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Breast Tuberculosis in Women: A Systematic Review

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Abstract. Breast tuberculosis (TB) is rarely reported and poorly described. This review aims to update the existing literature on risk factors, clinical presentations, constitutional symptoms, diagnostic procedures, and medical and surgical treatments for breast TB. In all, 1,478 cases of breast TB were collected. Previous history of TB was reported in 19% of cases. The most common clinical appearance of the lesion was breast lump (75%). The most common associated finding was axillary lymphadenitis (33%) followed by sinus or fistula (24%). The most common symptoms were pain and fever, reported in 42% and 28% of cases, respectively. The most used diagnostic method was fine-needle aspiration cytology (32%), followed by biopsy (27%), acid-fast bacteria Ziehl–Neelsen stain (26%), culture (13%), and polymerase chain reaction (2%). These tested positive in 64%, 93%, 27%, 26%, and 58% of cases, respectively. The majority (69%) of patients received a 6-month anti-TB treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol). Surgery consisted of excision in 39% of cases, drainage in 23%, and mastectomy in 5%. The great majority of patients had a positive outcome. It often mimics breast cancer, which makes it difficult to diagnose. Most patients, when diagnosed in time, respond to antitubercular therapy alone.

INTRODUCTION

Globally, tuberculosis (TB) is now the number one killer infectious disease. More than 95% of TB deaths occur in low- and middle-income countries (LMICs), where TB is among the top three causes of death for women aged 15 to 44.[1] Any organ can be affected by TB, but the breast is an uncommon extrapulmonary TB site.[2] The first case of breast TB was described by Cooper in 1829 as, "scrofulous swelling of the bosom of young women,"[3] but the first detailed description of the disease was not reported until the end of the 19th century by Richet[4] and Powers.[5] It is generally believed that the infection of the breast is usually secondary to a primary site elsewhere in the body, which may or may not be clinically apparent[6,7]; however, breast TB may be the primary site when no demonstrable tuberculous focus exists elsewhere. Lymphatic spread by retrograde extension from the axillary lymph nodes is considered the most common way the disease spreads. Propagation from cervical and mediastinal lymph nodes has occasionally been reported.[2]

There are no well-defined clinical features suggestive of breast TB. Because of its protean clinical presentations, establishing a diagnosis is difficult. For instance, it may be confused with breast carcinoma or pyogenic abscess.[2,8] The diagnostic delay can last months, and patients often undergo numerous investigations and unsuccessful treatments before a definitive diagnosis is made.[9,10] The most common clinical presentation is a lump, with or without a duct, painful or not.[6] The lump can mimic carcinoma, being hard, with irregular borders, and fixed to either the skin or the muscle or even to the chest wall.[8,11] Other presentations include diffuse breast swelling and edema, diffuse nodularity, nipple retraction, fistulization, multiple sinuses, skin ulcers, and recurrent abscess with or without axillary involvement.[12–15]

There are different ways to diagnose and follow up breast TB, although none are ideal because of a combination of technical limitations and no or limited availability, particularly in LMICs. The gold standard for diagnosis is the detection of *Mycobacterium tuberculosis* by acid-fast bacteria Ziehl–Neelsen stain (AFB) or the isolation of the organism from the lesion on culture, but the former lacks sensitivity in paucibacillary samples, and the latter is relatively expensive and impractical in some low-resource settings.[2,8] An alternative is polymerase chain reaction (PCR) to identify the *M. tuberculosis* genetic material, but it is rarely used.[15] Fine-needle aspiration cytology (FNAC)—which detects the presence of epithelioid cell granulomas and necrosis—is often used instead, but has drawbacks—differential diagnosis is difficult in cases of granulomatous mastitis and sarcoidosis, for instance.[16,17] Histopathology on biopsy identifies a chronic granulomatous inflammation (with caseous necrosis and Langhans-type giant cells).[8] Investigations such as ultrasonography, mammography, computed tomography, and magnetic resonance imaging do not give a conclusive diagnosis and, once again, are not widely available in LMICs.[12,15,18–21] Treatment generally involves anti-TB medications with or without surgery.[2,6] Medical treatment often consists of an intensive four-drug, 2-month phase with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a two-drug, 6-month (or longer) continuation phase with isoniazid and rifampicin.

Despite several published literature reviews of breast TB,[7,10,18,22,23] a systematic review has not been conducted. Therefore, we aimed to update and expand the existing evidence base by systematically reviewing the English, Spanish, and French literature about risk factors and clinical, diagnostic, and therapeutic aspects of breast TB in women.

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METHODS

Searches were undertaken in PubMed, Embase, and Web of Science. A search strategy was developed using a combination of free-text and predetermined terms, adapted for each database. We used the following search strategy: (tuberculosis OR TB) AND (breast OR mammary OR mastitis) AND (women OR female). Included were reports of studies published in English, Spanish, and French between 1990 and March 2018. Additional studies were identified by contacting the authors and by searching the reference lists of primary studies. The process of study selection is summarized in Figure 1. Title and abstracts identified through the searches were reviewed independently by two reviewers (G. Q. and D. P.). If there were duplicate publications of the same study, the most recent publication which reported full data was included. Full-text copies of the selected studies were retrieved and independently reviewed against the inclusion criteria by two reviewers from a team of three (G. Q., D. P., and G. P.).

