# A review of breast cancer care and outcomes in Latin America

American Cancer Society

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Regional Office of the World Health Organization

SLACOM

Sociedad Latinoamericana y del Caribe de Oncología Médica
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# ACKNOWLEDGEMENTS.

This document was written by Nahila Justo MPhil MBA, OptumInsight, Nils Wilking MD PhD, Karolinska Institutet, Prof. Bengt Jönsson PhD, Stockholm School of Economics.

This study would have not been feasible without the heartfelt and generous contributions of Alessandra Durstine, American Cancer Society (ACS), Silvana Luciani, Pan American Health Organization (PAHO), and Eduardo Cazap, Latin-American & Caribbean Society of Medical Oncology (SLACOM).

We are also greatly thankful to the clinical experts that provided us with valuable input on breast cancer treatment, service configuration and outcomes in their countries: in Argentina Dr. Maria Viniegra; in Brazil Dr. Antonio Bassani and Dr. Antonio Buzaid; in Chile Dr. José Miguel Reyes and Dr. Roberto Torres Ulloa; In Colombia Dr. Hernán Carranza; in Costa Rica Dr. Gonzalo Vargas and Dr. Denis Landaverde Recinos; in Ecuador Dr. Hernán Lupera and Dr. Fernando Checa; in Mexico Dr. Flavia Morales-Vásquez and Dr. Benito Sánchez; in Peru Dr. Henry Gomez Moreno and Dr. Carlos Vallejos; in Uruguay Dr. Graciela Sabini and Dr. Gabriel Krygier; and Venezuela Dr. Carlos Montesino Acosta and Dr. Karen Kubicek.

Finally, the patients view was greatly informed by a number of patients' organizations that, overcoming their sometimes limited access to official or aggregated data, helped us gain a better understanding of their constituents' understanding. We are grateful to the following organizations: Instituto Oncoguia, Asociación Mexicana de Lucha contra el Cáncer de Mama (CIMAB), Asociación Mexicana de Lucha contra el Cáncer (AMLCC), Yo Mujer, Esperantra, Fundación Nacional de Solidaridad contra el Cáncer de Mama (FUNDESO), Fundación Anna Ross, Rehabilitación Integral en Patología mamaria (RIPAMA), FUNCAMAMA and FUNDASENO.

Both, clinical experts and NGOs, participated through a survey that significantly contributed to the study.

All opinions expressed in this report, along with the conclusions and recommendations are those of the primary authors and may not reflect the views of those who contributed to this report.

The study was financed by unrestricted grants from F. Hoffmann-La Roche International.

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# SECTION 1.
# INTRODUCTION

## 1.1. Background

The burden of breast cancer, as well as the management and organization of breast cancer (BC) care in 18 countries [Brazil, China, Denmark, Finland, France, Germany, Hungary, Italy, Mexico, the Netherlands, Norway, Poland, the Russian Federation, Slovenia, Spain, Sweden, Turkey and the UK] was presented recently in a global report titled "A Review of Breast Cancer Care and Outcomes in 18 Countries in Europe, Asia and Latin-America"[1]. The best available data on outcomes of BC care were analyzed together with initiatives to increase early diagnosis and rapid access to evidence-based treatment; along with limitations in patient access to the most appropriate diagnostics and treatment.

Supported by data from Globocan 2002[2], that report states that BC is the most common form of cancer in women; affecting approximately 1.2 million women. Breast cancer, with 4.4 million survivors up to 5 years following diagnosis, remains the most prevalent cancer in the world. A few months after that global report was finalized, the International Agency for Research on Cancer (IARC) published GLOBOCAN 2008[3], which revealed that in 2008 1.38 million new BC cases were diagnosed, 23% of all cancers. The difference in incidence rates between developed and developing countries is still remarkable. As Figure 1 shows, age-standardized incidence rates in Western Europe are still almost 5 times higher than those in Eastern Africa (89,9 per 100 000 woman compared with 19,3), while Latin America and Caribbean (LAC) is somewhere in the middle with 40/100,000 women.

As documented in the literature, a mixture of demographic, hereditary, environmental and lifestyle risk factors account for this variability [4, 5] but differences regarding detection and diagnosis as well as case and death registration, also have an impact on the disease burden.

The burden of BC remains considerable, both in terms of suffering for patients and their relatives and an economic burden to society. Along with the increase in BC incidence, more women died from breast cancer in 2008 than in 2002; 458,000 women died from BC in 2008 worldwide, an increase of 47,000 women than in 2002 as reported by IARC in Globocan. Despite the large difference in BC incidence, mortality rates are similar between developing and developed regions because the latter countries have managed to improve survival (see Figure 1). The high direct costs of BC exposed in the global report also present a significant variability across the countries in the study in relation to the overall spending on healthcare and we found that, as the majority of women affected with BC are of working age, the indirect costs are considerable, estimated to be as much as twice the direct costs of BC based on recent assessments in some European countries.

The review of treatment patterns and the organization of BC care were hampered by the lack of available data, so it was concluded that there is a need for cancer registries that capture not only cancer incidence and mortality but also clinical practice in relation to more specific outcome measurements, including patient-rated outcomes such as quality of life. As for the guidelines for the organization and treatment of breast cancer, the global report found that they are available in almost all countries, but only monitored in a minority of them. These guidelines often refer to international guidelines such as the St. Gallen expert consensus meeting (for adjuvant therapy), ESMO (European Society for Medical Oncology), ESO (European School of Oncology) and the guidelines published by NCCN (National Comprehensive Cancer Network) in the United States, though, they are adapted to the local resource availability and/or how rapidly novel clinical evidence is incorporated. Evidence-based best practices for the design and implementation of patient-focused cancer care are limited in many countries. Although there are trends in many countries toward more patient-focused cancer care, as of now the patient perspective is not taken fully into

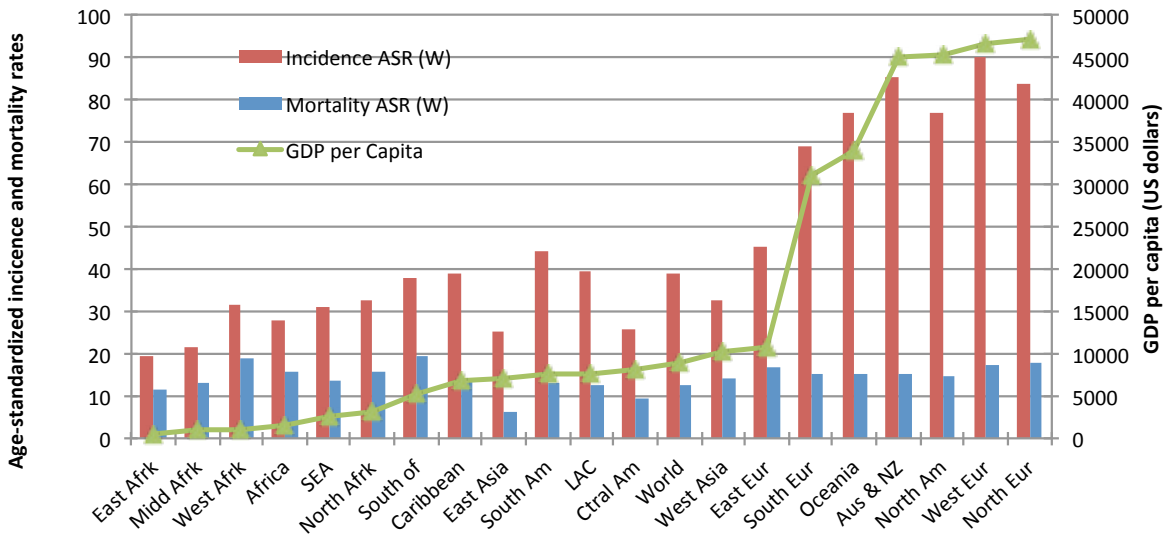
account; patient satisfaction regarding aspects such as communication, continuity, accessibility and response times need to be captured and analyzed as input to the re-organization of cancer care. The fragmented organization and management of BC care has been acknowledged by many countries and there have been extensive efforts to analyze and re-organize cancer care, resulting in the development of nationally coordinated strategies ("cancer plans"), for example the UK, France, Denmark or Norway.

When it comes to prevention, the global report found that primary prevention of BC is still an area under debate. We have information from several well-performed prevention trials providing evidence that prevention is feasible, although it seems that those treatment options currently available are still not targeted to the right population. Secondary prevention through the early detection of BC via mammography screening has been in place for more than 20 years in many countries. However, many women still do not have access to screening programs. There is a positive relationship between the stage of cancer at diagnosis and outcome. In some, especially developing countries, many patients are still diagnosed at an advanced stage of disease, resulting in a poor overall outcome. The area of BC diagnosis and sub-typing of the disease is likely to change over the next few years as understanding of BC biology increases and the use of biological markers expands.

It was also determined in the global study, that the major reason behind the dramatic progress observed in the outcomes of BC over the last 20-30 years has been the introduction and the improvements made in adjuvant therapy with chemo-, endocrine and now also biological therapy. Drugs like tamoxifen, the anthracyclines, the taxanes, aromatase inhibitors and now also HER2-interacting drugs, have all contributed to the marked reductions seen in BC relapses. Access to adjuvant therapy varies greatly, in spite of evidence based guidelines about their use, even many years after the drugs have been approved.

Finally, and in spite of the advances we have seen in the curative treatment of breast cancer, a significant number of women will suffer a relapse and many will develop metastatic disease. For these women it is extremely important that there is easy access to specialized care. We now have a huge therapeutic arsenal of treatments for palliation of symptoms and supportive therapy. These treatment options include surgery for metastatic complications and palliative radiotherapy but most of all a number of anti-tumour as well as supportive care drugs.

**FIGURE 1.** Breast cancer incidence and GDP per capita, 2008.



Almost all anti-cancer drugs are developed in metastatic BC as first- or second-line interventions and all adjuvant drugs have proven to be of clinical benefit in the metastatic stage before they are developed as adjuvant drugs. Some drugs, like the bisphosphonates, have had a major impact on quality of life of BC patients and these drugs may also have a possible role in the adjuvant setting.

The global report concluded that the introduction of new technology will put pressure on healthcare systems, regardless of the country. Of course this is especially true in countries with limited resources such as developing countries, where it will be increasingly important to continuously assess the effect of new treatments and medical interventions in clinical practice to be able to link treatment patterns to outcome. Health technology assessments and economic evaluations need to be used to guide decision makers in priorities, and to ensure that new treatments that are cost effective gain market access quickly. It is also important that such evaluations do not delay the introduction of new treatments more than necessary.

## 1.2. Study rationale

Given the relatively high degree of uncertainty and cross-country variation, it became evident that a study with geographical focus that included more countries in each region would facilitate the BC situational diagnosis among countries facing similar challenges with similar resources. A number of Europe-wide studies have been published and thus, an indepth analysis of BC care and outcome in Latin-America was carried out.

This study is an expansion of the previous research that only included Brazil and Mexico, where we could already anticipate that the burden of breast cancer, the optimal pattern of care, and the identified issues regarding patient access to the latest and efficacious treatment innovations present Latin America with significant challenges. They need to be better documented and further discussed in order to identify the most viable opportunities for improvement.

## 1.3. Study objective

This report aims to give an overview of the burden of BC and of BC care and outcomes with the focus on Latin America. Additionally, the current practices are described and assessed against evidence based best practice strategies in BC management. Finally, areas which require further improvement are identified. Using the data available, relationships between care elements such as treatment patterns, care organization and patient experiences are examined.

The countries covered in the study are Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay and Venezuela. The selection of countries was based on data availability and accessibility.

## 1.4. Materials and methods

The study is based on a review of literature and public databases, and a survey of clinical experts and patient organizations. The literature review, focusing specifically on treatment patterns and costs of BC in each study country, was conducted in MEDLINE, LILACS and SciELO but included also grey literature targeting data and information on the epidemiology of the disease and its outcomes in the region as well as treatment guidelines, cancer control plans, and documentation on the cost of breast cancer.

The Pan American Health Organization, the American Cancer Society and the Latin-American and Caribbean Society of Medical Oncology provided information, data and contacts for the interviews and other global sources were consulted. All data available in consolidated databases offer the advantage of consistent comparisons and uniform format, thus, data available from such sources were used whenever possible. However, if local data sources were available and had significantly different data from those in the international databases, the differences are reported.

Finally, a series of structured interviews/surveys were conducted. Two clinical experts in each study country were contacted and asked to participate in the project by providing answers to the questionnaire developed for

the Global report. As in the global report, input from the national clinical experts is presented in different parts of the report, and referenced as such. In order to capture the patients' perspective on BC care in the study countries, a questionnaire directed to patients' organizations was completed.

This study faces a number of limitations mostly due to the lack of data. Perhaps the most important to bear in mind when reading this report is the publication bias. Many factors influence the research and intellectual production in the countries under study resulting in very diverse volumes of evidence [6, 7] and, while for some countries rich materials and data have been identified, for others, only a few and scattered articles were found.

# SECTION 2.

## Health and economic burden of breast cancer in Latin America

## SUMMARY


- *An estimated 114,900 women are diagnosed and an estimated 37,000 women die of breast cancer every year in Latin-America and the Caribbean (LAC).*
- *Breast cancer is the most common and kills more women than any other cancer type in the Region.*
- *Despite the scarcity of cancer registries, we could corroborate that in most countries, breast cancer incidence and mortality are increasing. Number of deaths from BC is expected to double by 2030, to 74,000 every year.*
- *Ageing is the principal risk factor of BC. Changes in the demographical structure will cause epidemiological shifts i.e. in Brazil or Mexico and by 2020, BC will approach epidemic proportions in LAC.*
- *BC burden affects countries differently. In Peru, Mexico, Colombia and Brazil, for example, younger age at diagnosis and death deprives societies of numerous productive years; as does the high occurrence of the disease in Argentina and Uruguay.*
- *The economic burden is also significant, and it can be clearly observed that countries today allocate insufficient resources to tackle the disease. Women go undiagnosed, uncared for or treated with suboptimal therapies; which results in high morbidity and the associated societal costs*
- *Universal health-care coverage is still lacking in many countries in the region and, even in those countries where the entitlement to BC health services is guaranteed by law, it is not accompanied by the necessary resources.*
- *Vast inequities exist in access to BC health care in the region and within countries which translates in unequal results in BC outcomes.*


### 2.1 Epidemiology

BC is the most common cancer form in women worldwide and Latin America is no exception. An estimated 114,900 women are diagnosed every year and 37,000 die of the disease in the Region [3].

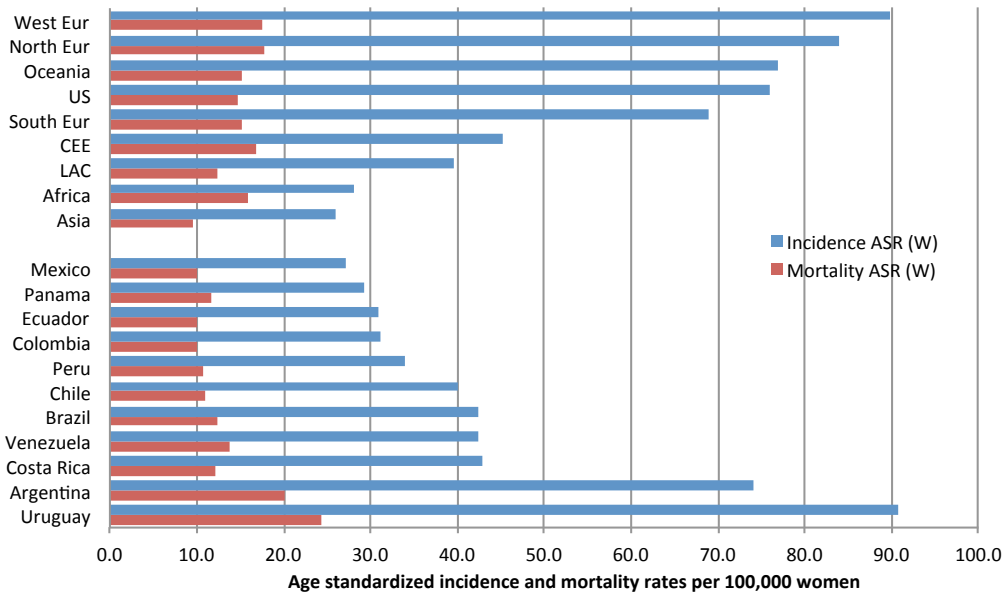
The variability within the Region is as large as that between Latin America and other regions of the world as can be seen in Figure 2. Uruguay and Argentina's crude incidence rate are five- to six-times higher than those of Panama and Mexico, and at the level of Europe and the USA. Incidence in the region seems to cluster geographically. The lower rates in some parts of Latin America (Mexico, Panama, Ecuador, Colombia) are at levels comparable to those from Asia, Africa and slightly less than Central and Eastern Europe; while the high incidence in the south of Latin America (Uruguay, Argentina, Chile) are at levels similar to those of Europe or the USA. Costa Rica appears as an exception; probably due to their demographic structure, which resembles more that of the Southern Cone rather than its neighbours. We will analyse all potential explanations in detail in Section 2.2, but it is worth mentioning that by 2020 countries like Brazil and Mexico will have a similar demographic structure as Argentina's today [8]. If their epidemiological profile shifts consequently, the occurrence of BC will approach epidemic proportions in the region.

Mortality in the region is also dissimilar. Driven by their high incidence, Argentina's and Uruguay's rates even surpass those of the countries with the highest incidence in Europe and the USA. The other countries converge around 10-13.7 deaths per 100,000 women, below European and North American levels.

According to Lozano Ascencio and colleagues [9], BC incidence and mortality have been increasing steadily in the region throughout the past 25-30 years. Jacques Ferlay and the Globocan team specifically warn against interpreting their successive incidence estimates as a time trend and no other source produces longitudinal data on BC incidence in the region. Thus, we can only analyse the evolution of incidence over time where national or regional registries provide comparable data. In the recently published report "III Atlas de Incidencia del Cáncer en el Uruguay 2002 – 2006", Barrios and colleagues estimated 1760 average annual new cases for those years, representing an incidence rate of 105/100,000 [10]. Compared with the period between 1996 and 1997 when the average annual cases were 1730 and the incidence rate was 105.7 [11], the incidence of BC seems to have stabilized in Uruguay. In contrast, Brazil's incidence rate has tripled in 15 years according to Ruffo Freitas-Junior and colleagues who estimated that the crude incidence of the state of Goiânia, Brazil has increased at an average 7.6% compound annual growth rate (CAGR) from 22.9/100,000 in 1988 to 68.2 in 2003 [12]. Similarly, Chile's Ministry of Health reports that the crude incidence rate had been growing at an average 10.7% CAGR from 28.9/100,000 in 2000 to 39.2/100,000 in 2003[1] [13]. Finally, Costa Rica's incidence has been increasing steadily since the mid nineties as can be appreciated in Figure 3, at an average 5.1% CAGR from 23.64/100,000 in 1995 to 35.2 in 2003 [14].

Given that the difference in incidence rates between developed and developing countries is due to a combination of demographic, hereditary, environmental and lifestyle risk factors, and that, in many newly-industrialized countries and transition economies rapidly changing lifestyles expose more and more women to breast-cancer specific risk factors, we can expect further increases in the incident cases in the years to come in the region. In Figure 4 we can observe that fertility has been decreasing steadily in all the countries under study [15]. Effectively, Sylvia Robles and Eleni Galanis [16] found that at the population level, fertility rates are inversely associated with BC incidence in Latin America; which is consistent with the longitudinal

**FIGURE 2.** Age-standardized incidence and mortality rates, new cases/deaths per 100,000 women.




Source: Globocan 2008, IARC

[1] Estimate based on cases registered by the public health system that covers 68.4% of the population. Female population for the period was taken from CEPALSTAT.

evolution of the variables. Socioeconomic development and the consequent adjustments in reproductive behaviour as well as other women's-lifestyle changes such as higher alcohol consumption, sedentarism and overweight increase significantly the individuals' risk of developing BC. When these phenomena occur on a country-aggregated basis, BC incidence grows.

hese trends affect all the countries in the region where BC incidence is expected to increase. However, the current situation of BC risk factors in each country differs and, in Section 2.2, we will analyse them in detail.

Before closing this Section we need to introduce a word of caution. IARC's estimates constitute the basis of this study for consistency purposes. However, the lack of a national consolidated registration system in most of the countries under study, may lead to incidence under- or over-estimations. Of the countries studied in this report, Brazil, Colombia and Costa Rica appear to be the only countries for which local data is produced from their own cancer registries. In the rest, IARC's estimates were produced using models that extrapolate data from neighbouring countries. This is the case even in Uruguay, where the National Registry reports incidence and mortality based on the registries of all the public and private hospitals, oncology clinics, radiotherapy centres, clinical pathology laboratories and Death Certificates.

