Original Article

Health System Delay and its Effect on Clinical Stage of Breast Cancer: Multicenter Study

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BACKGROUND: The objective of this study was to determine the correlation between health system delay and clinical disease stage in patients with breast cancer. **METHODS:** This was a cross-sectional study of 886 patients who were referred to 4 of the largest public cancer hospitals in Mexico City for the evaluation of a probable breast cancer. Data on time intervals, sociodemographic factors, and clinical stage at diagnosis were retrieved. A logistic regression model was used to estimate the average marginal effects of delay on the probability of being diagnosed with advanced breast cancer (stages III and IV). **RESULTS:** The median time between problem identification and the beginning of treatment was 7 months. The subinterval with the largest delay was that between the first medical consultation and diagnosis (median, 4 months). Only 15% of the patients who had cancer were diagnosed with stage 0 and I disease, and 48% were diagnosed with stage III and IV disease. Multivariate analyses confirmed independent correlations for the means of problem identification, patient delay, health system delay, and age with a higher probability that patients would begin cancer treatment in an advanced stage. **CONCLUSIONS:** In the sample studied, the majority of patients with breast cancer began treatment after a delay. Both patient delays and provider delays were associated with advanced disease. Research aimed at identifying specific access barriers to medical services is much needed to guide the design of tailored health policies that go beyond the promotion of breast care awareness and screening participation to include improvements in health services that facilitate access to timely diagnosis and treatment. ***Cancer* 2015;121:2198-206.**

KEYWORDS: breast cancer, clinical stage, delay, early diagnosis, time intervals.

INTRODUCTION

Although breast cancer (BC) is most common in high-income countries (HICs), most BC deaths occur in low and middle-income countries (LMICs).[1] This is mainly because diagnoses occur at more advanced stages.[2] The question that remains is why cancer patients are diagnosed in such advanced stages. Most study findings in HICs demonstrate an association between advanced clinical stages of BC and long times between symptom discovery and treatment start (total delay).[3] This interval has been broken into 2 main intervals, which have been studied independently: the patient interval, defined as the time between symptom discovery and the first medical consultation, and the health system or provider interval, defined as the time between the first medical consultation and the beginning of cancer treatment. Like total delay, patient delay >3 months is associated with more advanced-stage cancer and reduced survival.[3-5] The impact of health system delay on patient prognosis is less clear.[3,6,7]

There are few studies on this matter, and the variability of interval measurements complicates comparability. A Canadian study that analyzed the time from an abnormal screening mammography to the confirmation of cancer diagnosis reported a U-shaped distribution: intervals shorter than 4 weeks were associated with an increased risk of advanced-stage disease (first arm of the U); then, the risk diminished between weeks 4 and 20 (bottom part of the U); and, after 20 weeks, as time lengthened, the risk of advanced-stage disease increased linearly (last arm of the U).[8] Two additional studies in

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Germany and Thailand that included symptomatic patients reported a significant, bivariate correlation between provider delay and advanced clinical stage, although the analyses were not conclusive.[9,10]

The objectives of the current study were 1) to quantify the time intervals from the detection of a possible BC to the beginning of cancer treatment and 2) to determine the correlation between the prolongation of these intervals (delay) and advanced cancer stage. Our hypothesis was that not only patient delay but also health system delay is associated with advanced clinical stage.

Background

In Mexico, as in most Latin American countries, BC is the main cause of female cancer death.[1] Among the problems that contribute to the existing BC burden in Mexico are diagnosis in advanced stages, low coverage of screening mammography, limited access to treatment, insufficient physical and human resources for clinical care, and poor quality control of health services.[11,12] Cancer data in Mexico are scarce, because there is no national cancer registry, and time intervals for medical attention among patients with BC are unavailable except for a small sample study at a single institution.[13]

The Mexican health system is inequitable against the lower income groups and is fragmented into 3 sectors: 1) social security services, 2) services offered by the Ministry of Health (MoH), and 3) private services.[14] Public services generally are organized into primary, secondary, and tertiary care facilities. Health services covered by social security schemes are provided by different institutions. The largest of these is the Mexican Institute of Social Security (IMSS), which is available for the formally employed in the private sector and their families.[14] The IMSS covers approximately 30% of the population[15]; an additional 7% of the population is covered by other social security institutions[15]; and, in general, affiliates to 1 scheme cannot access the services provided by others.[16]