With respect to study designs, we included any retrospective and prospective analyses of medical records and case reports. Outcome measures included 1) risk factors for breast TB, 2) clinical appearance of the lesion and clinical presentations, 3) constitutional symptoms, 4) diagnostic procedures, and 5) anti-TB and surgical treatments. The inclusion criterion was articles published in English, French, and Spanish from 1990 to March 2018. The exclusion criteria were articles published in languages other than English, French, and Spanish; cases of breast TB described in association with other mammary diseases (cancer, granulomatous mastitis, etc.); and male case reports; however, articles which described cases of male TB within a large number of TB female cases were instead included. Purely qualitative studies were excluded.

Each of the included studies was coded with a predetermined rating sheet with relevant data extracted and recorded by two reviewers. Data extracted included name of the first author, year of publication, country where the study was conducted, prevalence (entente as the number of breast TB among the total number of mammary conditions treated in the centers reporting case series), general participant characteristics (age and gender), risk factors (multiparity, pregnancy, lactation, HIV+, and previous history of TB), breast affected (right, left, and bilateral), breast quadrant affected (superior, inferior, and peri-areolar), clinical appearance of the lesion (lump, abscess, and disseminated), clinical presentations (sinus or fistula, skin ulceration, nipple retraction, and discharging sinus), constitutional symptoms (fever, decreased appetite, decreased weight, and pain), duration of symptoms, previous empirical antibiotic treatment, chest X-ray results (negative, positive (active TB), and features of previously healed TB), diagnostic procedure (biopsy, FNAC, AFB, culture, and PCR), type and duration of anti-TB treatment, and, finally, surgical treatment (none, excision, incision and drainage, and mastectomy).

We generated a summary of the results in a table to describe the characteristics and results of each of the included studies. The review collected series and individual case reports. Most of the articles featuring series were included in the database as a single study. However, some series, typically those with few cases, have described these cases in a very detailed way; for these articles, each case was included independently in the database. Because of the heterogeneity in the presentations of case reports and series, a decision was made not to perform meta-analysis, but instead to summarize the results as simple averages in tables. Age was calculated as a weighted mean to account for sample size heterogeneity across studies. Between-test agreement was calculated using the Cohen's kappa coefficient. Because this is a systematic review of nonanalytical studies, that is, case series and case reports, the assessment of publication bias might not be practically applicable.[24] The Grading of Recommendations, Assessment, Development, and Evaluation and the approach by the Agency for Healthcare Research and Quality are not suitable for our systematic review of nonanalytical studies. For this reason, we have not performed a formal evaluation of the quality of the included studies.[24]

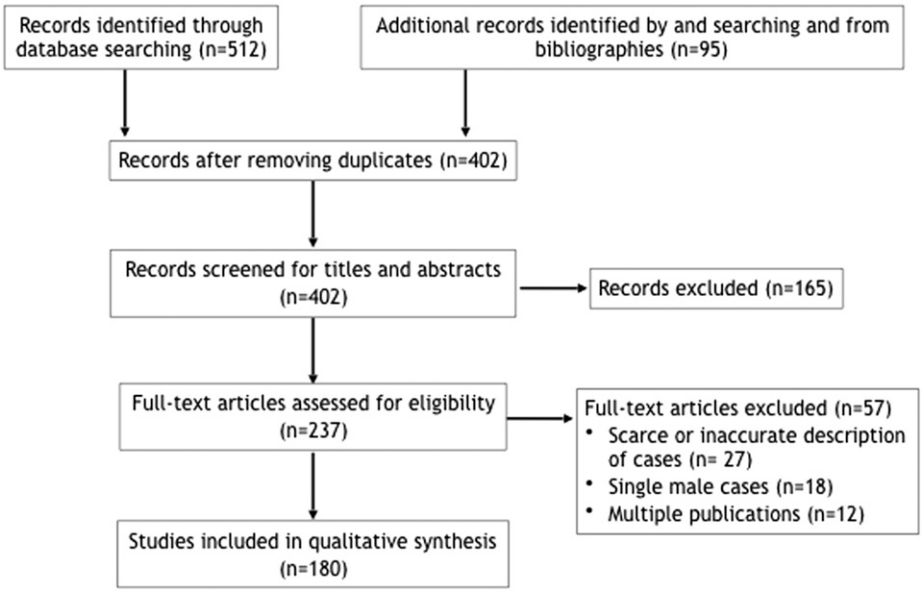

FIGURE 1. Flow diagram for study selection.

