

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Understanding Linkage to Biopsy and Treatment for Breast Cancer after a High-risk Tele-Mammography Result in Peru: A Mixed-Methods Study
AUTHORS	Errea, Renato; Garcia, Patricia; Pace, Lydia; Galea, Jerome; Franke, Molly F.

VERSION 1 – REVIEW

REVIEWER	Anderson, Benjamin Fred Hutchinson Cancer Research Center, Public Health Sciences
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	<p>This study provides valuable information about delays between the obtaining of a mammogram for which a biopsy has been recommended (BIRADS 4 or 5) and about reasons for those delays as illuminated through a well-executed qualitative research study. The findings regarding the reasons for delay certainly apply to other regions of Peru outside of the capital Lima and likely apply to other countries with similar health systems to that of Peru.</p> <p>The biopsy statistics and findings are themselves revealing and could be more fully explored in the manuscript. The authors note that they could only find evidence of biopsy among 48.4% of patients in whom biopsy was recommended; and of the 62 patients who underwent biopsy, 51 (82%) were positive for cancer. This positive biopsy rate is extremely high and suggest that there is a significant group of patients with cancer who are not being diagnosed. In established mammographic programs using the BIRADS scale, between 20 and 35% of BIRADS 4 ("suspicious") lesions should be positive. BIRADS 5 ("malignant") lesions should be positive in 95% of cases. It would be helpful for the authors to state what fraction of the biopsied patients were BIRADS 4 vs 5. Is there an unusually high fraction of patients with BIRADS 5 lesions in this cohort, is the BIRADS 4 designation being overused in comparison to BIRADS 5, or is there some other selection process occurring here and skewing the data? The authors should discuss why they believe the positive biopsy rate was so extreme and should consider what this means about the patients who either did not undergo biopsy or left the public system and were diagnosed some other way. The authors speculate that more patients may have been diagnosed and treated than they were able to identify, i.e., the situation is better than the numbers appear. The extreme positivity results suggests that the opposite could be true as well, i.e., there may be a significant number of women with cancer who (so far) have gone undiagnosed</p>
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	<p>and are more likely to present in the future with advanced stage disease.</p> <p>The authors correctly make the critical point that robust tracking and information systems are required to evaluate programmatic performance. Given the investigator's experience in public health, it would be meaningful if the authors could expand on what features a tracking system needs to have in order to achieve the desired goal.</p> <p>It should also be pointed out that the sensitivity of mammography for detecting cancers is approximately 85%. Women with dense breasts (more common among younger women) are more likely to have negative mammograms. These women would not be included in this study cohort, since patients with BIRADS 1, 2 and 3 mammograms were excluded.</p> <p>The authors comment that their study could be the first such study from a middle-income country. Unreferenced in this manuscript is the 2017 study from Trujillo in Northern Peru (Romanoff et al. Association of Previous Clinical Breast Examination With Reduced Delays and Earlier-Stage Breast Cancer Diagnosis Among Women in Peru. JAMA Oncol. 2017; 3(11): 1563-7.), in which delays in initiation of breast cancer diagnosis and treatment were similarly examined and were found on average to exceed a year from the development of symptoms to the initiation of treatment, and for which 8 months of delay could be attributed to the health system itself. A notable finding was that over 90% of women were symptomatic and had self-detected cancers. The current study does not report on whether patients were asymptomatic and underwent screening mammograms or had symptoms and were undergoing diagnostic mammograms. This distinction is important, especially if a country is hoping to initiate a mammographic screening program. While the authors may consider some of these points out of scope for the current study that is focusing on the qualitative issues leading to delays in initiating treatment, the findings are nonetheless relevant to future studies and therefore should be explored at some level in the Discussion.</p>
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REVIEWER	Paz-Soldan, Valerie Tulane University, Global Community Health and Behavioral Sciences
REVIEW RETURNED	24-Aug-2021

GENERAL COMMENTS	This is a well written paper with minor revisions that are VERY minor. The paper reads well and portrays a very important issue in the health care system in Peru: the need for a monitoring and evaluation system that allows providers to determine follow up of patients, the delays and problems in the system, and the challenges faced by women diagnosed with breast cancer trying to comply with doctor's orders.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

