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# Understanding Linkage to Biopsy and Treatment for Breast Cancer after a High-risk Tele-Mammography Result in Peru: A Mixed-Methods Study

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## ABSTRACT

**Objectives:** This mixed-method study aimed to understand the effectiveness of linkage to biopsy and treatment in women with a high-risk mammography result (BI-RADS 4-5) in the national tele-mammography program and to explore women's experiences during this process.

**Setting:** Quantitative component: we collected and linked health data from the tele-mammography reading center, the national public insurance, the national center for disease control and the national referral cancer center. Qualitative component: we interviewed participants from 4 different provinces of the country representing diverse social and geographical backgrounds.

**Participants:** Quantitative: data from all women who underwent tele-mammography between July 2017 and September 2018 and had high-risk results (BI-RADS 4-5) were collected. Qualitative: in-depth interviews with women with a high-risk tele-mammography result, healthcare providers and administrators.

**Outcomes measures:** Quantitative: we determined biopsy and treatment linkage rates and delays. Qualitative: we explored factors explaining non-linkage and delays.

**Results**: Of 126 women with high-risk results, 48.4% had documentation of biopsy, and 37.5% experienced a >45-day delay in obtaining it. Of 51 women with breast cancer diagnosis, 86.4% had evidence of treatment initiation, but 69.2% initiated treatment >45 days after biopsy. Travelling to major cities for care, breast cancer misconceptions, and administrative factors impeded timely, continuous care for breast cancer

**Conclusions:** Strengthened breast cancer care capacity outside the capital city, improved dissemination of guidelines among providers, enhanced patient education, standardized referral pathways and ensured financial support for travel expenses are required to secure linkage to the breast cancer care continuum. Robust tracking and information systems are needed to evaluate the program´s performance.



**Key words:** breast cancer; mammography; linkage to care; delays; Peru

**Article summary**

***Main findings***

- This study evaluated the linkage to biopsy and treatment in the Ministry of Health Tele-mammography Program.
- Delays in biopsy or treatment initiation and non-linkage to breast cancer care were explained by centralization of services in the capital city, policy and program implementation gaps, and insufficient patient education about breast cancer.

***Strengths and the study***

- This study is among the first to evaluate linkage to biopsy and treatment for breast cancer after high-risk mammography results in a middle-income country.
- This study is an exhaustive evaluation that used both quantitative and qualitive research methods to comprehend the program's situation in different geographical settings in Peru.

***Limitations of the study***

- The lack of integration of the health information systems of the different Ministry of Health components related to the Tele-mammography Program challenged data collection and may have caused underestimation of the percentage of women who obtained care.

## INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women and the leading cause of cancer-related deaths worldwide.[1] To date, mammography screening is the only early detection method that has been proven to reduce mortality due to breast cancer.[2] Pooled results from randomized trials in the U.S, Canada, and Europe, show a 19% reduction in breast cancer mortality associated with mammography screening.[3] Currently, the World Health Organization (WHO) supports organized, population-based mammography screening as an essential tool for the control of breast cancer.[2]

For mammography screening to reduce breast cancer mortality, timely diagnosis and effective treatment must follow.[4] Cancer care is complex and requires coordination across multiple medical specialists, as well as adequate healthcare facilities and equipment.[5] Thus, patients in low- and middle-income countries (LMIC), where less than 5% of the necessary resources for cancer diagnosis and treatment are available,[6] may face the greatest difficulties securing care. Suboptimal diagnosis and treatment rates and delays could undermine the effectiveness of a screening program in reducing breast cancer mortality.

In 2017, the Peru Ministry of Health (MOH) launched a free telemedicine-based mammography program targeting women living outside of the major metropolitan area of Lima and receiving government-subsidized health insurance. The program aimed to circumvent the lack of radiologists in the provinces by digitally transferring mammography images to Lima, the nation's capital, for review. We examined rates of and time to biopsy and breast cancer treatment initiation after a high-risk tele-mammography result among women participating in

this national program and sought to understand women's experiences seeking diagnostic and treatment services.

## METHODS

### Study setting

In Peru, individuals living in poverty receive government-subsidized insurance, known as the Comprehensive Health Insurance (SIS). In 2012, breast cancer care (diagnosis, treatment, and palliative services) was added to the SIS health package;[7] however, most services remain centralized in Lima, where they are provided by the National Institute of Neoplastic Diseases (INEN).[8] Outside Lima, two regional cancer institutes and some general hospitals offer cancer services on a varied and limited basis. When services are not available at one of the general hospitals, patients are referred to the regional cancer institute or to INEN.

Peru's MOH tele-mammography program is the primary mammography provider among SIS recipients and as of September 2018, 14 hospitals in 11 regions participated in the program. At these hospitals, the cancer program staff conduct mammography testing, result reporting, follow-up, and referrals. Asymptomatic women aged 50 to 69 years old are invited for screening through routine clinical visits or community outreach activities. Symptomatic women may be referred for a diagnostic mammogram. Digital images are transferred securely via the internet to a reading center in Lima, where trained radiologists provide a result within a few days. Following international guidelines, individuals with a Breast Imaging Reporting and Data System (BI-RADS) result of 4 or 5 are supposed to be referred for biopsy.[9] If cancer is diagnosed, treatment is planned, including referrals, as needed.

## Study design

We conducted a mixed-methods study with a concurrent design.[10] We described the frequency and time required for biopsy and treatment initiation, and qualitatively explored the factors impeding and facilitating care.

## Study population

Quantitative component

We conducted a retrospective review of data collected from all women aged ≥18 years with SIS insurance, who underwent a tele-mammography through the MOH program between July 2017 and September 2018 and obtained a high-risk result.

Qualitative component

We used purposeful sampling to identify and interview 32 key stakeholders comprised of women with a high-risk tele-mammography result, healthcare providers (cancer program nurses and midwives, and physicians from the hospital oncology services), hospital program coordinators supervising the program, and current or former staff of the MOH directly involved in health policy and supervision of cancer activities, nationally. We included women known to have experienced barriers to obtaining care (as identified by the cancer program staff) and women who obtained care more easily. Informants came from eight cities, including Lima, and represented the country's three geographical regions: (coast, highlands, and rainforest).

**Key procedures**

Quantitative component

*Data sources:* Tele-mammography results and basic demographic information were obtained from the tele-mammography reading center in Lima (Villa El Salvador Hospital). Because there was no national database for tracking patients along the breast cancer continuum of care, person-data on biopsy and treatment were extracted from three independent data sources using the national identification number of each subject: SIS electronic databases, the National Cancer Surveillance registry of Peru's Center for Control of Diseases (CDC), and INEN medical electronic and paper records. Access to these data sources was requested to the corresponding institutions. These data sources include diagnostic procedures, biopsy results and treatments. Data from SIS, CDC, and INEN were available through December 31st, 2018; November 1st, 2019; and January 15th, 2020; respectively. Thus, each woman was followed for a minimum of 90 days and a maximum of 470 days following mammography. (Figure 1)

*Outcomes:* A high-risk tele-mammography result was defined as a BI-RADS result of 4 or 5.[11] The biopsy rate was defined as the proportion of women with a high-risk tele-mammography result who had evidence of a breast biopsy documented in the available data sources. The treatment initiation rate was defined as the proportion of women with confirmed breast cancer who had evidence of initiating chemotherapy, surgery, radiation, or hormonal therapy.

We calculated the time to biopsy and treatment initiation among those who secured these services. Adapting definitions from a consensus statement,[12] we defined the diagnosis interval as the time from tele-mammography result to biopsy result, the treatment interval as the time from biopsy result to treatment initiation, and the health system interval as time from tele-

mammography result to treatment initiation. For each interval, we calculated the proportion of women who experienced delays. Because delays >90 days from breast cancer symptom discovery to treatment initiation correlate with advanced stage at diagnosis and worse survival,[13, 14] we defined a health system delay as a health system interval >90 days, and diagnosis and treatment delays as >45 days. We calculated the frequency of women with suboptimal care, defined as the presence of biopsy or treatment delay or the absence of biopsy or treatment in spite of indication.

Qualitative component

*Data collection:* We conducted individual, in-depth interviews using semi-structured interview guides to explore the barriers and facilitators to biopsy or treatment initiation. For women with a high-risk tele-mammography, topics included the experience of pursuing and following referral for care; strategies for overcoming difficulties in seeking care; and recommendations for improvement. Interviews with healthcare providers and administrators covered how breast cancer care is administered and delivered; program strengths and weaknesses; and recommendations for improvement. The first author (RE) conducted face-to-face interviews in Spanish (local language and RE's native language). Interviews lasted approximately 50 minutes and were audio-recorded and transcribed verbatim.

**Data analysis**

Quantitative component

Data was cleaned thoroughly by RAE using Stata v14 and supervised by MFF. We reported descriptive statistics and analyzed data using Stata v14. We examined time intervals to biopsy and treatment both as continuous variables and also as binary variables to identify the proportion of women experiencing delays in care.

Qualitative component

We conducted content analysis on the transcripts uploaded to Dedoose.[15] A subset of interviews was open coded using short descriptive labels from which the first codebook draft was constructed. The draft codebook was piloted in a separate subset of interviews; codes were added, eliminated, or merged to create the final version used to code the dataset. The coded data were inductively analyzed to identify key themes related to the barriers and facilitators for obtaining a biopsy or initiating treatment. Using an iterative approach, the draft themes were revised, resulting in a set of final themes. Illustrative quotes for each theme were extracted and translated into English.

**Patient and public involvement**

Patients were not involved in the development of the research question or in the design, recruitment or conduction of the study. Personnel from the Ministry of Health were involved in study design and recruitment. Results will be disseminated among the Ministry of Health staff.

## Ethical considerations

The study protocol and instruments were approved by Institutional Review Boards from Harvard Medical School, Cayetano Heredia Peruvian University, INEN, and Villa El Salvador Hospital. For the quantitative component, the informed consent requirement was waived. Participants in qualitative interviews provided written consent. Women with high-risk mammography results participating in the interviews received 6 USD for time and transportation compensation.

