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Breast cancer in Latin America: global burden, patterns, and risk factors

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Abstract

Breast cancer is a major public health problem in Latin America (LA) and the most common form of cancer among women. An important variability according to ethnicity/race with respect to incidence/mortality, clinical characteristics, and prognosis is observed throughout LA. In addition, women are more likely to develop breast cancer (BC) at younger age and to be diagnosed at an advanced stage compared to western women. While little is known about specific risk factors, changes in reproductive pattern (parity, breastfeeding) and lifestyle factors including sedentary behaviours, unhealthy diet, and alcohol intake may contribute to the increase of BC incidence. In this paper we give an overview of the burden and patterns of BC, review the leading causes of BC and discuss the possible ways to improve BC prevention and control in LA.

Key words: breast cancer; incidence; mortality; clinical characteristics; risk; prevention; Latin America

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Resumen

El cáncer de mama (CaMa) es uno de los mayores problemas de salud pública en América Latina (AL) y el cáncer más frecuente en mujeres. Se observa una importante variabilidad en la incidencia/mortalidad, las características clínicas y el pronóstico según la etnia/raza a lo largo de AL. Además, las mujeres latinoamericanas son más propensas a desarrollar CaMa en edades más tempranas y a ser diagnosticadas en una etapa más avanzada, comparando con mujeres occidentales. Aunque poco se sabe sobre sus factores de riesgo específicos, cambios en los patrones reproductivos (paridad y lactancia) y estilos de vida, incluyendo los hábitos sedentarios, las dietas poco saludables y el consumo de alcohol, podrían contribuir al incremento de la incidencia del CaMa. En este artículo se da una visión general de la carga y los patrones del CaMa, se revisan las causas principales del CaMa y se discuten posibles vías para mejorar la prevención y el control del CaMa en AL.

Palabras clave: cáncer de mama; incidencia; mortalidad; características clínicas; riesgo; prevención; América Latina

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Latin America (LA) is the fastest growing demographic population in the world, accounting for 8.6% (about 582 million people) of the world's population.[1] It is estimated that by 2020, more than 100 million people aged 60 years and above will be living in LA and the Caribbean.[2] This growth and ageing of the population is accompanied by an increase in sedentary lifestyle, unhealthy dietary habits, smoking, alcohol consumption, environmental carcinogenic pollutants, sun exposure, and urbanisation.[3] These factors may contribute to the increase of non-communicable disease including breast cancer (BC). BC is the most common cancer among women in LA,[4,5] and heterogeneous geographical patterns of the incidence rate are observed. Despite the lower incidence rates observed in LA countries, the mortality burden is greater compared to other developed countries.[6-8] Large gaps are still apparent in the epidemiology of BC causes in LA countries; however a number of risk factors have been identified in particular among LA women in the US. The majority of them are related to hormone and reproductive behaviour, and lifestyle including diet, obesity, physical activity, tobacco smoking and alcohol consumption. In addition, there are genetic predispositions.[9,10]

LA women are more likely to develop BC at a younger age and to have an advanced stage diagnosis compared to western women.[11,12] This is likely due to limited access to health care, mammography and delayed follow-up after an abnormal mammogram.[13-15] Furthermore, health-care systems in LA are characterised by a lack of health-care coverage for the overall population.[16] Accordingly, primary prevention remains the leading public health priority. This paper aims: to give an overview of the burden, trends and type of BC, to review the leading causes of BC and to discuss the different ways to improve BC prevention and control in LA.

Materials and methods

We have used two sources of data. The burden and patterns of incidence and mortality presented were extracted from the GLOBOCAN 2008 database of the International Agency for Research on Cancer (IARC). This database presents the estimates of incidence and of mortality from 27 major cancers in 184 countries or territories worldwide for 2008.[5] Then, we conducted a MEDLINE and PUBMED search including all publications on BC to review the epidemiologic studies on BC in LA. Our core research consisted of key words related to BC combined with risk factors, outcome and LA.

