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Genetic Cancer Risk Assessment for Breast Cancer in Latin America

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Abstract

In Latin America, breast cancer is the most common malignancy in women, and limited available data suggest that up to 15% of all breast cancer cases in the region are hereditary. Genetic cancer risk assessment and counseling is a critical component of the appropriate clinical care of patients with hereditary breast cancer and their families. Unfortunately, genetic services are underdeveloped across Latin America, and access to genetic testing and counseling is very scarce in the region. Barriers contributing to the access to genetic care are high cost and lack of insurance coverage for genetic tests, insufficient oncogenetics training or expertise, nonexistence of genetic counseling as a clinical discipline and lack of supportive healthcare policies. In this review, we highlight relevant initiatives undertaken in several Latin American countries aimed at creating genetic cancer risk assessment programs. Additionally, we present a review of the scientific literature on the current status of breast cancer genomics in Latin America, with specific emphasis on demographic indicators, access to cancer genetic care, training and strategies to improve outcomes and international collaborations.

Keywords

Breast cancer; genetic counseling; genetic testing; healthcare disparities; Latin America

Introduction

Breast cancer is the most common malignancy in women worldwide, with nearly 1.7 million cases diagnosed in 2012, representing 25% of all female cancers (1). Over the next 20 years, the incidence and mortality of breast cancer in developing countries are projected to increase by more than 50% (2). In Latin America, breast cancer is also the most common malignancy and the leading cause of cancer-related mortality among women (3). The mean age at diagnosis in Latin America is generally 10 years younger than that reported in developed

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countries, which may be explained in part by a combination of demographics (greater proportion of younger women at risk), recent changes in lifestyle risk factors and an elevated frequency of hereditary cancer syndromes in some countries (4). Moreover, young women with breast cancer are more frequently diagnosed with triple negative breast cancer subtype, which has a worse prognosis when compared to other subtypes and a higher probability of being associated with hereditary cancer predisposition (5).

During the last 60 years, advances in early detection, novel therapies and diagnostic tools, and preventive care that includes genetic testing for cancer predisposition, have largely contributed to a remarkable improvement in breast cancer survival in the developed world (6). In contrast, the breast cancer incidence/mortality ratio in Latin America remains high, which can in part be attributed to more advanced disease at diagnosis and limited access to cancer care (3). Although, progress is being made in Latin America, access to genetic cancer risk assessment and testing services (GCRA) remains an underdeveloped component of cancer care (7).

Hereditary breast cancer accounts for approximately 10% of all breast cancers. The genes most commonly associated with hereditary breast cancer are *BRCA1* and *BRCA2* (*BRCA*) (8). Women who carry a pathogenic germline mutation in one of the *BRCA* genes is estimated to have a cumulative breast cancer risk between 43 and 76% by the age of 70 years, and up to a 59% risk to develop ovarian cancer (9).

The prevalence of BRCA mutations in Latin America is comparable to that of more developed countries, ranging from 1.2 to 4.9% in unselected breast cancer cases (10). Identifying women with increased breast and ovarian cancer risk due to an inherited *BRCA* mutation allows for more effective breast screening to facilitate the diagnosis of smaller, more curable cancers, and laparoscopic salpingo-oophorectomy, tamoxifen and mastectomy for cancer prevention, and enables the assessment of cancer risk among other family members, often prior to the onset of disease (11).

As a result, guidelines from the National Comprehensive Cancer Network (NCCN) and from several international societies recommend genetic testing for individuals who meet specific personal and/or family cancer history criteria (12). Unfortunately, diagnostic genomic tools and genetic counseling services require complex technology and specialized personnel that are unavailable for the majority of people living in limited resource settings (13).

The objective of this review is to provide an overview of GCRA for breast cancer in the Latin American region, with specific emphasis on demographic indicators, access to cancer genetic care, training and strategies to improve outcomes.

Breast Cancer Genetics in Latin America

Latin America is a heterogeneous region comprised of 33 countries with diverse health care systems, resources, socioeconomic status, culture, geography and ethnicity. The inhabitants of Latin America represent the most genetically admixed population in the world, reflecting a unique historical pattern of migration and interaction with other populations (14). Genetic studies have shown a wide range of variation in ancestry admixture by country. In Brazil, for

example, the highest levels of European ancestry are found in the south of the country, while African ancestry is higher in the northwest (Amazonia). In Chile, European and Native American ancestries are relatively uniform, although European ancestry is a little higher in urban areas. In Peru, Native American is the predominant ancestry throughout the country, while African ancestry is generally low except for in the northern coast. In Mexico, the highest Native American ancestry is found in the central and southern regions of the country, while European ancestry is more common in the north and African ancestry is found in the coastal regions. The distribution of these ancestral patterns is the consequence of a complex history marked by the European colonization of America (15). Given that European genetic ancestry has been associated with a higher breast cancer risk in Latin America (16), these ancestral patterns may contribute to an explanation for the geographic distribution of the disease.