The MoH offers health services against payment of income-related user fees for the uninsured and without cost for those covered by Seguro Popular, which is a federal program that entitles its affiliates to an explicit list of health interventions, mainly health promotion, prevention, and primary care services.[17] In addition, the Fund for Protection Against Catastrophic Health Expenditures covers high-cost health interventions like BC treatment for the uninsured.[17] Approximately 37% of the Mexican population is covered by Seguro Popular, and 25% of the population is uninsured.[15]

Private services are available for those who can afford them and are heterogeneous in the variety and quality of services offered.[16] Only 1% of the population is covered by private health insurance.[15] Most of the uninsured resort to MoH facilities and pay out of pocket for services and pharmaceuticals in the private sector.[16]

MATERIALS AND METHODS

Study Design

We conducted a cross-sectional study of patients who were referred with a probable BC to 4 of the largest public cancer hospitals in Mexico City. The study protocol was approved by the research and ethics review boards of the National University (UNAM) and the participating institutions: the Mexican National Cancer Institute, the General Hospital of Mexico (HGM), and the IMSS.

Study Participants

Both the Mexican National Cancer Institute and the HGM depend on the Health Ministry and offer BC services without cost to uninsured BC patients through the Fund for Protection Against Catastrophic Health Expenditures. They are 2 of the largest cancer services in the entire country. Both the IMSS National Hospital of Oncology and the IMSS Hospital of Gynecology and Obstetrics Number 4 offer BC medical services for women who are insured by the IMSS. The Hospital of Gynecology and Obstetrics Number 4 is a second-level care facility that also offers diagnostic studies and surgical treatment for BC. Patients who require chemotherapy and/or radiotherapy are referred to the National Hospital of Oncology, which offers the full spectrum of cancer care services.

All new patients with suspected BC were candidates to participate in the study. Reasons for exclusion and elimination are summarized in Figure 1.

Measures of Time Intervals

The time interval definitions we used agree with the majority of studies on BC delay, recent recommendations of a consensus,[18] and applicability for use in the context of a fragmented health system like that in Mexico. The *total interval* is defined as the time from identification of the problem (either through symptoms or screening) to the beginning of cancer treatment. The *patient interval* is defined as the time between identification of the problem and the first medical consultation. The *provider or health system interval* is defined as the time from the first medical consultation to the beginning of cancer treatment (although use of the term "provider" has been more widespread in the literature, we prefer the use of "health