Burden and patterns of incidence rates in LA

BC is the most common cancer in LA and the Caribbean, with an estimated 115 000 women diagnosed every year, representing 8.3% of all BC cases. The incidence rates vary considerably according to region and socioeconomic status, ranging from 15 to 90.7 per 100 000 women (table I). Uruguay and Argentina present the highest incidence rates (90.7 and 74 per 100 000 women respectively), which are similar to those observed in Europe and North America. Costa Rica, Venezuela, Brazil, Chile, Cuba, and Peru have intermediate rates whereas the lowest incidence rates were found in Guatemala, and Belize. Incidence rates increased in all LA countries for the period 1980-2010.[4,5] This increase was more pronounced in central LA. For example, the cumulative probability of BC incidence (for women aged 15-79 years) in 1980

Table I
Numbers, crude rate, ASR and cumulative risk of BC incidence by region

Population	*Numbers*	*Crude rate*	*ASR (W)*	*Cumulative risk*
Uruguay	2 258	130.3	90.7	9.56
Argentina	18 712	92.1	74.0	7.76
Puerto Rico	1 778	86.2	54.2	6.03
Paraguay	1 224	39.6	51.4	5.77
Costa Rica	931	41.9	42.9	4.71
Venezuela	5 404	38.6	42.5	4.54
Brazil	42 566	43.7	42.3	4.51
Chile	4 199	49.4	40.1	4.25
Cuba	3 028	54.2	38.6	4.10
Peru	4 300	29.9	34.0	3.61
Dominican Republic	1 422	28.7	32.7	3.42
Colombia	6 655	29.1	31.2	3.50
Ecuador	1 882	28.0	30.8	3.28
Panama	466	27.7	29.2	3.27
Mexico	13 939	25.3	27.2	2.91
Bolivia	896	18.4	24.0	2.58
Haiti	831	16.6	23.9	3.16
Nicaragua	468	16.4	22.9	2.48
Honduras	487	13.3	19.9	2.16
El Salvador	508	15.7	17.1	1.78
Belize	17	11.4	16.3	1.98
Guatemala	686	9.8	15.0	1.61

Source: reference 17
BC: Breast cancer
ASR: age standardized rate

was 2.2 (95%CI: 2- 2.6) and 5.5 (95%CI: 4.4- 6.2) in Mexico and Brazil, respectively. While in 2010 it was 4.6 (95%CI: 3.9- 5.5) and 7.9 (95%CI: 6.9- 9.1) in Mexico and Brazil respectively.[4,5] The population growth, improvement in diagnosis and changes in the women's lifestyle may partly explain these increased rates.

Burden and patterns of mortality rates in LA

BC is the leading cause of cancer mortality among women in LA. An estimated 37 000 women die each year from BC, representing about 14% of all cancer deaths.[5] Mortality rates show a heterogeneous distribution across countries, ranging from 5.7 to 24.3 per 100 000 (table II). Similar to incidences rates, the highest mortality rates were observed in Uruguay, Argentina and Puerto Rico while the lowest were seen in Guatemala, and Belize.

Table II
Numbers, crude rate, ASR and cumulative risk of BC mortality by region

Population	*Numbers*	*Crude Rate*	*ASR (W)*	*Cumulative risk*
Uruguay	729	42.1	24.3	2.69
Argentina	5 873	28.9	20.1	2.16
Paraguay	407	13.2	17.1	1.93
Cuba	1 332	23.8	15.5	1.65
Venezuela	1 727	12.3	13.7	1.47
Brazil	12 573	12.9	12.3	1.32
Puerto Rico	423	20.5	12.3	1.39
Costa Rica	274	12.3	12.2	1.34
Dominican Republic	522	10.5	12.1	1.31
Panama	189	11.2	11.6	1.27
Chile	1 248	14.7	11.0	1.17
Peru	1 365	9.5	10.8	1.15
Haiti	363	7.3	10.6	1.40
Mexico	5 217	9.5	10.1	1.10
Ecuador	628	9.3	10.0	1.07
Colombia	2 120	9.3	10.0	1.12
Nicaragua	173	6.1	8.6	0.94
Bolivia	280	5.8	7.6	0.84
Honduras	182	5.0	7.6	0.82
Belize	7	4.7	6.7	0.79
El Salvador	193	6.0	6.4	0.66
Guatemala	255	3.6	5.7	0.61