## Role of the funding sources

The funding sources did not play any role in the study design; in the collection, analysis, and interpretation of the data; in writing of the report; nor in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

# RESULTS

## Quantitative findings

Biopsy and treatment initiation rates and delays

From July 1st, 2017 to September 30th, 2018, 6899 tele-mammography tests were conducted through the MOH services. Of these, 147 women had a high-risk mammography result. After the exclusion of 21 individuals with data discrepancies or who did not meet the inclusion criteria

(Figure 2), 126 women were included for analysis. Their mean age was 53.3 years (standard deviation: 11.3).

We found evidence of biopsy in 62/126 (48.4%) women (Figure 2). Of these, biopsy result dates were available in 48, of whom 18 (37.5%) experienced a diagnosis delay (median diagnosis interval = 39.5 days [IQR= 5.5-65; range= 7-263]) (Table 1). Among the 62 women with evidence of biopsy, 49 had data on where the procedure was performed, and in 32 (65.3%) it took place in a different region from where they lived.

**Table 1. Time intervals and delays between mammography, biopsy and treatment initiation among 126 women with a high-risk tele-mammography result who obtained this care**

| Time interval | Median days (IQR; range) | Delay n (%) |
|---|---|---|
| **From tele-mammography result to biopsy result** (n=48, N=62) | 39.5 (25.5-65; 7-263) | 18 (37.5) |
| **From biopsy result to treatment initiation** (n=39, N=44) | 65.3 (32-118; 8-416) | 27 (69.2) |
| **From tele-mammography result to treatment initiation** (n=44, N=44) | 109.5 (69.5-168; 10-442) | 29 (65.9) |

N= total number of women who completed the corresponding step
n= number of women with dates available

Of the 62 women who had a biopsy, 51 were diagnosed with breast cancer, four had a benign condition, and seven did not have a result in her medical record. Of those diagnosed, we found evidence that 44/51 (86.3%) initiated treatment. Of these, the dates of the biopsy results and treatment initiation were available in 39, of whom 27 (69.2%) experienced a treatment delay (median treatment interval = 65.3 days [IQR= 32-118; range= 8-416]) (Table 1). Among the 44 women with evidence of treatment, data about the treatment hospital was missing for one

individual; of the 43 remaining, 35 (81.4%) initiated treatment in a different region than where she lived. Health system delays were observed in 29/44 (65.9%) women (median health system interval = 109.5 days [IQR= 69.5-168; range= 10-442]) (Table 1). Excluding 14 individuals with missing dates, 104/112 (92.4%) women appeared to have received suboptimal care: 35 with a biopsy or treatment delay and 69 with no evidence of biopsy or treatment initiation.

**Qualitative findings**

Study population

We interviewed 32 people: 13 women with a high-risk tele-mammography result, 13 healthcare providers, three hospital program coordinators, and three policymakers. Participants represented the different geographic areas of the country (the coast, the Andean highlands, and the Amazonian rainforest).

Findings

Undergoing biopsy and initiating breast cancer treatment was impeded by several factors clustering around three primary themes: A) the toll of getting care in major cities following referrals, B) patients' misconceptions and access to information, and C) administrative and operational barriers. Some of these factors primarily affected the diagnosis interval, others influenced mainly the treatment interval, while others impacted both intervals. This relationship is illustrated in Figure 3. Although scarce, a few facilitators were identified and are detailed in a fourth theme, D) facilitators.

*Theme A: The toll of getting care in major cities following referrals*

Insufficient financial resources and support for transportation, accommodation, and food

Referral to a hospital in a major city at some point during follow-up was inevitable for almost all patients living outside of Lima. Informants agreed that most women could not afford the transportation, housing, and food expenses associated with residence outside of their hometowns. Patients mentioned that they did not receive any subsidy from SIS for these expenses. Providers and administrators perceived these constraints as preventing patients from receiving care. (Table 2, quote #1)

Interviewees highlighted the need to find external sources of financial support. Sometimes families organized fundraising activities. Other times, non-profit organizations, churches, or local municipalities provided financial support for transportation or living expenses; however, interviewees agreed that these resources were limited due to restricted budgets and prioritization of other vulnerable populations such as pediatric patients. (Table 2, quote #2). The economic burden of these expenses forced families to take out loans and/or sell assets (Table 2, quote #3).

Being away from family and friends' emotional support

Close relatives and friends were a vital source of motivation and emotional support as patients sought breast cancer care. Patients noted that the presence of loved ones transmitted confidence. Interviewees acknowledged that this accompaniment was essential, especially around the time of diagnosis. (Table 2, quote #4)

When patients left their hometowns to reside in the cities, this support was frequently diminished. Patients described how the cost of travel and competing responsibilities prevented loved ones from accompanying them. Providers and administrators referred that the weakened support network put patients at risk of withdrawing from care. (Table 2, quote #5)

**Table 2. Barriers and facilitators for obtaining a biopsy and initiating treatment after a high-risk tele-mammography result**

| Theme | Subtheme | Excerpts |
|---|---|---|
| A. The toll of getting care in major cities following referrals | Insufficient financial resources and support for transportation, accommodation, and food | **Quote #1:** *They have to assume the expenses; they have to. So, often, because of the little money that they have, they don't go [to the city].* [midwife, highlands] |
| | | **Quote #2:** *There are some shelters here where patients can stay, but they have limited access for a group of patients; first the pediatric patients and then the rest.* [physician, Lima] |
| | | **Quote #3:** *We sold some animals. On the farm, we had sheep, cattle, and we sold everything, even the land we had to sell, to save her. If we hadn't made those efforts, my wife wouldn't be alive now. We did it to save her.* [patient's husband, highlands] |
| | Being away from family and friends' emotional support | **Quote #4** *Interviewer: How important do you think family support is during this time [before having the biopsy]?* *Interviewee: Well, you are desperate, you feel like dying, but they talk to you, they talk with you. They give you support, psychological support. It's as if they were saying, "Mom, you are not alone; you are with me".* [patient, highlands] |
| | | **Quote #5** *Interviewee: If they come from the provinces, they come alone. They can't come with all their family. Or they come to the first consult with a relative, and then they say things like "well, he is my husband, but he has to go back to my town to take care of my children." And they leave. That's the reality of the people who come from the provinces outside of Lima.* *Interviewer: How does it affect care?* *Interviewee: It affects care because the patient must think twice before continuing care. Either she abandons it or comes irregularly.* [physician, Lima] |
| | Challenges adjusting to and navigating the city | **Quote #6** *The cultural shock [of going to the city] is very strong. They feel overwhelmed; sometimes so overwhelmed that they prefer to leave care and go back to their towns.* [physician, highlands] |
| B. Patients' misconceptions and access to information | Misconceptions about breast cancer manifestations and progression | ***Quote #7*** *I did not give it too much importance because I did not have any pain. I thought that maybe they were wrong. I didn't give it importance, so I didn't do anything.* [patient, highlands] |
| | | **Quote #8** *Patients say that [having a biopsy] is worse, because when they prick you or take a piece of your breast that's when the cancer awakens. And that's why they don't want to have the biopsy.* [nurse, highlands] |
| | Misconceptions about the treatment | **Quote #9** *When you tell someone she has breast cancer, the first thing they think of is that it is daño [a sort of witchcraft], so they go first to the shamans and later, if they continue feeling sick, they come back.* [program coordinator, rainforest] |
| | Misconceptions about the prognosis | **Quote #10** |

| | | |
|---|---|---|
| | | *Many times, I've heard that when you have cancer you have it until the end. You just have to wait for your death. Once you have it there is no cure.* [patient, highlands] |
| | Limited information provided about the disease | **Quote #11**<br>*I would have liked for them to explain it to me more thoroughly, perhaps that way I would have gone, it would have encouraged me. Because sometimes, when they explained to you well, you are conscientious and go. But if they give you a test result that only says get another test because the first test wasn't normal, you don't give it adequate importance. […] They didn't say anything more than giving you a number, where I should go, and all of that.* [patient, highlands]. |
| C. Administrative and operational barriers | Delays for obtaining appointments and tests | **Quote #12**<br>*Interviewer: What happened the day that you went to the hospital? How did it go?*<br>*Interviewee: I went very early, very early, but the line was already long, and as I needed to work, I got fatigued and didn't go back. So, I haven't done the test. Nothing. I left it there.* [patient, highlands] |
| | | **Quote #13**<br>*For these tests, they have to come one day and for these others another day. And that's how the time passes by. […]. So sometimes when they are told to do one more test they say "Miss, I've been there, three months have passed, and I haven't started treatment yet".* [nurse, highlands] |
| | Low awareness of the program or of its guidelines among providers | **Quote #14**<br>*We had a patient with BI-RADS 4 who needed a biopsy, but the closest hospital didn't have biopsy services. So, we coordinated to refer her to a regional cancer center. After a lot of insistence, they could transfer her to the regional cancer center, and it happens that when she arrives at the facility they ordered a repeat mammography.* [policymaker, Lima] |
| | Lack of standardized referral pathways | **Quote #15**<br>*Interviewer: Did they ask you if you wanted to go to [region X] instead of Lima?*<br>*Interviewee: No, they didn't say anything. If I had known that in [region X] they had chemotherapy, I wouldn't have gone to Lima, because I didn't have enough money or someone to help me. If I knew they had it here, I would have stayed.* [patient, coast] |
| | Inconsistent tracking of patients | **Quote #16**<br>*Interviewer: What type of follow-up do you do here?*<br>*Interviewee: Once they have a biopsy in the [local] hospital, and it comes back positive, they call the patient or her primary care center to inform her of the result. They talk with the patient to see what's best: to send her to [the regional hospital] or Lima […]*<br>*Interviewer: And what happens once they are referred?*<br>*Interviewee: We don't do further follow-up. I'd be lying if I say we do. We don't do more follow-up.* [program coordinator, coast] |
| | | **Quote #17**<br>*The systems are divorced; they are not integrated. So, you are taking mammography tests but there is not a structure that integrates the screening with the treatment or with the diagnosis.* [policymaker, Lima] |
| D. Facilitators | Having family or a friend living in the city | **Quote #18**<br>*They say: "I don't worry much about the stay, Miss, I have family there." The majority that wants to go to [a major city] is because they have family there.* [midwife, coast] |
| | Collaborative and family-inclusive explanation | **Quote #19**<br>*The psychologist has helped me a lot […] The psychologist is part of your disease, [the psychologist] cheers you up. It is not only the doctor who helps, the psychologist too. [The psychologist] talks with you in a particular way and makes you understand.* [patient, highlands] |
| | | **Quote #20**<br>*Interviewer: How do you convince them [to obtain a biopsy]?*<br>*Interviewee: Taking your time and explaining kindly. Sometimes the patient accepts [undergoing biopsy], but the relative doesn't, so you need to explain it all to the family, too. […] You need to explain to every one of them because in their way of living, all the family influences, and then they accept.* [physician, highlands] |
| | Facilitated appointments | **Quote #21**<br>*Interviewer: How do patients from other regions get care here?*<br>*Interviewee: They just come and get an appointment. Here in the oncology department, we have a system that we called 'unlimited appointments.' We give an appointment to everyone who arrives before 9:00 a.m.*<br>*Interviewer: What day is the appointment?*<br>*Interviewee: For the same day. So, they don't have to come back another day.* [physician, highlands] |