In our search, we found data comparable to that of Globocan 2008 issued by local authorities that reported slightly different numbers. For example, the National Registry of Tumors from Costa Rica reported crude incidence and mortality rates for breast cancer of 37.7 and 10.2 per 100,000 women while with Globocan 2008 they result in 42.9 and 12.0 respectively. The difference between the two estimates is proportionally the same so the resulting mortality-to-incidence ratio (MIR) is practically the same. Unlike the case of Uruguay, where the National Cancer Registry –Urucan- reports that between 2004 and 2008, the annual number of cancer cases and deaths are 2200 and 829 respectively, while Globocan reports 2258 new cases and 729 deaths per year, resulting in slightly different mortality to incidence ratio (MIRs) i.e. 0.38 vs 0.32. A similar case is Brazil where the National Cancer Institute reports 48,930 new cases and 11,735 deaths in 2006. Compared to Globocan's estimates of 42,566 cases and 12,573 deaths, the yielded MIRs are 0.24 and 0.30 respectively. The differences are not substantial as the ranking does not change and all sources confirm the

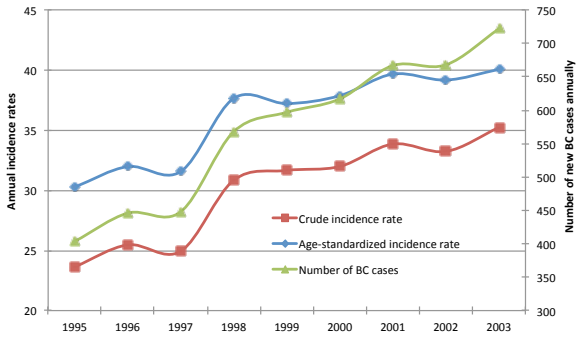



**FIGURE 3.**

Evolution of BC annual incidence in Costa Rica (incidence/100,000 women - number of cases).

Source: Costa Rica National Tumor Registry [14]

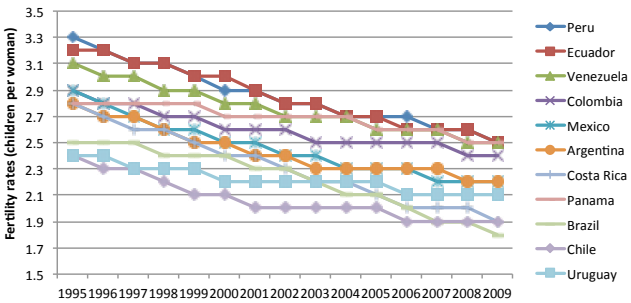



**FIGURE 4.**

Fertility rates in Latin America, 1995 through 2009

in-crescendo trend of both incidence and mortality but it is worth bearing in mind that these estimates are based on a number of assumptions and, therefore, carry uncertainty.

In a survey across 96 Latin American opinion leaders, Cazap reports that nearly 75% of them stated that some type of cancer registry was available [17]. Only Costa Rica and Uruguay count on a national comprehensive registry, and the latter publishes only 5-yearly statistics. Much of the data reported in the rest of the countries is estimated based on regional registries from small geographic areas and those data that are sometimes pooled and extrapolated to represent national figures. The generalizability of those records remains unclear, given the sometimes huge disparities within the countries which are not accounted for. Let's take the example of the countries for which geographically discriminated information is available. In 2007, the National Tumour Registry (Registro Nacional de Tumores) in Costa Rica reported age-adjusted incidence rates that range from 4.27/100,000 to 62.68/100,000 in Hojancha and Montes de Oca cantons, respectively [18]. In Brazil, the National Cancer Institute (INCA) also reports big differences between the 68/100,000 incidence rate in the south-east of the country compared to 16/100,000 in the north-west [19]. Finally, in Uruguay, age-standardized incidence rates in the capital Montevideo is also higher than that of the Department of Rio Negro (85.12/100,000 and 69.93/100,000 respectively) [10].

## 2.2 Risk factors and countries' risk profile

Many studies have explored a wealth of risk factors to which women in the different countries are exposed in varying degrees and which impact on the countries' incidence. We could classify them as demographic- and socioeconomic-related, genetic- and racial-related, hormone- and reproductive behaviour-related and lifestyle-related risk factors as presented in Table 1.

The main contributing factor to BC incidence remains age [5]. We found that mean age of the countries' female population is highly correlated with the occurrence of the disease which is consistent with the international literature, and illustrated in Figure 5. Uruguay's and Argentina's much higher incidence rates may partially be explained by their aging demographic structures. An interesting case is in Chile, where a relatively older society does not present a proportionately higher BC incidence rate. However, the steep increase in incident cases (and rates) experienced between the mid nineties and 2005 [13, 37], as presented in Section 2.1, indicates that this may change.

Demographical changes in the region may bring about an epidemiological transition and in the years to come most Latin American countries will have transitioned to the advanced aging stage. Issue 3 of the Demographic Observatory published by the Latin American and Caribbean Demographic Centre (CELADE), refers to the social and economic change that has been taking place in the region, which impacts the countries' age structures. Patterns such as small families, increased life expectancy and changes in intergenerational relations previously existed only in the most prosperous sectors in a few countries. Despite the

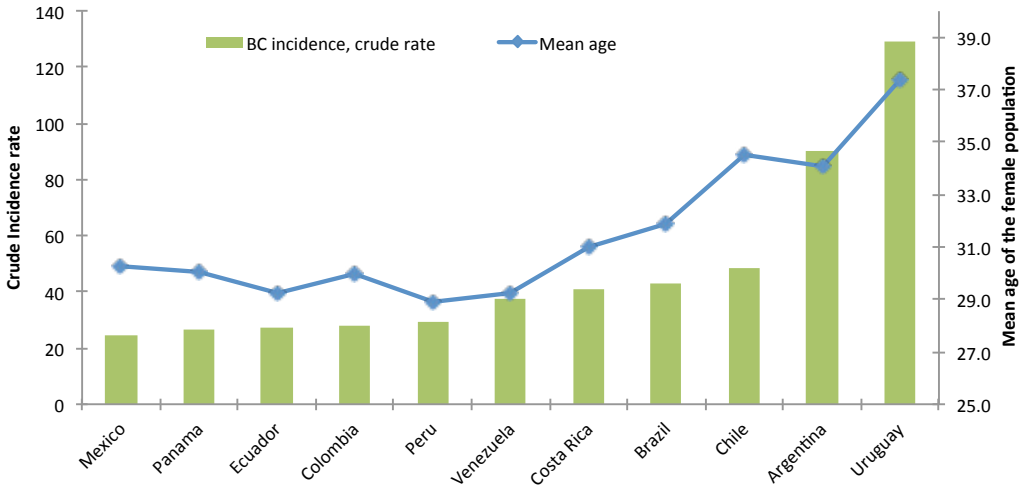
**TABLE 1.** BC risk factors [20-36].

| | |
|---|---|
| Demographic & Socioeconomic | Age (+), Female Gender (+), Higher Income (+), Higher Educational Level (+) |
| Genetic and racial | Family history of BC (+), White race (+), Mutations BRCA1 and BRCA2 (+) |
| Hormones and Reproductive behaviour | Early Menarche (+), Late menopause (+), Late first full-term pregnancy (+), Null parity (+), Parity rate (-), Exogenous hormone therapy (+), Estrogen/progesterone (+), Use of Oral Hormonal contraceptives (+), Breastfeeding (-) |
| Lifestyle-related | Overweight and Obesity (+), Alcohol Consumption (+), Physical Activity (-), Fat intake (+) |

persistence of such differences, these patterns are gradually spreading among sizeable sectors of the growing urban middle-classes. CELADE forecasts that the population ageing trend in the region, will continue and the proportion of persons aged over 65 (and their absolute numbers) will rise steadily in the coming decades, at a rate three times higher than the population as a whole in 2000-2025 and six times higher between 2000 and 2050. By then, one fifth of the population will be older than 65. Today, 10.5% of Argentina's and 13.9% of Uruguay's population respectively, are 65 years and older, while only 6.6% of Mexico's and 6.9% of Brazil's. By 2050, CELADE forecasts that people 65 years and older will represent 19% of the population in Argentina, 21% in Uruguay, 21.4% in Mexico and 22.6% in Brazil [8].

Limited by the availability of comparable data, we gathered or constructed a series of variables that approximate the well-documented BC predictive and risk factors described above. Those proxies are presented in Table 2, where it can be appreciated that the only significant correlations with the countries' incidence rates are their wealth and the women's education. The signs of the correlations are as predicted by the literature, except for the case of alcohol consumption (for which Ecuador appears as an exceptional case in the WHO data), but none of the rest of the proxies appear to be significant.

**FIGURE 5.** Crude incidence rate and mean age of the female population in selected Latin American countries.




This does not mean that reproductive and lifestyle-related risk factors, proven important by numerous studies, are irrelevant in the region. Rather that Latin America's considerable variation embedded within per-countries' averages, requires a different approach than population-based health indicators. In the countries under study, women in different socioeconomic strata are exposed to different risk factors. For example, while obesity tends to be higher among women in lower socioeconomic strata [42-45] but their birth rates are higher and they tend to be younger at delivery [46, 47]. Thus, there is no uniform prevention strategy, and policies to reduce BC risk need to be appropriately targeted and tailored for different needs of the population.

The lifestyle-related risk factor that has been extensively researched in Latin America is the impact of diet on the incidence of breast cancer. We have identified eight papers in Uruguay alone [48-55], eight more from Mexico [56-63] and some more general in the region. Torres-Sánchez and colleagues reviewed the literature from Latin America and the Caribbean (LAC) evaluating the associations between

BC and diet and concluded that the impact of specific foods and nutrients on the incidence of the disease is inconclusive [64]. However, the WHO has estimated that in 2004 in LAC, 5,195 and 4,618 BC deaths may be attributable to overweight/obesity and harmful use of alcohol , respectively [65]. Some of these cases overlap but, given that the total number of deaths reported by Globocan 2008 in the region is 37,000, it is estimated that more than 15% of BC fatality is due to modifiable risk factors which lead to overweight, obesity and harmful use of alcohol.

**TABLE 2.** Relation between BC incidences and some reproductive, socioeconomic and lifestyle risk factors.

| Country | Incidence Rate (ASR) | Births women under 30 | Childbearing Mean Age [15] | Fertility rate [15] | Overweight & Obesity* | Alcohol Consumption ** | Women's life expectancy | Per Capita GDP 2008 [39] | Female Education *** |
|---|---|---|---|---|---|---|---|---|---|
| Uruguay | 90.7 | 64.96% | 27,7 | 2,1 | 73,48 % | 12,7 lts | 79,9 | 8161 | 96,3 |
| Argentina | 74.0 | 65.83% | 27,9 | 2,2 | 77,28 % | 7,6 lts | 79,1 | 9885 | 93,3 |
| Costa Rica | 42.9 | 75.00% | 26,6 | 1,9 | 74,16 % | 7,8 lts | 81,3 | 5189 | 74,4 |
| Venezuela | 42.5 | 75.24% | 26,8 | 2,5 | 74,30 % | - | 76,8 | 5884 | 75,7 |
| Brazil | 42.3 | 76.58% | 26,9 | 1,8 | 68,40 % | 10,6 lts | 76 | 4448 | 89,4 |
| Chile | 40.1 | 65.74% | 28,0 | 1,9 | 76,66 % | 8,2 lts | 81,6 | 6235 | 82 |
| Peru | 34.0 | 63.53% | 28,5 | 2,5 | 78,88 % | 5,6 lts | 75,9 | 2924 | 89,9 |
| Colombia | 31.2 | 72.51% | 26,5 | 2,4 | 70,41 % | 4,7 lts | 76,7 | 2983 | 80,9 |
| Ecuador | 30.8 | 72.25% | 27,4 | 2,5 | 62,75 % | - | 78,1 | 1745 | - |
| Panama | 29.2 | 74.86% | 26,6 | 2,5 | 65,66 % | - | 78,3 | 5688 | 83,5 |
| Mexico | 27.2 | 71.79% | 26,8 | 2,2 | 79,95 % | 17,3 lts | 78,7 | 7092 | 79 |
| Correlation Coefficient | | -0.485 | 0.378 | -0.309 | 0.219 | 0,112 | 0.325 | 0.688 | 0.679 |
| P-value | | (0.1306) | (0.2519) | (0.355) | (0.5181) | (0.7912) | (0.3298) | (0.0193) | (0.0310) |

* Estimated Overweight & Obesity (BMI ≥ 25 kg/m$^2$) Prevalence, Females, Aged 30+, 2005 [40]

** Female per capita consumption of pure alcohol in liters, aged 15 and older; drinkers only [40]

*** Combined gross enrolment ratio in education, 2007 (%) [41]

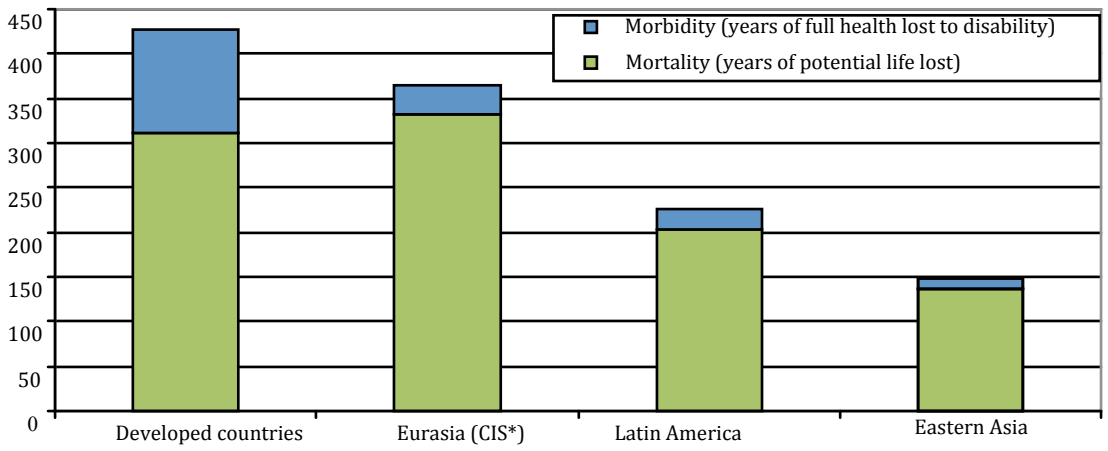
## 2.3 DALYs lost and age at diagnosis

DALYs is a measurement for the overall burden of disease that combines years of potential life lost due to premature mortality and years of productive life lost due to disability with the intention to quantify the gap between current health status and an ideal health situation [66].

Extracted from the global report, shows the estimated disease burden of BC in DALYs per 100,000 women, separated into years of life lost and years lost due to disability, in the relevant WHO MDG (Millennium Development Goals) regions. Although the overall burden per 100,000 women is highest in developed countries, where incidence rates are largest, it is worth noticing that the disease burden per BC case is higher in developing countries due to the higher mortality rates and the younger age of women at diagnosis. This holds true in Latin America as can be seen in Table 3, which presents WHO's estimates of the DALYs lost due to BC in absolute numbers and 3 additional measures in relation to: a) the total DALYs lost for all causes (as a percentage), b) the countries' population (as a rate per 100,000 women), and c) the number of BC incident cases (as average DALYs lost per BC case) in the countries under study. Countries are ranked following DALYs lost rates, in ascending order.

BC deprived LAC of 613,000 DALYs and, once again the variability within the region is remarkable. In the countries with the highest number of BC cases, Argentina and Uruguay, the disease presents the highest lost DALYs rates and a higher proportion of the total of DALYs lost to all causes including non-communicable diseases, injuries,

**FIGURE 6.** Age-standardized incidence and mortality rates, new cases/deaths per 100,000 women.




and communicable, maternal, perinatal and nutritional conditions. Up to 3% of all the DALYs lost in the female population of Uruguay and Argentina are due to breast cancer; between twice and three times higher than in any of the seven countries with lower incidence such as Ecuador, Colombia or Mexico.

So, we learn from Table 3, Table 4 and the epidemiological data presented that high BC incidence entails a heavy burden on society as in Argentina and Uruguay; but so do high BC mortality as in Brazil and Panama and young age at diagnosis and death as in Brazil, Peru and Mexico.

In Brazil, in spite of the relatively low BC incidence, the DALYs lost per 100,000 women nearly doubles that of most countries in the region. The country's high and increasing BC mortality, paired with the fact that both incidence and mortality among young women (<40 years old) have been reported to be on the rise by the population-based cancer registries in Brazil [12, 67], may account for the alarming DALYs losses. If more women of working age are being diagnosed, more productive years are being lost.

The average DALYs lost per BC case is also higher in Peru and Mexico because diagnosed women die younger than in the rest of the countries, as can be appreciated in Table 4. Finally, in Panama this is also the case, but mainly due to the higher proportion of cases that die of the disease as we will see in Section 3.2.

**TABLE 3.** Estimates of the burden of breast cancer in 2004 in Latin American countries in this study[66].

| Country | Estimated total DALYs lost due to BC | BC as a % of total women's DALYs lost | DALYs per 100,000 women due to BC | DALYs lost per BC case |
|---|---|---|---|---|
| Ecuador | 8 481 | 0,82% | 132 | 4,51 |
| Colombia | 30 943 | 0,98% | 138 | 4,65 |
| Mexico | 75 026 | 1,05% | 142 | 5,38 |
| Costa Rica | 3 298 | 1,34% | 158 | 3,54 |
| Chile | 13 925 | 1,44% | 171 | 3,32 |
| Panama | 2 722 | 1,26% | 173 | 5,84 |
| Venezuela | 24 050 | 1,35% | 184 | 4,45 |
| Peru | 26 644 | 1,19% | 198 | 6,20 |
| Brazil | 277 146 | 1,74% | 297 | 6,51 |
| Argentina | 64 360 | 2,33% | 328 | 3,44 |
| Uruguay | 7 444 | 3,00% | 433 | 3,30 |

**TABLE 4.** Women's mean age at diagnosis[1] and death[2] from breast cancer.

| Mean age at: | Mexico | Peru | Venezuela | Ecuador | Brazil | Colombia | Panama | Costa Rica | Chile | Argentina | Uruguay |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BC diagnosis | 52,7 | 54,0 | 54,5 | 55,9 | 56,1 | 56,7 | 56,7 | 57,8 | 58,0 | 60,2 | 61,0 |
| BC death | 57,1 | 58,4 | 58,2 | 60,2 | 59,5 | 58,5 | 62,8 | 62,7 | 64,1 | 66,4 | 63,2 |

Notes: 1. Data from IARC's database, Globocan 2008; 2. Data from PAHO's mortality database covering 2004-2006

The difference in age from breast cancer death is mainly due to the young age at BC diagnosis. In fact, previously reported in the global report we compared the cases in Sweden and Mexico. The total number of reported cases in Mexico in 2008 was 13,900 compared to 7,000 in Sweden in 2007, though Mexico has a population 10 times as large; but in Mexico, the average age at diagnosis of BC is 53 years while the average age at diagnosis in Sweden is 63 [1]. So, in Mexico, productivity losses due to younger age at death are exacerbated by the increased morbidity due to younger age at diagnosis.

Chile and Costa Rica have more moderate BC incidence rates, and age distribution is between that of Mexico and Uruguay. However, in Uruguay as in Chile, this is changing over time. Chile's mean age of patients diagnosed was 57.6 in 2000 and 59.2 in 2003; while in Uruguay it went from 62.8 in 1996-1997 to 64 in the years between 2002 and 2006. We have discussed the undergoing demographic transition in the region and its epidemiological consequences. We can expect that in the countries with younger populations, the burden of BC will increase rapidly, as life expectancy improves and lifestyle changes. Aging in countries like Mexico and Brazil may lower the average DALYs lost per BC case due to older age at diagnosis and death, but it will certainly increase much more the absolute number of DALYs lost due to BC as incidence approaches Argentina's, Uruguay's or Sweden's rates.

## 2.4 Mortality

Analyzing incidence levels and trends as well as age at diagnosis, we have explained part of the onerous burden of BC in Latin America. Incidence is very high in some countries while in others, where BC is less frequent, the disease affects younger women escalating the productivity losses due to the comparatively high morbidity among women of working age. BC mortality explains another component of the BC burden.

