

DATA SUMMARY:
SIGNIFICANCE OF FAMILY HISTORY IN BREAST CANCER DIAGNOSIS

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Significance of Family History in Breast Cancer Diagnosis

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Abstract

Background: Family history and its significance in Hispanic breast cancer cases with a known BRCA mutation has not been widely studied.

Methods: Family history, BRCA mutation and age data were obtained for a subset of 91 individuals derived from the ELLA Binational Breast Cancer Study population, in order to determine the importance of family history in the context of BRCA mutation status.

Results: A total of 8 different BRCA1 and BRCA2 mutations were found within the study population. Only 11 of the 91 participants (12.1%) were found to possess a BRCA mutation. Of these 11 women, 6 (54.5%) had a positive family history of cancer. This is greater than the expected percentage (23.5%) reported in the literature.

Conclusion: Over half of those individuals that were found to have a BRCA mutation also had a positive family history of cancer. Therefore, family history is an important component when assessing breast cancer risk in populations of Hispanic women but can often be obscured due to limited family structure. Family history could be evaluated more effectively in the ELLA Study through the use of a modified questionnaire that probes for family structure.

Introduction

Family history is an important component in assessing a woman's risk of developing breast cancer because it can provide a genetic basis by which to evaluate her likelihood of getting the disease. ¹Awareness of a positive family history is important not just for the woman being assessed but also for future generations in her family. ¹ Being informed allows her to take preventative measures to minimize her risk for breast cancer and it also allows her to pass on that information to younger generations of women and men in her family. Therefore, family history can be a very useful factor in risk assessment models.

Although there are many other risk factors to consider when evaluating a woman's risk for developing breast cancer, such as age and reproductive health, family history is one of the strongest determinants of individual risk.¹ In a clinical setting, a person with a positive family history of breast cancer is someone who has at least one first degree relative on the same side of the family with the same or related cancer.¹ Typically, an increased risk of breast cancer arises from having 2 or more relatives who have had breast or ovarian cancer.¹

Family history is usually assessed through the construction of a pedigree that covers at least 3 generations and/or a questionnaire that includes questions about familial cancers and the relationship of relatives with a prior cancer history to the patient.¹ The construction of a pedigree can often be difficult, though, particularly if the pedigree is produced by a physician with limited skills in genetic counseling or if the family structure of the patient is too large or limited.² If the family structure is large, it often helps if the patient is the "family informant" because usually, these individuals have enough familiarity with most, if not all members of a family and are able to provide information on most family member's medical past.² A limited family structure, which is defined as having less than two second degree relatives, can obscure a patient's family history assessment and suggest that the patient does not have a genetic component predisposing them to breast cancer or other cancers, when this may not be the case.² The use of a questionnaire can also give rise to limitations, especially if questions about family structure are not included.

Women who are informed of a prior family history of breast cancer early enough are more likely to maintain a regular screening routine than those that are unaware of their risk.³ According to a recent study conducted by Katapodi *et al.*, perceived risk appears to prompt many women, who would not get screened otherwise, to adopt routine screening.³ Many women who

are unaware of their previous family history of breast cancer often underestimate their risk, thinking that they are less likely than the average woman to develop breast cancer.³ This prevents them from adopting appropriate screening routines and this can have significant medical consequences.³ Women at high risk who underestimate their risk are also less likely to follow medical recommendations for screening and chemoprevention.³ These same women, once notified of their increased risk of breast cancer due to a positive family history, are also more likely to acknowledge their risk.³ Thus, it is very important for women to be informed of a positive family history of breast cancer because once they know of their risk, they are more likely to take preventative measures to protect themselves and reduce their risk of developing breast cancer.