The biopsy statistics and findings are themselves revealing and could be more fully explored in the manuscript. The authors note that they could only find evidence of biopsy among 48.4% of patients in whom biopsy was recommended; and of the 62 patients who underwent biopsy, 51 (82%) were positive for cancer. This positive biopsy rate is extremely high and suggest that there is a significant group of patients with cancer who are not being diagnosed. In established mammographic programs using the BIRADS scale, between 20 and 35% of BIRADS 4 ("suspicious") lesions should be positive. BIRADS 5 ("malignant") lesions should be positive in 95% of cases. It would be helpful for the authors to state what fraction of the biopsied patients were BIRADS 4 vs 5. Is there an unusually high fraction of patients with BIRADS 5 lesions in this cohort, is the BIRADS 4 designation being overused in comparison to BIRADS 5, or is there some other selection process occurring here and skewing the data? The authors should discuss why they believe the positive biopsy rate was so extreme and should consider what this means about the patients who either did not undergo biopsy or left the public system and were diagnosed some other way. The authors speculate that more patients may have been diagnosed and treated than they were able to identify, i.e., the situation is better than the numbers appear. The extreme positivity results suggests that the opposite could be true as well, i.e., there may be a significant number of women with cancer who (so far) have gone undiagnosed and are more likely to present in the future with advanced stage disease.

Thank you for noting this very important point. We have divided the answer to this comment in a few parts:

- It would be helpful for the authors to state what fraction of the biopsied patients were BIRADS 4 vs 5.

We have included these numbers in line #223 in the results section

- *Is there an unusually high fraction of patients with BIRADS 5 lesions in this cohort, is the BIRADS 4 designation being overused in comparison to BIRADS 5?*

Of the entire cohort (n=6899), 2.1% of the mammographs were BIRADS 4 and 5 results (added in line 206). We consider this is around the expected fraction according to the literature (added in lines 432-433).

References:

[Poplack SP, et al. Mammography in 53,803 women from the New Hampshire mammography network. Radiology 2000;217:832– 40]

[Eberl et. al. BI-RADS Classification for Management of Abnormal Mammograms. J Am Board Fam Med. 2006;19(2):161-4. doi: 10.3122/jabfm.19.2.161]

[Sirous M, Shahnani PS, Sirous A. Investigation of Frequency Distribution of Breast Imaging Reporting and Data System (BIRADS) Classification and Epidemiological Factors Related to Breast Cancer in Iran: A 7-year Study (2010–2016). Adv Biomed Res 2018;7:56.]

Of the 147 women with high-risk results, 73% had BIRADS 4 and 27% had BIRADS 5 (added in lines 207). Similarly, for the 126 women eligible for our analysis, 71% had BIRADS 4 and 29% had BIRADS 5 (added in line 209). The literature varies regarding the percentage of BIRADS 4 and 5 results, among high-risk results. A study in New Hampshire reports 91% of BIRADS 4 and 9% of BIRADS 5. A study in Iran reported similar percentages between BIRADS 4 (53%) vs BIRADS 5 (47%). While a study in Brazil reported the same results as ours: 71% of BIRADS 4 and 29% of BIRADS 5 (added in lines 428-430).

References:

[Poplack SP, et al. Mammography in 53,803 women from the New Hampshire mammography network.

Radiology 2000;217:832– 40].

[Milani et al. Presumed prevalence analysis on suspected and highly suspected breast cancer lesions in Sao Paulo using BIRADS criteria. Sao Paola Medical Journal. 2007;125(4):210-4]

[Sirous M, Shahnani PS, Sirous A. Investigation of Frequency Distribution of Breast Imaging Reporting and Data System (BIRADS) Classification and Epidemiological Factors Related to Breast Cancer in Iran: A 7-year Study (2010–2016). Adv Biomed Res 2018;7:56].

All in all, we consider that the total number of high-risk results of the cohort is around the expected number, and while the percentage of BI-RADS 4 vs BI-RADS 5 tends to be variable; our finding was similar to another Latin American study conducted in Brazil.

- ...or is there some other selection process occurring here and skewing the data?

The percentages of BIRADS 4 and 5 in the 147 women with high-risk results were 73% for BI-RADS 4 and 27% for BIRADS 5 (added in line 207); in the 126 eligible women were

71.4% for BI-RADS 4 vs 28.6% for BI-RADS 5 (added in line 209); while the percentage in women with evidence of biopsy (n=62) was 68% BIRADS 4 vs 32% had BIRADS 5 (added in line 223), leading to similar percentages in women without evidence of biopsy (n=64), 75% BIRADS 4 vs 25% had BIRADS. We consider all these percentages very similar, suggesting no skewness in the data selection. (comment added in lines 433-436).

- *The authors should discuss why they believe the positive biopsy rate was so extreme and should consider what this means about the patients who either did not undergo biopsy or left the public system and were diagnosed some other way*

To calculate the positive biopsy rate of the women with evidence of biopsy (n=62), we have to exclude the 7 individuals with unknown biopsy results. Of the remaining 55, 35 were BIRADS 4 and 20 were BIRADS 5, which led to a positivity rate of 89% for BIRADS 4, and a positivity rate of 100% for BIRADS 5 (added in lines 225-227). The 89% positivity rate is indeed higher than around 30% expected for this BIRADS category [Orel et al. BI-RADS categorization as a predictor of malignancy. Radiology 1999;211(3):845-50; Elezaby et al. ACR BI-RADS Assessment Category Subdivisions in Diagnostic Mammography. Radiology. 2018; 287(2): 416–422.] Of note, if we assume that the 7 unknown results (that were all BIRADS 4 as seen in the above figure) were negative, the positivity rate would be 74%.