RESULTS

We identified 512 potentially eligible citations from the database searches and 95 studies from hand searching and screening of bibliographies. We screened the titles and abstracts of the 402 remaining articles after removing duplicates and selected 237 publications for full-text screening, from which 180 articles were included in the final analysis (Figure 1). Only one prospective patient recruitment study was identified.[25] The final list of 180 relevant articles reported a total of 1,458 (98.6%) cases of breast TB in women and 20 (1.4%) in men. Of these 180 articles, 107 were single-case reports,[8,9,21,26–129] 38 reported between two and nine cases,[10,11,14,15,19,23,130–161] and 35 reported 10 or more cases[6,7,12,13,17,18,20,22,25,162–187] (Supplemental Appendix 1). The 10 articles with the largest series (ranging from 42 to 160 cases) reported 693 (46.9%) of the total 1,478 cases included in these 180 articles.[6,12,13,23,25–27,29,31,34] The amounts of information collected on different variables differ, as the publications did not provide full information on each variable. For the following variables: 1) breast affected, 2) breast quadrant affected, 3) clinical appearance of lesion, 4) chest X-ray, 5) antitubercular treatment, and 6) surgical treatment, the parameters were calculated for the population in which all variables were known. The majority of subjects (1,002, 67.9%) were from Asia, mainly India and Pakistan, followed by Africa with 249 (16.8%) of the cases, South America with 79 (5.3%, mostly from Peru and Brazil), Europe with 71 (4.8% mainly from the United Kingdom), the Middle East with 69 (4.7%, mainly from Iran), and the United States with eight (0.5%). Where described, the prevalence of breast TB among the total number of breast cases examined ranged from 0.2% to 6.8%, with an average of 1.7%.

Risk factors and clinical presentations. As described in Table 1, the mean age of included patients was 29 years (range 12–89 years). Among 185 single cases described, 125 (67.5%) were in the reproductive age range (14–45 years). Twenty-nine (4.5%) patients were pregnant, and 167 (14.7%) were lactating mothers. Multiparity was reported in 362 cases (70.2%). The HIV status was described in 211 cases, and 45 (21.3%) of them were HIV positive. Previous history of TB was reported in 111 cases (18.7%).

The most common clinical appearance of the lesion was breast lump (877, 74.9%) and breast abscess (174, 14.9%). Nearly half of the patients (431, 48.4%) presented with an involvement of the right breast. Bilateral localization was rare (38 subjects, 4.2%). The most common site was the superior quadrant (237, 60.4%). The most common associated finding was axillary lymphadenitis (377, 32.6%), followed by sinus or fistula (217, 23.9%), skin ulceration (103, 23.5%), and nipple retraction (83, 16.7%). The most common constitutional symptoms were pain, reported in 314 (42.5%) of the cases, and fever, reported in 175 (28.2%). The average duration of symptoms before seeking medical care was highly variable: on average, the delay in diagnosis was 7.1 months.

Diagnosis, treatment, and outcomes. Overall, 2,663 tests were reportedly applied to these 1,478 cases. As described in Table 2, the most common diagnostic method was FNAC, carried out in 842 cases (31.6%), followed by biopsy (723, 27.1%), AFB (687, 25.8%), culture (344, 12.9%), and PCR (67, 2.5%). Respectively, positive results were found in 64.1%, 92.8%, 26.6%, 25.9%, and 58.2% of the methods used (percentage of positivity found on the total of each test performed). Additional details were extracted for 412 cases, which were found positive on at least one of the tests they had been submitted to (1 test = 15% of cases, 2 tests = 32%, 3 tests = 30%, 4 tests = 18%, and 5 tests = 5%); they are shown in Table 3. In individual tests, biopsy was used in 29% of cases and found positive in 90%; AFB in 25%, positive in 59%; FNAC in 23%, positive in 59%; culture in 17%, positive in 56%; and PCR in 7%, positive in 61%. A single test was positive in 15% of cases. When two or more tests were combined, the sample was confirmed by two tests being positive in roughly half of the cases (59%, 55%, 46%, and 50% with two, three, four, and five tests, respectively). Diagnosis involved variable combinations of tests, most commonly between AFB and FNAC (n = 59), biopsy (n = 62), or culture (n = 69). As described in Table 4, the between-test agreement was low or very low. A chest X-ray was carried out in 1,026 subjects: 100 (9.7%) had a chest X-ray positive for active TB and 28 (2.7%) showed sequelae of past TB.

Of the 1,478 patients in this review, information on treatment—medical and/or surgical—was provided for 1,087 (73.5%). Of these, 1,050 patients (96.6%) received medical treatment; for the remaining 37, only surgical treatment was reported, whereas information on medical treatment was missing. Of 1,050 patients with anti-TB treatment, 733 (69.8%) received the standard 6-month anti-TB treatment (2 months of

TABLE 1
Risk factors, signs, and symptoms in 1,478 patients with breast TB

Variable	N (%)
Gender	
Female	1,458/1,478 (98.6%)
Male	20/1,478 (1.4%)
Age (years)	
Mean	29
Range	12–89
Risk factors	
Multiparity	362/516 (70.2%)
HIV+	45/211 (21.3%)
Previous history of TB	111/592 (18.7%)
Active breastfeeding	167/1,137 (14.7%)
Pregnancy at the time of diagnosis	29/641 (4.5%)
Breast affected*	
Right	431/891 (48.4%)
Left	422/891 (47.4%)
Bilateral	38/891 (4.2%)
Breast quadrant affected*,†	
Superior	237/392 (60.4%)
Inferior	118/392 (30.1%)
Peri-areolar	68/392 (17.3%)
Clinical appearance of the lesion*	
Lump	877/1,171 (74.9%)
Abscess	174/1,171 (14.9%)
Disseminated	120/1,171 (10.2%)
Clinical findings	
Axillary lymphadenopathy	377/1,157 (32.6%)
Sinus or fistula	217/909 (23.9%)
Skin ulceration	103/438 (23.5%)
Discharging sinus	138/743 (18.6%)
Nipple retraction	83/497 (16.7%)
Constitutional symptoms	
Pain	314/739 (42.5%)
Fever	175/621 (28.2%)
Decreased appetite	119/497 (23.9%)
Decreased weight	137/507 (27%)

TB = tuberculosis.
* Parameters were calculated for population in which all variables were known.
† The total is more than 100% because in some cases, the lesion involved more quadrants.

