Breast cancer is the most common cancer in women worldwide and 70% of breast cancer deaths occur in women from low-income and middle-income countries. Latin America has about 115,000 new cases of disease every year, with about 50,000 arising in Brazil. We examined the present status of breast cancer in Brazil as an example of the health effects of geographical, ethnic, and socioeconomic diversities on delivery of care. Our goal was to identify deficiencies that could be responsible for disparities in survival from breast cancer. We searched the English and Portuguese published work and reviewed national databases and Brazilian publications. Although the availability of publications specific to Brazil is low in general, we identified several factors that could account for disparities: delays in diagnosis due to low cancer awareness and implementation of mammography screening, unknown quality of surgery, and restricted access to radiotherapy and modern systemic therapies.

Introduction

Global statistics are based on data from high-income countries, where 76% of the women have access to private care and 24% have access to the public systems. In low-income and middle-income countries, only 12% of the women have access to private care and 88% access the public systems. In general, women in low-income and middle-income countries present with advanced disease due to lack of access to screening programs, and only a minority of such cases can benefit from this insurance and the public system. Cancer care through SUS is organized into state or regional referral centers that are responsible for providing diagnosis, staging, and treatment. Currently, there are 276 such centers in the country. According to a 2009 World Bank report, Brazil spent 9.8% of its gross domestic product (GDP) on total health expenditures and 45.7% of this sum was allocated to finance public health expenditures. By comparison with other countries, Brazil spent US$7.34 per head in 2009, which is substantially less than is spent in high-income countries such as the USA or UK (table 2).

Brazil has one of the fastest growing economies worldwide, and with economic growth the burden of infectious disease has lessened and the need to expand care for non-communicable diseases in an ageing population is becoming a priority. Furthermore, the demographics of Brazil have changed in the past decade, with the 2010 census showing an age pyramid that is weighted more towards adults and the elderly rather than children.

Breast cancer incidence and mortality

The Instituto Nacional de Cancer (INCA) branch of the Brazilian Ministry of Health provides epidemiological data for the distribution of cancer for the whole country, and by region, state, and state capital. This institute gathers yearly incidence and mortality statistics for breast cancer from population-based cancer registries and uses a repository for medical records within the national health system at municipal or state levels. Caveats are that for...
the 26 states and one district capital, there are 17 population based cancer registries, of which 16 are located in (and retrieve information from) the state capital only. Data collection varies between the different registries and within the same registry from one year to another. Furthermore, in the annual INCA publication of incidence and mortality estimations for the subsequent year, reported rates are not age-standardised. Age-standardised mortality rates are published by INCA in a separate index for the different regions and states within Brazil,26 with representation from all geographical regions and socioeconomic levels within Brazil. The median age of diagnosis was 58 years, compared with a median of 61 years in the USA.23 This study showed that women treated in public institutions had more advanced disease at presentation, less access to modern therapies, and worse overall survival than did patients treated at private institutions even after adjustment for stage and other known prognostic factors.27

Mammography screening and early diagnosis

The Brazilian Ministry of Health established national guidelines in 2004 recommending mammography screening at least every 2 years for women aged 50–69 years and every year starting at 35 years of age for women with a family history of breast cancer.28 Although screening guidelines were published in 2004, specific legislation was enacted only in 2008 to ensure access to mammography.

The number of women aged 50–69 years presently receiving mammography screening in Brazil is unknown. A recent audit of the public system showed that there are 1514 mammography machines in the country. More than 20% of mammography facilities in the northern and northeastern areas of Brazil are out of use, compared with 8.7% in the southern region.29 Moreover, the distribution of equipment is irregular; ranging from two mammography machines for the northern state of Roraima (population of 430 579 in 2010) to 335 machines in the southeastern state of São Paulo (population 41 262 199 in 2010).29,30