Knowledge of breast cancer associated gene mutations in the region is limited, and most studies have focused on *BRCA* mutations. *BRCA1* and *BRCA2* mutations are responsible of approximately 40% of hereditary breast and ovarian cancer cases in general, which are inherited in an autosomal dominant fashion (17). These gene mutations are found at a higher frequency among certain ethnic groups. For example, 1 in 40 unselected individuals of Ashkenazi Jewish decent carry one of the three founder mutations: 185delAG or 5382insC in *BRCA1* or 6174delT in *BRCA2* (18). In the Caucasian population, the prevalence of *BRCA* mutations is estimated to be 1 in 300 individuals (19). In Latin America, the prevalence in unselected breast cancer cases ranges from 1.2 to 4.9%, which is similar to that reported for the non-Hispanic population living in US (10). Table 1 shows the prevalence for *BRCA* mutations for selected countries in Latin America. Within the region, the highest frequency of *BRCA* mutations has been reported in The Bahamas with 23% of women with breast cancer and 2.8% of unaffected women with family history of breast/ovarian cancer having *BRCA* mutations (20, 21).

In the majority of Latin American populations, *BRCA1* is the gene most frequently found to have pathogenic mutations, with the exception of Costa Rica (22), Cuba (23), Puerto Rico (24) and Uruguay (25), where *BRCA2* is more common. The most common variants reported in Latin America are shared with other populations such as the Ashkenazi *BRCA1* founder mutations 185delAG and 5382insC, and the Spanish founder mutation R71G (26, 27), exemplifying again a pattern of historical population migration (10). However, there are other mutations that are frequent in Latin America and uncommon in other populations, such as *BRCA1* A1708E (10). Founder mutations have also been reported in Mexico (*BRCA1* ex9-12del) (28); in Colombia (*BRCA1* 3450del4, A17082 and BRCA2 3034del4) (29, 30); and in Brazil (*BRCA1* 5382insC and *BRCA2* c.156_157insAlu) (31, 32). Although the majority of BRCA mutations consist of single base changes or deletions/insertions of small numbers of bases, large rearrangements of DNA segments have been reported twice as frequently in the Latin American populations. Large rearrangements detected in Latin America are *BRCA1* deletions of exons 1–2, exons 9–12, exon 14, exons 16–17, as well as deletion of the entire gene (28, 33, 34).

The prevalence of other highly penetrant hereditary breast cancer genes, such as *PTEN* (Cowden's Syndrome), *TP53* (Li-Fraumeni syndrome), *STK11* (Peutz-Jeghers syndrome)

and *CDH1* (Hereditary diffuse gastric cancer) is largely unknown in Latin America (32). An exception to this is the finding of the *TP53* R337H founder mutation in Brazil. The spectrum of associated tumor types is slightly atypical for Li-Fraumeni syndrome and the prevalence of the allele has been calculated to be 1:300 individuals in the Rio Grande du Sul region, which is higher than the estimated worldwide prevalence (1:2000 –1:5000) (35, 36).

PALB2 has been recently described as a breast cancer predisposing gene with an average cumulative breast cancer risk of 35% (55% if there is a family history of breast cancer) (37). A recurrent *PALB2* mutation has been found in Hispanics, as well as in Italian and Nigerian families (38).

Access to Genetic Cancer Risk Assessment (GCRA)

Genetic cancer risk assessment (GCRA) is an interdisciplinary medical practice in which genetic and genomic tools are used to identify individuals and families at risk of having an inherited cancer syndrome. The clinical practice of GCRA includes risk assessment, genetic testing and management of individuals at risk (39). Although GCRA is available in most cancer centers in the United States and in other developed nations, this is not the case of low-and-middle income countries in Latin America, where access to GCRA is limited.

Availability of Genetic Testing in Latin America

The majority of gene mutations are detectable by standard methods such as Sanger sequencing of polymerase chain reaction (PCR) amplified DNA segments. In a few cases (large rearrangement mutations), alternative assays are required such as Southern blotting, multiplex ligation-dependent probe amplification (MLPA), quantitative PCR or comparative genomic hybridization (33). Historically, these are prohibitively expensive testing methods for low and middle-income countries. Commercial testing for BRCA in the United States has been available for 20 years. In Latin America, however, genetic testing for *BRCA* or other cancer-predisposing mutations is not widely available and, when offered, it is often unaffordable for patients (3). While technological advances such as next generation (massively parallel) sequencing (NGS) has rendered sequencing considerably cheaper, the cost of genetic testing in the United States still ranges from $249 to $5000 USD, depending on the type of test ordered (40, 41), and is not affordable for most public healthcare systems in Latin America. In order to overcome the barrier represented by the high cost of genetic testing, academic centers in the region have partnered with national or international collaborative research projects and offer testing as part of research initiatives (42).