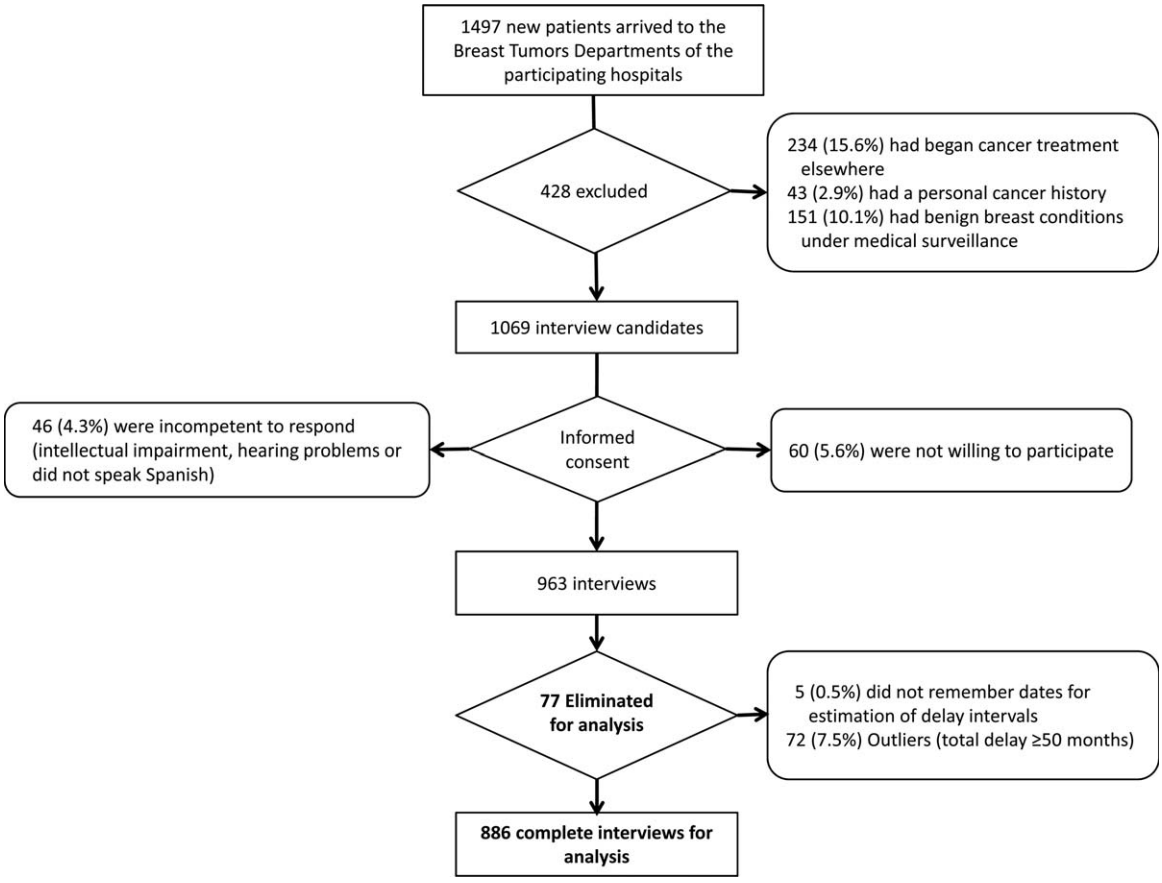

Figure 1. Inclusion, exclusion, and elimination criteria are illustrated for the current study.

system," because it better describes this interval in the Mexican context, in which patients typically receive care from different practitioners and different facilities). The *diagnosis interval* is defined as the time from the first medical consultation to cancer confirmation by histopathology. The *treatment interval* is defined as the time between diagnosis and the beginning of oncologic treatment (surgery, chemotherapy, radiotherapy, hormone therapy, or target therapy). The *prehospital interval* is defined as the time from the first medical consultation to arrival at the cancer service. The *in-hospital interval* is defined as the time between the first consultation at the cancer service and the start of treatment.

Data Collection

A validated questionnaire was used to measure dates for the estimation of time intervals.[19] The questionnaire was administered through face-to-face interviews conducted by trained interviewers in private rooms at the hospitals. The interviews took place at the Mexican National Cancer Institute between July 2009 and June 2010, at HGM between January and December 2010, and at both IMSS hospitals between October 2010 and May 2011. To minimize recall bias, study participants were asked to remember dates with the aid of a calendar. Information on final diagnosis, cancer stage, and dates of diagnosis and treatment start was extracted from patients' hospital records.

Statistical Analysis

Descriptive statistics were estimated for all variables. Kaplan-Meier curves were estimated for the total interval by clinical stage. Treatment start was considered the censoring event, and a Cox regression model was used to evaluate the significance of differences in interval lengths between different stages. Finally, we used logistic regression analysis to estimate the average marginal effects of patient and health system delays on the probability of being diagnosed with advanced-stage BC (stages III and IV). Standard errors were clustered at the hospital level. The following factors were controlled for: means of problem identification (symptoms vs screening), patient age, school education (<9 years vs >9 years), house

TABLE 1. Demographic and Disease Information

Variable	No. of Patients (%)	Total No. (%)
Age, y		
Mean ± SD [range]	50.9 ± 13.7 [18-91]	886 (100)
<40	158 (17.8)	
40-49	287 (32.4)	
50-59	211 (23.8)	
60-69	140 (15.8)	
≥70	90 (10.2)	
Education, y		
<6	194 (21.9)	886 (100)
6	176 (19.9)	
7-9	189 (21.3)	
>9	327 (36.9)	
Occupation		
Housewife	494 (55.7)	886 (100)
Employed	392 (44.3)	
Monthly family income		
≤3 Minimum wages[a]	474 (53.5)	886 (100)
3-5 Minimum wages	158 (17.8)	
6-8 Minimum wages	122 (13.8)	
Did not respond	132 (14.9)	
State of residence		
Mexico City DF	507 (57.2)	886 (100)
State of Mexico	230 (26.0)	
Other states	149 (16.8)	
Hospital of care		
INCAN	475 (53.6)	886 (100)
HGM	205 (23.2)	
IMSS Oncology Hospital	96 (10.8)	
IMSS Clinic of Gynecology	110 (12.4)	
Means of problem detection		
Patient self-discovery	670 (75.6)	886 (100)
Screening CBE or mammogram	216 (24.4)	
Final diagnosis		
Cancer	597 (67.3)	886 (100)
Benign disease	289 (32.7)	
Cancer stage		
0-I	82 (13.7)	597 (100)
II	214 (35.8)	
III	212 (35.6)	
IV	49 (8.2)	
Unknown	40 (6.7)	