TABLE 2
Diagnosis and treatments in patients with breast TB

Variable	*N* (%)
Delay in diagnosis	
Mean (months)	7.1
Range	0.25–78
Previous empirical antibiotic treatment	85/251 (33.8%)
Chest X-ray*	
Negative	855/983 (87.1%)
Positive (active TB)	100/983 (10.2%)
Sequelae findings of past TB†	28/983 (2.7%)
Method of diagnosis‡	
Biopsy	671/723 (92.8%)
Fine-needle aspiration cytology	540/842 (64.1%)
Acid-fast bacteria Ziehl–Neelsen	183/687 (26.6%)
Culture	89/344 (25.9%)
Polymerase chain reaction	39/67 (58.2%)
Type of antitubercular treatment*	
Two months of isoniazid, rifampicin, pyrazinamide, and ethambutol + 4 months of isoniazid and rifampicin	733/1,050 (69.8%)
Other antitubercular regimen§	207/1,050 (30.2%)
Antitubercular treatment duration	
Mean (months)	6.1
Range	2–24
Surgical treatment*,‖	
None	350/977 (35.8%)
Excision	377/977 (38.6%)
Incision and drainage	226/977 (23.1%)
Mastectomy (partial or total)	45/977 (4.6%)

TB = tuberculosis.
* Parameters were calculated for population in which all variables were known.
† Calcified parenchymal nodules, calcified radiological scars, calcified hilar lymph nodes, etc.
‡ Percentage of positivity found on the total of each test performed.
§ Other antitubercular regimen: different from the standard treatment in terms of type of used drugs.
‖ The total is more than 100% because some patients received more than one treatment.

HRZE isoniazid, rifampicin, pyrazinamide, and ethambutol, and 4 months of HR) and 317 (30.2%) received a modified anti-TB treatment in terms of type and duration. The average treatment duration was 6.1 months, ranging 2–24 months. Among the 1,050 cases with medical treatment, 491 (47%) received medical treatment only and 559 (53%) also underwent surgery (excision, incision, and mastectomy). Surgery consisted in excision in 377/559 cases (67.4%), drainage in 226 (40.4%), and mastectomy in 45 (8%); 63 patients underwent two different surgical interventions. Information relating to previous antibiotic treatment was reported for 251 subjects, of whom 85 (33.8%) received empirical antibiotic treatment before the final diagnosis of breast TB was made. The treatment outcome was reported for 792 (67.9%) subjects: 762 (96.3%) were cured, with the others lost to follow-up.

DISCUSSION

The present review identified 1,478 breast TB cases reported in the literature. To our knowledge, this is the first time a systematic review has been carried out of the risk factors and clinical, diagnostic, and treatment aspects of breast TB. The average reported prevalence was 1.7%, ranging from 0.2%[20] to 6.8%.[35] The prevalence in Western countries is less than 0.1%.[2,6] Breast TB more commonly affects women of childbearing age (average age 29 years in this review). Elderly women may also be affected,[8,38,63] whereas the disease is very rare under the age of 18.[62,96,172] Tuberculosis of the male breast is an extremely rare condition.[12,63,170,188] Lilleng et al, in a study of 809 cases of male breast mass, did not find a single case of TB.[189]

In pregnant and lactating women, the increased vascularity of the breast with dilated ducts predispose to infection.[190] Pregnancy suppresses the T-helper 1 pro-inflammatory response, which may increase susceptibility to a new infection or reactivation of TB.[191] It is difficult to understand from this review whether this might be the case: on the one hand, a small percentage were either pregnant or lactating, and on the other hand, more than 70% were multiparous, and, considering the long diagnostic delays, breast TB might have been triggered by a previous pregnancy. HIV infection carries an increased risk for primary TB, for reactivation of previous TB, and for second episodes of TB from exogenous reinfection.[192–194] Breast TB as a presenting manifestation of HIV is extremely rare.[33,195] In the present study, the HIV status was described in 211 cases, and approximately one in five were positive.