Challenges adjusting to and navigating the city

For some patients, residence in a metropolitan area represented a major cultural change and logistical challenges. Informants described how many patients pursuing care in the cities were accustomed to country life. Living in and navigating a new city, at times in a different language, was perceived by providers and program coordinators as a “cultural shock” for patients which interfered in their care. (Table 2, quote #6)

*Theme B: Patients' misconceptions and access to information*

Misconceptions about breast cancer manifestations and progression

Some misconceptions about how breast cancer manifests and progresses contributed to delays in pursuing a biopsy. For example, a high-risk mammography result was recognized as serious by some patients but denied by others in the absence of symptoms, preventing them from seeking further care. (Table 2, quote #7) Other patients felt that touching or manipulating the breast "awakens" the disease, preferring to "let it rest" instead of obtaining a biopsy. (Table 2, quote #8)

Misconceptions about treatment

Providers reported that women looked for therapies with herbs and shamans as their first treatment option. They felt that this caused disengagement from facility-based health care with women returning only when no improvement was seen with this traditional treatment, at which point symptoms had often worsened. (Table 2, quote #9)

Misconceptions about the prognosis

Prior experiences with breast cancer led some women to perceive the disease as a non-curable condition. Whether because they had heard about others' negative experiences with breast cancer or had personal experiences, many women expressed feeling that the ultimate outcome of breast cancer was certain death (Table 2, quote #10). This fatal conception of breast cancer made some women question the utility of treatment, creating delays for accepting care.

Limited information provided about breast cancer

Many patients noted the limited information about mammography findings, breast cancer treatment and prognosis communicated to them by the clinical team. Instead, they felt that communication was focused on conveying information about the next administrative steps. As some referred, a better explanation would have led to making good choices earlier. (Table 2, quote #11)

*Theme C: Administrative and operational barriers*

Delays in obtaining appointments and tests

Informants relayed difficulties in obtaining appointments. For example, in 'first come, first served' medical services, many had to arrive at the facility very early in the morning and wait in

long lines without the guarantee of an appointment that day. Some women expressed frustration with this process, noting that it led them to discontinue seeking care. (Table 2, quote #12)

When appointments could be booked in advance, they were often scheduled for several weeks later, with test results delayed up to a month or more. One nurse described a patient's onerous experience trying to complete the tests requested (Table 2, quote #13).

Limited awareness of the program among providers

Not all physicians reported awareness of the MOH tele-mammography program. Those unfamiliar with the program doubted the validity of mammography results (thinking that they were reported by untrained radiologists) and usually ordered a second mammography at their hospital. (Table 2, quote #14) In other cases, the cancer program's nurses and midwives wanted to "double check" each abnormal tele-mammography result so they would order a breast ultrasound before referring for biopsy, contrary to national guidelines. These extra procedures contributed to delays and the administrative burdens on the patient.

Lack of standardized referral pathways

There is no formal standardized referral pathway for high-risk tele-mammography results. The providers' choice of referral hospital, particularly for treatment, was usually based on his/her perceptions of available services or quality of care. As noted by most informants, INEN was often the hospital of choice. Policymakers agreed that this approach did not take advantage of the

resources available at closer regional hospitals. One woman's comment illustrated how this system failed to account for patients' convenience. (Table 2, quote #15)

Inconsistent tracking of patients

The follow-up of women did not occur uniformly along the continuum of care. While the cancer program staff closely followed patients who received care in the local hospital, program coordinators agreed that tracking patients in upper-level hospitals was less rigorous. (Table 2, quote #16)

The programmatic follow-up tool, created by the MOH to strengthen tracking activities, was not used consistently and scarcely monitored by the MOH officials. In addition, policymakers reported that tracking of patients through health information systems would not be possible due to a "divorce" between the MOH's and hospitals' digital data systems (Table 2, quote #17).

*Theme D: Facilitators*

Having family or a friend living in the city

Interviewees expressed that having a relative or a close friend living in the city where patients were referred facilitated access to care. When patients could stay with friends or family, it alleviated much of the financial hardship. (Table 2, quote #18) Also, patients felt secure in knowing that someone could help them navigate the city or take care of them once treatments started.

Collaborative and family-inclusive approaches to care

Addressing patients' concerns about breast cancer through a multidisciplinary approach was seen by providers as useful for improving the patient's understanding of the disease and for making prompt medical decisions. Collaborative work among clinicians, psychologists, and social workers facilitated communication around diagnosis and expectations for future care. Patients highlighted the benefit of receiving psychological support upon diagnosis (Table 2, quote #19), Providers emphasized that involving the family was necessary given its determinant role in health decision making. (Table 2, quote #20)

Facilitated appointments

Some hospitals and providers expedited appointments for their patients. In two hospitals, the medical appointments were scheduled within one day for patients coming from remote areas. In another, all patients arriving early were guaranteed to be seen that day. In other cases, providers coordinated appointments to reduce the administrative burden on the patients or leveraged their influence to secure a spot. These approaches, although not perfect, helped reduce appointment delays. (Table 2, quote #21)

## DISCUSSION

We evaluated linkages to breast cancer diagnostic and treatment services in the largest national tele-mammography program in Peru. To our knowledge this is the first such study from a

middle-income country. In women with a high-risk tele-mammography result among whom biopsy is indicated, we found evidence that biopsy was performed among fewer than half. Among women with breast cancer, we found evidence of treatment initiation in 86□3%. Delays in obtaining these services were common. Overall, the vast majority (92□4%) of women experienced suboptimal care (delayed care or no evidence of linkage to care). Our quantitative findings are complemented by qualitative evidence of substantial barriers to care. Through a mixed-methods design, we elucidated the ways in which diagnosis and treatment services for breast cancer were not easily accessible for women living in poverty throughout the country. These included travel barriers, administrative obstacles and patients´misconceptions about breast cancer.

In our study, many women with breast cancer did not have evidence of biopsy or treatment, and centralization of cancer services in Lima and a few other major cities likely contributes to delays and interruptions in care. Living outside Lima and/or in rural areas of the country has been shown to place individuals with cancer at higher risk of discontinuing care.[16, 17] Centralization of cancer care facilities has also been found to disproportionately affect socioeconomically vulnerable populations and may contribute to persistent care disparities for breast cancer care in LMIC.[18-20] In our study, although cancer services were offered free-of-charge, patients lacked the means for traveling to obtain those servicers. According to the National Cancer Control Plan, SIS should subsidy the costs for transportation and for staying at the cities; however, this economic support was not received by any of the patients interviewed. A recent study on cervical cancer in Peru highlighted the same policy-implementation gap in women with cervical cancer.[21] Given that five in ten women in Peru live in poverty (<150 USD per month),[22] our finding that insufficient economic resources for the expenses

associated with centralized care in cities (e.g., transportation, accommodation, and food) challenged care is not unexpected. Reducing inequalities for breast cancer care access in middle-income countries must incorporate the existing free diagnostic and treatments services with decentralization of these resources to bring them closer to those that need them.

Among women for whom we could confirm care, delays were common. Our finding that 65% of women experienced a health system delay is consistent with reports from other LMIC, where over 70% of patients start treatment three or more months after the first abnormal finding (a high-risk screening mammography or symptoms discovery).[13] Long health system delays leads to advanced disease stage, a known risk factor for death from breast cancer.[23] Efforts to decrease delays would be expected to increase breast cancer survival rates.

Our results raise several opportunities to improve the outcomes of the tele-mammography program by facilitating follow-up care for those with a positive mammography. For instance, unorganized referrals and patient tracking could be improved by a monitoring and evaluation plan along the entire care continuum.[24] Also, a unified health information system across the different MOH hospitals could allow a more accurate, and even real-time patient follow-up.[25] Low compliance to guidelines among the MOH's providers could be remedied by nationwide campaigns to build awareness of the program, its processes and goals. Appointment systems could be reconsidered to prioritize a patient-centered approach. Finally, multidisciplinary and culturally-tailored patient education, incorporating family members or supporters as appropriate, may correct misconceptions about breast cancer that contributed to delays. Overall, a real comprehensive tele-mammography program should not be seen as a separate breast cancer service but as part of the whole breast cancer continuum of care.

Evaluating breast cancer care using routinely collected data was challenging due to a lack of integration of health information systems of the different MOH components that managed and provided healthcare to the population subsidized by SIS. Although we used multiple national data sources to capture care access through different pathways, due to varying levels of follow-up and data completeness, we may have underestimated the proportion of women who obtained care. Thus, the quantitative results presented here were our best intent to disentangle the current health information puzzle existing in the public healthcare sector. Nonetheless, this study is a comprehensive evaluation that used both quantitative and qualitive research techniques to understand the situation in diverse geographical settings in Peru. Thus, this study provides a close perspective of challenges in Peru, which may be broadly applicable to other middle-income countries with similar resource levels and health systems.

The benefit of mammography screening can only be realized if women with abnormal findings are successfully linked to high-quality and timely diagnostic and treatment services. Our study underscores the need for strengthening the breast cancer diagnostic and treatment capacity of regional hospitals outside Lima to remove barriers and facilitate access to timely comprehensive breast cancer care. It also highlights the need for a strong patient education strategy and better dissemination of the information about the program among providers nationwide. Finally, a unified health information system is needed to allow better tracking of patients after the mammography and along the breast cancer continuum of care. Ensuring timely linkage to diagnosis and treatment for women with an abnormal result in the tele-mammography program will be critical to securing the screening program's success.