A low-cost genetic screening tool that incorporates 115 recurrent BRCA mutations observed in Hispanic women (HISPANEL) has been developed and implemented throughout Latin America (30, 43–46). HISPANEL is a panel of 114 recurrent Hispanic BRCA mutations analyzed by a Sequenom MassARRAY platform and a PCR assay to screen for the large genomic rearrangement of *BRCA1* exon 9–12. This test has been reported with a sensitivity of 68% to detect *BRCA* mutations in a Mexican population, at a cost of $20USD (43). Another potentially cost-effective solution would be to perform the HISPANEL genetic test followed by a full sequencing of the gene if HISPANEL negative on an Ion Torrent PGM

platform and analyzing the copy number of variations (CNV) by MLPA. The cost of this approach has been calculated to be $25 USD for mutations found by HISPANEL and $117.25 for the samples requiring MLPA (47). This panel is currently available for research purposes in five Latin American countries (Brazil, Colombia, Mexico, Peru and Puerto Rico).

Regional Guidelines

Paradoxically, even though genetic testing is seldom available and not included in public insurance schemes, several Latin American countries have national guidelines recommending genetic counseling and testing in selected cases based on personal and family history of cancer (48–51). Additionally, these guidelines include risk reduction interventions recommendations for women with hereditary breast cancer syndromes, many of which are also not covered by public health insurance (40).

Table 2 summarizes national recommendations for genetic testing and risk reduction intervention in selected countries.

GCRA Programs in Latin America

Clinical Cancer Genetics in Latin America is a less developed field than in other regions of the world. Some of the barriers precluding its development in the region are: limited awareness of GCRA by patients and physicians; unavailability of genetic testing; limited or lack of coverage for costly testing; genetic counseling not being recognized as a clinical discipline; few educational opportunities in cancer genetics; absence of health care policies and lack of infrastructure (10, 40, 52, 53). In addition, most existing programs are located in academic hospitals in large urban areas, making them practically inaccessible to people living in rural regions (10, 54). While most Latin American nations do not have organized GCRA programs, various successful GCRA efforts have been implemented in the regions.

Argentina

In 2011, the National Plan for Hereditary and Familiar tumors (PROCAFA) was created by the National Cancer Institute of Argentina. The aims of PROCAFA are training healthcare professionals in cancer genetics; developing diagnostic and therapeutic guidelines; creating a network of genetic services across the country and starting a hereditary cancer registry. Two years after PROCAFA was instituted, the Argentinean Familiar Cancer Network (RACAF) was created to address the last two objectives (creating a network of services and a registry). As of 2015, RACAF included 44 health professionals from 36 public and private institutions distributed all over the country. RACAF's programs are aimed at promoting patient case discussions and developing educational activities for healthcare providers (54).

Brazil

Clinicians from Brazil are pioneers in genetic cancer counseling in Latin America. GCRA in Brazil started in the 90's with few individual academic clinics funded by research grants. Researchers and clinicians from those centers became organized in the Brazilian Hereditary Cancer Network (BHCN), which in 2011 published the first Brazilian guidelines for the

detection, diagnosis, counseling, testing and surveillance of hereditary cancer syndromes. Currently, ten centers from cities across Brazil provide GCRA to patients enrolled in the federal universal Public Health Care System (SUS). One of the major challenges that this network has faced since its inception is financial constraint due to little coverage for genetic testing in public health plans. However, since 2012 genetic testing is included in private insurance schemes, which provide coverage to approximately one third of the Brazilian population (55).