The clinical presentation of breast TB is generally poorly described in the literature, and clinically important features are not uniformly reported or not reported at all. The average duration of symptoms before diagnosis is highly variable, spanning from a few weeks in Europe[93,96,154] to more than 7 months in India and sub-Saharan Africa.[12,14,170] This includes both patient and health system delays, and reflects the range of cultural, psychological, and economic components, as well as the diagnostic challenges. One-third of the patients about whom this information was collected received empirical antibiotic therapy at some point during their clinical history, typifying the challenges to the final diagnosis. The disease is generally mono-lateral and can equally affect either breast.[67,94,159] A lump is the most common presentation, with other less common forms being cold abscess and diffuse breast inflammation. Breast lumps are mostly misdiagnosed as fibroadenoma, malignancy, or breast abscess. One-third of the cases also have axillary lymph nodes. The rate of nipple–areola involvement in the present review is 17.3%. For comparison, in the carcinoma literature, studies showed a rate of gross nipple areola involvement of 12.5% (41/326 cases) in Laronga et al.[196] and 8% (99/1,291 consecutive cases) in Santini et al.[197]

This review shows a low prevalence of constitutional symptoms. This, combined with the low presence of concomitant active pulmonary TB (less than one in 10 was chest X-ray positive), or previous history of TB (less than one in five),

TABLE 3
Cases positive on at least one of the diagnostic test

Test	No. tested	% tested	No. positive	% positive	1 test	2 tests	3 tests	4 tests	5 tests
Fine-needle aspiration cytology	93	23%	55	59%	17	32	25	15	4
Biopsy	119	29%	107	90%	36	37	26	16	4
Culture	68	17%	38	56%	4	21	27	12	4
Acid-fast bacteria Ziehl–Neelsen stain	104	25%	61	59%	4	39	38	19	4
Polymerase chain reaction	28	7%	17	61%	0	3	7	14	4
Total (%)	412	–	–	–	61 (15)	132 (32)	123 (30)	76 (18)	20 (5)

TABLE 4
Test agreement between different diagnostic tests

Test		Polymerase chain reaction	AFB	Culture	Biopsy
Fine-needle aspiration cytology	Tested	18	59	36	34
	Concordance	39%	63%	72%	26%
	Kappa	–0.11	–0.06	–0.62	0.00
Biopsy	Tested	18	62	56	–
	Concordance	50%	42%	21%	–
	Kappa	–0.11	–0.06	–0.62	–
Culture	Tested	12	69	–	–
	Concordance	58%	45%	–	–
	Kappa	0.29	–0.01	–	–
AFB	Tested	25	–	–	–
	Concordance	48%	–	–	–
	Kappa	0.00	–	–	–

AFB = acid-fast bacteria Ziehl–Neelsen stain.

further contributes to the diagnostic delay. Pain is the most common constitutional symptom. Typically, its manifestation is a noncyclical mastalgia, that is, not linked to the menstrual cycle (as in fibrocystic disease, periductal mastitis, or breast abscess). Localized pain is very rare in breast cancer.[198]

As mentioned previously, the protean presentation of breast TB leads to significant diagnostic delay. This is compounded by multiple possible differential diagnoses, especially in resource-limited settings. The main differential diagnoses to be considered are fibroadenoma[199,200]; breast cancer; inflammatory diseases, such as idiopathic granulomatous mastitis, sarcoidosis, Wegener's granulomatosis, and giant cell arteritis[187,201–203]; and other infectious diseases, such as brucellosis, actinomycosis, mycotic infections, and fat necrosis.[199,204,205] The coexistence of carcinoma and breast TB is rare. The clinical situations include the presence of carcinoma and breast TB, carcinoma in the breast with axillary tuberculous adenitis, or both.[73,206,207] In the absence of a gold standard, the main question regarding the diagnosis of breast TB is whether it requires the detection of the microorganism or whether distinctive pathological changes suffice. The two most common diagnostic techniques are FNAC and biopsy, which in this review were positive in approximately 64% and 93% of cases, respectively.

With the proviso that a relatively small proportion of cases underwent more than one test, this review allowed for the comparison of diagnostic agreement between tests, which was very low. Using PCR or culture as standards by default, no test has satisfactory sensitivity and limited specificity. Of the *M. tuberculosis* detection methods, microscopy with AFB has, probably, the best balance between sensitivity (~80%) and specificity (35–65%). Biopsy has the best sensitivity (90% or more) but very low specificity, whereas FNAC has low sensitivity and specificity. However, the use of culture or PCR as standards might be questioned. One caveat is that it is not clear whether evidence of the presence of *M. tuberculosis* is mandatory to confirm the diagnosis of breast TB, especially if in the presence of definitive histological/cytological changes.[6] It has been argued[208] that the low sensitivity of direct detection techniques (especially in paucibacillary lesions) may cause delays in diagnosis and underdiagnosis. In the articles reviewed here, culture was positive only in about one in four cases, and PCR in just over half. By contrast, in various series included in this review,[17,22,141,162,166,167,182] in most cases, the diagnosis was made based on pathology and confirmed ex juvantibus as they responded to anti-TB therapy. Therefore, generally, pathological examination appears to be of more practical use than bacteriology, especially considering that both culture and PCR are technically challenging and cannot be applied in many settings in LMICs. This conclusion, however, is challenged by the very low agreement (29%) and concordance (kappa = 0.02) between FNAC and biopsy in the 34 cases in which both tests were conducted. To our knowledge, GeneXpert has not been tested on breast TB. A Cochrane systematic review and meta-analysis of the use of GeneXpert on extrapulmonary TB found variable sensitivities and specificities against culture depending on the type of specimen. When tested on lymph nodes, sensitivity and specificity ranged widely (56–100% and 39–100%, respectively); pooled sensitivity and specificity (95% credible intervals) were 87.6% (range 81.7–92.0%) and 86.0% (range 78.4–91.5%), respectively.[209]