Two other unpublished Peruvian studies conducted at INEN (the National Cancer Institute) and at the Regional Hospital in Arequipa have also reported high positivity rates for BIRADS 4 mammography results. The study conducted in INEN in 2013 found a positivity rate of 64% for BIRADS 4; while the study conducted in Arequipa in 2019 reported a mean positivity rate of 74% for BIRADS 4A, 4B and 4C results.

Available at:

INEN Study: <https://repositorio.urp.edu.pe/handle/urp/548>

Arequipa Study:

<https://repositorioslatinoamericanos.uchile.cl/handle/2250/3268049?show=full>

While we cannot be certain, we do not believe this high positivity rate for BIRADS-4 is attributable to inadequate training in our study, as radiologists were employed by the MOH and read the mammographs in compliance with MOH guidelines and standards. Likewise, most biopsies were taken at INEN, a national referral center for cancer, staffed with appropriately trained cancer pathologists (added in lines 439-443)

In conclusion, we are not sure why the positivity rate is high for the women with BIRADS 4 results and evidence of biopsy in the databases used in this study. Thus, we believe this observation merits further research. This is especially true given that many women with BI-RADS 4 did not have record of biopsy and therefore may remain undiagnosed and untreated, supporting the need for a robust tracking information system (added in lines 446-449)

The authors speculate that more patients may have been diagnosed and treated than they were able to identify, i.e., the situation is better than the numbers appear. The extreme positivity results suggests that the opposite could be true as well, i.e., there may be a significant number of women with cancer who (so far) have gone undiagnosed and are more likely to present in the future with advanced stage disease.

As mentioned above, we agree with this comment and this support the need of a robust tracking information that enables the program to come to precise number of women undiagnosed or untreated.

The authors correctly make the critical point that robust tracking and information systems are required to evaluate programmatic performance. Given the investigator's experience in public health, it would be meaningful if the authors could expand on what features a tracking system needs to have in order to achieve the desired goal

Thank you for this suggestion. We have included more details about the characteristics that we consider a tracking system for this breast cancer program should have in lines 456-461. We also added in lines 488-491 the ultimate use of this data management system.

It should also be pointed out that the sensitivity of mammography for detecting cancers is approximately 85%. Women with dense breasts (more common among younger women) are more likely to have negative mammograms. These women would not be included in this study cohort, since patients with BIRADS 1, 2 and 3 mammograms were excluded *Thank you. We agree; however, due to the journal's word count recommendation we have not expanded the discussion to include this point.*

The authors comment that their study could be the first such study from a middle-income country. Unreferenced in this manuscript is the 2017 study from Trujillo in Northern Peru (Romanoff et al. Association of Previous Clinical Breast Examination With Reduced Delays and Earlier-Stage Breast Cancer Diagnosis Among Women in Peru. JAMA Oncol. 2017; 3(11): 1563-7.), in which delays in initiation of breast cancer diagnosis and treatment were similarly examined and were found on average to exceed a year from the development of symptoms to the initiation of treatment, and for which 8 months of delay could be attributed to the health system itself. A notable finding was that over 90% of women were symptomatic and had self-detected cancers. The current study does not report on whether patients were asymptomatic and underwent screening mammograms or had symptoms and were undergoing diagnostic mammograms. This distinction is important, especially if a country is hoping to initiate a mammographic screening program. While the authors may consider some of these points out of scope for the current study that is focusing on the qualitative issues leading to delays in initiating treatment, the findings are nonetheless relevant to future studies and therefore should be explored at some level in the Discussion *Thanks so much for this comment. We also think that distinguishing how many were symptomatic and how many were not, is worth mentioning, however, this information was not available in the databases obtained for our study. Nonetheless, per verbal communication from the different program staff, the majority of the women were asymptomatic, as the main goal of the program is to actively capture asymptomatic women to screening mammography, but of course, with no exclusion of already symptomatic women.*

Thank you for kindly sharing the Romanoff et al. study. We have incorporated this paper in lines 427-429.

Reviewer 2:

This is a well written paper with minor revisions that are VERY minor. The paper reads

well and portrays a very important issue in the health care system in Peru: the need for a monitoring and evaluation system that allows providers to determine follow up of patients, the delays and problems in the system, and the challenges faced by women diagnosed with breast cancer trying to comply with doctor's orders.