Nationwide, 50% of all women older than 50 years have had at least one mammogram but few receive regular screening.23 Regional screening rates confirm these trends; only 30–35% of women aged 50–69 years receive appropriate screening (mostly in the private sector) and 80% of women reported not having a doctor’s referral as the main barrier to screening.23,25
An INCA report suggested that 45% of screening mammographies in Brazil were undertaken in women younger than 50 years, although most new breast cancer cases are diagnosed in women aged 50 years or older. A report from the Information System for the Control of Breast Cancer (SISMAMA) showed that, between 2009 and 2010, half of more than 1.5 million screening mammographies undertaken through the public system were done for women aged 50–69 years. This number corresponds to about 755,000 mammograms for an estimated 15.8 million eligible women in this age group in 2010, or 4.78% of the target population of the national screening guidelines. Reimbursement data available from SUS for January to December, 2010, show that there were 3039269 screening bilateral mammographies authorised in the country. If, according to the findings from the INCA and SISMAMA studies, only half of these procedures were undertaken in the target population, the screening rate would be estimated at 9.6%. Nonetheless, these two rates are underestimates because there are no data available for the number of women that undergo screening through the private system. However, the rates are substantially lower than the WHO recommendation to screen more than 70% of the target population and the INCA goal to screen 60% of all eligible women. By comparison, 51.4% of women aged 50–69 years in the European Union underwent mammography screening from 2000 to 2008 as did 74.2% of women aged 50–64 years and 65.4% of women aged 65 years or older in the USA in 2008. That doctors in Brazil report that 80% of breast cancer cases are brought directly to their attention by patients is not surprising.

Breast cancer care

Delays in diagnosis

One issue that potentially affects clinical outcomes is the time delay between the initial suspicion of cancer to diagnosis and, subsequently, the time to treatment. Delays of longer than 12 weeks are believed to affect stage and consequently outcomes and survival. After suspicion of a cancer, referral from a community health centre to a large subspecialty institution is needed and delays do occur. Observational studies suggest the median time from presentation to diagnosis is 72–185 days. Delays between mammogram and imaging interpretation last up to 30 days for 66% of screening mammograms and 67% of diagnostic mammograms. One survey of doctors reported that delays of more than 3 months occur 20% of the time.

Stage at diagnosis

The Amazone study reported that 20.2% of patients in Brazil were diagnosed with stage I breast cancer and 46.8% had stage II, 24.6% had stage III, and 5.5% had stage IV disease. Comparatively, 61% of women in the USA present with localised disease, 31% with regional disease, and only 5% with metastatic spread. With regard to socioeconomic characteristics, the number of women with advanced breast cancer is higher in the public system than it is in the private health-care system in Brazil. Almost 37% of patients in public institutions were diagnosed with stage III–IV disease versus 16.2% from private institutions. Unpublished data from this study also suggest that there are regional differences in stage at presentation. In the north, only 8.4% of women were diagnosed with stage I disease and up to 46.2% were diagnosed with stage III–IV disease. The centre-west region also had lower rates of stage I disease (12.3%) and higher rates of stage III–IV disease (31.9%). These rates contrast with 24.7% for stage I disease and 25.1% for stage III–IV disease in the south.

Diagnostic accuracy and effect on treatment

The quality of biopsy sampling and testing for predictive tumour markers, especially hormone receptors and HER2 expression, is crucial for diagnosis, prognosis, and treatment decisions. Although breast cancer is now the most frequent cancer diagnosis in women in the country, there are no official national programmes in place aimed at standardisation of these procedures. Information available from the published work is also sparse. 22% of fine-needle-aspiration biopsy procedures obtained inadequate material for cytopathological analysis. Regional variations occur and higher rates of inadequate biopsy procedures were reported in Bahia state (37%) and Goiás state (38%). This overall rate is raised because insufficient sampling is expected in only 4–13% of palpable breast lesions and 36% for non-palpable lesions.