Breast TB overall has a good prognosis. No specific guidelines are available for chemotherapy of breast TB; the most common approach is the standard TB treatment with 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. Some authors prefer the 9-month regimen (2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, and 7 months of isoniazid and rifampicin) because of a lower relapse rate in general.[13,166] Infection with multidrug-resistant TB has been reported.[47,123] The continuation phase may be extended, commonly to 12 months, but up to 18 months in cases with slow clinical response. In general, complete resolution is obtained in most patients.[2,143] Only 4.6% of the cases required radical surgical treatment (subtotal or total mastectomy). A minority of patients needed a combination of minor surgical procedures such as cold abscess aspiration and resection of sinus formation or necrotic tissue (63/559, 11.3%). Most cases which underwent surgical treatments went to a clinician several months after the development of their first symptoms; because of this delay at presentation, the lesion had already been complicated by abscess or sinus formation, for which surgical intervention proved necessary. Of all surgical cases, 38.6% underwent lump excision. However, as most of the series were retrospectively reviewed, in many cases, these procedures were performed as an initial step during the workup of the patient diagnosis, and as a consequence, they cannot be fully intentionally included in the treatment plan.[12,13]

To the best of our knowledge, this is the first study which attempts to review prevalence, risk factors, symptoms,

diagnosis, and therapy of breast TB in a systematic manner. However, our review is not without its limitations. Inevitably, as there is only one prospective study, there was an element of poor recall in each report, particularly for the case series. The main difficulty was dealing with a wide range of different study objectives, methods, and results presentations leading to a high, but heterogeneous, number of cases reported. Moreover, the different presentations of results, sometimes as cumulative findings, made it very difficult to standardize analyses; hence, the denominators change for different variables as the information for each of them was not fully available from all studies.

To improve future research on breast TB, there is a need for standardization in data collection as part of routine monitoring and evaluation. There is also a need for more prospective studies. Ideally, such data should capture information on possible risk factors, symptoms, and clinical presentations for a better differential diagnosis with other breast diseases, mainly granulomatous mastitis and carcinoma. Qualitative studies should be considered to clarify the reasons for the delay in diagnosis. Finally, diagnostic algorithms that could be applied in LMICs should be investigated, comparing different diagnostic approaches systematically.

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The following are supplemental materials and will be published online only

SUPPLEMENTAL APPENDIX 1
Summary of reported series of breast TB

Author, year and reference	Country	Number of cases	Type of lesions presentation	Localization			Clinical presentation					Diagnosis						Treatment	
			Lu*	R	Le	B	Sf	Su	Nr	Dis	Ly	X-ray	FNAC	Biop	Cult	AFB	Ex	Inc	Mast
Kakkar, 2000[162]	India	160	160/160	U	U	U	U	U	U	U	16	U	118/160	31/31	U	6/28	U	U	U
Shinde, 1995[13]	India	100	85/100	U	U	2	9	16	5	9	U	2/100	21/60	61/61	6/9	21/100	21	15	4
Ben Hassouna, 2005[163]	Tunisia	65	55/65	22	42	1	U	U	U	3	7	1/65	2/8	65/65	U	0/0	28	37	0
Ramaema, 2015[164]	South Africa	65	17/65	33	30	0	U	U	U	U	21	15/47	18/65	61/65	0/0	7/65	0	3	0
Metha, 2010[165]	India	63	46/63	U	U	2	13	U	4	4	27	7/63	47/54	16/16	0/0	3/4	34	8	1
Khanna, 2002[12]	India	52	39/52	26	26	2	28	U	U	4	21	7/52	52/52	0/0	0/4	0/4	17	5	2
Jalali,2005[166]	Pakistan	50	30/50	U	U	U	1	U	U	U	19	1/50	U	U	U	U	2	U	U
Khan, 2014[167]	Bangla-desh	50	40/50	26	23	1	20	U	U	U	20	6/50	5/5	0/0	0/0	0/5	30	10	0
Kilic, 2016[168]	Turkey	46	34/46	17	28	1	10	U	8	9	8	3/46	0/0	29/31	9/46	4/46	12	5	0
Puneet,2005[169]	India	42	U	U	U	0	U	U	U	U	U	U	42/42	0/0	U	28/42	U	U	U
Harris, 2006[170]	India	38	33/38	23	14	1	9	U	U	U	14	5/38	28/28	9/9	1/22	2/22	0	8	2
Longman, 2017[171]	UK	33	20/33	U	U	U	U	U	U	U	U	U	4/16	10/17	U	U	U	U	U
Tewari,2005[6]	India	30	22/30	U	U	U	4	11	U	U	18	0/30	11/30	23/23	0/0	0/0	11	8	0
Afridi,2008[172]	Pakistan	30	6/30	14	14	2	14	2	U	14	7	4/30	6/6	12/12	3/30	4/30	12	9	0
Muro,2013[173]	Peru	29	8/29	U	U	U	8	2	1	U	4	10/29	U	U	U	U	4	6	0