## Contributorship statement

RAE, PJG and MFF conceptualized the study. RAE collected the data and wrote the first draft of the article. MFF, PJG, LEP, JTG, helped to synthesize evidence, interpret results, and critically revise the manuscript. RAE secured funding for the study. All authors approved the final draft.

## Competing interests

All authors declare no competing interests.

## Data sharing statement

No additional data is available

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Figures' legends

Figure 1.


SIS, Comprehensive Health Insurance (government-based insurance); CDC, Center for Epidemiology and Control of Disease- National Cancer Surveillance registry; INEN, National Institute of Neoplastic Diseases

Figure 2.

ID, National Identification Number; SIS, Comprehensive Health Insurance (the government-subsidized insurance)

[I was requested to include a legend for Figure 3, but it does not have a legend, just a title which is already included in the Fig3 document]

**Figure 1. Availability of biopsy and treatment information from the three study data sources**

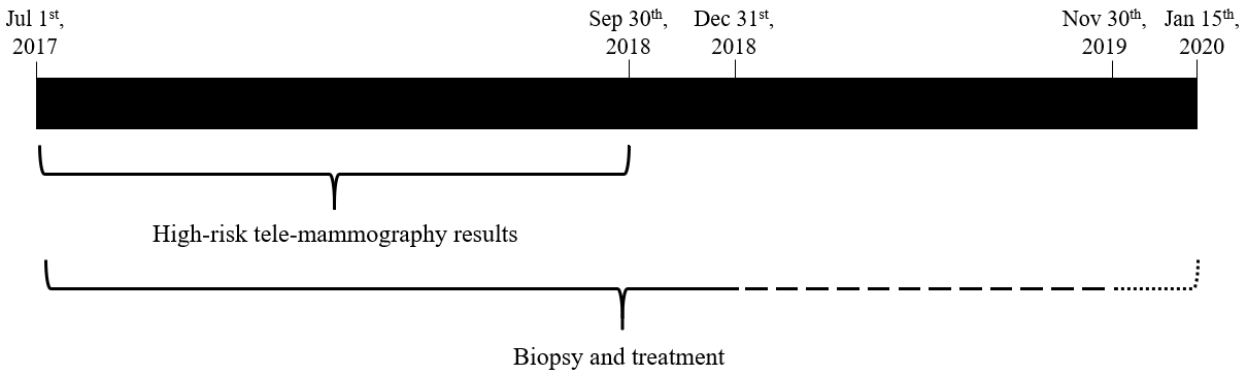

**Fig 2. Flowchart of biopsy and treatment initiation rates among women with a high-risk tele-mammography result**

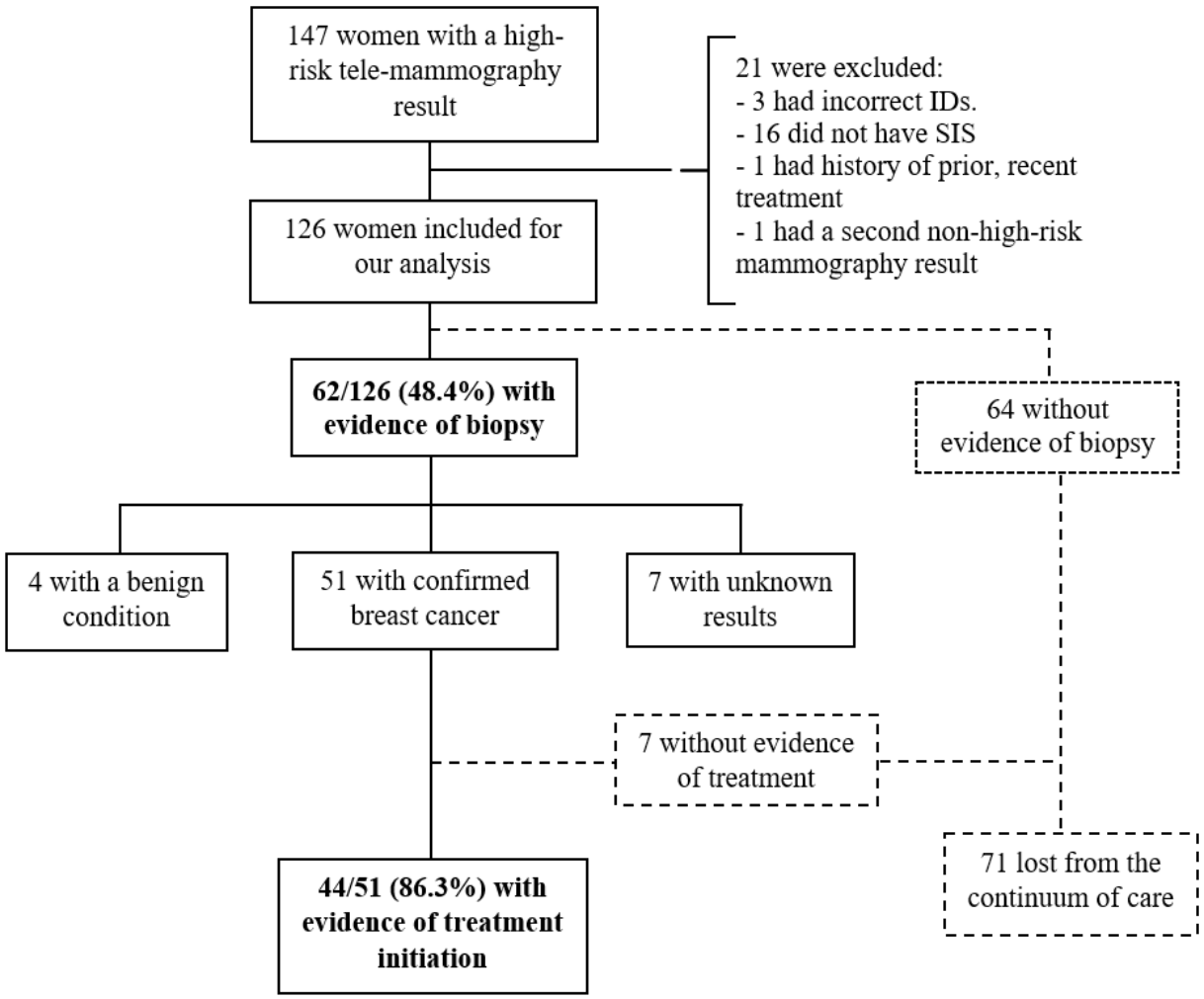

**Fig 3. Barriers for obtaining a biopsy and initiating treatment and related affected intervals after obtaining a high-risk tele-mammography result**

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | 1.1 Abstract, 'setting' section (page 2)<br><br>1.2 Abstract, 'Participants' section (page 2)<br><br>1.3 Abstract, 'Setting' section (page 2) |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including | | | |

| | | | | | |
|---|---|---|---|---|---|
| | | periods of recruitment, exposure, follow-up, and data collection | | | |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | 6.1. "Data sources" section (page 7)<br><br>6.2. No validation studies were conducted.<br><br>6.3. A graphic representation of the databases merge is included in Figure 1. |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | 7.1. No confounders or effect modifiers were included. Exposures and outcomes are explained in the "outcomes" section (page 7) |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details | | | |

| | | | | | |
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| | | of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | | | |
| Study size | 10 | Explain how the study size was arrived at | | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database | 12.1 ‘Data sources’ section. (page 7) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | population used to create the study population.<br><br>RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | 12.2 "Data analysis' section (quantitative component) (page 7) |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | 12.3 "Data analysis' section (quantitative component) (page 7) |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | 'Biopsy and treatment initiation rates and delays' section (page 10) |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | | | |

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| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over | 'Discussion' section (5th paragraph). |

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| | | | | time, as they pertain to the study being reported. | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | See 'Data sharing statement' (page 24) |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

# Understanding Linkage to Biopsy and Treatment for Breast Cancer after a High-risk Tele-Mammography Result in Peru: A Mixed-Methods Study



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# Understanding Linkage to Biopsy and Treatment for Breast Cancer after a High-risk Tele-Mammography Result in Peru: A Mixed-Methods Study

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## ABSTRACT

**Objectives:** This mixed-method study aimed to understand the effectiveness of linkage to biopsy and treatment in women with a high-risk mammography result (BI-RADS 4 and5) in the national tele-mammography program and to explore women's experiences during this process.

**Setting:** Quantitative component: we collected and linked health data from the tele-mammography reading center, the national public insurance, the national center for disease control, and the national referral cancer center. Qualitative component: we interviewed participants from different provinces of the country representing diverse social and geographical backgrounds.

**Participants:** Quantitative: women who underwent tele-mammography between July 2017 and September 2018 and had high-risk results (BI-RADS 4-5) were collected. Qualitative: women with a high-risk tele-mammography result, healthcare providers, and administrators.

**Outcomes measures:** Quantitative: we determined biopsy and treatment linkage rates and delays. Qualitative: we explored barriers and facilitators for obtaining a biopsy and initiating treatment.

**Results**: Of 126 women with high-risk results, 48.4% had documentation of biopsy, and 37.5% experienced a >45-day interval prior to biopsy. Of 51 women diagnosed with breast cancer, 86.4% had evidence of treatment initiation, but 69.2% initiated treatment >45 days after biopsy. Travelling to major cities for care, administrative factors, and breast cancer misconceptions, among other factors, impeded timely, continuous care for breast cancer. A multidisciplinary and culturally tailored patient education facilitated understanding of the disease and prompt decision making about subsequent medical care.

**Conclusions:** Strengthened breast cancer care capacity outside the capital city, standardized referral pathways, ensured financial support for travel expenses, and enhanced patient education are required to secure linkage to the breast cancer care continuum. Robust information systems are needed to track patients and to evaluate the program´s performance.