Concordance in diagnosis between two pathologists for 329 breast biopsy cases in one study was only 60%. The highest rates of concordance were with invasive breast cancer (81%) and the highest rates of discordance occurred with premalignant lesions (lobular carcinoma in situ 70% and atypical epithelial hyperplasias 61%). A straightforward tutorial that reviewed diagnostic criteria for premalignant lesions and representative images improved diagnostic concordance in five pathologists. With regard to biomarker analyses, immunohistochemistry testing for HER2 is not standardised in Brazil and is not available at all centres. When available, low

### Table 3: Age-standardised incidence, mortality, and ratio of mortality to incidence ratio

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence per 100 000 women</th>
<th>Mortality per 100 000 women</th>
<th>Mortality-to-incidence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>42.3</td>
<td>12.3</td>
<td>0.291</td>
</tr>
<tr>
<td>South America</td>
<td>44.3</td>
<td>12.2</td>
<td>0.298</td>
</tr>
<tr>
<td>USA</td>
<td>76.0</td>
<td>14.7</td>
<td>0.193</td>
</tr>
<tr>
<td>UK</td>
<td>89.1</td>
<td>18.6</td>
<td>0.209</td>
</tr>
<tr>
<td>European Union</td>
<td>77.1</td>
<td>16.6</td>
<td>0.215</td>
</tr>
</tbody>
</table>

Adapted from GLOBOCAN 2008. GLOBOCAN data can be verified at http://globocan.iarc.fr/
concordance of HER2 testing might occur between local laboratories and the reference centre; a 34% concordance rate was reported between local and central testing of 500 consecutive cases.46

Breast cancer surgery
Breast cancer surgical techniques are important for staging and for locoregional control, which both affect survival. Women treated by breast surgical specialists have a lower risk of death than those treated by general surgeons.47 Poor quality surgery is also associated with increased use of radiation and systemic therapy, which increase the cost of care.48 Positive margins have been associated with increased rates of nodal irradiation and adjuvant systemic therapy.50 The number of women treated by specialists versus general surgeons and the quality of surgery needs further investigation. Our search did not find studies analysing quality of surgery in Brazil. According to official reimbursement data from SUS in 2010, 65% of therapeutic breast surgeries were mastectomies and 35% were lumpectomies.51 Only one study compared surgical differences between the public and private health systems.52 Results from this study suggested that rates of mastectomy are lower in the private system (40·1%) than they are in the public system (51·7%).

Radiotherapy
Radiotherapy provides local control and improves overall survival in early and locally advanced breast cancers. The availability of radiotherapy establishes whether breast conservation is an option. In general, there is a shortage of radiotherapy resources in developing countries and this might increase rates of mastectomy.53 Types and quality of available radiation equipment have not been adequately reported in Brazil. Linear accelerators and cobalt-60 machines are used. Although the number of radiation units in Brazil (0·93 per million population) is comparable with the median number in other Latin American countries (0·45–2·73 per million), there are fewer radiotherapy centres in Brazil than the USA (8·85 per million).54 INCA’s Consultive Council has established that one of the priorities for radiotherapy in Brazil is to increase the number of centres and their capacity for care.4 In the Amazone cohort, 76% of women received adjuvant radiotherapy.55

Systemic treatment
For patients with hormone-receptor positive tumours, tamoxifen is widely available in Brazil for adjuvant therapy, independent of women’s menopausal status. Tamoxifen is preferred mainly because it is off-patent and thus cost effective. Aromatase inhibitors used sequentially or in place of tamoxifen for postmenopausal women improve relapse-free survival and might improve overall survival in some subgroups compared with tamoxifen alone.56 Cost-effectiveness analyses comparing 5 years of upfront anastrozole to 5 years of tamoxifen have concluded that anastrozole therapy in early disease is cost effective in Brazil for patients who are publicly or privately insured.57–59 More than 88% of patients with breast cancer in Brazil receive adjuvant chemotherapy.60 However, substantial differences exist in the chemotherapy regimens used. More than half the patients treated in public institutions receive first-generation regimens, such as cyclophosphamide, methotrexate and fluorouracil or doxorubicin and cyclophosphamide, compared with less than a third of patients treated in private institutions.61 While taxanes were still patented, they were used in only about 14% of patients from public institutions compared with more than 23% from private institutions.62 Since generic taxanes are now available, whether such disparities in access between the public and private systems still exist is uncertain.