Source: reference 17
BC: Breast cancer
ASR: age standardized rate

BC mortality rates among women have been increasing rapidly during the period 1980-2010 in many countries of LA,[4,5] and BC survival is on average 20% lower in LA than in the US and Western Europe. The high mortality rates observed in several of these countries may have been attributed to poor survival due to the lack of or limited access to early detection services and treatments. It has been reported that only small number of new BC diagnoses are made at stage 1. Coleman and colleagues, have shown that only 40% of women in Campinas (Brazil) survive 5 years after a diagnosis of BC,[18] compared with 89% of women in the US and more than 82% of women in Northern and Central Europe.[19]

Clinical characteristics of BC in LA

High mortality-to-incidence ratios (MIRs) signify poor survival, partly because of the late stage at diagnosis and poorer access to treatment.[11,20] The time delay between the initial suspicions of BC to diagnosis is one of the strong points that can affect clinical outcomes. Several studies suggested that there is delay in the diagnosis of BC.[21,22] Studies from Brazil and Mexico, showed that the average delay between presentation to a doctor and diagnosis of BC was around 6-7 months,[23,24] and 4-5 months in Peru;[25] whereas delays in diagnosis of longer than 12 weeks are considered to affect stage and consequently outcomes and survival.[26] More recently, Justo and colleagues reported that, the majority of BC cases are detected at advanced stages, and approximately 30-40% of diagnoses are metastatic disease in LA.[11] As an example, in Mexico an estimated 50-60% of all BC were diagnosed at advanced stage[27] and the average overall time from symptom onset to treatment was 8.4 months; 8.6 months for early stage disease and 7.5 months for late stage disease.[23] In contrast, 61% of women in the USA are diagnosed with localised BC, 31% with regional, and only 5% with metastatic spread.[12] The all-cancer mortality to incidence ratio for LA was 0.59 compared with 0.43 for the European Union and 0.35 in the US.5 In addition to these characteristics, LA women were also more likely to develop their BC at young ages.[28-30] Lara-Medina and colleagues evaluated the clinical and pathologic characteristics of 2074 BC patients. This study demonstrates that the age at diagnosis of Mexican patients with BC is younger compared to those reported in other populations, with a median age at BC diagnosis 11 years younger than the average age reported in the US.[31] A decade ago BC was considered as a relatively homogenous disease. Perou and colleagues[32] were the first to describe the various molecular sub-types or molecular profiles of BC. They identified subgroups of BC (according to oestrogen receptor (ER), progesterone

receptor (PR) and human epidermal growth factor receptor 2 (HER2)) that differed by molecular features and clinical characteristics: Luminal A, Luminal B, Normal-like, HER2-positive and Basal-like subtypes.[32,33] Studies from US have shown that triple-negative BC represents between 10-20% of invasive BC and has been associated with African American and Hispanic race, deprivation status, younger age at diagnosis, more advanced stages, higher grade, high mitotic indices, family history of BC and BRCA1 mutations.[34-37] However, to date, detailed genetic and molecular biology of BC has not been systematically taken into account in studies of BC in LA. Only one study conducted in Mexico reported a prevalence of 22% triple negative BC among 2 074 women with BC who attended the National Cancer Institute in Mexico City.[31]

Risk factors associated with BC in LA

Understanding factors that contribute to the development of BC become crucial in LA, where the majority of BC cases are diagnosed at advanced stages, resources are limited, and the rate of mammography screening are very low. Despite the huge number of studies, the majority of BC causes remain poorly understood. There are however few numbers of risk factors for BC that have been consistently identified (table III).

