

Genetics of breast cancer: Applications to the Mexican population

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Abstract

Breast cancer research has yielded several important results including the strong susceptibility genes, BRCA1 and BRCA2 and more recently 19 genes and genetic loci that confer a more moderate risk. The pace of discovery is accelerating as genetic technology and computational methods improve. These discoveries will change the way that breast cancer risk is understood in Mexico over the next few decades.

Keywords: breast neoplasms; genetics; BRCA1; BRCA2; oncogenes; Mexico

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Resumen

La investigación en cáncer de mama ha dado varios resultados importantes incluyendo los genes fuertemente susceptibles, BRCA1 y BRCA2, y más recientemente 19 genes y loci genéticos que confieren un riesgo moderado. El ritmo de los descubrimientos se acelera conforme mejora la tecnología y métodos computacionales. Estos descubrimientos cambiarán la forma en que la investigación del cáncer es comprendida en México en las próximas décadas.

Palabras clave: neoplasias de la mama; genética; BRCA1; BRCA2; oncogenes; México

Evidence of a genetic effect for breast cancer

Family studies and twin studies can suggest a genetic contribution to the risk of breast cancer. Relatives of women with breast cancer have an increased risk of developing the disease,¹ suggesting a genetic effect on risk. Women with one first degree relative with breast cancer have approximately 2-fold higher risk of breast cancer compared to the general population. The risk among women with second degree relatives with breast cancer is also increased ~1.5-fold compared to

the general population. Women with multiple affected relatives and women with relatives who are affected at a younger age tend to have higher risk.²⁻⁴

Twin studies are a unique case of family studies in which monozygotic (MZ) twins are compared to dizygotic (DZ) twins. Both MZ and DZ twins share environmental influences but MZ twins share 100% of their genome while DZ twins only share 50% of their genome. Thus, if the risk among women with an affected MZ twin is higher than the risk of women with an affected DZ twin, a genetic effect is strongly suspected to underlie this. Monozygotic twins of women with breast cancer

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have a higher risk of developing the disease compared with dizygotic twins of women with breast cancer.^{5,6} Lichtenstein *et al.* identified a 13% risk of breast cancer among MZ twins if the other twin had breast cancer, whereas the risk for DZ twins was 9%, a difference that was statistically significant. Heritability, the proportion of a trait that is attributable to genetic factors, can be estimated from twin studies. Analyzing data from twin studies, Lichtenstein *et al.* estimated that heritability for breast cancer is approximately 27%.⁵ However, the estimate of heritability makes many assumptions and these have been criticized to lead to underestimates of the importance of genes.⁷ Other investigators, also using twin data, have argued that a higher proportion of breast cancers attributable to genetic factors.⁶ For example, Peto and Mack compared the risk of breast cancer among MZ twins, DZ twins and the risk of breast cancer in the contralateral breast of an affected woman. They found that the risk of breast cancer in the contralateral breast of an affected woman is the same as the risk in each of the breasts of her MZ twin. Based on this, they concluded that most breast cancers have some genetic effect.

Population genetics of Mexico

Mexicans are a complex population genetically.⁸ Historically, Mexico has included an Indigenous population, Spanish migrants and African migrants, originally brought as slaves. Using genetic markers, it is possible to estimate the genetic ancestry of a group or of an individual.⁹ Such estimates are most efficiently made with a set of markers that are selected to be specifically informative for continental ancestry,¹⁰⁻¹³ but can also be ascertained from dense whole genome polymorphism data from SNP (single nucleotide polymorphism) arrays.¹⁴ Using these genetic markers, it is possible to see the ancestral components of Indigenous, European and African ancestors in modern day Mexicans and Mexican Americans. For example, a recent study of U.S. "Latinos" in the San Francisco Bay Area including Mexican Americans demonstrated that approximately 55% of the ancestry among Mexican Americans is European, approximately 40% is Indigenous American and approximately 5% is African.¹⁵ However, the proportions of ancestry may vary substantially. For example, in a study of breast cancer in Mexico, the investigators found a much higher proportion, ~60%, of Indigenous American ancestry.¹⁶ Furthermore, the proportions of ancestry may vary dramatically by geographic location and other factors. For example, individuals from Northern Mexico have much higher European ancestry and much lower Indigenous American ancestry compared to those from Southern Mexico.¹⁷