Abbreviations: CBE, clinical breast examination; DF, Federal District; HGM, Mexican General Hospital; IMSS, Mexican Institute of Social Security; INCAN, Mexican Cancer Institute, SD, standard deviation.
[a] The minimum wage in Mexico is approximately 5 US dollars per day.

ownership, state of residence (Mexico City vs other states), and religion (Catholic vs other). We controlled for hospital fixed effects and interviewer fixed effects. Income was excluded because it had colinearity with school education.

RESULTS

In total, 1497 new patients arrived at the breast departments of the participating hospitals for study of a suspected BC. Of these, 1069 of 1497 patients (71.4%) were good interview candidates, 963 of 1069 (90.1%) were interviewed, and 886 of 963 (92%) were included in the current analysis (Fig. 1). Demographics as well as the patient, prehospital, and diagnosis intervals were available for all participants (Table 1); clinical stage for 557 of 597 patients with confirmed BC diagnosis; and the total, health system, treatment and in-hospital intervals were available for 540 of the 597 BC patients (90.4%) who received treatment at the participating institutions.

The median durations of intervals were 7 months for the total interval, 10 days for the patient interval, and 5 months for the health system interval (Fig. 2). Nearly 90% (484 of 540 participants) experienced total delays >3 months, and 57% (308 of 540 participants) experienced total delays >6 months. The greatest delays occurred between the initial medical consultation and diagnosis confirmation, with a median interval of 4 months. In 73.7% (546 of 850 participants), the diagnosis interval was >3 months; and, in 36% (306 of 850 participants), it was >6 months.

Longer total delays were associated with more advanced cancer stages in the bivariate analysis (Fig. 3). The Cox regression hazard ratios indicated that, compared with patients who had stage I BC, those with stage II, III, and IV BC had 24%, 42%, and 45% less probability, respectively, of beginning treatment at any point in time (Table 2).

The logistic regression analysis (Table 3) indicated that the most important risk factor for advanced cancer was identification of the problem through symptom discovery compared with screening. In addition, both patient and provider delay and the patient's age were significant. With all other variables being held constant, identifying the problem through symptom discovery instead of through screening caused a 31% average increase in the probability of beginning treatment in advanced stages (III and IV) versus early stages (0, I, and II). For every increase of 1 month in the patient interval, there was a 1.8% rise in the probability of beginning cancer treatment in advanced stages, whereas each increment of 1 month in the provider interval increased this probability by 1%. Finally, for every additional year of the patient's age, the probability of starting treatment in advanced stages diminished by 0.4%. Note that these results were upheld after controlling for hospital and interviewer fixed effects (see Table 3, column 4). Hence, we can rule out the possibility that the effects of patient and provider intervals on advanced clinical stage could have been because of systematic differences between hospitals or interviewers.

Figure 4 illustrates the predicted probability of advanced cancer stage as a function of patient delay and health system delay. In our sample, if a patient delayed