Hormone and reproductive behaviour

Reproductive factors are one of the main factors that can affect BC risk and contribute to the heterogeneous distribution of BC. There is evidence that early menarche (menstrual periods that start earlier), late first full-term pregnancy (after 30 years old), nulliparity (never having children) and absence of breastfeeding are associated with the risk of developing BC.[38-40] Multiparous (more than five children) is associated with a 30% decreased risk of BC. In the Mexican study, Romieu and colleagues reported that parous women who had ever breastfed had a reduction in BC risk (age-adjusted odds ratio (OR) =0.39, 95% confidence interval (CI): 0.25-0.62) compared with parous women who had never breast-fed.[41] A small decreasing trend of BC risk in relation to duration of lactation (p <0.001) was observed. Compared with parous women who had never breast-fed, women who had breast-fed for 12-24 months had an age-adjusted OR of 0.47 (95% CI: 0.27-0.83). This study also detected

Table III
Summary of breast cancer risk factors in Latin American countries

	Risk factors	*Premenopausal*	*Postmenopausal*
Hormone and reproductive behaviour	Early menarche	Increase	Increase
	Parity	Decrease	Decrease
	Breastfeeding 4-12 months versus never	Decrease	Decrease
Lifestyle*	High Healthy Lifestyle index versus low	Decrease	Decrease
	Physical activity	Decrease	Decrease
	Alcohol ever versus never		
	Increase	Increase	
	Overweight and obesity	Inconsistent	Inconsistent
Food and nutrients	Carbohydrate intake high versus lowest	Increase	Increase
	High glycaemic load versus low	Increase	Increase
	Folate high versus low	Decrease	Decrease
	Vitamin B(12) high versus low	Decrease	Decrease
	Red meat	Increase	Increase
	Omega 6	Increase	Increase
	Omega 3	Decrease	Decrease
	Vitamin D	Decrease	Decrease
Predisposition	Personal history of breast cancer	Increase	Increase

* Lifestyle include the following variables dietary pattern, physical activity, alcohol consumption, and tobacco smoking

a strong protective effect with lactation duration for the first live birth (for 4-12 months of lactation, ORs=0.56 (95%CI:0.32-0.96) and 0.48 (95%CI:0.29-0.81) in pre- and postmenopausal women, respectively). Others factors that may increase the risk of BC include use of contraceptives and use of menopausal hormonal therapy (HRT), especially combined oestrogen and progestin therapy. The IARC classified combined estrogen-progestogen contraceptives and combined HRT as carcinogenic for humans.[42,43] However less is known about the effect of hormone therapy on BC in LA.

Lifestyle

Studies have analysed the effect of behavioural and lifestyle risk factors such as dietary pattern, physical activity, tobacco smoking, and alcohol consumption on the risk of BC. Using the Mexican population-based case-control study, Sanchez-Zamorano and colleagues[44] have assessed the effect of four variables (dietary pattern, physical activity, alcohol consumption, and tobacco smoking) as components of "Healthy Lifestyle" index on the risk of BC. It was considered healthy to practice moderate and vigorous-intensity physical activity, to belong to the lowest tertile of the Western dietary pattern, to have smoked less than 100 cigarettes, or to have never smoked and to have never consumed alcohol. This index was constructed by means of principal component analysis. This analysis detected a protective effect among women with high Healthy Lifestyle Index. The ORs=0.50 (95%CI:0.29-0.84) and 0.20 (95%CI:0.11-0.37) in premenopausal and postmenopausal, respectively when highest versus lowest quintiles were compared.[44]

