in the present study could have been more resourceful than women in average. If diagnostic delay is a problem among the more resourceful segments of the population, it is reasonable to think that it is also present in the population in general."

You say:" Women with advanced cancer might not have participated in the study." By adding a table as I suggested, you would get information on this.
Answer: We do not have data on this, according to ethical restrictions. We have added this sentence to the discussion: "It is a limitation to the study that we cannot compare those participating with the 14 non-respondents. Serious disease might have hindered participation."

Please explore the symptoms of breast cancer a bit more (see my comments above). You say "Awareness of symptoms other than lumps must be improved." Symptoms such as?
Answer: As described above, we have added: "Other symptoms known to represent breast cancer, such as retraction of the nipple or skin, nipple discharge, skin discolouring or change in texture, mastalgia, a palpable lump in the axilla or a changed breast contour, had only been recognized as breast cancer symptoms after having the cancer diagnosis."

Reviewer: 2 Maria C. Katapodi

Few recommendations for improvement:
1) Most participants were from urban or semi-urban settings. This is described in the limitations. It would be better mentioned under recruitment.
Answer: We have moved this information to “recruitment”.
2) Give some examples of questions asked during the interviews. Was there an interview guide?
Answer: We have rewritten the paragraph to clarify our use of an interview guide and which questions that was asked: “Following a semi-structured interview guide, the women were invited to tell their breast cancer story, including what kind of breast cancer symptoms they had reacted to. Other questions were about their views on mammography screening and reactions towards having interval breast cancer.”
3) Was information about medical treatments based on self-report or extracted from medical records?
Answer: Information about medical treatments was based on self-report, which have now been clarified in the findings section and in the new table 1: “Based on the women’s reports during the interview, all had been surgically treated, either with mastectomy or with breast conserving surgery, 21 women had gone through radiation therapy, and 14 had chemotherapy (Table 1).”
3) p. 6, ln. 55-57. The sentence "The women...mutually exclusive." is not clear. Please elaborate further.
Answer: We have changed the sentence to “Each woman could have several explanations for what she retrospectively saw as her delay in help-seeking.”
4) p. 7. ln. 55-57. The sentence "This suggests that...their identity." is not clear. Please expand.
Answer: We have added a sentence to expand the content: “Rather than being perceived as hypochondriacs, they would delay help-seeking for uncertain symptoms.”
5) p. 9. ln. 13-15. The sentence "The two women....screening participants" is not clear. Please expand.
Answer: We have expanded as follows: “Both women who had waited six months before seeking medical advice explained their delay with being screening participants. This suggests that some women who participate in screening place responsibility for cancer detection with the screening programme, potentially trusting too much in the design of the programme.“

6) please expand on Clinical implications.
Answer: We have added “Although the design of our study does not tell about the magnitude of the delay problem, it clearly identifies a problem which deserves closer attention. In line with conclusions from other studies 27-29, it also points in the direction of an upgrading of the importance of women’s self- examinations and of further education regarding breast cancer symptoms. ”

VERSION 2 – REVIEW

REVIEWER	Mette Kalager University of Oslo Institute of Health and Society Department of Health Management and Health Economics, Norway and Telemark Hospital, Norway and Harvard School of Public Health Department of Epidemiology, Boston, US I declare I have no conflict of interest
REVIEW RETURNED	07-Sep-2012

THE STUDY	No need for better reporting in the manuscript, and does not raise questions about the work

GENERAL COMMENTS	Minor comments: 1. In your revised manuscript (ms) you say “Rayson et al found poorer survival in true interval breast cancer compared to screen-detected cancers. The findings of adverse prognostic factors like higher grade and stage, receptor negativity and high mitotic index in true interval cancers might contribute to poorer survival outcome6;7. Diagnostic delay may also be a factor.” (last sentences in the 1st paragraph of the introduction). Further, in the 1st paragraph in the discussion “True interval breast cancer could have poorer survival compared to screen-detected cancers 6”. Interval cancers will always have poorer survival than screening detected cancers. Firstly, lead-time will affect survival and despite of a real survival benefit or not, survival will be improved (survival is estimated as time since diagnosis to an event or the end of follow-up). Secondly, screening will introduce length time (screening will be more likely to detect slower growing tumors), this will increase survival. Thirdly, overdiagnosis will increase survival as this will include cancers without any potential to kill (both survival time and number of cancers will increase). (The healthy screenee bias will not influence comparison of survival among screen-detected and interval cancers). This is a minor comment regarding what you are studying and the point you are making is that interval cancer might even have poorer prognosis that cancers detected without screening. I do agree with your reasoning that delaying diagnosis might influence prognosis. However, many scientists and physician does not understand that comparing survival in screen and not-screen detected cancers is not valid (Wegwarth et al. Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. Ann Intern Med 2012; 156:340-9). I believe you would be better off not making the same mistake as many others (including Rayson et al (your ref 6)). Please rephrase these two sentences. 2. In your new table 1 I suggest you move column with surgery+radiation+chemotherapy to the right, so this column appears closest to the column with the total numbers.

VERSION 2 – AUTHOR RESPONSE

Minor comments:
1. In your revised manuscript (ms) you say “Rayson et al found poorer survival in true interval breast cancer compared to screen-detected cancers. The findings of adverse prognostic factors like higher grade and stage, receptor negativity and high mitotic index in true interval cancers might contribute to poorer survival outcome6;7. Diagnostic delay may also be a factor.” (last sentences in the 1st paragraph of the introduction). Further, in the 1st paragraph in the discussion “True interval breast cancer could have poorer survival compared to screen-detected cancers 6”. Interval cancers will always have poorer survival than screening detected cancers. Firstly, lead-time will affect survival and despite of a real survival benefit or not, survival will be improved (survival is estimated as time since diagnosis to an event or the end of follow-up). Secondly, screening will introduce length time (screening will be more likely to detect slower growing tumors), this will increase survival. Thirdly, overdiagnosis will increase survival as this will include cancers without any potential to kill (both survival time and number of cancers will increase). (The healthy screenee bias will not influence comparison of survival among screen-detected and interval cancers). This is a minor comment regarding what you are studying and the point you are making is that interval cancer might even have poorer prognosis that cancers detected without screening. I do agree with your reasoning that

delaying diagnosis might influence prognosis. However, many scientists and physician does not understand that comparing survival in screen and not-screen detected cancers is not valid (Wegwarth et al. Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. Ann Intern Med 2012; 156:340-9). I believe you would be better off not making the same mistake as many others (including Rayson et al (your ref 6)). Please rephrase these two sentences.
Answer: We have added the reference to Wegwarth et al, and changed the two sentences to “On the other side, survival rates in the screen detected groups are biased (lead and length time bias and overdiagnosis), leading to misinterpretation of the true effectiveness of screening. 8” And “True interval breast cancer has poorer survival compared to screen-detected cancers. 6;8”
2. In your new table 1 I suggest you move column with surgery+radiation+chemotherapy to the right, so this column appears closest to the column with the total numbers.
Answer: We have changed table 1 accordingly.