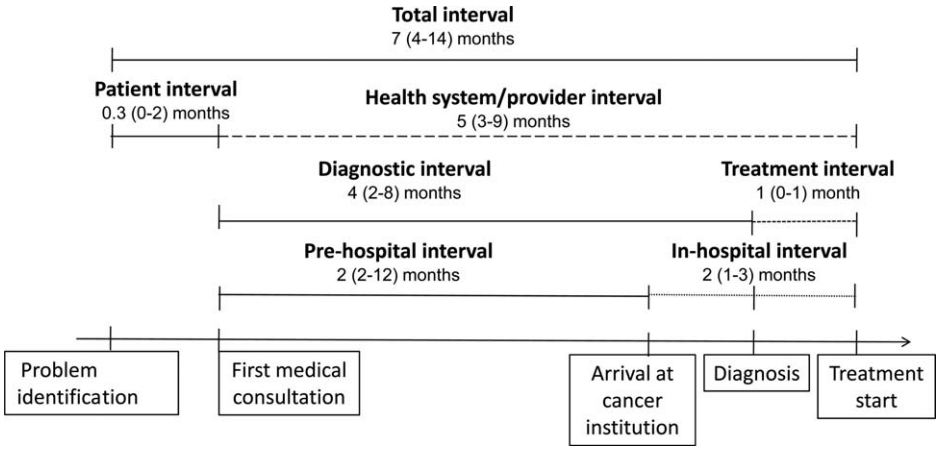

Figure 2. Estimates of total, patient, health system/provider, diagnostic, treatment, prehospital, and in-hospital intervals for patients with breast cancer are illustrated. Reported measures indicate the median interval, with the 25th percentile to 75th percentile indicated in parenthesis. The depicted bar lengths are proportional to the time length of the intervals.

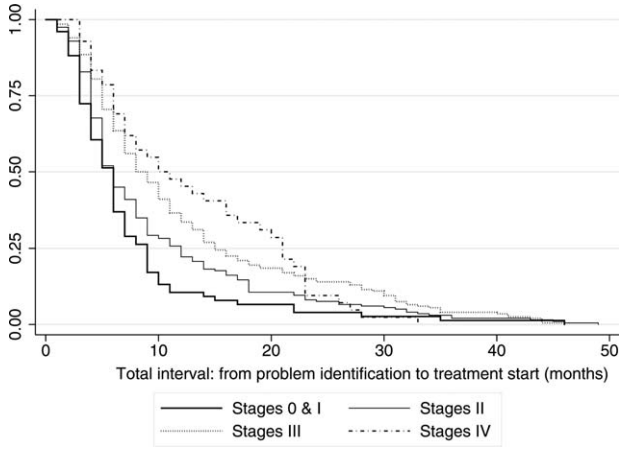

Figure 3. Kaplan-Meier curves for the total interval are indicated according to clinical disease stage.

TABLE 2. Bivariate Analysis of Total Interval and Clinical Stage

Cancer Clinical Stage[a]	HR	SE	*P*	95% CI
II	0.763	0.103	.046	0.585-0.995
III	0.585	0.079	.000	0.448-0.764
IV	0.553	0.107	.002	0.378-0.809

Abbreviations: CI, confidence interval; HR, Cox regression hazard ratio; SE, standard deviation.
[a] The reference category was stage 0 and 1.

seeking help by as little as 1 month, then the probability of advanced disease was already 45%, as indicated in the figure. Similarly, a 1-month delay between the first medical consultation and the beginning of treatment was associated with a 40% probability of advanced-stage cancer.

DISCUSSION

In this study, the proportion of patients who began treatment with delay was much higher than that in HICs and was similar to that in other LMICs. The median total interval was 7 months. In contrast, France and the United States report total interval medians of 34 days[20] and 48 days,[21] respectively. Studies in other LMICs like Brazil and Malaysia have reported median total delays of 7.6 months[22] and 5.5 months,[23] respectively, similar to our findings.

It is noteworthy that although the median total delay for our participants was very different from the delays reported for HICs, the patient interval was almost identical. Our study participants had a median patient interval of 10 days, similar to Germany (16 days)[5] and the United Kingdom (9 days)[24] and very different from other LMICs with median times of 2 to 3 months like Egypt[25] and Malaysia.[23]

In contrast, the greatest proportion of delays in our sample occurred within the health system interval, with a median of 5 months. This is strikingly different from what occurs in HICs like Canada,[8] France,[20] Germany,[9] and the United States,[21] where the reported median provider intervals range between 10 days and 42 days. Our findings are more similar to what has been described for other LMICs like Brazil[22] and Colombia,[26] with median intervals of 5 months.