Food and nutrients

Food and nutrient factors including high intake of carbohydrates, high glycaemic load (GL), low intake of folate and vitamin B12 have been suggested to increase the risk of BC, in particular postmenopausal BC.[42,45-48] In a population-based case-control study in Mexico carbohydrate intake was directly associated with BC risk.[49] Compared with women in the lowest quartile of total carbohydrate intake, the OR of BC for women in the highest quartile was 2.22 (95%CI:1.63-3.04) in all women, 2.31 (95%CI:1.36-3.91) in premenopausal women and 2.22 (95%CI:1.49-3.30) in postmenopausal women. Regarding dietary GL the multivariate adjusted OR for all women comparing the highest quartile of dietary GL with the lowest quartile was 1.62 (95%CI:1.13-2.32), with a significant trend (*p* test for trend=0.02). In postmenopausal women, the OR comparing the extreme quartiles was 2.18 (95%CI:1.34-3.55; *p*-test for trend=0.005).[45]

High intake of folate, vitamin B(6), and vitamin B(12) have been associated to lower the risk for BC. Compared with women in the lowest quartile, the OR for BC for all women in the highest quartile of folate intake was 0.64 (95%CI, 0.45-0.90; *p* test for trend =0.009) and 0.32 (95%CI, 0.22-0.49; *p* test for trend <0.0001) for vitamin B(12) intake.[46]

Studies from Uruguay have shown that the consumption of red meat could increase the risk of BC.[50,51] Ronco and colleagues[50] reported an OR of 4.16 (95% CI: 2.26-7.67) among the highest red meat consumers, after adjusting by calories. The increase of risk was even stronger for fried meat (OR=5.31,95%CI:2.77-10.2) compared to broiled meat (OR=2.21,95%CI:1.18-4.14), however, there was no effect found for boiled meat, characteristic of stew (OR=1.02, 95%CI:0.47-2.20).

Other nutrients such as omega 3 and 6 fatty acid, and vitamin D could play an important role on the risk of BC. Chajes and colleagues,[52] reported an increased risk of BC associated with increasing ω-6 polyunsaturated fatty acids (ω-6 PUFA) in a population-based case–control study conducted in Mexico. An increased risk of BC was observed with increasing ω-6 PUFA intake in premenopausal women (OR=1.92, 95%CI:1.13-3.26; *p*=0.04). A decreased risk of BC was significantly associated with increasing ω-3 PUFA intake in obese women (OR=0.58, 95%CI:0.39-0.87; *p*=0.008) but not in normal weight nor in overweight women (P heterogeneity=0.017).

The results of the large Mexican population-based case-control study indicate an inverse association between circulating vitamin D levels and BC risk among pre- and postmenopausal Mexican women.[53] Serum 25-hydroxyvitamin D [25(OH)D] (25(OH)D) concentration (per 10 ng/mL increase) showed a strong inverse association with risk of BC among all (*p* trend =0.001), pre- (*p* trend=0.006) and postmenopausal women (*p* trend=0.0001). Compared with a predefined lower concentration of 25(OH)D (<20 ng/mL), higher levels (>30 ng/mL) were associated with lower overall (OR=0.53, 95%CI:0.28-1.00; *p* trend=0.002), pre- (OR=0.60, 95%CI:0.16-2.17; *p* trend=0.07) and postmenopausal (OR=0.37, 95 %CI:0.16-0.82; *p* trend=0.004) BC risk.

Physical activity

It has been suggested that both moderate and vigorous intensity physical activity reduce the risk of BC. Data from LA countries (including Chile, Peru, Argentina, and Brazil) and the multi-country PAHO study showed a high prevalence of adult physical inactivity, 50-91%.[54] However, LA women spend on average, more time on household physical activity,[55] which is considered as moderate-intensity.[56] Further confirmation came

from Angeles-Llerenas and colleagues who reported a decrease in the risk of BC for every 3 h per week of moderate-intensity physical activity.[57] The ORs=0.96 (95%CI:0.92-0.99) and 0.90 (95%CI:0.86-0.93) in pre- and postmenopausal women, respectively.