Access to anti-HER2 therapy is very restricted in the public health system. In 2006, only 5·6% of patients with HER2 positive tumours received anti-HER2 therapy in the public health-care system compared with 56% in the private sector.63 Trastuzumab is costly for the public health system and this cost has largely precluded its adoption as a standard.

Palliative care
For advanced cancer, health systems need to offer palliative care to alleviate pain and unnecessary morbidity. WHO recommends that every country offer a comprehensive national palliative-care programme. The availability of palliative-care services varies between Latin American countries and little research has been done in this area. Brazil only has 14 centres offering palliative care and had the lowest ratio of hospice or palliative-care services per population in 21 countries examined in the Americas and Caribbean (one service per 13 315 000 patients in Brazil, 7 645 000 in Mexico, 90 000 in the USA, and 65 000 in Canada).64 More than 70% of Brazilian doctors reported in a survey65 that palliative care is “not a priority in formulation of health care policy” and “not a priority in health care education”.

Breast cancer research
Overview
Clinical research specific to Brazil could guide when, how, and in whom to use new treatments. Doctors and policy makers around the world could best address health needs of the local population by use of evidence-based medicine relevant to their country. Table 4 shows a summary of publications about breast cancer from Brazil compared with other emerging countries and the USA.

Funding for clinical research
94% of oncologists practising in Latin America reported that there was insufficient clinical-epidemiological research on breast cancer in their country.66 Important barriers to research were insufficient financial support (78·7%) and lack of dedicated time (61·8%). Only 1% of research was stated to occur at universities or in co-operative groups.67
Although further investment in clinical research is needed throughout Latin America, Brazil is already a leader in this area, with the highest number of clinical trials for breast cancer in the region: according to ClinicalTrials.gov, 105 clinical trials were open for breast cancer in Brazil in November, 2011, compared with 74 in Argentina, 67 in Peru, 39 in Chile, 29 in Colombia, nine in Venezuela, five in Uruguay, three in Ecuador, and one in Bolivia. 83 (79%) of the 105 registered trials in Brazil for breast neoplasms (one trial per 1 800 000 people) were funded by industry. By contrast, 2726 clinical trials were registered in the USA (one trial per 110 000 people) and 835 (31%) of these were funded by industry.

Apart from government funding, charity contributions for research have a major role in high-income countries. In Brazil, there are no statistics that document the amount of philanthropic funding for breast cancer research. However, general information on private funds for cancer care in Brazil suggests that most funding is directed towards care of patients and not research.

Research from clinical trials

Many Brazilian clinical trial sites have higher enrolment rates than do those in the USA or Europe. One reason for these high accrual rates is the disparity in access to good standard therapies in many public services, making the participation in clinical trials an attractive option for patients.

Although high accrual rates make Brazil an ideal country to undertake clinical research, doctors need to be aware of factors that could propagate disparities in care. Although Brazil is one of the countries labelled as a pharmaceutical industry in 2008, access to new medications is often restricted to patients with private insurance or financial means to pay expenses out-of-pocket. The ethics of clinical trials in developing countries should be reviewed when patients from low-income and middle-income countries, despite contributing to clinical trials, will not have access to new drugs once they are marketed. For example, 88% of new drugs launched in 2005–09 were used by the American, European, and Japanese markets.