Author, year and reference	Country	Number of cases	Type of lesions presentation	Localization			Clinical presentation					Diagnosis					Treatment		
Pinto Paz, 2013[25]	Peru	28	6/28	18	10	0	2	22	U	0	0	0/28	0/0	28/28	2/28	2/28	24	2	0
Tanrikulu, 2010[174]	Turkey	27	11/27	11	12	4	U	U	U	U	U	U	2/27	22/27	1/27	0/0	22	5	0
Lin, 2010[175]	Taiwan	26	17/26	13	12	1	2	U	U	U	U	0/26	0/2	11/24	1/15	3/17	0	9	16
Gupta, 1999[17]	India	22	22/22	U	U	U	U	U	U	U	1	U	22/22	0/0	U	5/22	U	U	U
Tandon, 2012[176]	India	22	8/22	14	7	1	3	3	4	4	11	4/22	U	U	U	U	3	7	0
Khodabakhshi, 2014[177]	Iran	22	13/22	4	16	2	6	U	U	5	7	U	0/0	18/22	2/22	U	18	0	11
Meerkotter, 2011[18]	Safrica	21	7/21	11	9	1	1	U	U	1	15	U	21/21	0/0	13/21	2/21	U	U	U
Da Silva, 2009[7]	Brasil	20	5/20	11	9	0	15	U	U	U	7	0/1	0/0	19/19	U	1/20	U	U	0
Mehmood, 2009[178]	Pakistan	17	14/17	7	10	0	2	2	3	3	16	U	9/15	13/13	U	U	0	15	0
Basarkod, 2012[179]	India	16	6/16	8	7	1	5	U	U	U	6	5/16	12/14	16/16	0/0	0/0	9	7	0
Ben Brahim, 2008[180]	Tunisia	15	2/15	10	5	0	U	U	U	3	5	3/15	1/15	15/15	0/0	0/15	U	U	U
Bhatti, 2010[181]	India	15	5/15	10	5	0	U	U	U	3	3	U	U	U	U	U	U	U	U
Morsad, 2000[182]	Morocco	14	12/14	U	U	2	2	U	U	3	10	0/14	2/2	14/14	1/7	U	12	6	0
Ahmed, 2006[183]	Pakistan	14	10/14	7	5	2	2	U	0	2	10	3/14	10/10	4/4	0/0	5/14	0	2	0
Al Marri, 2000[22]	Qatar	13	13/13	4	9	0	0	0	5	2	1	0/13	4/8	5/5	5/13	2/13	7	3	0
Methre, 2011[184]	India	11	8/11	3	8	0	2	U	1	2	4	1/11	U	U	0/0	4/4	7	0	1
Chandanwale, 2012[185]	India	11	7/11	8	3	0	U	U	U	U	3	0/11	5/11	11/11	1/5	6/11	0	0	0

Author, year and reference	Country	Number of cases	Type of lesions presentation	Localization			Clinical presentation					Diagnosis					Treatment		
Sakr, 2004[20]	Egypt	10	6/10	U	U	U	1	U	2	4	4	2/10	U	U	U	U	3	U	U
Zekri, 2010[186]	Morocco	10	9/10	3	7	0	U	U	U	U	2	1/10	2/2	10/10	0/0	2/2	9	1	0
Seo, 2012[187]	Korea	10	7/10	5	5	0	U	3	U	U	5	U	1/6	9/9	0/0	4/8	9	0	0
Elsiddig, 2003[14]	Sudan	9	9/9	U	U	U	3	3	U	1	7	U	9/10	1/1	U	0/9	U	U	U
Bani-Hani, 2005[15]	Jordan	9	7/9	3	6	0	U	U	U	U	3	0/9	3/7	8/9	0/0	3/9	9	0	1
Hussain Naqvi, 2007[130]	Pakistan	9	8/9	U	U	U	4	U	U	U	5	3/9	9/9	9/9	0/0	1/9	9	0	0
Raza, 2016[131]	India	9	5/9	7	0	2	5	0	2	2	2	1/2	3/3	5/5	0/0	2/2	0	2	0
Supe, 2002[132]	India	8	0/8	U	U	U	U	1	U	1	U	0/8	U	1/1	3/7	0/7	0	7	0
Fadaei-Araghi, 2008[133]	Iran	8	8/8	4	3	1	2	3	1	2	1	U	4/8	4/8	1/8	0/8	4	2	0
Hawilo, 2012[134]	Tunisia	8	4/8	3	5	0	2	4	4	2	2	0/8	0/0	8/8	2/8	0/0	2	0	0
Atamanalp, 2010[135]	Turkey	7	7/8	4	3	0	5	U	U	2	4	1/7	5/5	2/2	U	U	5	2	0
Cakar, 2016[136]	Turkey	7	7/7	3	3	1	0	0	0	3	U	0/7	2/2	5/5	0/0	0/0	5	0	0
Popli, 1999[137]	India	7	5/7	4	3	0	1	U	1	1	1	0/1	3/5	3/3	1/1	0/0	0	0	0
Gupta, 2003[138]	India	7	6/7	2	4	1	2	U	U	U	U	1/6	5/5	2/2	0/2	2/2	0	1	0
Mankanjuola, 1996[19]	Saudi Arabia	6	1/6	U	U	U	1	U	6	U	U	U	U	U	U	U	4	2	0
Marrakchi, 2004[139]	Tunisia	6	6/6	U	U	U	U	U	U	U	U	U	U	6/6	U	U	U	U	U
Gill, 2012[140]	India	6	5/6	4	2	0	1	U	1	U	U	U	6/6	0/0	U	1/6	1	0	0
Kalac, 2002[141]	Turkey	5	5/5	3	2	0	U	1	2	2	4	2/5	0/0	5/5	0/2	0/3	5	0	0
Jah, 2004[11]	UK	5	4/5	1	4	0	1	U	U	U	1	U	1/4	1/2	0/1	1/4	0	2	0