Globocan 2008 reveals that in LAC and estimated 36,952 women die each year of breast cancer, about 14% of all cancer deaths. BC has the highest mortality among cancers in LAC; about 16.5% greater than cervical cancer. Cervical cancer has long been a priority of governments, as well as international donors, but as increase in incidence and mortality shifts to other cancers such as BC, focus in terms of cancer control (governance, financing & service delivery) should be put on these types of cancer. Colombia, Ecuador, Mexico and Peru have very similar age-adjusted mortality rates around (10/100, 000), followed by Chile and Panama (11/100,000), Costa Rica and Brazil (12/100,000) and Venezuela (13/100,000). Then, and as a result of their several times-fold higher incidence, are Argentina (20/100,000) and Uruguay (24/100,000). The variability within the region is still important but much less than that registered in the incidence estimates. The ratio between the highest to the lowest incidence age-standardized rate to the World population (ASR (W)) is 3.35, while the ratio between the highest and lowest mortality ASR (W) is 2.25. This can be explained by many factors and the fact that the countries with higher incidence have better outcomes is one of them. In Section 3 we will analyse in detail the available information on survival and other BC outcomes and Section 4 will review the reasons behind those results. We will describe the whole BC care pathway from prevention to end-of-life care.

According to Lozano-Ascencio and colleagues, the analysis of mortality trend between 1979 and 2005 in the region, countries can be classified in three groups: a) those where mortality is decreasing as Argentina, Bahamas and Uruguay; b) those where the trend is steady as Cuba, Chile, Trinidad y Tobago and Barbados; and c) those where mortality is on the raise, which are all the remaining countries [9]. Particularly steep is the increase in Mexico (84%) and Venezuela (54%),

followed by Brazil, Costa Rica and Colombia. However, Francisco Franco-Marina ascertains that BC mortality rates in Mexico have stabilized in most age groups since 1995 and attributes the observable rising trend to better diagnosis and reporting since the mid-nineties, mainly related to the cohort and age effect of women born between 1940 and 1955 [70].

In any case, unlike in Europe and in the US, BC mortality is still on the rise in most of the selected countries in Latin America, with very few exceptions. This is confirmed by numerous country specific studies and reports [10, 11, 71-75] and by the WHO [66]. The WHO Global Burden of the Disease project has recently published their latest update of the projected deaths and DALYs lost for main diseases and they forecast that in the Latin American and Caribbean region as a whole, the number of deaths due to BC will double by 2030, as can be seen in Table 5.

**TABLE 5.** DALYs lost and deaths due to BC in 2004 and projected for 2015 and for 2030 in LAC [66].

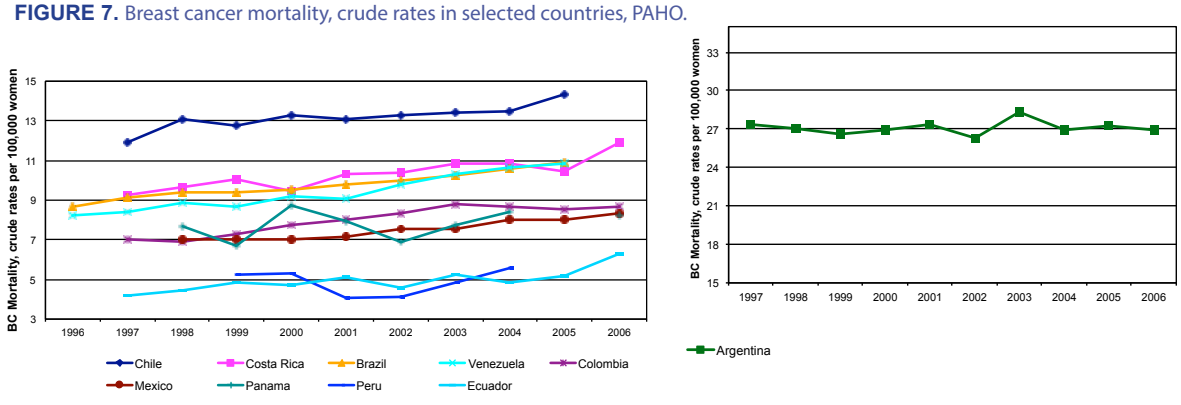
| | Number of deaths | | DALYs lost | |
|---|---|---|---|---|
| 2004/2008 | 36 952 | | 612 816 | |
| 2015 | 57 782 | Change: 99% | 726 480 | Change: 38% |
| 2030 | 73 542 | | 848 665 | |

The demographic transition that we were discussing before, explains the fact that the consequent increment of DALYs lost due to the disease will be lesser. They expect that more women will die of BC but they will be older. Figure 7 presents historical series of mortality rates built with data provided by country Ministries of Health to the Pan American Health Organizations. We chose not to correct the data with the world age-standard because we are focusing on the longitudinal dimension of the variable as opposed to cross-sectional. Thus, the demographic evolution both globally and in the countries under study does not play any role when assessing the way in which these countries experience the rise in BC fatalities as a proportion of their population.

Observing the evolution of the crude rates, we can see that more women die from BC in Latin America every year. The exception is Argentina where we noticed that mortality seems to stabilize at around 27/100,000 women.

Unfortunately, this upward trend in mortality will continue and the World Health Organization (WHO) estimates that by 2030 BC will account for about 73,542 deaths; twice as many as in 2008 [66].

**FIGURE 7.** Breast cancer mortality, crude rates in selected countries, PAHO.



## 2.5 Economic burden

The health burden that BC imposes has also an economic impact, which has been previously described in the global report for several European countries. Lidgren, Wilking and Jönsson [76] estimated that the total cost of BC in Sweden in 2002 was €320 million considering both direct costs (the costs directly linked to treatment, detection, prevention, or care) and indirect costs of the disease (predominantly the cost of lost productivity due to the patients' disability and illness, sometimes also including premature mortality). In Germany the total cost of BC in 2006 ascended to €1,906 million [77]; while in France the healthcare cost of BC in 2004 was calculated to be €1,456 million and the indirect cost due to production losses, €1,652 million [78]. So the average healthcare cost per BC case was €14,000 in Sweden (2002), €29,000 in France (2004), and €33,500 in Germany (2006); and the average per-case indirect costs were more than twice the direct costs in Sweden and about 110% in France and Germany. As for the composition of these costs, from the French study we could learn that 55% was due to hospital care and 45% was due to primary health care. Surgery represented approximately 34% of the total hospital care, drugs and their administration (37%), and radiotherapy (13%). However, these 5-7 year old estimates may be outdated, considering some of the recent relevant changes in the treatment of breast cancer, specifically when it comes to the range of drugs available to patients.

Unfortunately, the economic burden that BC imposes on Latin American societies is not well documented and the estimation is difficult. The overall cost of BC can be estimated by identifying and measuring all health care costs, patient and family costs and costs occurring in other sectors. To establish the cost of an illness, two methods are commonly used, the bottom-up approach and the top-down approach. The former utilizes patient-level data obtained from registries and/or self-reported measures and multiplies the cost per patient by the prevalence of the disease in a group of similar patients and repeats the operation for all groups, to finally aggregate the results and obtain the cost of illness of a disease. The top-down approach, on the other hand, utilizes financial data and allocates total hospital costs down to the department level [79] or national budgets down to the disease area level. With relatively homogeneous treatment patterns and universal and equal access to healthcare, the budget allocated to BC should be enough to cover the bottom-up estimated cost multiplied by the number of patients. This is not the case in Latin America. Little or no data is available for most countries, but with a couple of examples we can see that the money available is not enough to treat everyone and with the same standard of care. Some BC patients in these countries go undiagnosed, unattended, untreated, and uncared for and other patients receive suboptimal treatment. These patients receiving suboptimal or no care, generate an additional burden both in terms of health outcomes and in terms of indirect costs due to increased and avoidable morbidity and mortality. The avoidable increased morbidity and mortality increases the expenses of primary care facilities, emergency care, and other sectors in healthcare system and deprives society of many productive years.

### • BRAZIL CASE STUDY

The first case to look into in depth is Brazil where cost of BC care in the public sector differs from the private because of the access to treatment alternatives, as discussed in the Brazil case study presented in Section 2.6. Table 6 summarizes the results of a retrospective study of 199 women with BC treated at a private practice in Rio de Janeiro, Brazil [80] resulting in a weighted average annual cost per patient of US$15,426. Costs of treating stage IV BC patients are four times higher than at stage I. When compared to the public setting, these costs are relatively high, mainly because private health plans in Brazil provide access to more sophisticated healthcare facilities and in some cases more modern equipment and treatment.

Since 1988, under Brazilian law, all citizens have a legal right to healthcare provided by the Unified Health System (Sistema Único de Saúde – SUS) and breast cancer treatments available within the public health care system are reimbursed through an Authorization for High Complexity Procedures (APACs). Each APAC represents one month treatment for one patient. Adding the value of all

**TABLE 6.** Costs of BC treatment in Brazil (private clinic) by BC stage at diagnosis [80].

| | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|
| % of patients per BC stage | 48% | 34% | 2,5% | 15,5% |
| Mean direct medical care cost and duration per treatment | US$ 21,659 (mean 2.48 years) | US$ 48,295 (mean 2.76 years) | US$ 63,662 (mean 2.34 years) | US$ 63,697 (mean 1.77 years) |
| Mean annual healthcare cost | US$ 8,733 | US$ 17,498 | US$ 27,206 | US$ 35,987 |

the APACs approved by the SUS between October 2009 and September 2010, we estimated the total annual public expenditure on BC. According to Globocan 2008, 42,566 women are diagnosed every year and more than 75% of them have no private insurance so they depend exclusively on the public system financed through the SUS. Table 7 presents the estimation of the mean public spending in the treatment of a BC patient in Brazil.

Thus, SUS' endowment does not exceed US$4,760 per BC patient per year; far from the US$15,426 weighted mean annual cost per BC patient in the private clinic in Rio mentioned above. Although the federal government pays lower prices than private facilities [81], part of the SUS cancer budget is also used by patients with a private insurance [82] and it has been demonstrated that SUS patients present with more advanced disease compared to patients with a private health insurance [83, 84]. So the gap between the per-patient cost in private practice and the per-patient budget in the public sector that we estimated in US$10,669 ($15,426-$4,757) might probably be wider. We might conclude that the SUS budget may not be enough to provide the same standard of care for all breast cancer patients as in the private sector with all the therapeutic alternatives.

**TABLE 7.** Brazil's public expenditure for BC treatment (10/2009 to 09/2010) Brazil Ministry of Health[1].

| | |
|---|---|
| Total value of reimbursed Chemotherapy in the period (APAC value approved) | R$ 200 322 795 |
| Total value of Hormonal Therapy in the period (APAC value approved) | R$ 92 952 405 |
| Total value of Surgery in the period (APAC value approved) | R$ 10 448 494 |
| Brazil's total public BC treatment expenditure | R$ 303 723 694 |
| | |
| Total in US$ (Exchange rate annual average 2009 IADB) | US$ 151 861 847 |
| Number of patients who need treatment under SUS (assuming 75% of incidence) | 31 925 patients |
| Per-patient mean public expenditure | US$ 4 757 |

Note: 1: "Situação da base de dados nacional em 01/11/2010" and "Situação da base de dados nacional em 01/12/2010" Ministério da Saúde - Sistema de Informações Ambulatoriais do SUS (SIA/SUS).

## • MEXICO CASE STUDY

Another interesting case is Mexico. Felicia Marie Knaul and colleagues [85] have estimated that US$11,4392 was the mean per-case healthcare costs of BC patients treated in 2002 at the Mexican Social Security Institute (Instituto Mexicano del Seguro Social - IMSS). Some of these results are presented in Table 8, broken down by BC stage. Once again, later stage at BC diagnosis is associated with higher per-patient and per-year BC treatment costs. We can see that the estimates for earlier stages are not far from those in Brazil, especially if we adjust Mexico's 2005 values to 2010 (which is when the Brazilian study was published). However, the cost of treatment of metastatic BC in the Mexican public is significantly less than in the Brazilian private sector.

Additionally, Knaul and colleagues aggregated the per-patient costs to calculate the total cost of care of BC for the 16,346 patients who received care in the IMSS in 2002 (comprising both ambulatory and inpatient settings), which amounted to $MX 1,806 million, or US$187 million; which is 1,7% of the IMSS budget [85].

However, Cahuana-Hurtado and colleagues, using a different methodology that could be described as top-down, estimated that the total healthcare expenditure in BC in 2003 was only US$63.7 million [86].

Moreover, Puentes-Rosas and colleagues estimated that in 2002 only 29.5% of Mexicans were covered by the IMSS [87] and many of their co-nationals remained uninsured. In 2004, in the framework of a historic healthcare reform, the Popular Health Insurance (Seguro Popular de Salud - SPS) was introduced. The SPS is a programme aimed to deliver health insurance, regular and preventive medical care, medicines, and health facilities to 50 million uninsured Mexicans and, by doing so, to reduce the prevalence of catastrophic health expenditures. Affiliated families are entitled to well-defined benefit packages for a number of health interventions and medicines and the otherwise catastrophic medical expenses associated with certain diseases. BC is one of those diseases and although the system is still not fully rolled out, efforts to evaluate its impact, such as the study by Gary King and colleagues, start to show positive results. But Paul Farmer and colleagues question the real impact of Mexican initiative stating that the delivery of cancer services is suboptimum and the financial sustainability of novel entitlement schemes for the poor, a challenge [88].

In any case, according to the National Committee for Health and Social Protection of the Secretary of Health (Comisión Nacional de Protección Social en Salud - Secretaría de Salud), by June 30th 2010, the treatment of 11,468 BC cases for a total of MX$1,302 million had been authorized. On average, the SPS covers US$8,400 per BC patient; which is the equivalent to approximately 65% of the mean cost of BC estimated by Knaul and colleagues and adjusted to 2010.

In Mexico as in Brazil, the health care budget estimated with a top-down approach may not be enough to pay for the treatment of all BC patients with the same standard. Many methodological issues in our estimations may explain this gap, but the issue of ensuring sufficient public funding for BC care remains important. Mexico and Brazil show poor evolution of BC outcomes, which will be discussed in Section 3.

**TABLE 8.** Estimated annual weighted-average health care cost per BC patient in Mexico [85].

| | Stage I | Stage II | Stage III | Stage IV | Mean cost |
|---|---|---|---|---|---|
| % of patients with established stage | 9% | 33% | 30% | 7% | |
| Healthcare cost 2002 ($MX) | 74,522 | 102,042 | 154,018 | 199,274 | 110,459 |
| Mean annual healthcare cost 2002 (US$)[1] | US$7,717 | US$10,568 | US$ 15,950 | US$20,637 | US$11,439 |

Note: 1: Exchange rates obtained from Centro de Estudios de las Finanzas Públicas de la Cámara de Diputados, with data from Banco de México.

## • COSTA RICA CASE STUDY

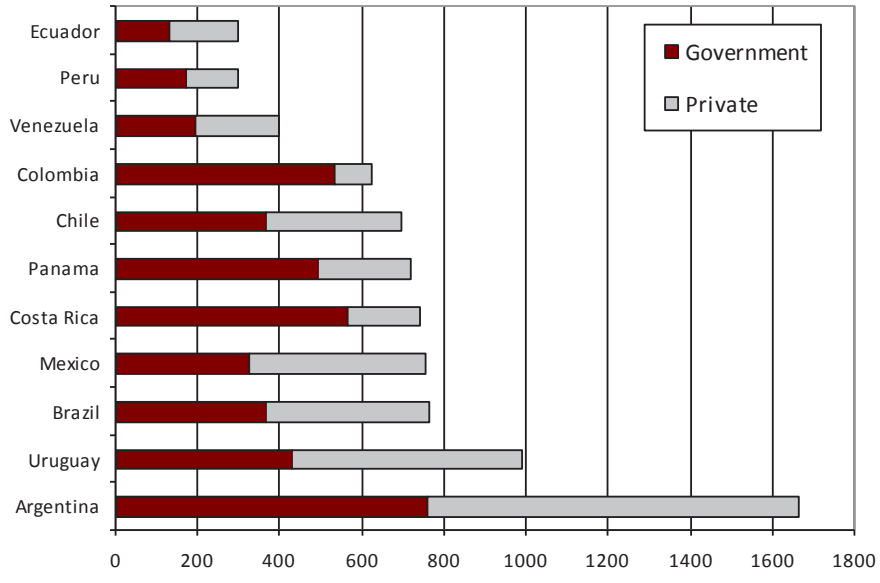
The last case we will look into is Costa Rica. The country's Ministry of Health produced an overarching report on cancer in 2006, divulging data on the country's investment in the disease. Public spending in cancer had risen from US$44.1 million in 2000 to US$60.7 million in 2003 and the share of cancer in the public health care budget had increased from 5.9% to 6.8% [89]. In 2008, the country's Social Security Agency showed that the public spending in cancer in 2007 had risen to US$9.5 million [90]. If we assume that the distribution of this budget is related to the incidence of the malignancies, and given that BC represents about 12% of all cancers of both sexes, Costa Rica spends about US$10,172 per BC patient per year. The Social Security Agency has announced that, in 2008 they spent US$4.572 million (out of a budget for new medicines of US$6.9 million) in the acquisition of Trastuzumab for the treatment of breast cancer [90]. Costa Rica's per-patient level of investment in BC is higher than in Brazil and Mexico. Costa Rica has a very positive evolution of BC outcomes.

If we look at Figure 8 we will see that Brazil's and Mexico's per capita overall expenditure on health care are very similar to that of Costa Rica but they devote less resources for each BC case.

Another compelling observation in this figure is the intra-regional differences. It is expected that countries like Ecuador or Peru devote less resources than richer Brazil, Mexico or Uruguay. However, the level of expenditure in healthcare in Argentina is a clear outlier. These numbers, when paired with the clinical outcomes, point to possible inefficiencies in the Argentine healthcare system since Uruguay and Chile achieve similar outcomes with much less resources, as is described in Section 3.2. Also, in Colombia, Panama and Costa Rica the public sector contributes the greater proportion to healthcare spending, reducing inequities and mitigating the financial burden on the population that catastrophic diseases such as cancer place on families without health insurance.

The notes that we present, provide an impression of the heavy burden of the disease in terms of the healthcare resources utilized for its treatment but, as explained above, the economic burden of BC includes other components that we are not accounting for here, due to the lack of data. First of all we lack data on the economic impact outside the health care system, in terms of private expenditures and income losses due to treatment, morbidity and premature mortality. Second, we lack data on the total resources used in the health care system for prevention, early detection and diagnosis, treatment and rehabilitation, as well as palliative

**FIGURE 8.** Per capita expenditure on health (purchasing-power parity international dollars).




Source: The World Health Report 2006 - Working together for health, WHO Statistical Information System (WHOSIS), based on National Health Accounts.

care. While there is some data on the cost of different stages of the disease, we lack incidence based costing studies, which describe for example the cost for a patient with metastatic breast cancer from diagnosis to death. Such studies will show the costs related to different treatment patterns, and are important for further studies assessing cost-effectiveness where treatment is related to outcome.

Investments in improved management of BC should be shifted to early stages of the disease, where the opportunities to improve outcome is greatest.

Finally, we know from the global report that indirect costs have been estimated to be over twice the cost of healthcare services in Europe34; but the total cost of a disease in a specific country is related to "price and income level" in that country. Lower income gives lower health care spending and lower estimates of loss of production. In spite of the fact that indirect costs of BC have not been estimated in Latin America, we have already established in Section 2.3 that they are significant because of the younger age at diagnosis and death. Additionally, new innovative drugs may consume a higher share of direct costs since their relative price compared to local salaries of doctors and other health care staff is higher.

## 2.6 Patients access to healthcare services

During the past 25 years, the region's health care systems have been experiencing a transformation towards the construction of a welfare state according to the countries' social and economic development. In a recently published report, Giedion, Villar and Ávila review the multiple solutions that Latin American countries have been attempting. They classify their health care systems under four categories as depicted in Table 9.

Differences in shades remain within all 4 types of systems. For example, among countries with a segmented system, the poorest populations do not have healthcare insurance and rely on the state network financed with general taxes; while in some cases in the integrated systems, resources are very low and in practice, those poor populations also receive below-standard care. In this framework, private health insurance can play different roles; from being explicitly integrated into the strategy to extend insurance and/or healthcare in general (as is the case in Chile and Colombia) to just duplicating or being complementary or supplementary to that the public service (as is the case in Brazil, Mexico or Venezuela). The extreme form of these being Costa Rica's health care integration, where private health insurances were banned until 2009, when they were obliged to open the Social Security Agency's monopoly to enter a free trade agreement with the United States [92].