Genetic testing also plays a significant role in the assessment of family history because there are well-known mutations in particular genes that have been associated with an increased risk of breast cancer. The BRCA gene family is perhaps the best known example of genes whose biological properties and influence on breast cancer incidence and prevalence have been studied intensively. The BRCA1 gene is one of the genes of interest in this family.⁴ It stands for “breast cancer 1, early onset” and belongs to a class of genes identified as tumor suppressor genes.⁴ The gene is responsible for producing a protein that helps prevent cells from growing too rapidly, as well as DNA repair.⁴ Mutations in this gene that result in breast cancer are usually caused by the production of a shorter version of the BRCA1 protein, amino acid changes, or DNA deletions from the BRCA1 gene.⁴ This affects the control of cell growth and division, as well as DNA repair, all of which can result in the formation of a tumor.⁴ The BRCA2 gene (breast cancer 2, early onset) also belongs to the same class of tumor suppressor genes.⁵ The protein produced by BRCA2 is responsible for control of cell growth and division as well.⁵ Mutations in this gene

usually result from DNA deletions and insertions in the BRCA2 gene, which alter BRCA2 protein production.⁵ When this protein is altered, uncontrolled cell growth can result, leading to the formation of a tumor.⁵

Mutations in BRCA1 and BRCA2 genes account for approximately 5-10% of breast cancer cases.¹ Many epidemiological studies have been conducted on the BRCA genes, mostly in populations of Caucasian women.⁶ BRCA gene studies have been conducted on other ethnic groups, but most have been performed on populations of African American women.⁶ To date, there have not been many BRCA studies conducted in populations of Hispanic individuals.⁶ One study published by Weitzel *et al.* found that the prevalence of BRCA mutations in a subset of the Hispanic population is about 34%.⁶ Therefore, the study of BRCA mutations and their relevance to family history assessment in populations of Hispanic women is an area of particular interest.

Methods

Description of ELLA Study Population

Participants for this study were obtained from the ELLA Binational Breast Cancer Study. The ELLA population consists of women of Mexican descent who have been diagnosed with breast cancer within 12 months prior to consenting to participate in the study. Participants must also be at least 18 years of age or older in order to be eligible to participate. There are 5 different sites that collaborate and recruit participants for the ELLA study and they include the Arizona Cancer Center in Tucson, AZ, MD Anderson Cancer Center in Houston, TX, the University of Guadalajara in Guadalajara, Jalisco, MX, the University of Sonora in Hermosillo, Sonora, Mexico and the Instituto Tecnológico de Sonora in Ciudad Obregon, Sonora, Mexico.

Description of 5 Study Sites

All 5 sites for the ELLA study work together in a collaborative research effort. The Arizona Cancer Center is designated as a Comprehensive Cancer Center by the National Institute of Health and is a leader in research on many different cancers, including breast cancer. The M.D. Anderson Cancer Center in Houston, TX is also designated as a comprehensive cancer center by the National Institute of Health. It has been ranked as the number one hospital for cancer care at least six times and is known for its cutting edge cancer research and patient care. The University of Guadalajara in Guadalajara, MX is one of the top public universities in Mexico and is a leader in medical education and research. The University of Sonora in Hermosillo, MX is one of the top 5 universities in Mexico and it has a special center dedicated to the study of nutrition and its impact on health. This center works directly with the investigators of the ELLA Study to provide assistance with conducting the study in Hermosillo. The Instituto Tecnológico de Sonora in Ciudad Obregon, MX is a public university with many high quality programs in biotechnology and medicine, to name a few.

Selection of Family History Study Participants

A representative subset of individuals from the ELLA Study population were chosen as participants for this study. Approximately 91 women of Mexican ancestry who were diagnosed with breast cancer under the age of 50 years were selected and screened for common ancestral germline mutations of the BRCA gene family. Family history data for each participant was also determined prior to their selection for this study. Data on family history was collected and recorded according to whether the participant had a positive family history of cancer or not. All data obtained for each participant was de-identified prior to any measures and no links to

participant level information and gene testing were retained, other than age as a category and information on family history, which was identified as having any first degree relative with breast or ovarian cancer.

Family History Ascertainment

Family history information was obtained for each participant through the use of the ELLA Binational Breast Cancer Study risk factor questionnaire. Following their consent to participate in the study, participants were asked a series of questions contained under the “family history of cancer” section in the risk factor questionnaire. Potential participants are asked questions regarding their adoption status and the cancer history of first and second degree relatives. The participant is asked to denote the type of cancer each affected family member had, the age at diagnosis and if they are unsure of the type of cancer their family members had, they can respond “don’t know”. Cancer history is obtained for both maternal and paternal relatives.