**Key words:** breast cancer; mammography; linkage to care; delays; Peru



**Article summary**

***Strengths of the study***

- This is among the very limited studies evaluating linkages to care after high-risk mammography results in a middle-income country.
- This study is an exhaustive evaluation that used both quantitative and qualitive research methods.
- This study collected user´s the perspectives from different geographical settings in Peru

***Limitations of the study***

- The lack of integration of the health information systems in the Ministry of Health may have caused underestimation of the percentage of women who obtained care.
- The follow-up time for women who obtained a high-risk tele-mammography result was heterogenous

## INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women and the leading cause of cancer-related deaths worldwide.[1] To date, mammography screening is the only early detection method that has been proven to reduce breast cancer mortality.[2] Pooled results from randomized trials in the U.S, Canada, and Europe, show a 19% reduction in breast cancer mortality associated with mammography screening.[3] Currently, the World Health Organization (WHO) supports organized, population-based mammography screening as an essential tool for the control of breast cancer.[2]

For mammography screening to reduce breast cancer mortality, timely diagnosis and effective treatment must follow.[4] Cancer diagnosis and treatment are complex and requires coordination across multiple medical specialists, as well as adequate healthcare facilities and equipment.[5] Thus, patients in low- and middle-income countries (LMIC), where less than 5% of the necessary resources for cancer diagnosis and treatment are available,[6] may face great difficulties securing care. Suboptimal diagnosis and treatment rates and delays could undermine the effectiveness of a screening program in reducing breast cancer mortality.

In 2017, the Peru Ministry of Health (MOH) launched a free telemedicine-based mammography program targeting women living outside of the major metropolitan area of Lima and receiving government-subsidized health insurance. The program aimed to circumvent the lack of radiologists in the provinces by digitally transferring mammography images to Lima, the nation's capital, for review. We examined rates of and time to biopsy and breast cancer treatment initiation after a high-risk tele-mammography result among women participating in

this national program and sought to understand women's experiences seeking diagnostic and treatment services.

## METHODS

### Study setting

In Peru, individuals living in poverty receive government-subsidized insurance, known as the Comprehensive Health Insurance (SIS). In 2012, breast cancer care (diagnosis, treatment, and palliative services) was added to the SIS health package;[7] however, most services remain centralized in Lima, where they are provided by the National Institute of Neoplastic Diseases (INEN).[8] Outside Lima, two regional cancer institutes and some general hospitals offer cancer services on a varied and limited basis. When services are not available at one of the general hospitals, patients are referred to the regional cancer institute or to INEN.

Peru's MOH tele-mammography program is the primary mammography provider among SIS recipients and as of September 2018, 14 hospitals in 11 regions participated in the program. At these hospitals, the cancer program staff conduct mammography testing, result reporting, follow-up, and referrals. Asymptomatic women aged 50 to 69 years old are invited for screening through routine clinical visits or community outreach activities. Symptomatic women may be referred for a diagnostic mammogram. Digital images are transferred securely via the internet to a reading center in Lima, where trained radiologists provide a result within a few days. Following international guidelines, individuals with a Breast Imaging Reporting and Data System (BI-RADS) result of 4 or 5 are supposed to be referred for biopsy.[9] If cancer is diagnosed, treatment is planned, including referrals, as needed.

## Study design

We conducted a mixed-methods study with a concurrent design.[10] We described the frequency and time required for biopsy and treatment initiation, and qualitatively explored the factors impeding and facilitating care.

## Study population

Quantitative component

We conducted a retrospective review of data collected from all women aged ≥18 years with SIS insurance, who had a tele-mammography through the MOH program between July 2017 and September 2018 and obtained a high-risk result.

Qualitative component

We used purposeful sampling to identify and interview 32 key stakeholders comprised of women with a high-risk tele-mammography result, healthcare providers (cancer program nurses and midwives, and physicians from the hospital oncology services), hospital program coordinators supervising the program, and current or former staff of the MOH directly involved in health policy and supervision of cancer activities, nationally. We included women known to have experienced barriers to obtaining care and women who obtained care more easily; all of them had undergone a mammography through the tele-mammography program. 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. To ensure we had perspectives from different part of the country, informants from diverse geographical areas of the country were selected.

**Key procedures**

Quantitative component

*Data sources:* Tele-mammography results and basic demographic information were obtained from the tele-mammography reading center in Lima (Villa El Salvador Hospital). Because there was no national database for tracking patients along the breast cancer continuum of care, person-data on biopsy and treatment were extracted from three independent data sources using the national identification number of each subject: SIS electronic databases, the National Cancer Surveillance registry of Peru's Center for Control of Diseases (CDC), and INEN medical electronic and paper records. Access to these data sources was requested to the corresponding institutions. These data sources include diagnostic procedures, biopsy results and treatments. Data from SIS, CDC, and INEN were available through December 31st, 2018; November 1st, 2019; and January 15th, 2020; respectively. Thus, each woman was followed for a minimum of 90 days and a maximum of 470 days following mammography. (Figure 1)

*Outcomes:* A high-risk tele-mammography result was defined as a BI-RADS result of 4 or 5.[11] The biopsy rate was defined as the proportion of women with a high-risk tele-mammography result who had evidence of a breast biopsy documented in the available data sources. The treatment initiation rate was defined as the proportion of women with confirmed breast cancer who had evidence of initiating chemotherapy, surgery, radiation, or hormonal therapy.

We calculated the time to biopsy and treatment initiation among those who secured these services. Adapting definitions from a consensus statement,[12] we defined the diagnosis interval as the time from tele-mammography result to biopsy result, the treatment interval as the time from biopsy result to treatment initiation, and the health system interval as time from tele-mammography result to treatment initiation. For each interval, we calculated the proportion of women that experienced delays. Because delays >90 days from breast cancer symptom discovery to treatment initiation correlate with advanced stage at diagnosis and worse survival,[13, 14] we defined a health system delay as a health system interval >90 days, and diagnosis and treatment delays as >45 days. We calculated the frequency of women with suboptimal care, defined as the presence of biopsy or treatment delay or the absence of biopsy or treatment despite the indication.

Qualitative component

*Data collection:* We conducted individual, in-depth interviews using semi-structured interview guides to explore the barriers and facilitators to biopsy or treatment initiation. For women with a high-risk tele-mammography, topics included the experience of pursuing and following referral for care; strategies for overcoming difficulties in seeking care; and recommendations for improvement. Interviews with healthcare providers and administrators explored how breast cancer care is administered and delivered; program strengths and weaknesses; and recommendations for improvement. The first author (RE) conducted face-to-face interviews in Spanish (local language and RE's native language). Interviews lasted approximately 50 minutes and were audio-recorded and transcribed verbatim.

## Data analysis

Quantitative component

Data was cleaned thoroughly by RAE using Stata v14 and supervised by MFF. We reported descriptive statistics and analyzed data using Stata v14. We examined time intervals to biopsy and treatment both as continuous variables and also as binary variables to identify the proportion of women experiencing delays in care.

Qualitative component

We conducted content analysis on the transcripts uploaded to Dedoose.[15] A subset of interviews was open coded using short descriptive labels from which the first codebook draft was constructed. The draft codebook was piloted in a separate subset of interviews; codes were added, eliminated, or merged to create the final version used to code the dataset. The coded data were inductively analyzed to identify key themes related to the barriers and facilitators for obtaining a biopsy or initiating treatment. Using an iterative approach, the draft themes were revised, resulting in a set of final themes. Illustrative quotes for each theme were extracted and translated into English.

## Patient and public involvement

Patients were not involved in the development of the research question or in the design, recruitment or conduction of the study. Personnel from the Ministry of Health were involved in study design and recruitment. Results will be disseminated among the Ministry of Health staff.

## Ethical considerations

The study protocol and instruments were approved by Institutional Review Boards from Harvard Medical School (IRB19-0589), Cayetano Heredia Peruvian University (#104252), INEN (INEN 20-02), and Villa El Salvador Hospital (#01744-2019). For the quantitative component, the informed consent requirement was waived. Participants in qualitative interviews provided written consent. Women with high-risk mammography results participating in the interviews received 6 USD for time and transportation compensation.

## Role of the funding sources

The funding sources did not play any role in the study design; in the collection, analysis, and interpretation of the data; in writing of the report; nor in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

# RESULTS

## Quantitative findings

Biopsy and treatment initiation rates and delays

From July 1st, 2017 to September 30th, 2018, 6899 tele-mammography tests were conducted through the MOH services. Of these, 147 (2.1%) women had a high-risk mammography result (72.8% with BI-RADS 4 and 27.2 with BI-RADS 5). After the exclusion of 21 individuals with data discrepancies or who did not meet the inclusion criteria (Figure 2), 126 women were included for analysis (71.4% with BI-RADS 4 and 28.6% with BI-RADS 5). Their mean age was 53.3 years (standard deviation: 11.3).

We found evidence of biopsy in 62/126 (48.4%) women (Figure 2). Of these, biopsy result dates were available in 48, of whom 18 (37.5%) experienced a diagnosis delay (median diagnosis interval = 39.5 days) (Table 1). Among the 62 women with evidence of biopsy, 49 had data on where the procedure was performed, and in 32 (65.3%) it took place in a different region from where they lived.

**Table 1. Time intervals and delays between mammography, biopsy and treatment initiation among 126 women with a high-risk tele-mammography result who obtained this care**

| Time interval | Median days (IQR; range) | Delay n (%) |
|---|---|---|
| **From tele-mammography result to biopsy result** (n=48, N=62) | 39.5 (25.5-65; 7-263) | 18 (37.5) |
| **From biopsy result to treatment initiation** (n=39, N=44) | 65.3 (32-118; 8-416) | 27 (69.2) |
| **From tele-mammography result to treatment initiation** (n=44, N=44) | 109.5 (69.5-168; 10-442) | 29 (65.9) |

N= total number of women who completed the corresponding step
n= number of women with dates available

Of the 62 women who had a biopsy (67.7% with BI-RADS, 51 were diagnosed with breast cancer, four had a benign condition, and seven did not have a result in their medical record. Of the 35 women who had BI-RADS 4 mammography results and had a known biopsy result, 85% were found to have breast cancer, while among the 20 women with BI-RADS 5 mammography results and documented biopsy, 100% had breast cancer. Of those diagnosed with breast cancer, we found evidence that 44/51 (86.3%) initiated treatment. Of these, the dates of the biopsy results and treatment initiation were available in 39, of whom 27 (69.2%) experienced a treatment delay (median treatment interval = 65.3 days) (Table 1). Among the 44 women with evidence of treatment, data about the treatment hospital was missing for one individual; of the 43 remaining, 35 (81.4%) initiated treatment in a different region than where she lived. Health system delays were observed in 29/44 (65.9%) women (median health system interval = 109.5 days) (Table 1). Excluding 14 individuals with missing dates, 104/112 (92.4%) women appeared to have received suboptimal care.

**Qualitative findings**

Study population

We interviewed 32 people: 13 women with a high-risk tele-mammography result, 13 healthcare providers, three hospital program coordinators, and three policymakers. See table 2 for details on the geographic areas were informants belonged to.