In synthesis, coverage has been increasing in general in the region through two processes. The reforms of the state health care systems to advance towards universal health insurance with a basic service package; and the growing participation of the private sector in LAC's health system, both contributed to the coverage improvements [93]. Though, universal health coverage is still not the rule and, even in those systems where the entitlement to access health services is guaranteed by law or even a constitutional

**TABLE 9.** Classification of health care systems in LAC. Extracted from U. Giedion, M. Villar and A. Ávila [91].

| | | System Integration | |
|---|---|---|---|
| | | Integrated | Segmented |
| Private sector participation in:<br>- Service delivery (SD)<br>- Insurance (I) | Yes | Brazil (SD) Uruguay (SD, I) | Chile (SD, I), Colombia (SD, I), Peru (I), Argentina (I), Nicaragua (SD, I), Dominican Republic (SD, I), Paraguay (SD, I) |
| | No | Antigua y Barbuda, Barbados, Costa Rica, Cuba, Dominica, Grenada, Guyana, Haiti, Jamaica, St. Kits & Nevis, St. Vincent & Grenadines, Trinidad & Tobago | Mexico, Ecuador, Bahamas, Belice, Bolivia, El Salvador, Guatemala, Honduras, Panama, St. Lucia, Surinam, Venezuela |

right, it is not accompanied by the resources that level the playing field with the private sector or among different regions within a country.

We are now introducing a brief description of the current state of health care in a few countries in the region.

## • ARGENTINA

Argentina presents an interesting case because of the extraordinary levels of healthcare spending, which is unparalleled in the region, and amounts to 10.1% of the country's GDP in 2006 (Figure 9). According to data published in 2007 by the WHO's Global Health Observatory, Argentina's physicians density 31.6 per 10,000 population is higher than the US (26.7) and Japan (21.2), and close to Germany (34.8). In the region, only Uruguay surpasses it with 36.5 physicians per 10,000 people. As for health care infrastructure, approximated with the number of hospital beds per 10,000 population, Argentina (41) tops Italy (39.4), the US (30.5) and even Sweden (21), with no match in the LAC region.

In Argentina, a minimum package of health services is guaranteed by law to the whole population. The so-called Compulsory Medical Plan (Plan Médico Obligatorio - PMO) establishes that the reimbursement of drugs will reach at least 40% in acute conditions, 70% in chronic diseases and 100% in hospital drugs as well as special treatments such as oncology [1]. So, all BC patients in Argentina have free access to oncology treatment by law. Yet, a survey with 95 medical oncologists revealed that there is much heterogeneity in what they think is the best treatment and what they could indicate to their patients [94].

In a recent study conducted by Innovus, for which the Institute for Clinical Effectiveness and Health Policy (IECS per its acronym in Spanish) contributed, Argentina's healthcare is described as a multi-tier system divided in three large sectors [95]: a) public sector b) private sector and c) social security.

The publicly-funded sector is decentralized so the federal government, through its Ministry of Health (MoH) has a rather limited role in health-policy design or implementation. This is shared with 23 provinces and the government of the autonomous city of Buenos Aires, as well as with numerous municipalities. About 34% of Argentines with no health insurance rely solely on the public health sector of each province or district [96], for free and irrespective of their origin or nationality. But provinces and municipalities have very different health budget endowments, thus geographical inequalities in health care arise.

The private sector is composed of private providers, private insurances (Empresas de Medicina Prepaga – EMP) and out-of-pocket expenses, which account for two thirds of health expenditures [95].

The social security sector (Obras Sociales – OS) aims at providing care to workers formally employed through about 300 different funds (OS) and the retirees and the disabled through an entity similar to the American Medicare (PAMI). The OS vary in sizes and scope and mostly managed by trade unions. They are primarily funded by a compulsory payroll contribution from employees (3% of their salary) and employers (additional 6%), defined by sector of the economy or profession. Thus, significant differences across the various OS arise from the wide range of average wages (and number of dependents for each worker) which in turn vary following a social gradient.

In order to address this matter and compensate for the differences that result in potential health inequities due to the disparities in earnings for each of the OS, a "redistribution fund" (Fondo Solidario de Redistribución - FSR) composed of 10 - 15% of each payroll contribution, is transferred from the more wealthy to the poorer OS [95] in order to close the gap between the contribution of the affiliated worker and the PMO prime.

Table 10 shows Argentina's peculiar healthcare system highly decentralized and characterized by the inarticulate co-existence of subsystems that not only duplicate (sometimes even triplicate) coverage but also bureaucracy. Inefficiencies become evident when we see the similar outcomes achieved by countries such as Uruguay, Chile or Costa Rica with a much lower per-capita investment in health care.

[1] Argentina Resolution 310/2004.

**TABLE 10.** Argentina healthcare spending (2006) and coverage (2005) per sector [91].

| | Million US$ PPP 2006 | % | Coverage |
|---|---|---|---|
| Public | 8,940 | 26 | 34% |
| Federal | 1,446 | 16 | |
| Provinces | 6,323 | 71 | |
| Municipalities | 1,171 | 13 | |
| National Security | 12,578 | 38 | 56% |
| National OS | 6,562 | 52 | |
| Provincial OS | 3,292 | 26 | |
| PAMI | 2,724 | 22 | |
| Private | 12,010 | 36 | 10% |
| Total | 33,528 | 100 | 100% |

## • BRAZIL

Being a federal republic with 26 states and one federal district, Brazil also has a multi-tiered healthcare system managed and operated at federal, state and municipal levels. The country's healthcare sector is a mix of public and private services with 7,000 hospitals, more than 12,000 diagnostic clinics and 250,000 registered doctors. Healthcare spending amounts to US$ 55 billion per annum (public 60%: private 40%), which is equal to almost 7% of the country's gross domestic product. The hospital services segment alone is responsible for US$ 9 billion of sales every year [95].

The Unified Health System (Sistema Único de Saúde – SUS) was implemented ipso facto based on universalization and decentralization principles. SUS services are provided for free through public and government contracted private healthcare facilities and are sought primarily by individuals with low incomes. The private or "supplementary" healthcare sector provides care to patients who have private insurance (individually or through their employers) or who pay out-of-pocket. According to the National Agency of Supplementary Health (Agência Nacional de Saúde Suplementar - ANS), about 25% of Brazilians are enrolled in private healthcare plans [97] and the private healthcare system is geographically concentrated in southern regions. Table 11 confirms that Brazil exhibits differences in coverage that range from over 38% in São Paulo to one-digit rates in the North and Northeast.

**TABLE 11.** Coverage rate by private health plans in Brazil, by state , 2007 [95].

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| São Paulo | 38,4% | Rio Grande do Sul | 16,3% | Amazonas | 8,7% | Rondônia | 6,3% |
| Rio de Janeiro | 30,3% | Mato Grosso do Sul | 13,7% | Alagoas | 8,3% | Acre | 5,4% |
| Distrito Federal | 28,1% | Pernambuco | 12,2% | Bahia | 8,3% | Piauí | 4,7% |
| Espírito Santo | 23,2% | Rio Grande do Norte | 11,7% | Mato Grosso | 8,3% | Maranhão | 3,9% |
| Santa Catarina | 19,8% | Ceará | 9,4% | Paraíba | 8,2% | Tocantis | 3,7% |
| Minas Gerais | 19,4% | Sergipe | 9,4% | Amapá | 7,7% | Roraima | 2,1% |
| Paraná | 19,0% | Goiás | 9,3% | Pará | 7,6% | | |

The reimbursement of cancer treatment under SUS is governed by the High Complexity Discharge Authorization (Autorização para Procedimentos de Alta Complexidade - APAC). Table 12 presents the mean APAC for BC treatment estimated in US$148. These APAC expressly mention different surgical procedures, various lines of chemotherapy and hormonal therapy but there is no mention to biologic therapy. The current APAC amount is not sufficient to cover the costs of new technologies in the treatment of breast cancer. Thus, due to the restricted federal reimbursement, some states provide additional treatments for cancer care, such as the wealthier state of São Paulo. Since 2009, the

Secretary of Health of this particular state incorporated 7 new oncological drugs to the treatments offered in their hospitals (rituximab for NHL, bevacizumab, temozolomida, trastuzumab, cetuximab, sinutinibe and sorafenibe)[1] . This practice is good news for the citizens of São Paulo, but unfortunately it is an exception in Brazil and the majority of the other states do not provide such additional coverage to the federal SUS package. Due to the limited public funding in the SUS and this state-by-state delivery of services, strong regional differences in healthcare result in Brazil, where the Constitution guarantees everyone the right to health

The SUS was created to provide full and comprehensive healthcare to Brazilian citizens, including pharmaceutical services. But different interpretations of the term comprehensiveness, justify on the one hand the limits to treatments covered and, on the other, the lawsuits patients often pursue in order to get access to specific medications. According to L. Cruz Lopes and colleagues, the amounts spent with lawsuits in 2007 were over R$500 million (~US$250 million) in the federal, state and local administrations. And matters are getting worse since the amount spent yearly in the Ministry of Health alone went from R$188,000 in 2003 to R$52 million in 2008 [98]. This may be the salvation for just a few but it comes at a too high (and inefficient) cost. Besides, the unrestricted supply of medication through legal suits privileges segments of health service users with more financial resources to pay for attorney's fees, or that have more access to information, to the detriment of the needy segment of the population.

Summarizing, three facts contradict the principle of equity on which SUS was created 1) The private sector has a statutory obligation to comply with higher standards than the SUS, 2) Only some states (as Sao Paulo) offer more treatment alternatives in their public hospitals, and 3) Some informed patients do get the more expensive (i.e. biological) treatments, but only by taking legal action against the government.

**TABLE 12.** Mean APAC value for BC treatment 01/10/2009-30/09/2010 (Brazilian Ministry of Health).

| | |
|---|---|
| Total value of APACs approved for systemic and surgical treatment of BC | R$ 303,723,694 |
| Total quantity of APACs approved for systemic and surgical treatment of BC | 1,028,635 procedures |
| Mean value per APAC for treatment of BC | R$ 295 |
| Mean APAC for treatment of BC in US$ (exchange rate 2009 IADB) | US$148 |

Source: "Situação da base de dados nacional em 01/11/2010" and "Situação da base de dados nacional em 01/12/2010" Ministério da Saúde - Sistema de Informações Ambulatoriais do SUS (SIA/SUS).

## • COLOMBIA

The public and private sector in Colombia are explicitly integrated to extend health care coverage. This system dates to its origins in the profound reform introduced by the Act 100 in 1993[2] , when the healthcare market (including public sector and social security) was opened for private agents to provide health services. By 2005, there were about 58,500 health-service delivery agents registered; 43,639 of which are independent professionals and the rest are institutions (Instituciones Prestadoras de Servicios de Salud - IPS). About 70% of the country's IPS and 41% of hospital beds are private [91]. It was the same Act 100 that anticipated universal healthcare coverage of Colombia's system, by dividing it in 3 regimens[3] :

A) Contributive regimen for about 42% of the Colombian population, and financed with employees' and employers' contributions.

B) Subsidized regimen for about 44% of the population, those without the capacity to pay the insurance prime, receives a subsidized health provision. This kind of service is provided by companies that promote subsidized health (Empresa Promotora de Salud Subsidiada - EPSS) through transfers that the national state sends to the municipalities. And 60% of these resources ought to be devoted to the health assistance of the population in need.

C) Special regimen for the military and employees of the Colombian Oil Company (Ecopetrol), which amount to 4%.

The remaining 10% of the Colombian population had no

[1]: http://www.saude.sp.gov.br/content/assistencia_farmaceutica.mmp
[2]: http://www.caprecom.gov.co/sitio/filesnormatividad/Ley-100-de-1993.pdf
[3]: http://www.fosyga.gov.co/Consultas/RegimenSubsidiadoBDUA/tabid/338/Default.aspx

coverage in 2008 and some people in the contributive regimen have private insurance as well [91].

The Colombian universal health insurance has included treatment for cancers in the mandatory health plan with a subsidized scheme providing specific entitlements for the poor, since 2004. The government's goal is to attain a coverage rate of 94% by 2012, from 85% in 2008 [99]. According to calculations based on Barón's publication (2007) and published by the Colombian-based think-tank ANIF (Asociación Nacional de Instituciones Financieras) [100], the process of increasing the public participation in the total of health care expenses has been sustained since 2003. Then, 52% of health care spending was out-of-pocket, the Social Security-Contributive System was 26% and the budgetary share was 22%. By 2003, they were already 16%, 44% and 40% respectively. However, the enforcement of the patient's right to access certain technologies is achieved through a lawsuit [88], as in the case of Brazil.

## • PERU

According to the latest national Survey on Health Care Infrastructure and Resources (Censo de Infraestrucura Sanitaria y Recursos de Salud), in 2005 there were 8,041 health care centres, 93% of which belong to the public sector. The Ministry of Health (MINSA) represents 85% of the total health infrastructure and it counted with 31,431 hospital beds, that is 11.1/10,000 population according to the WHO's Global Health Observatory. About 90% of MINSA's health care centres were in urban areas, while only 7% and 3% were located in marginal urban and rural areas respectively. In 2001 Peru's government created the Integral Health Service (Servicio Integrado de Salud – SIS) precisely to provide coverage to the marginal and rural population in poverty [91]. The SIS is a subsidized service targeting the poor population but, effectively, it is only those with geographical access to their facilities who can benefit from this scheme.

The aforementioned report by Giedion and colleagues presents the data reproduced in Table 13, where we can see that, even when the creation of SIS provides coverage to 16.3% of the population, its overall effect on the number of people uninsured is marginal. In 2005, about 64% Peruvians remained without health care coverage and can only get emergency care in public hospitals.

Legislation guarantees universal access to healthcare (Ley No 29344 - 2009) and the SIS is required to provide those basic healthcare services established in the Basic Health Insurance Plan (Plan Esencial de Aseguramiento en Salud – PEAS). Two months later, the PEAS is regulated and in Section 4, Title 3, it establishes that only the diagnosis of BC is covered, but not the treatment. So, in Peru, an estimated 64% of the population does not have public access to cancer treatment.

**TABLE 13.** Health care coverage in Peru in 2000 and 2005 [91].

| | Percentage in 2000 | Percentage in 2005 |
|---|---|---|
| INSURED | 32.3 | 35.3 |
| EsSALUD (Social Security) | 19.7 | 15.3 |
| EPS (Private Social Security) | 1.5 | 1.8 |
| Army and Police | 1.3 | 1.6 |
| SIS | | 16.3 |
| Private Insurances | 1.6 | 1.7 |
| Other | 9.3 | 0.4 |
| NOT INSURED | 67.7 | 64.4 |
| TOTAL | 100 | 100 |

# SECTION 3.

## Outcomes of breast cancer care

## SUMMARY


- *Long term prognosis for BC patients has improved significantly over the last 50 years, 5 year survival rates are now over 85% in those countries with best outcome (international benchmark)*
- *In LA, data on survival is scarce and fragmented and what is available shows a wide disparity across and also within countries. Yet, the evidence signals that only in a few countries 5-year survival surpasses 70%*
- *The reduced survival in LA is partly due to the fact that around 30%-40% of patients are only diagnosed in metastatic phases III and IV; while in Europe such late diagnosis accounts for only 10% of the cases*
- *BC outcomes have improved during the last decade, as evidenced by comparison of the mortality-to-incidence ratios (MIR) between 2002 and 2008. Costa Rica is the country where most progress is seen, while Brazil, Mexico and Panama have not seen significant improvement in MIR ratio over the past years*
- *Quality of Life (QoL) is severely affected by a BC diagnosis and, in the region, the associations most clearly established in the literature is between the surgical procedure undergone by the patient and her QoL. As breast preservation or reconstruction techniques continue progressing, we may see this changing*


### 3.1 Survival

In the global report we concluded that the long-term prognosis for BC patients has improved significantly over the last 50 years. In the countries with the best outcome such as Norway, 10-year survival rates are now 80% and in most European countries, Canada, the US, Australia and Japan 5-year survival exceeds 80%. This progress is explained by the combination of two positive developments: 1) enhanced treatment and 2) earlier diagnosis. Regarding enhanced treatment, it has been estimated that the introduction of adjuvant systemic chemo-, endocrine- and biologic therapy account for a 25% increase in overall survival and an almost 50% increased survival in women younger than 70 years of age [101]. A recent study from Norway has indicated that the effect of adjuvant treatment actually may constitute the major part of the survival improvement seen [102].

As for earlier diagnosis, the largest improvements in outcome have been seen during the last 20-30 years and this is mainly due to the introduction of population-based mammography screening leading to earlier diagnosis. A number of randomized studies have demonstrated increased BC survival due to earlier diagnosis with screening [103-107]. However, it has also been shown that screening leads to a certain overdiagnosis, e.g. detection of BC that would have remained asymptomatic (cancers in situ), and therefore survival rates are not completely comparable

between countries with population-based screening programs in place and those countries without screening programs in place [108].

In the case of Latin America, apart from the varying screening policies that we describe in Section 4, information on survival is extremely difficult to come across and whatever little was found is partial and fragmented so the interpretation of the results should be cautiously read. Through an expert survey we could gather some estimates produced with diverse methodologies. A number of articles and abstracts presented in ASCO have also been screened and data has been abstracted, as presented in Table 14.

The most complete study with the largest and most representative sample is that of Dr. Sankaranarayanan that surveyed several countries in the developing world including Costa Rica. The availability of data provided by the population-based national registry represents a unique opportunity in the region for obtaining unbiased estimates given its ample coverage accounting for geographical and socioeconomic disparities as well as patients treated in both private and public settings.

The second largest study is the one conducted in Peru by Dr Henry Gómez Moreno and colleagues. In fact, even though the patient selection in the abstract presented by Vallejos and his colleagues only included premenopausal patients, the outcome of the disease seems to be consistent with the results of that larger study conducted in the same centre. In a personal communication, Dr. Henry Gómez Moreno provided us the data of a study he is undertaking with Dr Vallejos and their colleagues in the Instituto Nacional de Enfermedades Neoplasicas – INEN (National Institute of Neoplastic Diseases). In a large sample of patients diagnosed between 2000 and 2002, they found that 10% of those with evaluable clinical stages were diagnosed in Stage IV and 53% in Stages I and II. A publication with the results of the study is in press. As for Chile, Serra's work seems to be comprehensive but may potentially have a selection bias. This is because even when the patient population comprises all women operated for BC between 1994 and 2005 in two public hospitals in Santiago de Chile, the situation and outcomes may be different outside the capital; epidemiological and socioeconomic differences within the country may affect the generalizability of this estimate.

Dr. Krygier presents impressive results in Uruguay. Although all the patients were treated in a single institution corresponding to the private sector, so it cannot be assumed that this high survival is representative of the whole Uruguayan population, given that we have no information on the outcomes in the public setting. The Mexican study calculated a 59% 5-year survival in women admitted between 1990-1999 to a single hospital in Mexico City but statistics from a hospital in Guadalajara, the second biggest city in Mexico, presents a 5-year survival rate of 72% with follow-up until 2009 [115]. The differences between the estimations in Mexico City and Guadalajara may be due to underlying differences in the populations, to dissimilar practice patterns in the management of breast cancer, or just be accounted for by the different study designs.

This is also the case across the Brazilian registries and studies. The estimate that Coleman and colleagues produced based on two regional registries is questioned by the authors who warn against the data provided by the Registry in Campinas where 26% of patients had to be excluded with errors.

**TABLE 14.** 5 year overall breast cancer survival in selected Latin American countries [37, 109-114].

| Country | Health care setting | 5-year survival | Period | # of Patients | Reference |
|---|---|---|---|---|---|
| Brazil | General | 58,0% | 1990-1994 | 806 | Coleman: 2008 |
| Mexico (DF) | Public | 58,9% | 1990-1999 | 432 | Flores-Luna: 2008 |
| Peru | Public | 68,0% | 2000-2002 | 518 | Vallejos: 2010 |
| Peru | Public | 67,8% | 2000-2002 | 2056 | Gómez Moreno: 2010 |
| Costa Rica | General | 70,0% | 1995-2000 | 2462 | Sankaranarayanan: 2010 |
| Chile | Public | 76,2% | 1994-2009 | 1485 | Serra: 2009 |
| Uruguay | Private | 89,3% | 21 yrs follow-up | 1906 | Krygier: 2007 |

Brazil is a large country with infinite variations across the different states and regions and, in the absence of national survival data, we present in Table 15 the results of a number of studies produced in different regions. Unfortunately, all studies identified reflect the situation of the wealthier regions and no studies from Brazil's North or Northeast regions were available and we expect survival to be lower there, given the poorer access to up-to-date treatment technologies.