Brazil has a conservative approach to clinical research approval with a strict and lengthy regulatory process. The average time for regulatory approval of a research protocol in Brazil is 6–7·5 months compared with 2–3 months in the USA. This has an important effect in the competitiveness of the Brazilian clinical research community: many projects are not done in the country because of this delay. The balance between careful ethical scrutiny and timely approval is delicate, and should be the subject of continued discussions and reassessment.

Discussion

In developing countries such as Brazil where the health system serves a diverse population, a systematic approach to cancer services will improve long-term outcomes. The need for epidemiological research that correlates clinical outcomes with trends in prevention, screening, diagnosis, and treatment should be recognised and addressed. Interventions that improve cancer outcomes should be implemented. Increased public awareness of breast cancer and expansion of access to screening are strategies that will reduce breast-cancer mortality. The Ministry of Health in Brazil and non-governmental organisations have already initiated efforts to improve early diagnosis and promote breast cancer screening and education in Brazil. The Brazilian Government has recently announced increased investments until 2014 for breast and cervical cancer screening.

The role of mammography for screening in low-income and middle-income countries is controversial. To be effective, screening programmes have to target women who will most probably benefit. With regard to the burden of disease, benefits of screening must be weighed against costs of a national programme. Improvements in treatment in developed countries have had a greater effect on breast cancer mortality than has mammography screening. Thus, some international public health officials suggest that there should be more investment in breast cancer treatment rather than screening in low-resource settings and that the harms of screening must be weighed against any benefits. Since Brazil already has a large number of mammography machines installed, reasons for the low screening rates need investigation to determine how to best use the existing equipment. For public investment in screening programmes to be cost effective, screening rates must be improved and the use of existing resources optimised.

Reasons why some regions have lower incidence of breast cancer than do others need to be examined. Differences have been attributed to dietary habits, socioeconomic status, parity (ie, having borne children), and ethnic ancestry. Other issues might include differences in the age distribution of the female population within the country. Competing illnesses such as cervical cancer, which remains the most frequent cancer in women in the north of Brazil, might also have a role. Internal migrations in search of health care also occur and are largely unaccounted for in the data analyses. Finally, bias caused by improved accuracy of diagnosis or data collection in the southern regions cannot be ruled out as explanations for these trends.
Educational differences and disparities in access to screening between the public and private sectors and between different regions and how they might affect rates of early diagnosis of breast cancer in Brazil needs to be clarified. In high-income countries, socioeconomic factors seem to affect breast cancer stage: women with a low socioeconomic status are most likely to present with late-stage disease.72

Frequent delays in the public health system could result in advanced cancer at diagnosis. Factors that contribute to delays between the suspicion of cancer and therapy need to be identified and addressed. Successful experiences such as the patient navigation programme that reduced late-stage disease presentation and increased early disease detection would be of interest to study in Brazil.73

Diagnosis of breast cancer needs to be accurate and low pathological concordance rates could be improved. In low-resource countries, inaccuracies such as a 34% HER2 concordance rate in diagnosis will increase overall costs and decrease the effectiveness of treatment. Our Review emphasises the need to standardise and ensure that high-quality biopsy sampling, pathological assessment, and immunohistochemistry testing are done.

Diagnostic procedures need to be standardised. Additional research into surgical characteristics and trends are required. Access to radiotherapy should be expanded and innovative ways to deliver therapy should be explored for areas where resources are restricted. For example, accelerated partial breast irradiation might provide similar outcomes to conventional radiotherapy and allows for a shorter period of treatment.74 Experimental techniques such as adaptation of the use of electron intraoperative radiotherapy (ELIOT) to a conventional linear accelerator have been reported in Brazil, but need to be properly assessed in a randomised trial.75 Discussion is needed about the appropriate ways to increase the number of available radiotherapy machines. Although linear accelerators are the predominant technology in high-income countries, use of cobalt-60 machines is accepted in low-income settings and might have lower costs.76 Conversely, cobalt-60 machines are technically more restricted in their ability to deliver some treatments and can result in an increase in radiation-related complications.77 INCA suggests that there is a trend in Brazil favouring linear accelerators.78