We appreciate your comment.

Overall

This is a great paper tackling an important problem in breast cancer – and all health conditions that require continuous care in multiple types of health facilities in the country. It is clear and well written. The quantitative outcomes are clearly defined. The qualitative section flows well and there are rich quotes for the different sections. And the implications of this work are clear: this is beyond a “woman with breast cancer” problem – it is a problem of the entire system.

Thanks for highlighting this important message: it is the system as a whole that should be addressed

Introduction

Line 32: may face the greatest difficulties securing care – consider replacing with “may face great difficulties securing care”

We have modified it as suggested (lines 69-70)

P7, line 46-53: questions: 1) you identified women who experienced barriers and those who did not – were these barriers specifically through this tele-mammography program or who were going through cancer treatment in general? 2) How did the women actually get recruited? It seems that the cancer program staff identified them to the team – and then the research team introduced themselves?

The barriers were from getting a mammography (through this tele-mammography program) to initiating treatment. All of the women interviewed had undergone the mammography through the tele-mammography program. (added in lines 118-119)

Regarding the second question, it is correct. Potential participants were first identified by the tele-mammography program staff and provided a brief explanation of the research. After a first verbal acceptance, the research team visited them at their homes to formally invite them to participate (added in lines 119-121)

P8, lines 35-55: nice, clearly defined outcomes. You may even want to put them in a table to highlight these more, but fine as they are and clear.

Thanks for this recommendation. We prefer not to incorporate many tables/figures as recommended by the journal guidelines.

P11, lines 11: It seemed unusual to say that the “informed consent requirement was waived” for the quantitative component since it was a secondary data review – would it be more appropriate to say that it was a secondary data review with publicly available data? (Was it identifiable data?)

Data was not publicly available, but we submitted permission to each institution to obtain one identifiable variable (the national identification number) for the only purpose of merging the different study databases. The national identification number was then removed from the main study database.

P12: More of an editorial comment: considering you have a clear table with IQR, range, delay, etc, it is not necessary to repeat all that information in the text. You might consider keeping the main points but remove the IQR from the text.

Thanks for this suggestion. We have followed the recommendation

P13: line 13: it says there are 69 with no evidence of biopsy or treatment initiation, but it seems this should be a 64. You refer to 64 later in the paper, and out of 126, you mention that 62 did receive a biopsy, so it seems to be a typo.

-In total, 62 had evidence of biopsy and 64 did not

-The 69 mentioned, is part of the study definition “women with suboptimal care” (lines 152-154), which includes women with delays or with no biopsy or treatment, so it comes from adding up women with those events and deleting duplicates. We have decided not to mention such specific number as it may be confusing (deleted in lines 236-237)

P14, Lines 24-29: In the description of the study population on page 14, we learn that there were 13 women interviewed, and these represent the different geographic areas of the country. 1) Could you provide a table or a breakdown of how many women from each of the geographic areas? 2) I would be careful with the word “represented” in the sentence “Participants represented the different geographic areas of the country” – because it is not representative and almost sounds like it. Indeed, Peru is diverse and has many different regions, so the authors could say: “To ensure we had perspectives from different parts of the country, women from diverse geographic areas of the country were selected...” I forget if the limitations section addresses the fact that this is a small number of women and there are experiences of women in more remote areas that might be even more difficult...

We have included a table with the characteristics of the informants in general. (Table 2)

We have also changed the suggested sentence. (lines 121 to 123)

We did consider some women leaving remotely; however, women from very remote areas may have been excluded. (added in lines 482-483)

P18, lines 16-18: “This fatal conception of breast cancer made some women question the utility of treatment, creating delays for accepting care.” After reading the quotes and the earlier sections of this paper, I wonder: is it that the fatal conception of breast cancer makes them question the utility of treatment, or is it that they have seen and KNOW that care will be complex, delayed, “divorced” between systems, and so it feels like a death sentence because they know how hard it will be to try to manage this in a flawed system. No need to change it, but it just made me think that there may be a real reason for this “fatal conception”...

This is a very important point. We have discussed some more about this topic in lines 465-470

P22: lines 7 and 10: formatting went off on both percentages – the period replaced by a square!

Thanks for catching this typo. We have corrected it (lines 400 and 401)

P22, line 22: Again, is it a “patient misconception of breast cancer” or is it truly a deep awareness of the reality of treatment in the country...?

We have commented and discussed more about this topic in lines 465-470

P22, line 46: SIS should SUBSIDIZE (vs subsidy)?

We have corrected it (line 415)

Of note, we have slightly modified Fig 2 to make it simpler and have uploaded a better formatted version of Fig 3 without any change on the content.