In Table 15 we included 2 studies from Minas Gerais because they were conducted by the same team, with a patient population sampled in the same city during the same years. The results are different so calculating a weighted average of the estimates, we could conclude that 5-year overall survival in Minas Gerais is 76%. In Santa Catarina, with the largest sample of all the studies, the two most advanced oncology centers in Florianópolis were included in the study, both providing assistance in the framework of the universal healthcare service (SUS). The study conducted in Rio de Janeiro is old and small to account for the most heavily populated of these cities and with one oncology centre.

So, the lack of national registries also affects the assessment of BC care outcomes and the few more reliable estimations indicate that 5-year survival in LA fluctuates around 70%, considerably less than Northern Europe, France, Italy, Spain, North America, Japan and Australia, and also below Eastern European countries such as Poland or Slovenia that are reaching 75% 5-year overall survival [1].

**TABLE 15.** 5-year overall breast cancer survival in selected Brazilian states.

| | 5-year survival | Period | # of Patients | Follow-up | Reference |
|---|---|---|---|---|---|
| Minas Gerais | 81,8% | 1998-2000 | 734 | At least 5 yrs | Guerra: 2009 [116] |
| Minas Gerais | 71,9% | 1998-2000 | 869 | Till Dec 2005 | Guerra: 2007 [83] |
| Santa Catarina | 76,2% | 2000-2002 | 1002 | Till Dec 2007 | Schneider: 2009 [117] |
| Rio de Janeiro | 75,0% | 1995-1996 | 170 | 93% > 4 yrs | Mendonça: 2004 [118] |
| Goiania | 65,4% | 1990-1994 | 631 | Till 1999 | Coleman: 2008 [111] |
| Campinas | 36,6% | 1990-1994 | 175 | Till 1999 | Coleman: 2008 [111] |
| Uruguay | Private | 89,3% | 21 yrs follow-up | 1906 | Krygier: 2007 |

## • STAGE AT DIAGNOSIS

One of the common conclusions among these studies is that the stage at diagnosis is an important predictor for overall survival as can be seen in Table 16. Stage I and II are referred to as early BC disease, at which point it is possible to completely remove the tumour and cure rates are high. Stage I disease is defined as a primary tumour less than 2 cm in diameter. In Stage II, the primary tumour is more than 2 cm in diameter but has not spread outside of the breast, or the primary tumour is less than 5 cm but with metastases identified in 1-3 axillary lymph nodes. Stage III is the classification for locally advanced disease when the tumour has spread to lymph nodes and/or to the skin or chest wall and Stage IV is advanced disease with distant metastases, most commonly skeletal, liver or lung metastases. Since advanced BC has the poorest survival rate and is the most resource-intensive to treat, measures that lead to earlier diagnosis, including greater awareness of the importance of early detection and improved access to mammography screening, are considered to deliver the greatest overall benefit in terms of survival in relation to cost [119].

Most of these studies are based on small samples or on a patient population with non-generalizable characteristics so we will not interpret the absolute number. However, it is interesting to see that the largest difference in outcomes across countries is in the late stages and, particularly when distant metastasis has settled in.

Given that stage at diagnosis is determinant of outcomes and, therefore, of the burden that BC imposes on societies, we'll look into the proportions of women diagnosed in each stage (in some countries for which we could find data) and compare it to the reality in the country with the best outcomes.

**TABLE 16.** 5 year overall breast cancer survival in selected Latin American countries [37, 109-114].

| | Stage I | Stage II | Stage III | Stage IV | Reference |
|---|---|---|---|---|---|
| Brazil-Rio Grande doSul | 97,0% | 74,7% | 73,0% | 57,0% | de Moraes:2009 [120] |
| Brazil-Minas Gerais | 92,8% | 88,6% | 70,9% | 61,3% | Guerra:2009 [116] |
| Brazil-Sta Catarina | 93,6% | 87,8% | 62,5% | 27,3% | Schneider:2009 [117] |
| Brazil-Rio de Janeiro | 96,3% | 86,2% | 64,3% | 21,0% | Brito:2008 [121] |
| Brazil-Curitiba | 90,0% | 78,9% | 47,4% | 14,9% | Schwartsmann:2001 [122] |
| Argentina | 96,0% | 82,0% | | | Iturbe: 2008 [123] & 2009 [124] |
| Colombia | | 87,0% | | 34,0% | EBC:Kimmel:2000 [125]-MBC:Cardona:2008 [126] |
| Mexico (DF) | 82,0% | 68,2% | 45,9% | 15,0% | Flores-Luna:2008 [110] |
| Uruguay | 96,0% | 92,0% | 71,0% | 39,0% | Krygier:2007 [114] |

stage (in some countries for which we could find data) and compare it to the reality in the country with the best outcomes. The global report presented Norway's data as a case of best practice given that it is one of the countries with the highest BC survival rates. According to the Institute for Population-Based Cancer Registry of their Cancer Research Institute (Kreftregisteret Institutt for Populasjonsbasert Kreftforskning, 2009), in Norway in the early 2000s, only 10% of BC patients presented with stage III or IV at diagnosis, and 90% with early breast cancer. As can be appreciated in Table 17, Latin America's reality is very different.

Once again, sample sizes vary and generalizability of these estimates can be questioned. Nevertheless, Table 17 shows some interesting features. In Peru twenty years ago, 1 out of every 2 BC patients was diagnosed when the disease had spread. After 15 years, women are diagnosed earlier in terms of disease progression but Peru's situation is still among the poorest in the region. Chile, on the other hand, has improved BC diagnosis as early BC cases went from representing 43% of all cases in 1999 to 70% of all cases in 2003. There may be several factors that have had an influence, but the fact that in 2001 mammography screening was introduced in the primary care program and clear quality standards were set, was probably the most important. Finally, Uruguay and certain wealthier regions in Brazil diagnose women earlier but still far from Norway's benchmark.

Some experts point to patient delay [69] and limited mammography screening capacity and compliance [128, 129] as reasons behind the high proportion of woman presenting with more advanced stage at diagnosis [122]. Also, the figures presented in Table 17 are not population-based estimates, therefore, the data may overestimate the share of patients with advanced disease as it is likely that the most advanced cases are referred to the major hospitals, while those diagnosed in early stages are treated at smaller hospitals. However, the data has come from hospitals in some of the biggest cities in each country and it is possible that awareness of BC and access to care is better in the cities than in the countryside thus increasing representativeness of data.

There is further potential for improvement, based on better diagnostic tools and more effective treatment, but also through better selection of at-risk groups who would most benefit from medical prevention measures.

**TABLE 17.** 5-year overall breast cancer survival in selected Brazilian states.

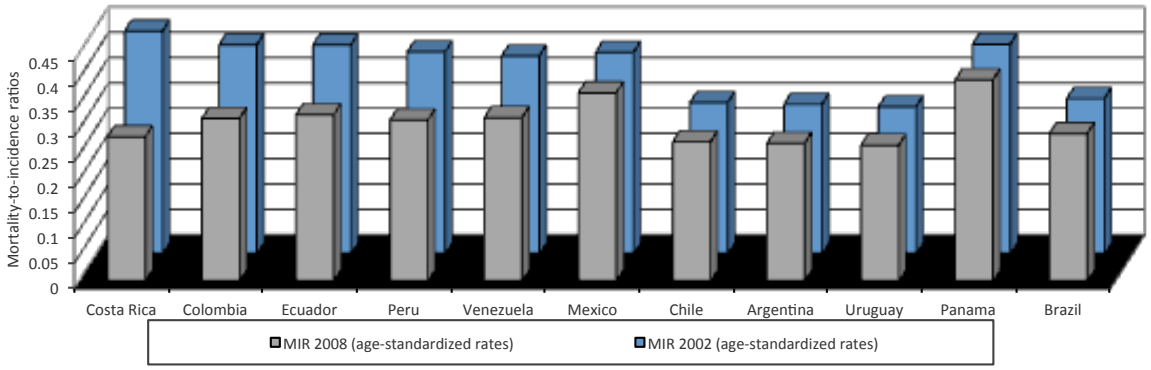
| | Stage I | Stage II | EBC | Stage III | Stage IV | Reference |
|---|---|---|---|---|---|---|
| Norway (benchmark) | | | 90% | | | Kreftristeret Institutt:2009 |
| Brazil-Minas Gerais | 16,8% | 46,0% | 62,8% | 30,5% | 4,2% | Guerra:2009 |
| Brazil -Porto Alegre | 16,0% | 54,0% | 70,0% | 19,0% | 11,0% | Schwartsmann:2001 |
| Brazil –RGdS | 19,8% | 57,6% | 77,4% | 15,1% | 7,5% | de Moraes:2006 |
| Brazil -Rio de Janeiro | 9,4% | 43,0% | 52,4% | 34,3% | 13,3% | Brito: 2008 |
| Brazil -Sta Catarina | 18,1% | 46,2% | 64,3% | 24,3% | 11,4% | Schneider:2009 |
| Brazil -Sao Paulo | 27,1% | 33,2% | 60,3% | 27,9% | 8,2% | Fund Oncocentro de São Paulo'09 |
| Chile (1999) | 14,1% | 28,8% | 42,9% | 35,8% | 20,7% | Pietro:2006 [13] |
| Chile (2003) | 19,7% | 50,1% | 69,8% | 23,9% | 5,1% | Pietro:2006 [13] |
| Colombia (Bgtá) | 21,8% | 39,6% | 61,4% | 17,0% | 3,4% | Gonzáles Marino:2005 [127] |
| Mexico (DF) | 9,7% | 52,7% | 62,4% | 34,8% | 2,8% | Flores-Luna:2008 |
| Mexico (DF) | 10,2% | 59,5% | 69,7% | 29,4% | 0,9% | Rodríguez-Cuevas: 2001 [68] |
| Peru (1985-1997) | 9,0% | 42,0% | 51,0% | 33,0% | 16,0% | Schwartsmann:2001 |
| Peru (2000-2002) | | | 60,8% | 31,9% | 7,3% | Moreno Gómez:2010 |
| Uruguay | 40,1% | 41,8% | 81,9% | 16,6% | 1,5% | Krygier:2007 |

## 3.2 Mortality-to-Incidence Ratio

The mortality-to-incidence ratio (MIR) has been extensively used in the literature, especially for cross-sectional comparisons. Besides, one can interpret it rather intuitively. Let's take the countries under study. In the previous section, we learned that Argentina's mortality was between 4 and 5 times higher than that of Mexico or Panama (Error! Reference source not found.). However, for every 100 women diagnosed with BC in Uruguay or Argentina only 27 will die of the disease while in Mexico 37 and in Panama 40 will die of the disease (Figure 9). In general, the treatment and care for BC patients in Argentina saves comparatively more lives than in Mexico or Panama.

The grey bars in Figure 9 represent the MIR in 2008, when Panama (0.397) and Mexico (0.371) presented with the poorest outcomes and Uruguay (0.268), Argentina (0.271), Chile (0.274) and Costa Rica (0.284) with the best results. When comparing the outcomes of Globocan 2002 with 2008, Figure 9 illustrates the positive development that is evident in the whole region. However, this proxy-survival evolved more favourably in some countries than in others. Costa Rica shows a dramatic improvement in their results dropping closer to the levels of Uruguay, Argentina or Chile. Colombia, Ecuador and Peru are also improving but still lagging behind and Brazil is the country where the least progress is seen.

**FIGURE 9.** Breast cancer mortality to incidence ratio in 2002 and 2008 (Globocan).




## 3.3 Quality of life

As Mandelblatt and colleagues wrote, quality of life (QoL) has been an implied medical outcome since the time of Hippocrates but it was Karnofsky's work that featured the first significant landmark. He made the first explicit effort coming from physicians to systematically assess the impact of cancer treatments on the patient's QoL and not quantity of life [130]. The study of QoL and development of cancer specific tools has been advancing ever since, particularly for breast cancer. The first instruments to measure cancer patients' performance status and quality of life were physician-rated [131, 132]. QoL research evolved into the current methodology based on patient questionnaires in the late 1980s and early 1990s [133]. Since then, several instruments have been developed for the assessment of health-related quality of life in cancer and specifically to evaluate the impact of breast malignancies. Given the multi-dimensional nature of BC management, the detection of significant changes in patient reported outcomes along with the different phases of the disease management, often requires the use of alternative instruments. As we presented in the global report, the health domains most commonly considered in a quality of life assessments are: 1) somatic concerns, such as pain and symptoms; 2) functional ability; 3) family well-being; 4) emotional well-being; 5) spirituality; 6) treatment satisfaction, including financial impact of illness; 7) future orientation; 8) sexuality, intimacy, and body image; 9) social functioning; 10) occupational functioning; and 11) preferences. Published quality of life studies have encompassed the major stages of BC care: screening, local treatment, adjuvant treatment, treatment of metastatic disease, and survivorship and surveillance [130]. Decisions about alternative therapies, in particular in metastatic BC when the objective of treatment is not cure but prolonged survival, often encompass quality of life considerations. Although health-related quality of life is today considered an important endpoint in cancer clinical trials, due to methodological problems with many studies lacking a predefined specific endpoint, quality of life considerations so far have limited impact on the evaluation and approval of drugs. Thus, there is a clear need for expanded research on outcomes measures.

In Latin America, research on QoL is meager and the production and use of health-related QoL assessments in BC is marginal to say the least, except for Brazil where numerous studies have been identified and, to a less extent Colombia and Mexico. Apart from the general QoL research trying to identify QoL deterioration drivers, most of the rest deals with the aftermath of surgical procedures. We found only one Latin-American article addressing radiation therapy that rejects the hypothetical benefits of multivitamins to improve radiotherapy-related fatigue [134]. We also found two ASCO abstracts, one which discusses QoL improvements associated to the use of Capecitabine in patients with metastatic disease [135]; and the other abstract addresses

the QoL of patients in ambulatory treatment and their personality dimension in Peru [136].

Two of the Brazilian articles that studied factors that interfere with the QoL of BC survivors provide some interesting findings. Marques Conde and colleagues ascertain that BC survivors 6 months after complete oncologic treatment exhibit a good QoL in general with scores as high as 82.7/100 in physical functioning and 75.8/100 in social functioning but also 61.9/100 in vitality and 58.5/100 in body pain. The most prevalent symptoms reported were nervousness, and hot flashes and factors associated with poorer QoL were as dizziness, postmenopausal status, and breast conserving therapy (in the physical component) as well as insomnia and being married (in the mental component) [137]. Rabin and colleagues also worked with survivors after 3 years on average and found no statistical significance among the demographic variables (age and educational background), time of disease, staging and chemotherapy but patients who underwent mastectomy indicated lower QoL scores in the physical and psychological domains and depressive symptoms were significantly associates with lower QoL scores in all domains [138].

We will briefly address the evolution of surgical procedures in Section 4 but let us advance that, in general, progress in this field improved the QoL of survivors rather than survival as such. Some of the main physical sequelae of BC and its surgical treatment are upper-extremity dysfunction, lymphoedema, pain and pulmonary sequelae [139]. In the psychological dimension, the main stressors identified in Brazil by da Silva and dos Santos have to do with conflicts with self-image and alteration in the feeling of autonomy, fear in relation to the evolution of the condition, feelings of guilt about the disorder generated in the family, experience of disturbing social situations and a desire to return to their professional occupation [140]. Additionally, after surgically treated women see their sexuality also affected and two Brazilian studies examined its impact on their QoL. Ribeiro Huguet and colleagues evaluated first the QoL of the patients depending on their sociodemographic characteristics and the procedure they underwent and found that the QoL of the patients was not significantly different due to their age, education, and type of surgery; but women with stable marital relationship got better scores in the psychosocial and social relationships areas and higher socioeconomic level influenced the QoL concerning physical appearance and environment. Then, when looking into sexuality, stable marital status revealed to impact positively as did age and higher schooling. Finally, women submitted to quadrantectomy or mastectomy with immediate breast reconstruction showed higher scores relating to attractiveness than those who did not receive reconstructive surgery [141]. Their conclusions were consistent with the findings of Manganiello and colleagues who used a different instrument and still observed that higher education had a significant impact on the women's functional capacity, vitality, emotional limitations and mental health and that higher education and breast reconstruction had a significantly positive effect on women's sexual satisfaction and functioning, the contrary to what happened with the age of the patient's partner [142]. And, finally, an interesting study by Rabin and colleagues revealed that partners of women with BC may be viewed as reliable surrogates to assess patient's QoL [143]. Apparently, when they administered the WHO QoL instrument and another to assess depression (the Beck Depression Inventory), there were no differences between the perceptions of QoL between the patients and their partners and it was only in the cases where the patient was depressed that this congruence was interfered.

One more issue is whether different surgical procedures have different impact on patient's QoL. Rodrigues Paim and colleagues documented that incidence of postlymphadenectomy complications such as impaired shoulder strength and range motion, pain, fibrosis and lymphedema was higher after auxiliary lymph node dissection (ALND) than sentinel lymph node biopsy (SLNB) and winged scapula only occurred among patients who underwent ALND [144]. Consequently, QoL of ALND patients was lower due to its high correlation with pain and impaired shoulder strength. More details are provided by a Mexican study that observed that patients with a benign lesion who underwent lumpectomy demonstrated a favourable body image perception when compared with the malignant lesion group. Also, conservative surgery and breast reconstruction proved to improve QoL but only in young patients and educational level of the patient also affects the results. Medina-Franco and colleagues realized that what affects the patients' body image and QoL the most, is the cancer diagnosis itself [145].

In general, the BC diagnosis itself disturbs a woman's life

and affects her QoL, mainly in the psychological and even phychosocial dimensions. But it is after surgery when the QoL of a patient deteriorates most, in all dimensions. Under certain conditions education level, socioeconomic strata or having/not having a partner may mitigate or exacerbate that deterioration. In any case, the evolution of treatment alternatives seems to bring new technologies that address QoL, as is the case with new surgical techniques (see Section 6.1).

# SECTION 4.

## Framework for breast cancer care

## SUMMARY


- *Evidence based treatment guidelines, which adhere to international standards, receive high compliance and are regularly updated, are key to promote the rational use of resources and equality in access to BC treatment services. Additionally, guidelines must be relevant to the locally available resources and conditions.*
- *In LA, most countries have medical care standards (MCS) published by governmental authorities, cancer institutes, or national, professional or scientific associations. The challenge in the region is to implement policies and control mechanisms to ensure compliance and their applicability to the whole population.*
- *National Cancer Control Plans (NCCP) are the fundamental building blocks to an organized governance, financing and health delivery for cancer care. There is a marked absence of NCCP in LA.*
- *Organization of BC care delivery: evidence has shown that a multidisciplinary team approach yields better results, improves patient satisfaction, decreases waiting times from diagnosis to treatment and improves spending efficiency. The organization of BC care delivery in the region varies and, in general, is not up-to the standards observed in more developed countries*
- *Latin American patient groups fulfil an important task, especially where healthcare systems cannot or do not sufficiently assist BC patients. Further improvements are needed for patient information services and involvement of patient groups in policy decision making.*


### 4.1 Treatment guidelines

BC care is complex and a multidisciplinary team approach to diagnosis and treatment is necessary for ensuring best practice outcomes. In Latin America, maximizing results with limited resources presents the challenge of balancing the right level of investment in prevention, early detection, detailed and accurate diagnosing, the most efficacious and safest surgical, radiation, systemic, and biological therapies, as well as the safeguard of the patients' quality of life. This is the framework of the ongoing debate among analysts and experts.

The Breast Cancer Research Foundation sponsored two studies conducted by SLACOM in 12 Latin American and Caribbean countries. The second study (BCRF II) presents a systematic review of the norms, recommendations and guidelines that are considered medical care standards (MCS) for breast cancer. The article concludes that most countries under study count with MCS published by governmental authorities; cancer institutes; or national, professional or scientific associations. However, the challenge in the region is to implement policies and control mechanisms to ensure compliance with those MCS and their applicability to the whole population [146]. With a smaller sample, we conducted a survey among experts in the region and found that, in general, the use of regularly updated evidence-based treatment guidelines are in line with internationally

accepted standards. Most authors and experts convey the need for further coordination and better use of scientific evidence in the diffusion of medical care standards across the region, but there is no mention of the need for new MCS [129, 147]. The documents researched, as well as the experts, often referred to the guidelines produced by the National Comprehensive Cancer Network (NCCN) in the United States.

The BHGI (Breast Health Global Initiative) has developed BC treatment guidelines for low and medium income countries, which stratifies prevention and treatment options according to available resources [148-152]. Internationally referenced treatment guidelines often assume unlimited resources, so such an adjustment is necessary. In some of the study countries, BC treatment guidelines are formulated as so called 'care programs' that include also treatment pathways and organizational aspects of BC care, while in other countries the guidelines are predominantly clinically oriented, focusing on which diagnostic investigations should be performed, and what treatment should be provided depending on diagnostic results.