The relationship between breast cancer risk and genetic ancestry has been investigated in Mexico and in Mexican Americans. Fejerman *et al.* found that among Mexican women with higher European ancestry there was a significantly higher risk of breast cancer compared to Mexican women with lower European ancestry and high Indigenous American ancestry.¹⁶ No significant association was found with African ancestry. The association between ancestry and risk was attenuated in multivariate regression models by known non-genetic risk factors such as reproductive history and hormone use. Therefore, part of the association between genetic ancestry and breast cancer in Mexico is explained by the prevalence of different non-genetic risk factors among sub-populations within Mexico. However, some of the association between genetic ancestry and breast cancer risk remained statistically significant after accounting for known non-genetic risk factors. Furthermore, this association was also seen in U.S. populations of Mexican and Central American origin.¹⁸ Thus, there may be genetic variants that are more common among women with European ancestry that increase the risk of breast cancer.

Breast cancer genetics

High risk susceptibility genes

Two high risk genes, BRCA1 and BRCA2, have been identified by linkage analysis.^{19,20} Women with mutations in these genes have a very high lifetime risk of breast cancer (~50-80%) and also a dramatically elevated risk of ovarian cancer (~20-40%). However, mutations in these genes are relatively rare and it is estimated that they account for only about 5% of breast cancer cases.²¹

Separately, other genes have been identified to increase breast cancer risk, including p53, PTEN, ATM and others.²² However, mutations in these genes are even less common than mutations in BRCA1 and BRCA2, so they likely account for a very small fraction of breast cancer cases.

High risk susceptibility genes in Mexico

Few studies exist of BRCA1 and BRCA2 mutations have been performed in Mexico. Ruiz-Flores *et al.* studied 51 Mexican women with breast cancer, including 36 women who developed breast cancer at age ≤ 35 .²³ They found 2 disease-causing protein truncating mutations, one in BRCA1 and one in BRCA2, which had not been reported before. Vildal-Millan *et al.* screened 40 women with

breast cancer and either family history of breast and/or ovarian cancer and found two mutations in BRCA1.²⁴ Both studies found additional genetic variants that alter the protein sequence but do not completely abolish the activity and thus may or may not increase the risk of breast cancer. Clearly, additional studies of BRCA1 and BRCA2 in Mexican women would be helpful to further delineate the contribution of these genes.

Additional information can be obtained from studies in the U.S. of breast cancer patients who are classified as "Latina" or "Hispanic." In the Southwestern United States, the majority of women in such studies are usually of Mexican American origin and therefore the mutations identified in these women may be helpful to understanding the risk contribution of BRCA1 and BRCA2 in Mexico. Several studies have identified a series of BRCA1 mutations in Hispanic American women.²⁵⁻²⁸ Some of these mutations have also been observed in other populations such as in Spain or in Jewish populations.²⁵⁻²⁸ Other mutations have not been observed before and may be of Indigenous American origin.²⁹

Additional data on BRCA1 and BRCA2 mutations in Mexico, as well as data on other high risk susceptibility genes (P53, PTEN, ATM) will be important to obtain in order to understand the contribution of these genes to breast cancer risk in Mexican families with breast cancer.

Moderate susceptibility alleles

Genome wide association studies (GWAS) have recently been used to identify new loci for breast cancer.³⁰⁻³⁷ To date over 19 loci have been identified (Table I). While these loci have modest effects they influence the understanding of breast cancer risk in potentially important ways. First, these genes may help us to understand the underlying biology of breast cancer by implicating new pathways that have not been previously considered to be associated with breast cancer risk. Second, while each polymorphism may not be a strong risk factor for breast cancer, together these polymorphisms may help to develop more precise risk information. For example, Wacholder *et al.* evaluated the proportion of women reclassified into high and low risk categories based on using the Gail model with and without 10 genetic variants.³⁸ They found that 19% of women were classified into a high risk category (>0.575% / year) with just the regular Gail model, but 27.7% were in that category if SNPs were added. Although they concluded that these risk SNPs were not quite ready for use in the general population, as more SNPs associated with breast cancer are identified, risk prediction will continue to improve. Thus, breast cancer prevention may be improved with the results of GWAS.