**Table 2. Characteristics of the 32 in-depth interview participants**

| | Patients | Providers | Program coordinators | Policymakers |
|---|---|---|---|---|
| **Provenance** | | | | |
| *Lima (capital)* | - | 4 | - | 3 |
| *Coast (North)* | 3 | 1 | 1 | - |
| *Highlands (Center)* | 3 | 2 | 1 | - |
| *Highlands (South))* | 4 | 4 | - | - |
| *Rainforest (East))* | 3 | 2 | 1 | - |

Findings

Undergoing biopsy and initiating breast cancer treatment was impeded by several factors clustering around three primary themes: A) the toll of getting care in major cities following referrals, B) patients' misconceptions and access to information, and C) administrative and operational barriers. Some of these factors primarily affected the diagnosis interval, others influenced mainly the treatment interval, while others impacted both intervals. This relationship is illustrated in Figure 3. Although scarce, a few facilitators were identified and are detailed in a fourth theme, D) facilitators.

*Theme A: The toll of getting care in major cities following referrals*

Insufficient financial resources and support for transportation, accommodation, and food

Referral to a hospital in a major city at some point during follow-up was inevitable for almost all patients living outside of Lima. Informants agreed that most women could not afford the transportation, housing, and food expenses associated with residence outside of their hometowns. Patients mentioned that they did not receive any subsidy from SIS for these expenses. Providers

and administrators perceived these constraints as preventing patients from receiving care. (Table 3, quote #1)

Interviewees highlighted the need to find external sources of financial support. Sometimes families organized fundraising activities. Other times, non-profit organizations, churches, or local municipalities provided financial support for transportation or living expenses; however, interviewees agreed that these resources were limited due to restricted budgets and prioritization of other vulnerable populations such as pediatric patients. (Table 3, quote #2). The economic burden of these expenses forced families to take out loans and/or sell assets (Table 3, quote #3).

Being away from family and friends' emotional support

Close relatives and friends were a vital source of motivation and emotional support as patients sought breast cancer care. Patients noted that the presence of loved ones transmitted confidence. Interviewees acknowledged that this accompaniment was essential, especially around the time of diagnosis. (Table 3, quote #4)

When patients left their hometowns to reside in the cities, this support was frequently diminished. Patients described how the cost of travel and competing responsibilities prevented loved ones from accompanying them. Providers and administrators referred that the weakened support network put patients at risk of withdrawing from care. (Table 3, quote #5)

**Table 3. Barriers and facilitators for obtaining a biopsy and initiating treatment after a high-risk tele-mammography result**

| Theme | Subtheme | Excerpts |
|---|---|---|

| | | |
|---|---|---|
| A. The toll of getting care in major cities following referrals | Insufficient financial resources and support for transportation, accommodation, and food | **Quote #1:** *They have to assume the expenses; they have to. So, often, because of the little money that they have, they don't go [to the city].* [midwife, highlands] |
| | | **Quote #2:** *There are some shelters here where patients can stay, but they have limited access for a group of patients; first the pediatric patients and then the rest.* [physician, Lima] |
| | | **Quote #3:** *We sold some animals. On the farm, we had sheep, cattle, and we sold everything, even the land we had to sell, to save her. If we hadn't made those efforts, my wife wouldn't be alive now. We did it to save her.* [patient's husband, highlands] |
| | Being away from family and friends' emotional support | **Quote #4** *Interviewer: How important do you think family support is during this time [before having the biopsy]?* *Interviewee: Well, you are desperate, you feel like dying, but they talk to you, they talk with you. They give you support, psychological support. It's as if they were saying, "Mom, you are not alone; you are with me".* [patient, highlands] |
| | | **Quote #5** *Interviewee: If they come from the provinces, they come alone. They can't come with all their family. Or they come to the first consult with a relative, and then they say things like "well, he is my husband, but he has to go back to my town to take care of my children." And they leave. That's the reality of the people who come from the provinces outside of Lima.* *Interviewer: How does it affect care?* *Interviewee: It affects care because the patient must think twice before continuing care. Either she abandons it or comes irregularly.* [physician, Lima] |
| | Challenges adjusting to and navigating the city | **Quote #6** *The cultural shock [of going to the city] is very strong. They feel overwhelmed; sometimes so overwhelmed that they prefer to leave care and go back to their towns.* [physician, highlands] |
| B. Patients' misconceptions and access to information | Misconceptions about breast cancer manifestations and progression | ***Quote #7*** *I did not give it too much importance because I did not have any pain. I thought that maybe they were wrong. I didn't give it importance, so I didn't do anything.* [patient, highlands] |
| | | **Quote #8** *Patients say that [having a biopsy] is worse, because when they prick you or take a piece of your breast that's when the cancer awakens. And that's why they don't want to have the biopsy.* [nurse, highlands] |
| | Misconceptions about the treatment | **Quote #9** *When you tell someone she has breast cancer, the first thing they think of is that it is daño (a sort of witchcraft), so they go first to the shamans and later, if they continue feeling sick, they come back.* [program coordinator, rainforest] |
| | Misconceptions about the prognosis | **Quote #10** *Many times, I've heard that when you have cancer you have it until the end. You just have to wait for your death. Once you have it there is no cure.* [patient, highlands] |
| | Limited information provided about the disease | **Quote #11** *I would have liked for them to explain it to me more thoroughly, perhaps that way I would have gone, it would have encouraged me. Because sometimes, when they explained to you well, you are conscientious and go. But if they give you a test result that only says get another test because the first test wasn't normal, you don't give it adequate importance. […] They didn't say anything more than giving you a number, where I should go, and all of that.* [patient, highlands]. |
| | Delays for obtaining appointments and tests | **Quote #12** *Interviewer: What happened the day that you went to the hospital? How did it go?* *Interviewee: I went very early, very early, but the line was already long, and as I needed to work, I got fatigued and didn't go back. So, I haven't done the test. Nothing. I left it there.* [patient, highlands] |
| | | **Quote #13** *For these tests, they have to come one day and for these others another day. And that's how the time passes by. […]. So sometimes when they are told to do one more test they say "Miss, I've been there, three months have passed, and I haven't started treatment yet".* [nurse, highlands] |

| | | |
|---|---|---|
| C. Administrative and operational barriers | Low awareness of the program or of its guidelines among providers | **Quote #14**<br>*We had a patient with BI-RADS 4 who needed a biopsy, but the closest hospital didn't have biopsy services. So, we coordinated to refer her to a regional cancer center. After a lot of insistence, they could transfer her to the regional cancer center, and it happens that when she arrives at the facility, they ordered a repeat mammography.* [policymaker, Lima] |
| | Lack of standardized referral pathways | **Quote #15**<br>*Interviewer: Did they ask you if you wanted to go to [region X] instead of Lima?*<br>*Interviewee: No, they didn't say anything. If I had known that in [region X] they had chemotherapy, I wouldn't have gone to Lima, because I didn't have enough money or someone to help me. If I knew they had it here, I would have stayed.* [patient, coast] |
| | Inconsistent tracking of patients | **Quote #16**<br>*Interviewer: What type of follow-up do you do here?*<br>*Interviewee: Once they have a biopsy in the [local] hospital, and it comes back positive, they call the patient or her primary care center to inform her of the result. They talk with the patient to see what's best: to send her to [the regional hospital] or Lima […]*<br>*Interviewer: And what happens once they are referred?*<br>*Interviewee: We don't do further follow-up. I'd be lying if I say we do. We don't do more follow-up.* [program coordinator, coast] |
| | | **Quote #17**<br>*The systems are divorced; they are not integrated. So, you are taking mammography tests but there is not a structure that integrates the screening with the treatment or with the diagnosis.* [policymaker, Lima] |
| D. Facilitators | Having family or a friend living in the city | **Quote #18**<br>*They say: "I don't worry much about the stay, Miss, I have family there." The majority that wants to go to [a major city] is because they have family there.* [midwife, coast] |
| | Collaborative and family-inclusive explanation | **Quote #19**<br>*The psychologist has helped me a lot […] The psychologist is part of your disease, [the psychologist] cheers you up. It is not only the doctor who helps, the psychologist too. [The psychologist] talks with you in a particular way and makes you understand.* [patient, highlands] |
| | | **Quote #20**<br>*Interviewer: How do you convince them [to obtain a biopsy]?*<br>*Interviewee: Taking your time and explaining kindly. Sometimes the patient accepts [undergoing biopsy], but the relative doesn't, so you need to explain it all to the family, too. […] You need to explain to every one of them because in their way of living, all the family influences, and then they accept.* [physician, highlands] |
| | Facilitated appointments | **Quote #21**<br>*Interviewer: How do patients from other regions get care here?*<br>*Interviewee: They just come and get an appointment. Here in the oncology department, we have a system that we called 'unlimited appointments.' We give an appointment to everyone who arrives before 9:00 a.m.*<br>*Interviewer: What day is the appointment?*<br>*Interviewee: For the same day. So, they don't have to come back another day.* [physician, highlands] |

## Challenges adjusting to and navigating the city

For some patients, residence in a metropolitan area represented a major cultural change and logistical challenges. Informants described how many patients pursuing care in the cities were accustomed to country life. Living in and navigating a new city, at times in a different language,

was perceived by providers and program coordinators as a “cultural shock” for patients which interfered in their care. (Table 3, quote #6)

*Theme B: Patients' misconceptions and access to information*

Misconceptions about breast cancer manifestations and progression

Some misconceptions about how breast cancer manifests and progresses contributed to delays in pursuing a biopsy. For example, a high-risk mammography result was recognized as serious by some patients but denied by others in the absence of symptoms, preventing them from seeking further care. (Table 3, quote #7) Other patients felt that touching or manipulating the breast "awakens" the disease, preferring to "let it rest" instead of obtaining a biopsy. (Table 3, quote #8)

Misconceptions about treatment

Providers reported that women looked for therapies with herbs and shamans as their first treatment option. They felt that this caused disengagement from facility-based health care with women returning only when no improvement was seen with this traditional treatment, at which point symptoms had often worsened. (Table 3, quote #9)

Misconceptions about the prognosis

Prior experiences with breast cancer led some women to perceive the disease as a non-curable condition. Whether because they had heard or seen others' fatal experiences with breast cancer,

many women expressed feeling that the ultimate outcome of breast cancer was certain death (Table 3, quote #10). This conception of breast cancer made some women question the utility of treatment, creating delays for accepting care.