When faced with decisions regarding the optimal allocation of limited healthcare resources, some countries in Europe, the US, Canada, Australia and others resort to Health Technology Assessments (HTA), which are more often being "hard wired" into resource allocation decisions, such as those about the reimbursement of drugs and other health technologies. In Latin America, the use and influence of HTA in decision making is increasing. Argentina, Brazil, Chile, and Mexico have HTA agencies affiliated to INAHTA (International Network of HTA agencies). HTA was formally used to shape benefit packages in Argentina, Uruguay, and Chile. A formal fourth hurdle system is in place in Brazil, Mexico, and Colombia that require evaluation of new technologies using HTAs [153]. In fact, in 2009 the Institute for Clinical Effectiveness and Health Policy (IECS) and Professors Sullivan and Drummond conducted a survey among 1,142 HTA researcher and users from nineteen LA countries, with a majority of the respondents from the public and private health sector, followed by academic and government sectors. They found that around one third stated that they use the HTA reports at an institutional level for decisions related to coverage and reimbursement of health technologies, one third used them at institutional level for other decisions not related directly to coverage (e.g., clinical practice guideline development), and another third used them for clinical decisions at the patient level [153].

The advancement of evidence-based best practices in the evaluation required for resource allocation decision making may, in turn, create economic incentives to stick to the treatment practices that are proven to work.

## 4.2 Organization of Breast Cancer Care

### 4.2.1 National cancer control strategies

The development of national public health programmes to reduce cancer incidence and mortality and improve quality of life, using evidenced-based strategies and making the best use of available resources, is recommended by the WHO. This is a means to not only manage the current burden of cancer, but to deal with the expected increased future burden of cancer, resulting from demographic changes and ageing population.

Professors Rifat Atun, Toshio Ogawa and Jose M Martin-Moreno produced a report on National Cancer Control Programmes (NCCP) in Europe that highlights WHO's efforts to respond to the cancer pandemic, given its human and economic cost. The Cancer Prevention and Control Strategy Resolution, adopted by the 58th World Health Assembly (WHA58.22, adopted in May 2005), which outlines "WHO's cancer control strategy at global, regional and national levels aimed at improving knowledge to implement effective and efficient programmes for cancer control, accelerating the translation of knowledge into a reduction of cancer burden and improving quality of life for cancer patients and their families" [154].

Atun, Ogawa and Martin-Moreno also present a useful analytical framework consisting of elements of a NCCP such as: a) governance and organization; b) financing; c) resource allocation and provider payment systems; d) service delivery; e) monitoring and evaluation; and f) resource

generation. Without comprehensive NCCPs, there is little basis for sustainable improvements in cancer control.

As we stated in Section 4.1 and following the findings and final remarks of the study conducted by the Breast Cancer Research Foundation (BCRF II) [146], most Latin American countries reported the use of similar medical care standards (MCS) for BC care. However, the challenge is not in generating new MCS, but in implementing policies and control mechanisms for compliance with existing MCS, guaranteeing their applicability to all populations. Robles and Galanis, agree concluding that countries in LA need to evaluate the feasibility of designing and implementing appropriate treatment guidelines and providing wide access to diagnostic and treatment services [129]. In fact, even very few comprehensive registries exist in the region. Antonio Mirra studied the historical evolution of the 42 cancer registries started in Latin America during the period 1950-1995 and concludes that about 43% of them failed due to lack of technical personnel, improper evaluation of (regional or national) possibilities and above all scarce financial support [156].

### 4.2.2 Multidisciplinary teams

Before the mid-1970s, early BC was managed almost exclusively by surgeons, while radiation and medical oncologists would be involved in the treatment of patients with advanced disease. Since then, the advances in the diagnosis and treatment of BC have made BC care increasingly successful but also more complex. In the process from prevention, diagnosis and treatment to rehabilitation or palliative care, a range of expertise needs to be involved, including surgeons, radiotherapists, medical oncologists, gynaecologists, diagnostic radiologists, pathologists, primary care physicians, specialised nurses, pharmacists, geneticists, psychologists, physiotherapists, and social workers.

Studies in the 1980s and 1990s demonstrated that BC patients managed by specialist surgeons, with a high load of BC cases per year, had better outcomes, since the specialist care resulted in a more holistic treatment approach and the patients were more likely to receive a combination of adjuvant therapies [157, 158]. A multidisciplinary treatment approach was something that evolved as it became evident that outcome was improving with the combination of different types of interventions. However, as BC care grew increasingly complex it became necessary to formalise the structures for cooperation over disciplines. Today, a multidisciplinary team approach, where specialists of the different disciplines meet regularly, discuss the files of current BC patients at the centre, and together decide on a treatment plan, is the recommended model for BC care as well as for most other forms of cancer. Additionally, it has been demonstrated that decisions made by a multidisciplinary team are more likely to be in accordance with evidence-based guidelines than those made by individual clinicians [157-160].

### 4.2.3 Streamlining the patient pathway

There are many possibilities for delays in the pathway from the time an individual acknowledges the presence of symptoms to warrant a visit to a doctor, until a diagnosis has been made and, if necessary, treatment is initiated. Potential delays include: the individual may hesitate in visiting a general practitioner; the general practitioner may dismiss or misinterpret the symptoms and not conduct the relevant examinations; there can be waiting times for diagnostic tests, the interpretation of the results and for transfer to a specialist for further diagnosis or in initiation of treatment. The different types of delays are referred to as, patient's delay, doctor's delay and system delay respectively [161].

Fragmentation, a lack of continuity, and long waiting times can be particularly evident for cancer patients since the care process is often long and involves different disciplines. Having to wait for the results of a diagnosis or for treatment to be initiated can be a large psychological strain. With ambitions in recent years to offer more patient-focused care, attempts have been made to create a so called seamless care process. Indeed, patients treated by multidisciplinary care teams have reported greater satisfaction, with decreased waiting times from diagnosis to treatment, and reduction in duplication of services [162, 163]. BC nurses, who often have a coordinating role in the teams and function as care coordinators and contact persons for the patients, seem to have a significant role in this [164, 165]. The aim is to ensure that the patient always knows what and when the next step will be and is not left unattended in the transfer from one medical department to another.

According to the BCRF II study [146], overall in Latin America, about 30% (range of 0%-64%) of patients waited for more than 3 months for a diagnosis at the country level. Other studies confirm this. In Mexico, long waiting times are a frequent problem in cancer care, as well as insufficient supply of drugs. Comprehensive data of available resources and access to services do not exist in Mexico, therefore the national institute of public health in Mexico is currently conducting a study to identify and map barriers to BC care [166]. In Brazil, Cintra and colleagues report an up to 12-week interval between diagnostic and first intervention [84].

### 4.2.4 Quality assurance processes

There may be many barriers to the introduction of clinical evidence into routine clinical practice. A change will often require comprehensive approaches at different levels: the policy environment; the hospital management; the specialist team; the individual physicians. Even if doctors are aware of the new clinical evidence and are willing to change, to alter well-established patterns of care is difficult, especially if the clinical environment is not conducive to change. It has been shown that important factors in order to improve clinical practice include overall emphasis on quality rather than cost of care, treatment guidelines, awareness-raising through education, monitoring of progress continuously or at regular intervals based on defined indicators for measurement of success and feedback of results [167, 168]. A difficulty with continuous follow-up of outcomes in cancer care is that outcome quality can so far only be measured indirectly by using surrogate parameters under the general assumption that better short- to medium-term structural quality and process quality will result in improved long-term outcome quality.

One important initiative is seen in Germany where, since 2003, a growing number of German hospitals and specialist breast centres with a focus on BC care have chosen to participate in a voluntary, external and independent scientific benchmarking system developed by the major German medical BC societies. Detailed requirements for breast centres have been formulated, based on evidence based guidelines and the EUSOMA requirements for specialist breast units, and a certification system has been established. The aim is to develop a comprehensive network based on voluntary self declaration of quality assurance data, to develop suitable indicators for benchmarking the quality of care delivered to BC patients, and to demonstrate that the quality of cancer care can be assessed, and subsequently improved, by means of a standardised collection and analysis of such voluntary data. Quality assurance includes both comprehensive documentation of all treatments and external analysis of the data. Certified centres need to demonstrate regularly that they live up to quality requirements [169, 170].

No initiatives with these characteristics have been identified in the Latin American countries studied for this report.

## 4.3 Patients' insight and involvement in treatment decisions

The Patient Experience Working Group of the Macmillan Cancer Support undertook a research project for the UK's Cancer Reform Strategy, that culminated with a number of recommendations for improving patients' experience of cancer care, including the following: (1) Providing information at key points along the care pathway, (2) Offering patients a choice of treatment and care packages, (3) Providing support for self-care and self-management, (4) Obtaining systematic feedback from patients by means of surveys, and (5) Involving service users in decisions about reconfiguration and service development [171].

Concerning the first of these points, it can be expected that the asymmetry of information between the patient and the physician, in combination with the seriousness of a cancer diagnosis, can give the patient a feeling of powerlessness in particular when the information provided about the disease and treatment options is felt to be insufficient. Therefore it is important that there is sufficient room for communication to allow the patient to get enough support and information to understand the situation and have the opportunity to plan treatment and care together with their physician.

In fact, a study conducted in Argentina explored the doctor-patient communication in oncology. Gercovich and colleagues created an ad-hoc questionnaire in order to evaluate the patient's expectations and preferences; and administered it to 436 consecutive ambulatory oncology

patients. They found that the highest ranked patient's preferences for receiving information were veracity (36%), clarity (20%), and frankness (18%) [172]. This is in line with the findings of other studies in several countries reported in the global report, which show that a great majority of BC patients want to be involved in treatment decisions; over half of all patients express that they want the doctor to take the final decision on treatment, but want to feel that their views are taken into account following discussion with their doctor as part of the decision process [173-176].

As for the patient involvement, we have established that well-informed patients are a prerequisite for their increased participation in treatment decisions; even when the information asymmetries persist. In our survey with clinical experts and non-governmental organizations (NGOs), we found that sometimes the gap between the public and private settings also impacts patients' involvement and, in some countries, patients are not entitled to a second opinion if they cannot afford to pay for it, they cannot choose the treatment centre and do not receive a written treatment plan. Also, information, emotional support and prosthetics and/or wigs are not always provided. In some cases this gap is filled by the patients' organizations.

Regarding patients' organizations, the American Cancer Society published in 2008 the findings on their 6-month market access research of NGOs and civil society in all the study countries except for Panama [177]. Their overall findings concluded that, in general, Latin American NGOs lack a leadership role in cancer control and that the lack of a survivorship movement, faulty patient information services and governmental failure to include them in policy-decision making need further improvements. The authors highlight the NGOs strengths such as a highly committed staff and volunteer base, expertise in pediatric cancer services, burgeoning BC movement and the emergency of innovative programs. In contrast, they found that the organizations' weaknesses are: their small size and limited community outreach, inadequate fundraising programs, lack collaboration among groups, inability to develop advocacy-based programs, lack of strategic media relations approaches and failure to develop patient information dissemination strategies among others. Some of these weaknesses do not accurately describe all the NGOs we worked with. In Brazil, Costa Rica, Mexico and Peru, strong organizations compile and produce information, advocate and cooperate with all the relevant stakeholders and provide patients with emotional support.

# SECTION 5.

## Prevention and diagnosis of breast cancer

## SUMMARY


- *In the region, there is no one-suit-all prevention strategy given the outstanding epidemiological contrasts in terms of disease occurrence, risks, and available resources both across but also within countries*
- *Population-based mammography has been shown to improve outcomes as it leads to a larger share of breast cancers being diagnosed at an early stage but in some LA countries with limited resources and low incidence, the best screening strategies differ. In countries like Argentina and Uruguay higher frequency, lower start age and shorter intervals than in countries like Ecuador, Peru, or Mexico are justified.*
- *Since affordability remains a liming factor in the region, recommendations from the BHGI and WHO highlight the role of prevention but contemplating several additional measures like health education and behaviour modification, breast self-awareness and clinical breast examination.*
- *Nowadays in LA, the majority of BC cases are detected when women seek care following onset of symptoms. Initiatives to increase the awareness of BC are extremely important so that women are attentive and do not postpone seeking care until the symptoms have reached a critical stage.*
- *In LA, contrary to the relatively low commitment to mammographic screening, post-diagnostic screening with hormone receptors and biologic marker determination is widely spread. However, not all the information obtained is put to good use, because of the limits on access to some treatments, especially some expensive targeted agents.*


### 5.1 Primary prevention

Primary prevention measures aim to reduce the risk factors for a specific disease and/or the individual perceptibility for such risk factors. Primary prevention of BC is more difficult to achieve than for some other cancer forms. Most of the BC risk factors are currently not amenable to primary prevention interventions. The life-style risk factors of BC that are susceptible to primary prevention measures include: breast feeding, obesity after menopause, diet, alcohol, physical activity, oral contraception close to menopause, and post-menopausal hormonal treatment [178].

- **Prevention in high-risk groups**

It is estimated that 20–30% of breast cancers are caused by genetic factors that in combination with life-style factors can trigger the development of the disease. Around 4-7% of BC cases are directly attributable to certain genetic mutations, most commonly in the BRCA1 and BRCA2 genes, which predispose women to a 60-80% life time risk of developing breast cancer, often already at a young age [28, 179, 180]. Women with a high genetic predisposition for BC can benefit from preventive measures including; more frequent screening, and at a younger age, or chemoprevention with endocrine therapy. These drugs however, may have limited impact since BRCA1 carriers are frequently endocrine unresponsive [181-184] and their elevated cost renders them prohibitive in most Latin American countries for prevention purposes. The most established strategy is preventive removal of the breasts, although the evidence base for this strategy is limited.

## 5.2 Secondary prevention/early diagnosis

The aim of secondary prevention is to reduce the severity of disease and the risk of dying from it. As discussed in Section 3.1, outcome is significantly better if the BC is detected before it has spread outside of the breast. However, early stage BC is not symptomatic in all patients. The principal secondary prevention measure in BC is population-based mammography which has shown to improve outcomes. It leads to a larger share of breast cancers being diagnosed at an early stage in the screened population [103-107].

In the BHGI's outline for program development in Latin America, prevention is highlighted but contemplating several additional measures like health education and behaviour modification, breast self-awareness and clinical breast examination. Screening mammography is still recognized as the only single modality proven to reduce mortality but its "prohibitive cost" in many settings leads to the recommendation that population and intervals be optimized within the scope of available resources [147]. This is perfectly in line with the WHO's recommended early detection strategies for low- and middle-income countries centred around awareness of early signs and symptoms and screening by clinical breast examination. The WHO also regards mammography screening as very costly and recommends it for countries with good health infrastructure that can afford a long-term programme. Additionally, WHO's BC Control recommendations sustain that key to the success of population based early detection are careful planning and a well organized and sustainable programme that targets the right population group and ensures coordination, continuity and quality of actions across the whole continuum of care [185]. Targeting the wrong patient group (such as younger women with low risk) could cause a lower number of breast cancers found per woman screened and therefore reduce its cost-effectiveness. In addition, targeting younger women would lead to more evaluation of benign tumours, which causes unnecessary overload of health care facilities due to the use of additional diagnostic resources [186]. And it is in this framework that their recommendation in favour of the practice of breast self examination is given; it empowers women, fostering their taking responsibility for their own health; and by doing so, awareness among women at risk is raised.

Robles and Galanis, make these concepts tangible assuring that in countries with low incidence, screening with mammography is not justified in women under 50 years of age [129]. Though, WHO's recommendation may need to be carefully interpreted in those middle-income countries with high and very high incidence as in the case of Argentina and Uruguay.

**TABLE 18.** Women who have had mammography or breast examination in Latin American countries, UN DATA, WHO.

| Country | Percentage |
|---|---|
| Brazil | 49% |
| Ecuador | 17% |
| Mexico | 21% |
| Uruguay | 54% |

Source: World Health Survey, Geneva, 2006 (http://www.who.int/healthinfo survey/whsresults/en/index.html)

According to the aforementioned expert survey conducted by SLACOM, access to mammography was reportedly available to 66% of the patients at the country level [128]. In Table 18 we present WHO's estimate of the percentage of the female population aged 40–69 years who have undergone a breast examination or mammography in the past three years. Uruguay and Brazil report significantly higher rates than Ecuador and Mexico.

In Mexico, this number may be an overestimation if we consider that in the year 2001 the Ministry of Health reported that 0.77% of 40-year old women and older had a mammography in the previous year and that only 25% of the installed capacity was being used. In contrast, according to the same report, one of every 3 women older than 25 had had a breast clinical examination [187]. In Mexico, mammography screening is recommended but there is no national population-base screening program and the overall adherence rate to mammography controls is low; a recent survey in Mexico City indicates that many women feel uncomfortable or worried about doing mammography screening [166, 188]. Aware of this situation, the Federal government published a norm[1] that establishes early detection through self-examination, clinical examination and mammography every two years for women aged 40 to 49 with 2 or more risk factors and every year for 50-year old women. The budget accompanied the norm and the number

[1]: Norma Oficial Mexicana NOM-041-SSA2-2002, Para la Prevención, Diagnóstico, Tratamiento, Control y Vigilancia Epidemiológica de Cáncer de Mama.

of mammography units went from 120 in 2001 to 413 in 2006. However, the slow organization of a National Early Detection Program and the required diagnosis and treatment services have been hampering the realization of this investment in terms of outcomes for the moment [189]. The norm is now under revision. Aiming at contributing in the design of the optimal screening policy, Valencia-Mendoza and colleagues have developed a model that generates cost-effectiveness information about 13 screening policies (plus "no screening" as baseline) composed by varying combinations of starting age (SA), percentage of coverage (PoC) and frequency in years (FiY). They conclude that the three best alternatives are SA/PoC/FiY: 48/25/2, 40/50/2, 40/50/1 [190]. One of the goals of Mexican healthcare for the period 2007-2012 is to triple the coverage of mammography screening in women 45-64 years old from the reported coverage of 22% in 2006 [191]. This is perhaps close enough to Valencia-Mendoza's recommended alternative 2.

A similar study conducted in Colombia to assess alternative screening strategies concluded that the most cost-effective is an opportunistic screening program with mammography every 2 years for women aged between 50 and 69 and annual breast clinical examination for women aged between 30 and 69 [192].

With a different approach, Puschel and colleagues propose a low-cost intervention that can boost coverage or, rather, adherence. They compared the effects on mammography screening rates of standard care, of a low-intensity intervention based on mail contact, and of a high-intensity intervention based on mail plus telephone or personal contact, in Chile, where BC screening has very low compliance. As a result of the intervention, mammography screening rates increased significantly from 6% to 51.8% in the low-intensity group and to 70.1% in the high-intensity group; which lead them to conclude that a relatively simple intervention could have a strong impact in BC prevention in underserved communities [193].

In Argentina, a BC Control Program is being initiated in October 2010 as an extension of Female Cancer Prevention Program. It was preceded by a survey on available resources for BC control performed between October 2009 and March 2010. One of the main conclusions of that report is that screening is mostly opportunistic even in territories with running programs. This is related to the lack of effective strategies to guarantee high coverage rates. The new National Program will cover 4 provinces with high mortality rates that account for approximately 20% of the country's total population [194].

Finally, Brazil's relatively high percentage is consistent with the data obtained from the Ministry of Health that reports that in 2008, 72.2% of women aged between 50 and 69 had had a mammography in the previous 2 years [195], and this relatively high coverage was relatively uniform across the territory with the lowest rate in Porto Velho (52.2%) and the highest in Belo Horizonte (83%). Surprising information if we bear in mind Brazil's relatively poor BC outcomes. Given that improvements in survival have been driven by early detection and enhanced systemic therapy, the remarkable efforts to improve in the former leave the latter as the main suspect to explain poor survival. So, to conclude, given Brazil's important efforts in secondary prevention, their poor health outcomes seem to be caused by a lack of enhanced systemic treatment rather than a lack of an early-detection strategy and screening compliance.

Also in countries with a high overall coverage, it has been shown that two groups in particular are under-represented in BC screening programs; women from lower socio-economic levels and first-generation immigrants [196, 197]. This has been proved in Colombia, where Ligia de Charry and colleagues assessed the equity in real access to breast-cancer early detection by comparing opportunity for and real access to mammography screening according to women's social health insurance affiliation (or lack of one). Inequality was substantiated and it affects the most vulnerable population, those poor uninsured and the illiterate were found to have lower probability of receiving mammography screening [198]. In Colombia in 1993, the Bill 100-1993 granted BC the condition of "Disease with Public Interest"[1] and Early Detection was introduced in 2000 by Resolution 412 and reinforced by Resolution 3384. However, according to Dr. Gutiérrez and colleagues, the text is imprecise due to the lack of clarity regarding the kind of screening and the failure to include women without health insurance [199].