The initial GWAS scans were focused on populations of mostly European ancestry.^{32,39,40} Subsequently,

Table I
MODERATE SUSCEPTIBILITY LOCI FOR BREAST CANCER

rs#	Gene / region	allele freq	OR (95% CI)	Ethnicity	Ref
rs2981582	FGFR2 / 10q26	0.39	1.26 (1.23 - 1.30)	Eur/EurAm	31
rs3803662	TRNC9 / 16q12	0.27	1.2 (1.16 - 1.24)	Eur/EurAm	31
rs13281615	8q24	0.4	1.08 (1.05 - 1.11)	Eur/EurAm	31
rs3817198	LSPI / 11p15	0.3	1.07 (1.04 - 1.11)	Eur/EurAm	31
rs889312	MAP3K1 / 5q11	0.28	1.13 (1.10 - 1.16)	Eur/EurAm	31
rs2107425	H19 / 11p15	0.4	1.08 (1.05 - 1.11)	Eur/EurAm	31
rs13387042	2q35	0.49	1.21 (1.14 - 1.29)	Eur/EurAm	40
rs10941679	5p12	0.29	1.19 (1.13 - 1.26)	Eur/EurAm	34
rs11249433	1p11.2	0.39	1.16 (1.09 - 1.24)	Eur/EurAm	36
rs999737	RAD51 / 14q24.1	0.23	1.06 (1.01 - 1.14)	Eur/EurAm	36
rs4973768	SLC4A7 / 3p24.1	0.47	1.16 (1.10 - 1.24)	Eur/EurAm	36
rs999737	COX11 / 14q24	0.76	1.06 (1.01 - 1.14)	Eur/EurAm	36
rs1011970	CDKN2BAS / 9p21	0.17	1.09 (1.04 - 1.14)	Eur/EurAm	30
rs10995190	ZNF365 / 10q21	0.85	1.16 (1.10 - 1.22)	Eur/EurAm	30
rs704010	ZIMZ / 10q22	0.39	1.07 (1.03 - 1.11)	Eur/EurAm	30
rs614367	11q13.3	0.15	1.15 (1.10 - 1.20)	Eur/EurAm	30
rs2380205	10p15.1	0.57	1.06 (1.02 - 1.10)	Eur/EurAm	30
rs2046210	5' ESRI / 6q25.1	0.37	1.29 (1.21 - 1.37)	Chinese	37

East Asian populations were also included in GWAS scans and have yielded new results.³⁷ In addition, there is an ongoing effort to map loci in African Americans.^{41,42}

To date, very little work has been published on the Mexican population and the effect of these common variants and breast cancer. However, in U.S. Latinas, it appears that at least some of them also predict risk.⁴³ More data is needed on how these risk variants affect risk in Mexican women. In addition, there may be additional polymorphisms that affect risk that may be discovered in Mexican women.

New approaches to identifying and characterizing breast cancer susceptibility genes

With the ongoing development of genetic technology, it is becoming feasible now to sequence the entire genomes of individual patients.^{44,45} As the feasibility of this technology improves, it will become possible to obtain more data from breast cancer cases that may ultimately help to identify new genes. In addition, sequencing of the tumor and understanding the relationship between the genetics of the tumor and the genetics of the patient in which it developed may also help to identify genes that increase the risk of cancer. Such approaches have recently yielded results in identifying PALB2 which is a risk factor in pancreatic cancer⁴⁶ and breast cancer.^{47,48} Large scale tumor sequencing efforts such as the Cancer Genome Atlas project may help to identify genes involved in cancer susceptibility and progression.⁴⁹

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