Limited information provided about breast cancer

Many patients noted the limited information about mammography findings, breast cancer treatment and prognosis communicated to them by the clinical team. Instead, they felt that communication was focused on conveying information about the next administrative steps. As some referred, a better explanation would have led to making good choices earlier. (Table 3, quote #11)

*Theme C: Administrative and operational barriers*

Delays in obtaining appointments and tests

Informants relayed difficulties in obtaining appointments. For example, in "first come, first served" medical services, many had to arrive at the facility very early in the morning and wait in long lines without the guarantee of an appointment that day. Some women expressed frustration with this process, noting that it led them to discontinue seeking care. (Table 3, quote #12)

When appointments could be booked in advance, they were often scheduled for several weeks later, with test results delayed up to a month or more. One nurse described a patient's onerous experience trying to complete the tests requested (Table 3, quote #13).

Limited awareness of the program among providers

Not all physicians reported awareness of the MOH tele-mammography program. Those unfamiliar with the program doubted the validity of mammography results (thinking that they were reported by untrained radiologists) and usually ordered a second mammography at their hospital. (Table 3, quote #14) In other cases, the cancer program's nurses and midwives wanted to "double check" each abnormal tele-mammography result so they would order a breast ultrasound before referring for biopsy, contrary to national guidelines. These extra procedures contributed to delays and the administrative burdens on the patient.

Lack of standardized referral pathways

There is no formal standardized referral pathway for high-risk tele-mammography results. The providers' choice of referral hospital, particularly for treatment, was usually based on his/her perceptions of available services or quality of care. As noted by most informants, INEN was often the hospital of choice. Policymakers agreed that this approach did not take advantage of the resources available at closer regional hospitals. One woman's comment illustrated how this system failed to account for patients' convenience. (Table 3, quote #15)

Inconsistent tracking of patients

The follow-up of women did not occur uniformly along the continuum of care. While the cancer program staff closely followed patients who received care in the local hospital, program

coordinators agreed that tracking patients in upper-level hospitals was less rigorous. (Table 3, quote #16)

The programmatic follow-up tool, created by the MOH to strengthen tracking activities, was not used consistently and scarcely monitored by the MOH officials. In addition, policymakers reported that tracking of patients through health information systems would not be possible due to a "divorce" between the MOH's and hospitals' digital data systems (Table 3, quote #17).

*Theme D: Facilitators*

Having family or a friend living in the city

Interviewees expressed that having a relative or a close friend living in the city where patients were referred facilitated access to care. When patients could stay with friends or family, it alleviated much of the financial hardship. (Table 3, quote #18) Also, patients felt secure in knowing that someone could help them navigate the city or take care of them once treatments started.

Collaborative and family-inclusive approaches to care

Addressing patients' concerns about breast cancer through a multidisciplinary approach was seen by providers as useful for improving the patient's understanding of the disease and for making prompt medical decisions. Collaborative work among clinicians, psychologists, and social workers facilitated communication around diagnosis and expectations for future care. Patients highlighted the benefit of receiving psychological support upon diagnosis (Table 3, quote #19),

Providers emphasized that involving the family was necessary given its determinant role in health decision making. (Table 3, quote #20)

Facilitated appointments

Some hospitals and providers expedited appointments for their patients. In two hospitals, the medical appointments were scheduled within one day for patients coming from remote areas. In another, all patients arriving early were guaranteed to be seen that day. In other cases, providers coordinated appointments to reduce the administrative burden on the patients or leveraged their influence to secure a spot. These approaches, although not perfect, helped reduce appointment delays. (Table 3, quote #21)

## DISCUSSION

We evaluated linkages to breast cancer diagnostic and treatment services in the largest national tele-mammography program in Peru. This adds to the very limited body of literature examining linkages to care among women undergoing breast cancer screening in a middle-income country. Identifying health system requirements for rapid breast cancer diagnosis is a priority for the World Health Organization's new Global Breast Cancer Initiative,[16] and our findings contribute to understanding of important barriers and facilitators of timely diagnosis in Peru and similar settings. In women with a high-risk tele-mammography result among whom biopsy is indicated, we found evidence that biopsy was performed among fewer than half. Among women with breast cancer, we found evidence of treatment initiation in 86.3%. Delays in obtaining these

services were common. Overall, the vast majority (92.4%) of women experienced suboptimal care (delayed care or no evidence of linkage to care). Our quantitative findings are complemented by qualitative evidence of substantial barriers to care. Through a mixed-methods design, we elucidated the ways in which diagnosis and treatment services for breast cancer were not easily accessible for women living in poverty throughout the country. These included travel barriers, administrative obstacles, and patients´ misconceptions about breast cancer.

In our study, many women with breast cancer did not have evidence of biopsy or treatment, and centralization of cancer services in Lima and a few other major cities likely contributes to delays and interruptions in care. Living outside Lima and/or in rural areas of the country has been shown to place individuals with cancer at higher risk of discontinuing care.[17, 18] Centralization of cancer care facilities has also been found to disproportionately affect socioeconomically vulnerable populations and may contribute to persistent care disparities for breast cancer care in LMIC.[19-21] In our study, although cancer services were offered free-of-charge, patients lacked the means for traveling to obtain those servicers. According to the National Cancer Control Plan, SIS should subsidize the costs for transportation and for staying in the cities; however, this economic support was not received by any of the patients interviewed. A recent study on cervical cancer in Peru highlighted the same policy-implementation gap in women with cervical cancer.[22] Given that five in ten women in Peru live in poverty (<150 USD per month),[23] our finding that insufficient economic resources for the expenses associated with centralized care in cities (e.g., transportation, accommodation, and food) challenged care is not unexpected. Reducing inequalities for breast cancer care access in Peru must incorporate the existing free diagnostic and treatments services with decentralization of these resources to bring them closer to those that need them.

Among women for whom we could confirm care, delays were common. Our finding that 65% of women experienced a health system delay is consistent with reports from other LMIC, where over 70% of patients start treatment three or more months after the first abnormal finding (a high-risk screening mammography or symptoms discovery).[13] This finding is also supported by one local study reporting even longer health system delays (around 8 months), albeit under different circumstances and using different definitions.[24] Long health system delays leads to advanced disease stage, a known risk factor for death from breast cancer.[25] Efforts to decrease delays would be expected to increase breast cancer survival rates.

The observed 2% prevalence of BI-RADS 4 and 5 results found in our study is comparable to what would be expected for mammography screening.[26-28] And, while the percentage of BI-RADS 4 vs. BI-RADS 5 tends to be variable,[26, 28, 29] our finding that 73% percent and 27% of women had BI-RADS 4 and 5, respectively, was very similar to another Latin American study conducted in Brazil.[29] In contrast, among women with biopsy results, the positivity rate found for women with BI-RADS 4 (89%), was higher than the expected. While at least 95% of biopsies of BI-RADS 5 results are typically positive, this statistic is much lower, around 20-30%, for BI-RADS 4.[30, 31] While we cannot be certain, we do not believe this observation of our study is attributable to inadequate training, as radiologists from the tele-mammography program were employed by the MOH and read de mammographs in compliance with MOH guidelines and standards. Likewise, most biopsies of our study were taken at INEN, a national referral center for cancer, staffed with appropriately trained cancer pathologists. This is also unlikely an artefact of selection bias induced by missing data: the percentage of BI-RADS 4 vs BI-RADS 5 results were comparable between women with and without evidence of biopsy. Nonetheless, this high positivity rate for malignancy for BI-RADS 4 results merits further research. This is especially

true given that many women with BI-RADS 4 did not have record of biopsy and therefore may remained undiagnosed and untreated, supporting the need for a robust tracking information system.

Our results raise several opportunities to improve the outcomes of the tele-mammography program by facilitating follow-up care and decreasing delays for those with a positive mammography. Patient tracking could be improved by implementing a unified health information system that tracks patients across the different public hospitals, allowing an accurate, full, and even real-time patient follow-up.[32, 33] Specifically for this breast cancer program, the tracking system should be a digital platform that enables data entry at the care steps (mammography, result, and patient reporting; biopsy referral, biopsy, result, and patient reporting; treatment referral, initiation, and completion), at the different public healthcare facilities and even at private hospitals, enabling also the calculation of the time elapsed between steps. Appointment systems could be reconsidered to prioritize a patient-centered approach. Low compliance to guidelines among the MOH's providers could be remedied by nationwide campaigns to build awareness of the program, its processes and goals. Finally, our data suggest some misconceptions about breast cancer treatment and prognosis. The source of these misconceptions is likely multifactorial and includes an unawareness of the success of breast cancer treatment when diagnosed and treated promptly. Thus, multidisciplinary and culturally tailored patient education, incorporating family members or supporters as appropriate, and continued work to ensure access to effective diagnosis and treatment, may correct misconceptions about breast cancer that contributed to delays and discontinuation seeking care. Overall, a real comprehensive tele-mammography program should not be seen as a separate breast cancer service but as part of the whole breast cancer continuum of care.

Evaluating breast cancer care using routinely collected data was challenging due to a lack of integration of health information systems of the different MOH components that managed and provided healthcare to the population subsidized by SIS. Although we used multiple national data sources to capture care access through different pathways, due to varying levels of follow-up and data completeness, we may have underestimated the proportion of women who obtained care. Thus, the quantitative results presented here were our best intent to disentangle the current health information puzzle existing in the public healthcare sector. Nonetheless, this study is a comprehensive evaluation that used both quantitative and qualitive research techniques to understand the situation in diverse geographical settings in Peru. Although particular challenges of very hard to reach women living in more remote areas may have note been explored, this study provides a close perspective of challenges in Peru, which may be broadly applicable to other middle-income countries with similar resource levels and health systems.

The benefit of mammography screening can only be realized if women with abnormal findings are successfully linked to high-quality and timely diagnostic and treatment services. Our study underscores the need for strengthening the breast cancer diagnostic and treatment capacity of regional hospitals outside Lima to remove barriers and facilitate access to timely comprehensive breast cancer care. It also highlights the need for a strong patient education strategy and better dissemination of the information about the program among providers nationwide. A unified health information system is needed to allow better tracking of patients after the mammography and along the breast cancer continuum of care. This information system should be part of an overall breast cancer data management system that facilitates program monitoring, evaluation, and research to guide appropriate and timely public health decisions and locally tailored policy development. All in all, ensuring timely linkage to diagnosis and treatment for women with an

abnormal result in the tele-mammography program will be critical to securing the screening program's success.