Nowadays in Latin America, the majority of BC are detected when women seek care after having noticed a breast lump. And to make matters worse, not always do they seek care immediately. A Colombian study with more than 1,100 women, of whom 80% consulted due to symptoms, patient delay was established in 20.3% of cases. Consequently, the

[1]: Ley 100 de 1993 ; "Enfermedad de Interés Publico".

majority had advanced-stage disease. Initiatives to increase the awareness of BC are extremely important so that women are attentive that breast lumps and other changes to the breasts can be a sign of cancer and do not postpone seeking care until the symptoms have reached a critical stage [69]. Early detection presents an opportunity for improvement in the region [193] and in some countries like Argentina, Brazil, Costa Rica, and Mexico actions are being taken in this direction [89, 189, 194, 200, 201].



## 5.3 Diagnosis

The recommended diagnostic approach in BC is the so called triple diagnosis with a combination of clinical investigation, radiological investigation and a biopsy, frequently fine needle cytology or a core biopsy, which distinguishes in situ versus invasive lesions. This diagnostic approach is essential in order not to miss small or non-palpable breast lesions. Additionally, testing for biological markers is recommended because it provides the basis for the selection of medical therapy. For estrogen-receptor positive and progesterone-receptor positive patients, endocrine therapy - drugs that interfere with the production of hormones or block their action - is the recommended treatment option [101].

Advances in molecular medicine in recent years have made it possible to identify genes that provide certain tumour-specific characteristics and in some cases to predict if an individual tumour will respond to certain treatments. Patients with tumors expressing human epidermal growth factor receptor 2 (HER2), previously a subgroup with poorer prognosis than the average BC patient, respond to treatment with trastuzumab which has significantly improved the outcome for these patients [202, 203]. Patients with so called triple negative disease, with estrogen-receptor, progesterone-receptor and HER2 negative tumors, have been identified as a subgroup that at present have limited treatment options and thus worse prognosis in certain settings [112, 204].

In Latin America, contrary to the relatively low commitment to mammographic screening, post diagnostic screening with hormone receptors and biologic marker determination is widely spread in the region according to an expert survey conducted by SLACOM [128], as well as our consultation with local key opinion leaders. If we follow the same reasoning as with mammography screening, to sustain that post prognostic screening needs to be done rationally, a closer look on case-by-case bases is necessary.

**TABLE 19.** Hormone-receptor status in studies in the region.

| | Estrogen Receptor + | Progesterone Receptor + | HER2+ |
|---|---|---|---|
| Brazil (Southeast region) | | 57% | |
| Argentina | 65% | 62% | 18% |
| Uruguay | 77.2% | 69.6% | 13.6% |
| Mexico | 61% | 59% | 25.5% |
| Central America and Caribbean | | | 28.3% |

Source: Based on multiple studies, details and references follow

Table 19 presents data on hormone receptor (HR) extracted from secondary sources. For example in Brazil, a study in the South-eastern Region sustains that testing for the two of the common breast cancer founder mutations (185delAG and 6174delT) in non-Ashkenazi women is probably not justified, given their very low prevalence [205]. Another study in the same region found that 57% of the patients are HR+ and 29% unknown [121], while a third study concluded that the crude hazard ratio for positive estrogen receptor (ER+) was 0.42 and for positive progesterone receptor (PR+) was 0.67 [118]. Similarly, in Argentina, a long-term follow-up study found that hormone receptors were ER+ in 65% and PR+ in 62% of the patients [124] and another study, cross-sectional this time and based on 2285 tumour samples provided by 82 oncologists and breast surgeons, found that HER2 (human epidermal growth factor receptor 2) was over

expressed in 18% of them, 6% scored 2+ and 18% scored 1+. Additionally, they found that HER2 over expression was associated with higher levels of ER/PR+ (38% compared with 64% among HER2-) and 24% were triple negatives [206].

In Uruguay, a study found a lower prevalence of HER2+ (13.6% of the 47% known) and similar ER+ (77.2% of the 94.6% known) and PR+ (69.6% of the 94.6% known) operable BC than in most American and European studies and that triple negative BC was correlated with younger age and higher histological grade [207]. In Mexico, a study based on data obtained from the pathology register found that from 1027 patients, 61% were ER+, 59% PR+ and 25.5% HER2+ (out of 966 patients measured for it); HER2 over expression was present in 21.8% of the 68.8% HR+ patients [208].

Finally, an immuno-histochemical study in 1426 patients from Central America and the Caribbean (Costa Rica, Dominican Republic, Cuba, El Salvador, Guatemala, Honduras, and Nicaragua) found that 28.3% were HER2+ (1+:13.7%; 2+:9.6% and 3+:18.7%) but that there were significant differences across countries and institutions which underscores the need for standardizing criteria in immuno-histocheminal assays interpretation [209].

It appears that the prevalence is high enough in all the countries under study to justify the testing of hormone receptors and biologic markers. In any case, further refinement in the classification of BC tumors will most likely take place based on the present development in genomics and proteomics. Already today some subtypes of BC are recognized by this strategy.

# SECTION 6.

## Treatment of early breast cancer

## SUMMARY


- *Breast conserving surgery and sentinel lymph node dissection are part of the standard practice in LA, though the availability of breast-cancer specialized surgeons, waiting times, node clearance policy and access to breast reconstruction vary greatly across countries and between public and private settings.*
- *Radiotherapy equipment is insufficient in most countries studied for this report, except for Uruguay, Chile and Venezuela. Scarcity of trained personnel and geographical concentration add to the challenge.*
- *Affordability remains a liming factor for generalized access to evidence based best practices, especially from an equity perspective.*
- *Adjuvant chemotherapy reduces the relative yearly risk of death by almost 40% for women <50 years and by 20% for women 50-69 years old. Endocrine therapy with tamoxifen in estrogen receptor positive patients results in a more than 30% relative risk reduction of mortality. Finally, one year of adjuvant treatment with trastuzumab in women with HER2 positive BC leads to a 50% reduced risk of recurrence.*
- *In Latin America, all systemic therapies are licensed and available but cost considerations limit the wide diffusion of the use of some of the latest developments. Treatments with anthracyclines are widely accepted; as is tamoxifen for patients with oestrogen receptor-positive tumours. However, new-generation hormonal treatment alternatives, like the aromatase inhibitors and biologicals are not accessible.*


### 6.1 Surgery

Breast tumors in early stages can be completely removed by surgical resection. Surgical procedures have been evolving to attend to the high levels of associated morbidity. It was back in 1894 that Halsted proposed the classic radical mastectomy that has been the predominant technique for over half a century, consisting in the removal of the breast, both pectoral muscles and clearance of the axillary lymph nodes [210]. This technique was associated with reduced range of motion of the shoulder, lymphedema, pain, numbness, and muscle weakness. So in the second half of the 20th century, the modified radical mastectomy was developed, which preserves the major or both pectoral muscles. As then, surgery became less extensive with breast conserving treatment consisting of the excision, auxiliary clearance and breast irradiation [139]. Pos-surgery morbidity was so reduced, but not completely eradicated. So finally, sentinel-node biopsy was introduced to predict lymph nodal status and avoid unnecessary axillary clearance if the sentinel node presents no metastasis [211-214]. Breast reconstruction can be performed at the time of tumour resection or later.

For most women with Stage I or II breast cancer, breast conservation therapy (lumpectomy/partial mastectomy plus radiation therapy) is as effective as mastectomy [215, 216]. However, breast-conservation surgery requires high-

quality breast imaging equipment and is as effective as mastectomy only in combination with radiotherapy thus, in settings with limited resource where this cannot be provided in combination with the breast surgery, modified radical mastectomy is recommended [151].

Lymph node dissection is part of the staging process and the results will determine subsequent treatment decisions. A sentinel lymph node biopsy is the identification and removal of the first lymph node(s) into which a tumour drains, which will most likely contain cancer cells if they have started to spread outside of the breast. This procedure requires a great deal of skill and experience. Axillary lymph node dissection is performed as part of the removal of Stage II tumours. Anywhere from about 10 to 20 lymph nodes are removed as with these numbers the false negative rate is considered to be acceptable. A possible long-term adverse effect of removing axillary lymph nodes is lymphedema, which develops in 25% of women who have had underarm lymph nodes removed [217].

In Latin America, both our and SLACOM's surveys confirm that surgery is the first treatment modality for stage I and II; more specifically, breast conserving mastectomy was reported as a common surgical option by most experts consulted in this study. For example, in the study conducted in Rio Grande do Sul, Brazil, 60% of the patients had had a total mastectomy with the Patey method (pectoral muscle preservation) and only 6.7% had no surgery [120]. In Minas Gerais, 32.6% had breast conserving surgery while the rest had radical procedures [116]. In contrast, in Neuquén, Argentina, 70% of women treated operated between 1978 and 2004 received conservative surgery with a 17 median number of nodes examined [124].

Sentinel lymph node dissection was also reported to be part of the standard practice by most experts, though the availability of breast-cancer specialized surgeons, waiting times, node clearance policy and access to breast

reconstruction vary greatly across countries and between public and private settings [128].

## 6.2 Radiotherapy

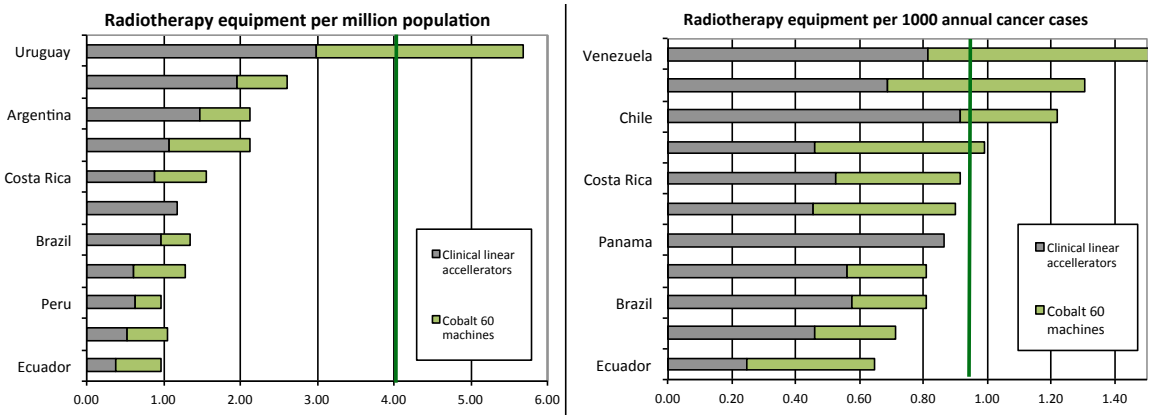
Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. This treatment may be employed to kill any cancer cells that remain in the breast, chest wall, or lymph node areas after breast-conserving surgery. Radiotherapy has gained an increased importance, and a recent meta-analysis revealed that radiotherapy as a complement to surgery decreased the risk of loco-regional relapse by two-thirds compared to surgery alone [218]. External beam radiation is the most common type of radiation therapy for women with breast cancer. If breast-conservation surgery was performed, the entire breast receives radiation, and sometimes an extra boost of radiation is given to the area in the breast where the cancer was removed to prevent it from coming back in that area. Depending on the size and extent of the cancer, radiation may include the chest wall and lymph node areas as well.

Brachytherapy, also known as internal radiation, is another way to deliver radiation therapy. Instead of aiming radiation beams from outside the body, radioactive seeds or pellets are placed directly into the breast tissue next to the cancer. It is often used as a way to add an extra boost of radiation to the tumour site along with external radiation to the whole breast. Tumour size, location, and other factors may limit who can get brachytherapy.

Linear accelerators are the device principally used for radiation therapy. In some countries cobalt machines are more frequently used because they cost less. European guidelines for radiotherapy equipment recommend that the coverage of linear accelerators should be at least four per million inhabitants. It has been estimated that 45%-55% of new cancer patients would benefit from radiotherapy [219, 220]. Both these European guideline benchmarks are represented by the green lines in Figure 10.

The BHGI outline for program development in Latin America states that there is a huge insufficiency of radiotherapy capacity in the region [147], and the left graph in Figure 10 seems to confirm this; we see that except for Uruguay, no other country counts with four linear accelerators or equivalent in cobalt machines per million inhabitants. However, Venezuela, Uruguay, Chile and Colombia possess more than 2 radiotherapy equipments per 900-1000 cancer patients in need of radiotherapy, and Costa Rica, Mexico and Panama are close to this level (Figure 10). A problem with the geographical concentration of these equipments

**FIGURE 10.** Breast cancer mortality to incidence ratio in 2002 and 2008 (Globocan).




Source: DIRAC (DIrectory of RAdiotherapy Centres). International Atomic Energy Agency, available at http://www.naweb.iaea.org/nahu/dirac/query.asp

may still be a substantial hurdle for patients' access to radiotherapy. Additionally, the level of adequately trained personnel [220] may hamper the opportunity to maximize the use of the equipment.

WHO recommends that in limited-resource countries medical facilities should initially be concentrated in relatively few places to optimise the use of resources, given the very high cost of establishing and maintaining sophisticated technology such as radiation and diagnostic equipment. Nonetheless, in countries with social and economic inequalities as most Latin American countries, high technology medical facilities may often be based in areas of the country where wealth is concentrated. This can result in a sharp contrasts in access to BC treatment between the wealthier and poorer segments in a country [221].

## 6.3 Medical therapy

Adjuvant treatment is systemic therapy given after surgery to patients with no evidence of cancer spread outside of the breast or the lymph nodes, with the purpose of destroying any microscopic cancer cells that might remain in the body and cause recurrence of the disease. Adjuvant therapy may consist of chemotherapy, endocrine therapy, and/or biological targeted therapies. Chemotherapy inhibits cell growth by different mechanisms and thus reduces the rapid cell proliferation that is a characteristic of cancer cells. Endocrine therapies (tamoxifen or aromatase inhibitors) block the effect of oestrogen or reduce hormone levels, and have effect in types of BC where tumour growth is stimulated by estrogen (about two thirds of all cases). Biological targeted therapies selectively attack genetic expression that is typical for cancer cells. Adjuvant treatment is not recommended for all BC patients with early disease; adjuvant treatment decisions are guided by a risk-benefit assessment, weighting a patient's risk of BC recurrence against adverse effects of adjuvant treatment [222, 223].

Adjuvant medical treatment in BC has evolved over a 30-40 year period. Combination regimens, of two to three drug types, with different mechanisms of action are recommended as adjuvant chemotherapy in breast cancer. The first generation of adjuvant chemotherapy evolved during the 1970s. Better regimens have been developed over time and at present, chemotherapy regimens containing taxanes and anthracyclines have been demonstrated as the most effective [224-227]. Endocrine therapy of BC started with tamoxifen in 1975 and it has established itself as the most cost-effective cancer treatment to date. Its broad indication in the treatment of advanced disease and as adjuvant treatment (as well as prevention in the US), represents a major breakthrough in the treatment of BC. Aromatase inhibitors, anastrazole, exemestane and letrozole, are now in part replacing tamoxifen, both in the treatment of advanced disease and in the adjuvant setting. Meta-analyses have demonstrated that adjuvant chemotherapy reduces the relative yearly risk of death by

almost 40% for women <50 years and by 20% for women 50-69 years old and that endocrine therapy with tamoxifen in estrogen receptor positive patients results in a more than 30% relative risk reduction of mortality [224, 227-231].

The biological therapy trastuzumab entered BC therapy in the late 1990s and has dramatically changed the outcome for women with HER2 over-expressing breast cancer. Trastuzumab is a monoclonal antibody that attaches to a growth-promoting protein known as HER2/neu which is present in larger than normal amounts on the surface of the BC cells in about 15-20% of women with early BC and 20-30% of women with advanced breast cancer. Trastuzumab can thus suppress HER2 stimulated tumour growth and may also activate the immune system to more effectively attack the cancer. In recent years, studies have shown that one year of adjuvant treatment with trastuzumab in women with HER2 positive BC leads to a 50% reduced risk of recurrence, although the follow-up period of these patients is still limited [232, 233].

Adjuvant chemotherapy is commonly given for a period of 6 months, followed by endocrine therapy for 5 years for hormone-sensitive patients, either 5 years of tamoxifen or anastrazole or a sequence of first tamoxifen and then exemestane or letrozole. Some high risk patients may also be subject to prolonged use with tamoxifen followed by letrozole with a total treatment time of up to 10 years. There is not enough evidence to establish the optimal period of adjuvant treatment with trastuzumab but it is usually given for a period of 1 year in combination with, or subsequent to, chemotherapy and may also be followed by endocrine therapy for 5 years.

Bisphosphonates, a cornerstone in the treatment of metastatic breast cancer, are a group of drugs that have come into focus also in the adjuvant treatment of breast cancer though not with curative intent but for pain reduction and fracture prevention in patients with osteometastasis. A recent study showed a clear reduction in metastatic event in premenopausal women receiving zoledronic acid [234, 235]. However, there are a couple of studies soon to be reported that will give additional information and define the role of bisphosphonates in the adjuvant setting [236].

In Latin America, all systemic therapies are licensed and available but cost considerations limit the wide diffusion of the use of some of the latest developments. The results of SLACOM's survey to 100 clinical experts in the region reveal that chemotherapy treatments with anthracyclines are widely accepted; as is tamoxifen for patients with oestrogen receptor-positive tumours. However, new generation hormonal treatment alternatives, like the aromatase inhibitors, and the biological therapy trastuzumab for women with HER2 over expressing breast cancer, which are also approved and widely accepted, are not accessible for all women in all the countries [128, 147].

For example, a pharmaco-economic analysis comparing Tamoxifen vs. Letrozol produced by the National Cancer Institute in Colombia states that it is not cost-effective to switch to the latter [237]. As described in Section 2.6, even Argentina, that has the highest per-capita health expenditure in the region and cancer treatment is provided free of charge by the government and the social security organizations in the public and private settings respectively, some patients may sometimes receive suboptimal treatment.

As we saw before, in Peru, about 70% of the population does not have access to cancer treatment altogether, let alone the more expensive interventions. In Colombia the new modern drugs are not included in the package guaranteed by the universal health insurance and patients would only have their right to be treated recognized through a lawsuit [88]. Also in Brazil, access to innovative treatments differs significantly depending on the insurance status of the patient. In the global report we learned that the public system usually does not reimburse modern drugs like trastuzumab, bevacizumab or lapatinib which, thus are rarely used. Private health insurances reimburse in general similar treatments as those used in Europe and in the US, but it is important to mention that, depending on the private insurance a patient has, different drugs will be available for their treatment [1]. Finally, in Chile, it was only in June 2010 that the Cancer Unit of the Secretary for Public Health established the inclusion of trastuzumab to be reimbursed by the National Health Fund (Fondo Nacional de Salud – FONASA) and, for the moment, in a selected high-risk group of 200 patients with maximal benefit [238].

Affordability and equity remain a challenge for generalized access to internationally accepted, evidence based best practices for BC treatment.

## 6.4 Patient follow-up

Regular follow-up is important in order to identify early signs of recurring disease. Follow-up is also important in order to identify toxicity of treatment, both short- and long-term. A recent systematic review of published evidence concluded that less intensive follow-up strategies based on periodical clinical exam and annual mammography were as effective as more intense surveillance schemes [239].

# SECTION 7.

## Treatment of advanced breast cancer

## SUMMARY


- *In metastatic breast cancer, medical treatment is, to a large extent, the same as those given in adjuvant therapy. In Mexico and Brazil, advanced BC (ABC) patients are typically treated in 1st line with anthracyclines and taxanes. Second line normally also involves chemotherapy and most likely, Capecitabine.*
- *Approval of new technologies is normally faster in metastatic setting and a new proven technology such as trastuzumab had already reached significant levels of uptake by the time it's indication for early disease was approved.*
- *In Latin America, uptake of new treatments is slow, almost marginal in some countries. This is related with the health care systems' coverage and limits.*
- *The top four barriers to the optimal management of cancer pain identified by clinicians from LA countries are: 1) inadequate staff knowledge of pain management (70%); 2) patients' inability to pay for services or analgesics (57%); 3) inadequate pain assessment (52%); and 4) excessive state/legal regulations of prescribing opioids (44%).*
- *Palliative care in the region is developing and efforts both at the institutional and individual level are a reality but the problems identified in 1993 were still there almost 10 years later.*


### 7.1 Treatment of Metastatic Disease

Locally disseminated BC can be surgically removed. The tumour is often pre-treated with neoadjuvant therapy – chemotherapy given before surgery - and radiation with the purpose of shrinking the tumour before surgical resection. Neoadjuvant chemotherapy can also give information on the effect of the selected therapy – around 20% of the patients with a complete pathological response have a significantly better survival compared with those who respond less well. Neoadjuvant chemotherapy has been shown to result in equivalent survival compared with the same adjuvant regimen [240].