Author, year and reference	Country	Number of cases	Type of lesions presentation	Localization			Clinical presentation					Diagnosis				Treatment		
Efared, 2017[161]	Maroc	5	2/5	U	U	U	U	U	U	U	2	U	1/1	4/4	0/0	0/0	1	2	0
Chung, 1996[142]	Korea	4	4/4	U	U	U	2	U	U	U	0	0/4	0/2	4/4	4/4	4/4	0	0	0
Mirsaeidi, 2007[143]	Iran	4	2/4	1	3	0	3	3	1	2	2	1/1	0/4	2/2	0/2	1/2	0	0	0
Bouti, 2012[144]	Turkey	4	3/4	4	0	0	1	U	1	U	U	1/1	0/3	4/4	0/2	1/1	0	0	1
Akcay, 2007[10]	Turkey	3	2/3	1	2	0	2	U	U	U	1	0/3	0/3	3/3	0/3	0/3	2	1	0
Ndungu, 2008[145]	Kenya	3	3/3	2	1	0	0	0	0	0	U	0/3	1/1	2/2	0/1	1/2	0	0	0
Sen, 2009[23]	Turkey	3	3/3	1	2	0	1	U	U	1	0	0/3	3/3	3/3	0/3	0/3	0	1	0
Kumar, 2012[146]	India	3	2/3	1	2	0	U	1	U	3	U	0/1	0/3	1/1	1/3	2/3	1	1	0
Seker, 2010[147]	Belgium	2	2/2	0	2	0	U	U	U	U	U	0/2	0/2	2/2	0/0	0/0	0	1	0
Zouhal, 2000[148]	Maroc	2	1/2	1	1	0	1	U	1	1	1	0/2	0/0	2/2	0/1	0/0	0	2	0
Escobedo, 2000[149]	Mexico	2	2/2	0	2	0	1	U	1	1	n	0/2	0/2	2/2	0/1	2/2	1	0	0
Chalazonitis, 2003[150]	Greece	2	2/2	1	1	0	U	U	1	U	1	U	1/1	1/1	2/2	0/0	0	0	0
Rakoto-Ratsimba, 2005[151]	Madagas-car	2	2/2	0	2	0	2	0	0	1	1	0/2	0/0	1/2	0/2	0/0	0	2	0
Gupta, 2006[152]	India	2	2/2	1	1	0	0	0	0	0	2	0/1	2/2	0/2	2/2	2/2	0	0	0
Morino, 2007[153]	Kenya	2	1/2	0	2	0	U	1	0	1	1	0/2	0/0	1/1	0/1	0/0	0	0	0
Soto, 2008[154]	Spain	2	0/2	2	0	0	U	U	2	1	U	0/2	0/1	2/2	0/2	0/2	0	0	0

Author, year and reference	Country	Number of cases	Type of lesions presentation	Localization			Clinical presentation					Diagnosis					Treatment		
Khair, 2010[155]	Maroc	2	1/2	1	1	0	U	U	1	U	U	0/2	0/0	2/2	0/0	0/0	0	0	0
Kapan, 2010[156]	Turkey	2	2/2	1	1	0	0	0	2	0	1	0/1	0/1	2/2	0/2	0/0	2	0	0
Hafidi, 2011[157]	Maroc	2	1/2	2	0	0	1	U	2	U	U	U	0/0	2/2	0/0	0/0	0	1	0
Zida, 2012[158]	Burkina Faso	2	2/2	1	1	0	U	1	U	U	1	0/2	0/0	2/2	0/0	0/0	1	0	1
Yanamandra, 2012[159]	India	2	2/2	1	1	0	1	1	U	U	U	0/2	1/2	2/2	1/1	2/2	1	1	0
Al-Roomi, 2009[160]	Kuwait	2	2/2	1	1	0	0	0	0	2	1	0/2	0/0	0/0	2/2	2/2	1	1	0

*=Lump lesions on the total of the case described; Lu=Lump lesion; L=Left; R=Right; B=Bilateral; Sf=Sinus or fistula; Su=Skin ulceration; Nr=Nipple retraction; Dis=Discharging sinus; Ly= Axillary lymphadenopathy; ATT=Antitubercular therapy; ATTO=Other antitubercular therapy; Biop=Biopsy; Cult=Culture; FNAC=Fine-Needle Aspiration Cytology; AFB=Acid-Fast Bacteria; PCR=Polymerase Chain Reaction; U=Unknown; Ex=Excision; Inc=Incision and drainage; Mast=Mastectomy.