Alcohol

Alcohol consumption has been recognized as a risk factor for BC by the IARC.[57] The association is present in both pre and postmenopausal women. However little is known about its relationship with BC among LA women. In 2010, Beasley and colleagues[59] supported emerging evidence that any alcohol intake was associated with increased odds of BC among Mexican women. Compared with never drinkers, women reporting ever drinking had a greater odds of BC Adjusted OR=1.25, 95% CI=0.99-1.58). In analyses stratified by menopausal status, there was no evidence for effect modification (*p* for interaction=0.83 for current drinking and p for interaction=0.80 for categorized alcohol). Lifetime alcohol use was associated with an increased risk of BC, as women who reported ever drinking one or more drinks a month for at least 1 year had 1.74 higher odds of BC (OR=95%CI:1.27-2.39). Folate intake appeared to modify the association between ever consuming any alcohol and BC (*p* for interaction=0.04). Women in the lowest tertile of folate intake (mean=197 μg/day) had a higher odds of BC (Adjusted OR=1.99, 95%CI=1.26-3.16) compared to women with highest tertile of folate intake (mean=532μg/day) (OR=1.12, 95%CI:0.69-1.83).

Tobacco

Tobacco smoking is a growing problem throughout LA countries. There are around 145 million smokers aged 15 years or more in LA.[59] It is one of the most important cancer risk factors, accounting for 26% of all cancer deaths. However there is no information on the effect of tobacco on BC in LA.

Overweight and obesity

Overweight and obesity have been associated with an increased risk of BC in postmenopausal, but with a decreased risk in pre-menopausal Caucasian women.[61,62] However, these associations remain unclear in LA populations. Previous studies conducted among Hispanic women in the US have shown different patterns, some study reported an inverse association[63] between obesity (BMI $\geq$ 30 kg/m^2) and BC, whereas others found no association in both pre- and postmenopausal women.[64,65]

Genetic predisposition

Hereditary BC comprises 10% of all BC diagnosis.[66] The most prevalent entity is Hereditary Breast and Ovarian Cancer (HBOC). BRCA1 and BRCA2 genes known as tumor suppressors are the most well-known genetic factors that increase the risk for BC[66,67] and others cancers. Despite the outstanding relevance of genetic screening of BRCA deleterious variants in patients with a history of familial cancer, this practice is less common in LA countries, probably due to the high cost of the screening and limitations in the countries health infrastructure. However a number of studies have reported a high prevalence of BRCA mutation in LA.[30,66,68-71] The prevalence of BRCA1 or BRCA2 mutation was 13% (4/31) among Brazilian women diagnosed with BC.[72] García-Jiménez identified a deleterious BRCA1 or BRCA2 mutation in 5.2% of Costa Rican BC patients.[73] This frequency of BRCA mutations is similar to that reported for familial BC cases from Mexico (3.9%)[74,75] and Costa Rica (4.5%).68 Recently, Vaca and colleagues found 10.2% BRCA mutations among 39 Mexican patients.[76] The family history of BC in first degree relatives was significantly associated with risk of premenopausal BC (OR=2.20, 95% CI 1.33-3.62).[77]

Conclusion

BC is the most common form of cancer in women and is a heterogeneous disease. The incidence is increasing, and women with BC either present with large, advanced tumours or do not present until the disease is at an incurable stage. Resources are limited and the treatment cost is high.[3] For these reasons, efforts and public health priorities are needed for primary prevention, early detection and diagnosis, and prompt and optimum treatment.

Primary prevention is one of the most-effective strategies for cancer prevention and should focus on modifiable risk factors and early detection. Among the important factors identified, physical activity, diet with low sugary food and drinks, low in fried meat and rich in vegetables should be promoted. In addition the consumption of alcohol should be limited. However, there is an urgent need for further research to identify the distribution of specific BC phenotypes in the LA women population. Detailed classification of tumour subtypes is necessary to refine phenotype and improve the identification of specific endogenous and exogenous risk factors. This information will be of crucial importance for the identification of susceptible women to focus prevention programs and improve BC

treatment. In parallel, increased public awareness of BC and expansion of access to screening are strategies that will reduce BC mortality.

Declaration of conflict of interests. The authors declare that they have no conflicts of interest.

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