Thus, it appears that an average woman in Mexico seeks care as promptly as does a woman living in Germany or in the United Kingdom, but she then faces extremely

TABLE 3. Logistic Regression of the Factors Associated With Advanced Clinical Stage

	1		2		3		4	
	Coef (SE)	AME (SE)	Coef (SE)	AME (SE)	Coef (SE)	AME (SE)	Coef (SE)	AME (SE)
Variable of interest								
Patient interval	0.111 (−0.045)[a]	0.022 (−0.002)[b]	0.103 (−0.046)[a]	0.020 (−0.008)[a]	0.111 (0.047)[a]	0.020 (−0.008)[b]	0.106 (−0.02)[b]	0.018 (−0.003)[b]
(Patient interval)[c]	−0.002 (−0.002)		−0.002 (−0.002)		−0.003 (−0.002)		−0.002 (−0.001)	
Provider interval	0.102 (−0.034)[b]	0.015 (−0.005)[b]	0.103 (−0.034)[b]	0.015 (−0.005)[b]	0.100 (−0.035)[b]	0.014 (−0.005)[b]	0.083 (−0.036)[a]	0.010 (−0.004)[a]
(Provider interval)[c]	−0.002 (−0.001)[a]		−0.002 (−0.001)[a]		0.002 (−0.001)[a]		−0.002 (0.001)[a]	
Means of identification: symptoms vs screening	1.501 (−0.331)[b]	0.312 (0.055)[b]	1.553 (−0.336)[b]	0.315 (−0.055)[b]	1.471 (−0.343)[b]	0.294 (−0.057)[b]	1.68 (0.274)[b]	0.310 (−0.043)[b]
Patient age	−0.015 (−0.007)[a]	−0.003 (−0.002)[a]	−0.019 (−0.008)[a]	−0.004 (−0.002)[b]	−0.018 (0.008)[a]	−0.004 (−0.002)[a]	−0.020 (0.008)[b]	−0.004 (−0.001)[b]
Inclusion of control variables								
Education >9 y	No	No	Yes	Yes	Yes	Yes	Yes	Yes
House ownership	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Religion	No	No	No	No	Yes	Yes	Yes	Yes
State of residence	No	No	No	No	Yes	Yes	Yes	Yes
Hospital fixed effects	No	No	No	No	No	No	Yes	Yes
Interviewer fixed effects	No	No	No	No	No	No	Yes	Yes

Abbreviations: AME, average marginal effects; Coef, regression coefficient; SE, hospital-clustered, robust standard error.

[a] $P < .05$.

[b] $P < .01$.

[c] Patient and provider intervals were included as numerical variables in months.

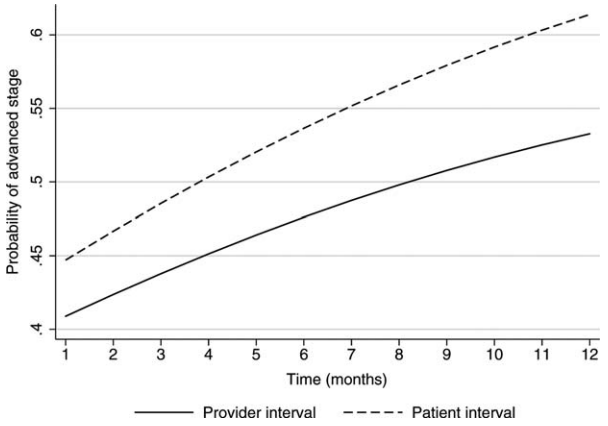

Figure 4. Predictions of advanced-stage disease are illustrated as patient and provider intervals increase. These estimates were calculated based on the estimated average marginal effects of the regression provided in Table 3. In fact, only the within-hospital and within-interviewer variation were exploited in the preferred specification (see Table 3, column 4).

long delays before her diagnosis is confirmed, similar to what happens in other LMICs. This goes against the idea that delay is mainly because of the patients' postponement to seek medical care, as is commonly believed.

Close to 45% of our participants were diagnosed in stages III and IV, similar to other LMICs like Brazil, Egypt, India, Libya, Nigeria, Peru, and Thailand, where between 31% and 75% of patients are diagnosed in these stages.[27] In contrast, in HICs like Canada, Norway, Sweden, and the United Kingdom, only between 8% and 22% of patients are diagnosed with such advanced disease.[28] Our multivariate analysis confirmed the independent effects on clinical stage of the means of problem identification, the patient delay, the health system delay, and the patient's age.