## Contributorship statement

RAE, PJG and MFF conceptualized the study. RAE collected the data and wrote the first draft of the article. MFF, PJG, LEP, JTG, helped to synthesize evidence, interpret results, and critically revise the manuscript. RAE secured funding for the study. All authors approved the final draft.

## Competing interests

All authors declare no competing interests.

## Data sharing statement

No additional data is available

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Figures' legends

Figure 1.

——— Data available for SIS, CDC and INEN

– – – Data available for CDC and INEN

····· Data available for INEN

SIS, Comprehensive Health Insurance (government-based insurance); CDC, Center for Epidemiology and Control of Disease- National Cancer Surveillance registry; INEN, National Institute of Neoplastic Diseases

Figure 2.

ID, National Identification Number; SIS, Comprehensive Health Insurance (the government-subsidized insurance)

[I was requested to include a legend for Figure 3, but it does not have a legend, just a title which is already included in the Fig3 document]

**Figure 1. Availability of biopsy and treatment information from the three study data sources**

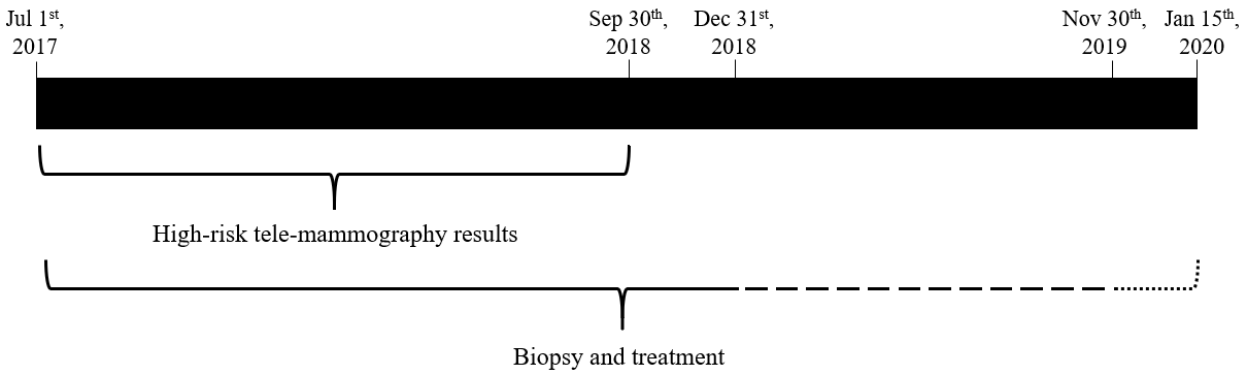


**Fig 2. Flowchart of biopsy and treatment initiation rates among women with a high-risk tele-mammography result**

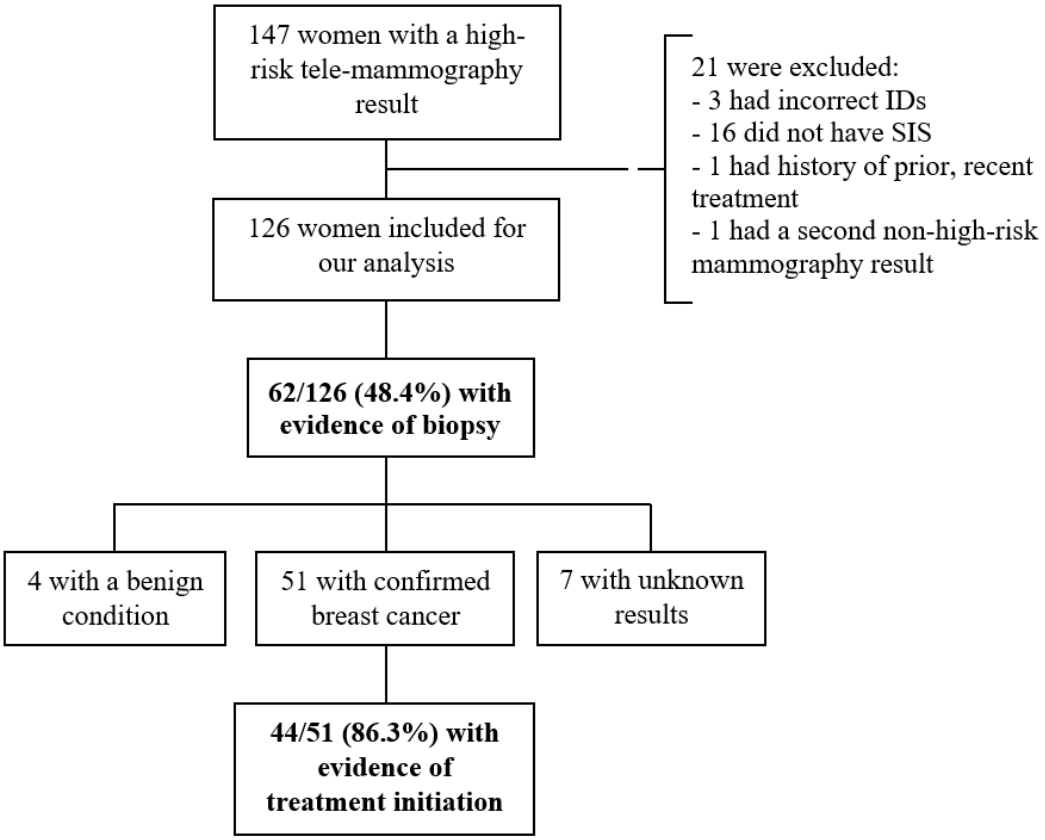
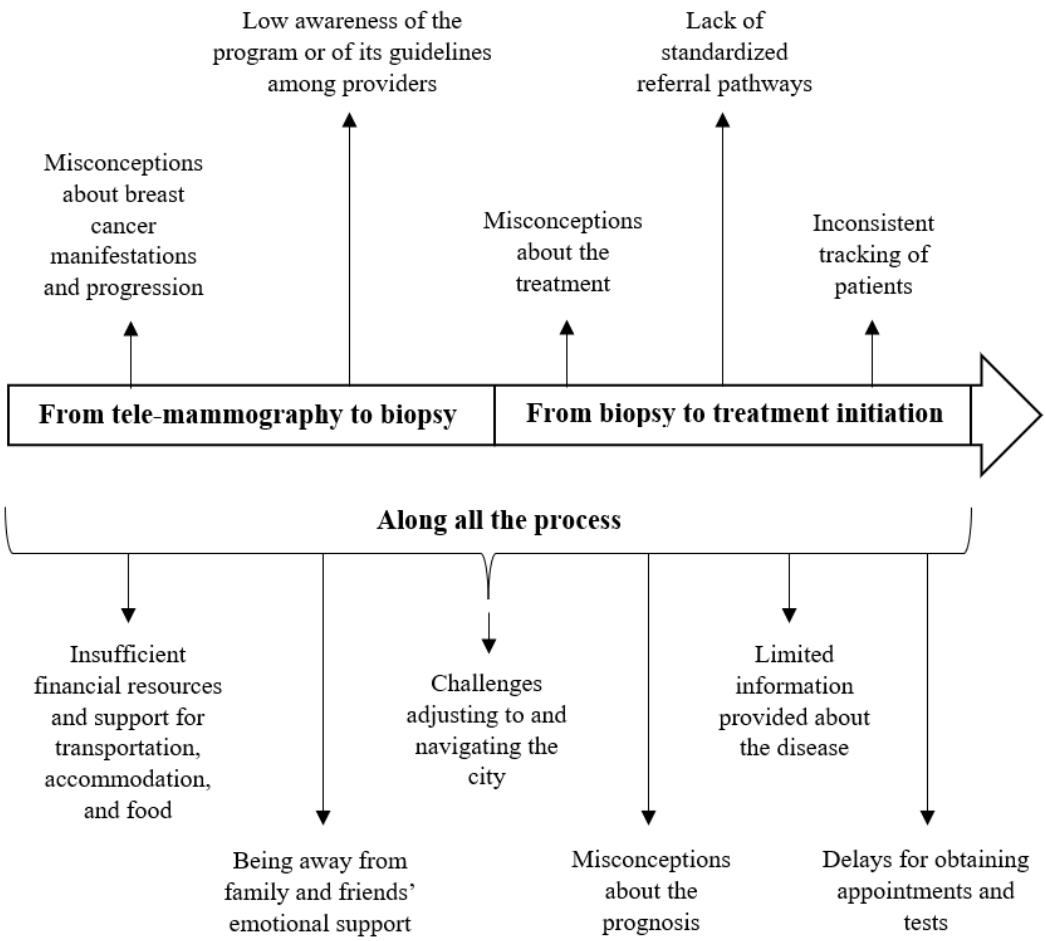


**Fig 3. Barriers for obtaining a biopsy and initiating treatment and related affected intervals after obtaining a high-risk tele-mammography result**



**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | 1.1 Abstract, 'setting' section (page 2)<br><br>1.2 Abstract, 'Participants' section (page 2)<br><br>1.3 Abstract, 'Setting' section (page 2) |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including | | | |

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| | | periods of recruitment, exposure, follow-up, and data collection | | | |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | 6.1. "Data sources" section (page 7)<br><br>6.2. No validation studies were conducted.<br><br>6.3. A graphic representation of the databases merge is included in Figure 1. |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | 7.1. No confounders or effect modifiers were included. Exposures and outcomes are explained in the "outcomes" section (page 7) |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details | | | |

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| | | of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | | | |
| Study size | 10 | Explain how the study size was arrived at | | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database | 12.1 ‘Data sources’ section. (page 7) |

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| | | | | population used to create the study population.<br><br>RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | 12.2 "Data analysis' section (quantitative component) (page 7) |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | 12.3 "Data analysis' section (quantitative component) (page 7) |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | 'Biopsy and treatment initiation rates and delays' section (page 10) |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | | | |

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| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over | 'Discussion' section (5th paragraph). |

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| | | | | time, as they pertain to the study being reported. | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | See 'Data sharing statement' (page 24) |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.