Delivery of effective systemic treatments and palliative care needs to be addressed. Cost-effectiveness analyses specific to Brazil are needed to guide therapy. Tamoxifen is the present standard in the public health system and treatment with aromatase inhibitors is restricted to postmenopausal women with metastatic disease because of its high cost. As generic aromatase inhibitors become available, adjuvant hormonal strategies such as tamoxifen-aromatase inhibitors switch or extended aromatase inhibitor therapy should be considered for women with early breast cancer. In the meantime, tamoxifen should remain the mainstay of hormonal therapy in Brazil’s public health system.

Availability of trastuzumab for women with HER2 tumours in the public health system should be expanded. Women with such tumours are ten-times more likely to receive trastuzumab if they are privately insured. Stakeholders need to find alternatives to overcome this disparity in access to targeted therapy. Standardisation of HER2 assessment, alternative anti-HER2 therapies, and schedules of administration, risk-benefit assessments, and cost-effectiveness analyses are all potential ways to achieve this endpoint.78–79 In addition to cancer therapies, palliative-care services need to be strengthened within Brazil. Access to pain medications and supportive therapies should be prioritised for patients with advanced cancer at the end of life.

Although investment in low-income and middle-income countries in a strong research infrastructure is a challenge, local research is important as it can help policy makers allocate limited resources and improve the effects on cancer outcomes. As patients enter the era of targeted cancer therapies, disparities in access to available therapies will continue to widen between and within countries. Pharmacoeconomic endpoints will be particularly important to establish what treatments should be available through public health-care systems.

The aim of our Review was to provide systematically gathered information about the scope of breast cancer care in the largest country in Latin America. Nonetheless, our Review had limitations. Specific data from low-income and middle-income countries are sparse, non-existent, or underreported, meaning we had to rely mostly on small studies that might not represent the country as a whole. Information was scattered, and although the main sources available were consulted, studies might have been missed, specifically those that are ongoing or have not been

Search strategy and selection criteria

We searched PubMed with the MeSH terms “breast neoplasms” and “Brazil”, “breast neoplasms/epidemiology” and “Brazil”, and “breast neoplasms/therapy” and “Brazil”. We also searched the Scientific Electronic Library Online (SciELO; a research database originally developed in Brazil that includes medical and scientific publications in Portuguese) with the terms “câncer de mama” [breast cancer], “neoplasia de mama” [breast neoplasms], and “tumores de mama” [breast tumours]. We obtained official cancer statistics, including incidence and mortality data, and population demographics for Brazil from published resources made available online by the Brazilian Ministry of Health, the National Institute of Cancer of Brazil (INCA), and the Brazilian Institute of Geography and Statistics. We also assessed data from Brazilian medical societies, WHO, and GLOBOCAN 2008, and manuscripts and abstracts from scientific conferences. We included information published between Jan 1, 1990, and May 31, 2011, in English or Portuguese.
indexed in peer-reviewed journals (i.e., publication bias). Ways to improve care presented in this Review are only suggestions, and decisions to implement these or other solutions require further discussion between governments and society. Conversely, the strength of this Review is that we discuss the present state of care for breast cancer in Brazil and provide one source of information that might be used not only by the Brazilian stakeholders, but also by other countries facing similar issues.

The growing burden of cancer in low-income and middle-income countries has emerged as a major public health issue. This disparity will only grow in the future, and every country or region must assess their specific needs and priorities to tackle such a challenge. Contributors

BLL and PERL did the literature search. BLL, PERL, CHS, and PEG planned the manuscript. All authors contributed to the writing of the report.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
PEG, DMF, and PERL are supported by The Avon Foundation New York, NY, USA, which had no role in the planning or writing of this manuscript. BLL would like to thank the Department of Medicine and Division of Global Health for supporting her clinical rotation in Brazil, and the Pontifícia Universidade do Rio Grande do Sul.

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