Our results confirm an effect of health system delay on clinical stage, in line with other study findings.[8-10] However, we did not observe the first arm of the U-shaped correlation between time and clinical stage that has been reported in other studies,[8,9] which represents the association between short intervals and advanced clinical stages. We do confirm the rest of the U-shape distribution in our data, in which the longer the time before patients started treatment, the more likely their cancer stage would be advanced. It has been proposed that the counterintuitive first arm of the U originates in the ability of physicians to quickly identify patients with more advanced cancer and somehow accelerate their care.[6] The absence of this finding in our data, together with the observation that most of the diagnosis delays occurred before the patients' arrival to the cancer hospital (Fig. 2), support the hypothesis that diagnosis delays are probably caused by problems in the first and second levels of health care (eg, waiting times to get appointments, accessibility barriers, quality of care, etc). It has been demonstrated that these kinds of barriers are relevant in a Thai study of provider delay[10] and in a previous qualitative study of uninsured Mexican patients with BC.[29]

It is also interesting to highlight the association we observed between age and BC stage: the younger the patient, the more likely for her to be in advanced stages. This effect was independent of both patient and provider delay and, thus, supports a biologic mechanism of age, as widely documented in previous studies reporting larger tumors and higher incidence of triple-negative BCs among young patients.[30]

Implications

This is 1 of the few studies to analyze the correlations between system delay and clinical stage in patients with BC. Strengths of our study include the use of accepted definitions for the intervals, the measurement of dates for estimating the intervals with a validated instrument, and a multivariate analysis of the correlations between delay, covariates, and cancer stage that controls for hospital and interviewer fixed effects. Our findings may reflect a similar situation regarding BC delays in other low and middle resource settings in which access to quality health services is inequitable.

Because not only the means of problem identification but also patient and health system delays affect cancer stage, possible solutions should include interventions that address all of these issues. Enhancing mammography screening is usually the proposed solution to improve early diagnosis of BC, but we will argue that this is probably not the solution for LMICs like Mexico. Only 24% of our sample identified their cancer through a screening mammography, comparable to the national screening coverage of 20%,[31] which is very low compared with the World Health Organization's recommended minimum of 70% coverage required to impact mortality.[32] Screening is useless if access to adequate diagnosis and treatment cannot be assured, and our study demonstrates that the majority of patients are receiving cancer treatment after very long delays. If mammography screening coverage were increased without accompanying improvements for early diagnosis and treatment, then delays could worsen, because more patients would be using the already insufficient health services and resources. To achieve a 70%

screening rate, there would need to be greater social and financial investment in training of highly qualified human resources and equipment. With the recent controversies in HICs regarding the real benefits of screening mammography on mortality,[33] it is highly questionable whether investing in mammography screening should be the priority in Mexico.

A more cost-effective strategy could be *early diagnosis* or *down-staging*, which has been endorsed for LMICs by the World Health Organization and the Breast Health Global Initiative.[32,34] This approach consists of a combination of strategies directed to the population, the health professionals, and the health system that may bring down the clinical stages in which cancer is diagnosed. At the *level of the population*, strategies aimed at enhancing earlier identification of BC symptoms are needed. Our findings indicate that the baseline risk for advanced-stage cancer is >40% (Fig. 4). This reflects the finding that women are not detecting symptoms as early as they could. The promotion of awareness of early symptoms among the public could increase first presentation at earlier stages. At the *health professionals' level*, strategies to improve primary care physicians' abilities to suspect BC earlier and strengthen breast-imaging services could aid prompter diagnosis. Finally, at the *health system level*, the improvement of procedures for referral and admission to tertiary care services could facilitate earlier cancer care.

Limitations

One limitation of our study is that it was not possible to determine causality between delay and clinical stage with a cross-sectional study design. Nevertheless, a cohort study to assess delay would be unethical and, thus, impossible to undertake. It could be argued that it is clinical stage that influences the time to care, because more advanced cancers may be treated more promptly. This does not appear to be the case in our data. We did not observe the correlation between advanced stages and shorter health system intervals that has been reported in other studies.[6,9]

Yet another study limitation was that we did not collect data on biologic tumor characteristics, like histologic grade, estrogen receptor status, progesterone receptor status, and human epidermal growth factor receptor 2 status. Thus, it was not possible to determine causality between delay and clinical stage, because the cancer subtype may have confused the correlation. More studies are needed. A follow-up study is underway in which data on biologic tumor characteristics, 5-year survival, treatment scheme, and adherence to treatment are being retrieved.

Research aimed at identifying specific access barriers to medical services is much needed, not only in Mexico but in LMICs. The identification of these barriers could guide the design of tailored health policies that go beyond the promotion of breast care awareness and screening participation to include improvements in health services that facilitate access to timely diagnosis and treatment.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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