Compared with treatment options for early-stage breast cancer, limited data exist regarding the optimal use of chemotherapy for metastatic breast cancer. Few appropriately powered randomised clinical trials have addressed the question of the sequential use of single cytotoxic agents versus combination chemotherapy. In contrast to adjuvant therapy, for which trials are designed to include thousands of patients to identify small absolute differences in disease-free survival, most studies that address metastatic BC involve smaller numbers of participants and are underpowered to detect potentially meaningful differences in progression-free interval and/or overall survival between combination and sequential approaches [241]. The outcomes of treatments for advanced BC should be evaluated from several standpoints together with the patient. For instance, therapeutic strategies

may be associated with similar survival but different toxic effects; alternatively, one therapy may yield better survival but more severe side effects, while another may offer poorer survival but better quality of life during the patient's remaining months or years. Thus, decisions about therapy options are often based on quality of life considerations, in addition to survival [242].

Patients with locoregional relapse of BC are a heterogeneous group. About half of these patients will become disease-free following surgery, radiotherapy and medical adjuvant treatment. In the remaining group of patients the local relapse is a lead in the development of disseminated metastatic disease and the patient will need treatment accordingly. For example, a Chilean study observed 283 BC patients and within a 60-month follow-up period, the survival of those with recurrences dropped to 40%, compared to 95% in the no-recurrence group. About 68% of the recurrences were local and 32% distant and 62% were stage II [243].

In metastatic breast cancer, medical treatment is the most important consideration. The drugs given are to a large extent the same as those given in adjuvant therapy; first-line treatment for pre-menopausal women with hormone-receptor positive metastatic BC is tamoxifen and for post-menopausal women aromatase inhibitors or tamoxifen.

Trastuzumab is indicated as first-line treatment for women with HER2 positive tumours in combination with taxanes-based chemotherapy or an aromatase inhibitor. Other biological targeted therapies that may be given as secondary options in metastatic BC are bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), which is a protein that helps tumours form new blood vessels, and lapatinib (conditional approval within EU), which like trastuzumab targets the HER2 protein and may be given as third line treatment to women whose tumours progress under treatment with chemotherapy and trastuzumab.

In Mexico, advanced BC (ABC) patients are typically treated with anthracyclines and taxanes (AT) in first line, however, a large number present with AT failure. Juárez García and colleagues have investigated the treatment patterns care for ABC patients after AT failure in the Mexican public healthcare system and found that about 15% receive surgery, 29% radiotherapy, 38% hormonetherapy and 76% chemotherapy. Capecitabine was used in 55% of the cases, followed by oral and intravenous vinorelbine (12% and 9% respectively), cyclophosphamide (3%), paclitaxel (3%), gemcitabine single agent and in combination with carboplatin (2.2% and 1.9% respectively) and others (15%) including trastuzumab, vinorelbine and cisplatine [244]. In Brazil, current treatment patterns for metastatic BC patients refractory to AT in the public healthcare system also comprises the use of capecitabine (53%), gemcitabine+cisplatin (17%), and tamoxifen (9%). Third line treatment contemplates the use of gemcitabine+cisplatin (23%), capecitabine (21%), vinorelbine (14%), tamoxifen (12%), paclitaxel (5%), and letrozol (5%) [245]. A similar study in Colombia revealed that between 1995 and 2006 36% of the patients underwent surgery, 70% received initial chemotherapy, 23% of them had to change it, 50% receive radiotherapy; tamoxifen and anastrazole were also used. From the patients receiving neoadjuvant treatment (36%), 89% got chemotherapy and 11% mixed chemo and radiotherapy while among those receiving adjuvant treatment (32%), 81% got the mix [126].

## 7.2 Palliative care

In the palliative treatment of metastatic breast cancer, radiotherapy plays a major role. Metastatic bone disease and brain disease are important indications for external palliative radiotherapy. Radiation is effective in locally controlling the tumours and reducing pain. In patients with skeletal metastases, bisphosphonates are also effective in reducing pain and may help to control disease. Bisphosphonates are recommended to be used extensively and early in metastatic disease in order to prevent skeletal complications such as pathological fractures, surgery for fracture or impending fracture, radiation, spinal cord compression as well as hypercalcemia [236, 246]. Dishabilitating symptoms such as pain, fatigue, nausea, physical impairment, and sleeplessness have been found to be persistent problems for women with advanced breast cancer [247-251]. BC patients have been found to experience moderate to severe pain with some being unaware that they can have strong analgesia and a reluctance to complain to health professionals [248].

In 1993, Dr. Bruera from WHO Palliative Care Program, wrote an article describing the situation of palliative care in Latin America that is still being quoted. In it, explained that in the previous 5 years, a number of palliative care programs had been developed in Latin America but they were all still dealing with financial problems, the lack of adequate knowledge of pain control and other palliative care issues, difficulties in communication and obstacles related to local legislation are common to all programs [252, 253]. Almost 10 years later, a cross-sectional survey of Latin American and Caribbean physicians aiming at identifying the barriers to the optimal management of cancer pain concluded that out of 10 potential barriers, the top four are: 1) inadequate staff knowledge of pain management (70%); 2) patients' inability to pay for services or analgesics (57%); 3) inadequate pain assessment (52%); and 4) excessive state/legal regulations of prescribing opioids (44%). Barriers were rated similarly by the majority of physicians regardless of whether they practiced in public or private hospitals or specialized cancer centres. Palliative care specialists ranked "medical staff reluctance to prescribe opiates" as either the first or second most important barrier in their settings, in contrast to those who do not specialize in palliative care. Furthermore, while restrictive prescribing related laws and regulations were reported as one of the principal barriers by 81% of Peruvian physicians, only 40% of Brazilian ranked this as one of the primary barriers [253].

Efforts in the region are being made and in 2001 the Latin American Association for Palliative Care was launched, and they established an office in Buenos Aires, Argentina. Their mission is to promote the development of Palliative Care in LA, through communication and integration of all those interested in improving the quality of life of patients with advanced life threatening diseases, and their families. Apart from the promotion of research, exchange of experiences, diffusion of best practices, advocacy, and provision of information on palliative care in general to patients, their families and physicians, they develop clinical guidelines for the region (http://www.cuidadospaliativos.org/). Another interesting initiative is that of PAHO's Program on Noncommunicable Diseases that in 2002 selected seven demonstration projects to serve as models of change in the region in order to expand the availability of palliative care services throughout LA.

Some positive cases are presented at WHO's Pain and Palliative Care Communication Program website. For example, in 2001, the International Association for Hospice and Palliative Care (IAHPC) recognized the work of a palliative care service in Chile with its Institutional Award. The Clinica Familia - Programa de Cuidados Paliativos in Santiago was distinguished because of its ability to forge alliances with health, academic and governmental institutions in its community. That same year, Dr. Isaias Salas-Herrera, chief of the National Pain and Palliative Care Center in Costa Rica, explains that the their government has signed into law a National Pain Control and Palliative Care policy, which makes it mandatory for public and private hospitals to implement clinical guidelines for pain relief and palliative care to improve the quality of life of patients with terminal illness.

A study from Argentina about palliative care in oncology reports that varying numbers of patients attended in a palliative care program required palliative surgical procedures (such as paracentesis, pleurodesis, nephrostomy, etc), palliative radiation therapy (mainly for pain relief or CNS metastasis), pain medication (NSD and opiates), chronic steroids, antibiotics, anticoagulants, antidepressants and oxygen supplementation. The median hospitalization length was 15 days, and much of the palliative care was successfully provided ambulatory and in their home setting; which resulted in improvements in their QoL and medical cost savings [254]. Another study, in Jalisco, Mexico, reported that the most frequent symptom for admission was pain followed by weakness, loss of weight, anorexia, and emesis (nausea and vomiting). Average stay in the program of patients who died was 67 days with a range of 1-707 days [255].

However, Drs. Wenk and Bertolino assure that in spite of the fact that the development of palliative care in the region stated around 1981, it is still not available to an acceptable number of patients. In many Latin American and Caribbean countries, quality of life during the end of life is poor, with fragmented assistance, uncontrolled suffering, poor communication between professionals, patients, and families, and a great burden on family caregivers [256].

# SECTION 8.

## Conclusions and recommendations

In this report we have studied the current epidemiological situation, and the management and organisation of breast cancer care in Latin America (LA), with a focus in 11 countries Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay and Venezuela.

114,900 women present with and 37,000 die of BC every year in the LAC region, which renders BC the more frequent cancer and also the neoplasm that kills more women than any other. In spite of the scarcity of national registries, we could corroborate that in most countries, incidence and mortality are increasing due to a number of factors that will steadily increment the headcount. Ageing is the principal risk factor of BC and expected changes in the demographical structure will cause epidemiological shifts; including countries vastly populated where BC incidence is today in the lower tier in the region, such as Brazil and Mexico. BC will approach epidemic proportions in LAC by 2020 and by 2030 the number of deaths from BC is expected to double, to 74,000 every year.

The variability within the LA is as large as that between LA and other regions of the world. Uruguay and Argentina's crude incidence rate are five- six-times higher than those of Panama and Mexico, and at the level of Europe and the US. Incidence numbers in the region seems to cluster geographically. The lower rates in the North of Latin America (Mexico, Panama, Ecuador, Colombia) at levels comparable to those from Asia, Africa; while the high incidence from the South (Uruguay, Argentina, Chile, Brazil) presents serious challenges similar to those faced by Europe, the United States and Oceania. Costa Rica appears as an exception and this is probably due to their demographic structure, which resembles more that of the South Cone rather than its neighbours'. These variations may reflect reality, but could also relate to insufficient or incomplete cancer registration.

Thus, the lack of clinical and epidemiological data in many of the LA is a limitation when estimating the burden of disease, identifying trends in cancer prevention, care, treatment and outcomes over time as well and when making inter-country comparisons. The only way to reduce the uncertainty on epidemiological data is, in our opinion, to build up prospective registration on number of new cases diagnosed as well as number of deaths due to breast cancer. There is also a need for registries that capture, not only incidence and mortality, but also treatment patterns in relation to more specific outcome measures, including patient-rated outcomes, such as quality of life. Before such data are available it will be difficult to further discuss the burden of breast cancer in the region in precise and rigorous terms.

Yet, what we can conclude so far is that the burden that BC presents Latin American countries with has different shapes. In Peru, Mexico, Colombia and Brazil, younger age at diagnosis and death deprives societies of numerous productive years; as does the high occurrence of the disease in Argentina and Uruguay. The economic burden is also significant, and it can be clearly observed that countries today allocate insufficient resources to tackle the disease. Women go undiagnosed, uncared for or treated with suboptimal therapies; which results in high morbidity and the associated societal costs.

Universal health-care coverage is still not pervasive in LA and, even in those countries where the entitlement to health services is guaranteed constitutionally or by law, it is not accompanied by the necessary resources. Vast inequities in the access to BC care in LA countries are corroborated. Even within the countries across different regions such variations in access to treatment exist, leading to unequal results in BC outcomes.

Over the last 50 years, long-term prognosis for BC patients has improved significantly and 5-year survival rates are now over 85% in those countries with best outcome such as North America, Australia, Japan, and northern Europe. In LA, data on survival is scarce and fragmented and what is available shows a wide dispersion across and also within countries. Yet, the evidence signals that only in a

few countries 5-year survival surpasses 70%. The reduced survival in LA is partly due to fact that around 30-40% of patients are diagnosed only in metastatic phases III and IV; while in Europe late diagnosis is only 10% of the cases. Additionally, the referred unequal access to appropriate treatment may reduce even further the overall survival estimations; as some BC patients die undiagnosed and/or uncared for.

When confronted with the lack of complete and consistently comparable survival data, we resourced to mortality-to-incidence ratios (MIR). Panama and Mexico presented with the poorest outcomes while Uruguay, Argentina, Chile and Costa Rica are at the other end. Albeit the lower-than-desired survival in the region, BC outcomes have improved during the last decade, as evidenced by comparison of the MIRs between 2002 and 2008. Costa Rica is the country where most progress is seen, while Brazil, Mexico and Panama have not been able to significantly improve MIR ratio over the past years.

Regarding quality of life, it is a BC diagnosis that affects it the most and, in the region, the association most clearly established in the literature is between the surgical procedure undergone by the patient and her QoL. As breast preservation or reconstruction new techniques continue progressing, we may see this changing.

Treatment patterns and the organisation of breast cancer care were assessed to the extent possible on the basis of identified observational studies available, clinical expert input, national treatment guidelines and cancer control plans. Overall the lack of available data hampers full assessment of the relationship between breast cancer care practices and disease outcomes. This also means that, before we have population based registry data, we can only predict that mortality (outcome) will relate to socioeconomic factors and the organization of the health care system. These factors will also be the major determinants of access to therapy, not only "basic" treatment including diagnostics, surgery, radiotherapy as well as cancer drugs, but especially when it comes to more innovative technologies like MRI, molecular characterisation, oncoplastic surgery, front line radiotherapy as well as the more recent cancer drugs like taxanes, trastuzumab and for example bevacizumab.

Evidence-based treatment guidelines -regularly updated in line with international standards, followed, and audited- are key to promote the rational use of resources and equality in access to treatment services, so long as compliance is reasonably high. Additionally, guidelines have to be related to local conditions and be followed. In LA, most countries count with medical care standards (MCS) published by governmental authorities; cancer institutes; or national, professional or scientific associations but, the challenge in the region is to implement policies and control mechanisms to ensure compliance and their applicability to the whole population.

National Cancer Control Plans (NCCP) are the fundamental building blocks to an organized governance, financing and healthcare delivery of cancer. There is a marked absence of NCCP in LA.

The fragmented organization and management of breast cancer care has been acknowledged by many countries and there have been extensive efforts to analyse and re-organise cancer care, resulting in the development of nationally coordinated strategies. Evidence has shown that a multidisciplinary team approach yield better results, improve patient satisfaction, decrease waiting times from diagnosis to treatment and improve spending efficiency. The organization of BC care delivery in the region varies and, in general, is not up-to the standards observed in more developed countries. There are many institutions that provide breast cancer care at an internationally top level, but one could not extrapolate the results from these institutions to the overall access to best breast cancer care within the individual LA countries.

Latin American patient groups fulfill an important task, there where healthcare systems cannot or do not sufficiently assist BC patients. Weak patient information services and the government's lack of full inclusion of these groups in policy decision making, as well as patient satisfaction regarding communication, continuity, accessibility and lead times, need further improvements.

In the region, there is no one-suit-all prevention strategy given the outstanding epidemiological contrasts in terms of disease occurrence, risks, and available resources both across but also within countries.

Primary prevention of breast cancer is still an area under debate. We have information from several well performed prevention trials providing evidence that medical

prevention is feasible, although it seems we are still not able to target the right population with those treatment options currently available. This is especially true in most LA in this study as many have a significant lower incidence (based on modelling) and a different age distribution. It thus seems that primary prevention (tamoxifen and raloxifene) is not at present feasible in LA. A similar conclusion was made by the European regulatory agency (EMA).

Secondary prevention through the early detection of breast cancer via mammography screening has been in place for more than 20 years in many countries in the Western world. Population-based mammography has been shown to improve outcomes as it leads to a larger share of breast cancers being diagnosed at an early stage but in some LA countries with limited resources and low incidence, the best screening strategies differ. In countries like Argentina and Uruguay higher frequency, lower start age and shorter intervals than in countries like Ecuador, Peru, or Mexico are justified. Since affordability remains a liming factor in the region, recommendations from the BHGI and WHO highlight the role of prevention but contemplating several additional measures like health education and behaviour modification, breast self-awareness and clinical breast examination.

Nowadays in LA, the majority of BC cases are detected when women seek care following symptoms onset. Initiatives to increase the awareness of BC are extremely important so that women are attentive and do not postpone seeking care until the symptoms have reached a critical stage.

Conversely to the relatively low commitment to mammographic screening, post-diagnostic screening with hormone receptors and biologic marker determination is widely spread. However, not all the information obtained is put to good use, because of the limits on access to some treatments, especially some expensive targeted agents. Furthermore, the area of breast cancer diagnosis and sub-typing of the disease is likely to change over the next few years as we increase our understanding of breast cancer biology and widen the use of biological markers. These innovations in breast cancer diagnosis may come at an initial high cost and we will as a result, at least in many developing countries, not have the resources for these new technologies, but will have to relay on more "mature" and less costly technologies.

Surgery has developed significantly over the last decades into a specialty of its own in many countries. This evolution in breast cancer surgery has introduced breast conserving surgery, sentinel node biopsies and an oncoplastic surgical approach. Although these innovations in surgical treatment have not led to an increased cure rate, women with BC have experienced a significantly increased quality of life, based on these improvements in surgical care.

In LA, breast-conserving surgery and sentinel lymph node dissection are part of the standard practice, though the availability of breast cancer specialized surgeons, waiting times, node clearance policy and access to breast reconstruction vary greatly across countries and between public and private settings

Radiotherapy has developed in a similar way as surgery over the last decades. The long-term side-effects of radiotherapy have been reduced with the introduction of new sophisticated dose planning and improved radiotherapy equipment. Thus, toxicity has been lowered for individuals treated but efficacy has not increased. We need to ensure that there is adequate access to at least palliative radiotherapy for metastatic breast cancer patients in all countries and in the future also make radiotherapy for breast conservation surgery available. But in LA, access to radiotherapy is still a critical issue with a lack of investment in equipment and staffing in most countries except for Uruguay, Chile and Venezuela; and scarcity of trained personnel and geographical concentration add to the challenge.

A major reason behind the dramatic improvement we have seen in the outcome of breast cancer over the last 20-30 years has been improvements in adjuvant therapy with chemo-, endocrine and now also biological therapy. Adjuvant chemotherapy reduces the relative yearly risk of death by almost 40% for women <50 years and by 20% for women 50-69 years old. Endocrine therapy with tamoxifen in oestrogen-receptor positive patients results in a more than 30% relative risk reduction of mortality. Finally, one year of adjuvant treatment with trastuzumab in women with HER2 positive BC leads to a 50% reduced risk of recurrence.

In Latin America, all systemic therapies are licensed and available but cost considerations limit the wide diffusion

of the use of some of the latest developments. Treatments with anthracyclines are widely accepted; as is tamoxifen for patients with estrogen receptor positive tumours. However, new-generation hormonal treatment alternatives, like the aromatase inhibitors and biologicals are not accessible for all women in all the countries.

The follow-up of women treated for breast cancer has been under debate and there is a trend not to follow these patients for as long as before. Although there is little scientific evidence showing that close follow-up improves outcome measured in survival terms, one should remember that many of these women are on adjuvant endocrine therapy for many years. Long-term side-effects of treatment are also a common cause of decreased quality of life for women treated for breast cancer.

In spite of the advances we have seen in the curative treatment of BC, a significant number of women will suffer a relapse and many will develop metastatic disease. For these women it is extremely important that there is easy access to specialised care. This is an especially important observation from this study on LA, as many of the BC patients diagnosed have advanced disease at time of diagnosis and a large proportion of patients will be in need of palliative treatment. We now have a huge arsenal of treatments for palliation of symptoms and also supportive therapies. These treatment options include surgery for metastatic complications and palliative radiotherapy and a number of anti-tumour drugs as well as supportive care drugs. Almost all anti-cancer drugs are also developed in metastatic breast cancer before they are developed as adjuvant drugs.

Approval of new technologies is normally faster in metastatic setting and a new proven technology such as trastuzumab had already reached significant levels of uptake by the time it's indication for early disease was approved. Still, in LA, uptake of new treatments is slow, almost marginal in some countries. This is related with the health care systems' coverage and limits.

Palliative care in the region is developing and efforts both at the institutional and individual level are a reality but the problems identified in 1993 were still there almost 10 years later. The top four barriers to the optimal management of cancer pain identified by clinicians from LA countries are: 1) inadequate staff knowledge of pain management (70%); 2) patients' inability to pay for services or analgesics (57%); 3) inadequate pain assessment (52%); and 4) excessive state/legal regulations of prescribing opioids (44%).

In conclusion, it is very important that regulations, priorities, funding, and organization of breast cancer care are coordinated to provide all patients with the most appropriate, cost-effective and evidence-based treatment with minimal delays.

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