Mexico

In 2016, the National Cancer Institute of Mexico (INCAN) opened the first Hereditary Cancer Clinic in the country. The clinic has a multidisciplinary team of healthcare professionals including genetic specialists, molecular biologists, cytogenetic experts and a general physician that coordinate the referral of patients with a suspicious diagnosis of hereditary cancer syndrome. Initiation of the GCRA program services was facilitated by a dissemination and implementation intervention, in collaboration with the Division of Clinical Cancer Genomics at the City of Hope Cancer Center in Duarte, California. This included Avon Foundation and Breast Cancer Research Foundation sponsored participation in an established intensive clinical training program, provision of *BRCA* gene testing for patients enrolled in a collaborative research registry, local infrastructure assessment and academic detailing for the administration and staff to promote GCRA program development and recognition. Genetic testing is performed to confirm or rule out the diagnosis and recommendations are made based on the testing results to both the patients and their families (56). More recently, in the north region of the country, a Hereditary Cancer Clinic was also established in Monterrey following the same working model used at Incan (57). In the short term, they also plan to replicate the model in another state of the country (Coahuila). Cancer genetic services are also available in the state of Jalisco, where clinician scientists from the *Instituto Jalisciense de Cancerología* and the Civil Hospital located at Guadalajara also participated in the GCRA program development intervention and are part of the City of Hope international collaborative research registry to study familial cancer epidemiology and clinical outcomes (58,59).

Peru

In 2008, the Genetic and Molecular Biology Unit at the National Institute of Neoplastic Diseases of Peru started the first genetic cancer program in the country, which serves as a referral center for patients with cancer diagnosis and their families' nationwide. Cancer genetic training and genetic testing have been facilitated through research collaboration with City of Hope. During the first five years, the program has provided genetic counseling for approximately 1000 families and, currently under the Plan Esperanza, which is a cancer specific public insurance, they have been able to recommend and cover risk reduction interventions to their patients with a personal history of cancer and cancer associated mutations (60).

Uruguay

The Uruguayan Collaborative Group is a non-profit organization aimed at providing clinical genetics services to Uruguayan patients with hereditary cancers. This group is composed by

clinicians who offer free GCRA in several hospitals throughout the country. In 2013, it was recognized by the ministry of Health, who provided funds for the group's operation. It has provided genetics services to approximately 14,000 patients (61).

Cancer Genetics Training in Latin America

The rapidly evolving scientific evidence behind cancer genomics increases the challenges faced by practitioners aiming to integrate it into their everyday medical practice. GCRA is a highly specialized discipline that requires knowledge of both genetics and oncology and specialized patient and family counseling (62). However, opportunities for formal training in GCRA are limited even in the US, and they are practically unavailable for those practitioners living in low-and middle-income countries (62). As a matter of fact, practitioners from Latin America have expressed that knowledge about GCRA is limited among patients and physicians, and that there is a lack of training and expertise in the field (53). However, collaborative efforts aimed at helping providers from LMIC overcome barriers to training and establishing effective GCRA programs have been established. One example of a successful international educational program is the Intensive Course in Cancer Risk Assessment organized by the Division of Clinical Cancer Genomics at City of Hope Comprehensive Cancer Center. This course is designed to train practitioners from underserved geographic areas, including Latin America, to integrate cancer genetics and oncology knowledge into their everyday clinical practice (62). As of 2016, forty-eight practitioners from Latin America have taken the course and they continue to be involved in other web-based educational sessions, including a multidisciplinary case review conference, topic sessions and an annual caner genetic conference. (Unpublished data).

Conclusion

As we have shown, cancer genetics is largely underdeveloped in Latin America (63, 64), and Latin American populations are poorly represented in genomic studies. Therefore, there is a great need to develop policies aimed at increasing the availability of clinical cancer genetics, as well as of research to better understand the prevalence, risks and outcomes of hereditary cancer in the region.

In spite of these challenges, some successful GCRA models have emerged in the region. In order to overcome these barriers, policy makers and healthcare authorities should:

1. Increase training and awareness in clinical cancer genetics- Provide training in clinical cancer genetics across all healthcare professions.
2. Integrate GCRA programs into the existing cancer care structure- Embed GCRA into existing cancer centers and cancer control programs.
3. Include GCRA in healthcare policies and plans- Include genetic testing and risk reduction interventions into existing healthcare coverage programs.

Advances in the field of genomics over the last years have led to substantial reduction in the cost of genome sequencing. As a result, genome-sequencing is becoming increasingly affordable, making it potentially more accessible for patients in developing countries,

including those in Latin America (65). In fact, several commercial laboratories offering genetic testing in the US have recently expanded their operations to Latin American countries. Nevertheless, even though testing may soon be available and more affordable, the cost of risk reducing strategies may still represent a barrier for the management of hereditary cancer syndromes. This is exemplified by the fact that while the cost of genome-sequencing is gradually descending, the cost of breast cancer drugs is rapidly rising (66). Policymakers in Latin America, where resources are limited, need to carefully balance the benefits and costs of interventions in the rational of cancer care.

In summary, there is an urgent regional need for the development and implementation of genetic cancer risk assessment programs. Improving the education of the healthcare personnel, a better allocation of existing resources, and the development of healthcare policies aimed at increasing the availability of genetic testing and counseling and cancer prevention are of the highest priority.

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Table 1

BRCA1/2 mutation prevalence in selected countries in Latin America

Country	Cohort selecting criteria	BRCA1/2 prevalence
Argentina(67, 68)	Personal or FH of BC/OC	19.04–28.3%
	BC/OC in ≤ 40 y); FH; or AJ ancestry	
Bahamas (20, 21)	BC	23%
	Unaffected women with FH of BC/OC	2.8%
Brazil (69–74)	BC unselected cases	2.3%
	FH of BC/OC	3.4%
	BC with FH	13%
	HBOC criteria	2.8–26%
	OC unselected	35.5%
Chile (75–78)	BC/OC with FH	7.1–20.4%
Colombia (29) (45) (30)	BC patients	1.2
	BC/OC families	24.5%
	OC patients	15.6%
Costa Rica (22)	BC with FH	4.5%
Cuba(23)	BC patients	2.6%
Mexico (43, 79) (80) (81) (46)	BC/OC unselected cases	4.3–28%
	Early BC	6%
	TNBC	23%
Peru(44)	Unselected cohort	5%
Puerto Rico(24)	BC and unaffected individuals with FH	47.8%
Uruguay(25)	BC with FH	17%
Venezuela (82)	BC cases with FH, early onset or bilateral BC	17.2%
US Hispanics(10)	Unselected BC patients	1.2–4.9%

* BC= breast cancer; FH= family history; HBOC= hereditary breast and ovarian cancer; OC= ovarian cancer.

Table 2

National practice guidelines for HBOC syndromes in selected countries in Latin America

Country	National Guidelines	Genetic Counseling Criteria	Screening and management recommendations	Healthcare public insurance coverage
Argentina(51)	Guidelines for the detection and study of high-risk hereditary breast cancer cases. National Intersociety Consensus for high risk of breast cancer. 2014	BC < 50 y; bilateral/multicentric BC; BC in male; BC in AJ; ≥ 2 first/second degree relative; BC + other primary or; TNBC < 60 y. Families with BC + OC; BC + endometrial or thyroid cancer; BC + pediatric cancer or; BC + GI cancer.	Annual breast MRI and mammogram RRM RRSO after child bearing completion (BRCA mutation) Chemoprevention if RRM not performed.	No
Brazil(50)	Operational Manual. National Hereditary Cancer Network. 2009	BC ≥ 3 cases + OC case; BC > 3 cases ≤ 50 y or; 2 sisters or mother and daughter < 50 y with one of the followings: 2 BC cases; or 2 OV cases; or BC + OC	Monthly breast self exam Annual or every 6 mo clinical breast exam Annual mammogram Breast MRI (6 mo after the mammogram) Transvaginal ultrasound + Ca 125 (every 6 mo)	No
Colombia(48)	Guideline for the early detection, treatment, follow-up and rehabilitation of breast cancer. (2013)	BC < 30 y; BC in 2 FDR <40 y; or 3 FDR <50 y; or 4 FDR < 60 y; or 6 relatives (any age); BR + FDR < 50 y; OC + BR in FDR < 50 y; OC in 2 FDR; bilateral OC recurrent OC after 2 y of initial diagnosis; OC < 40 y; BC or OC in AJ Ancestry; male BC or; BC or OC < 50 y + other BRCA related cancer (BC, OC, endometrium, colon, small bowel, gastric, biliary, pancreatic, prostate, melanoma or sarcoma).	Annual Breast MRI or Mammogram + US (if MRI is not available or contraindicated) RRM RRSO Chemoprevention	No
Mexico(49)	Mexican Official Norm (NOM-041-SSA2-2011) for breast cancer prevention, diagnosis, treatment and surveillance.	Personal history of BC < 40 y; bilateral BC, BC + OC; Family history of BC in ≥ 2 FDR; BC in male; relative with BC + OV; > 1 generations with cancer (colon, pancreas, prostatic); > 1 OC; AJ ancestry; high risk gene mutation;	Breast self examination; Clinical breast exam every 6 mo; Annual breast image (mammogram, ultrasound or MRI according to age and resources; Annual social and psychological support Chemoprevention; RRSO RRMO	No

*AJ= Ashkenazi Jewish; BC= breast cancer; FDR= first degree relative; GI= gastrointestinal; HBOC= hereditary breast and ovarian cancer; mo= months; MRI= magnetic resonance imaging; OC = ovarian cancer; RRMO= risk reduction mastectomy; RRSO= risk reduction salpingoophorectomy; TNBC= triple negative breast cancer; y= year

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