Results

Determination of BRCA Mutation Ancestry

BRCA mutation data was obtained for all participants in this study and after careful analysis of the data, a total of 8 different BRCA mutations were found in this representative population of 91 women. There were 4 BRCA1 mutations and 4 BRCA2 mutations identified amongst the study participants. The ancestry of 5 of the 8 distinct BRCA mutations was determined from a literature review. All information concerning the exact BRCA mutations found and whether the mutation was located on the BRCA1/BRCA2 gene was de-identified in order to protect the identity of ELLA Study participants.

All 5 mutations appeared to have their origin in one or two Latin American countries. One mutation, MUT02, found in individuals of Mexican/Spanish descent, also appears to be present in approximately 1% of individuals of Ashkenazi Jewish ancestry and could be due to the migration of many Jews to Spain in the early 6th century. ⁶ Information regarding the specific BRCA mutations, their ancestry and the frequency of these mutations in the study population may be found in Table I below.

Table I: BRCA Mutation Ancestry

<i>BRCA Mutation</i>	<i>Ancestry/Country of Origin</i>	<i>Frequency (%)</i>
MUT01	Mexico	2.2%
MUT02	Mexico/Spain	1.1%
MUT03	Mexico	1.1%
MUT04	Unknown	1.1%
MUT05	Mexico	3.3%
MUT06	Unknown	1.1%
MUT07	Unknown	1.1%
MUT08	Amerindian/Mestizo	1.1%

Only 11 of the 91 participants (12.1%) from this study were found to have a mutation on either the BRCA1/BRCA gene. The remaining 80 participants (87.9%) were found not to have any mutations on either the BRCA1 or the BRCA2 gene.

Mutation Frequency, Relative Age, and Family History

As previously stated, relative age and family history information was obtained for all 91 participants. Relative age is defined as the age range under which each participant falls, i.e. whether they are under the age of 40 years or over the age of 40 years. The data collected for age specifies age at diagnosis for each participant only, not age at which they consented to participate in either the ELLA study or this study. Family history data collected provided information as to whether the participant had a positive family history of cancer in their family. A positive family history is defined as having at least one first or second degree relative that has or has had breast or ovarian cancer.

Table II below contains information about each mutation in relation to age at diagnosis and family history. Overall frequency refers to how often the mutation was seen in the entire study population. Age at diagnosis is reported as being either over the age of 40 years or under the age of 40 years. Presence of family history refers to how many individuals had a positive family history of cancer. The percentages correspond to how many individuals with that particular mutation had the above characteristics.

In this study population, 11 of the 91 women (12.1%) were found to have a mutation on either the BRCA1 or the BRCA2 gene. Among these 11 women, there were 5 (45%) who were over the age of 40 years and 6 (55%) who were under the age of 40 years. Approximately 3 (60%) of the women who were over the age of 40 years had a positive family history of cancer,

whereas 3 (50%) of the women who were under the age of 40 years had a positive family history of cancer. Overall, 6 out of the 11 women (54.5%) had a positive family history of cancer.

Table II: Family History and Age at Diagnosis Across Mutations

<i>Mutation</i>	<i>Overall Frequency (%)</i>	<i>>40 yrs of age (%)</i>	<i><40 yrs of age (%)</i>	<i>Presence of Family History (%)</i>
MUT01 (n=2)	2.2%	100%	0	100%
MUT02 (n=1)	1.1%	0	100%	100%
MUT03 (n=1)	1.1%	100%	0	100%
MUT04 (n=1)	1.1%	0	100%	0
MUT05 (n=3)	3.3%	33.3%	66.7%	33.3%
MUT06 (n=1)	1.1%	0	100%	0
MUT07 (n=1)	1.1%	100%	0	0
MUT08 (n=1)	1.1%	0	100%	100%

Among the mutations that appeared to be most prevalent in the study population, namely, MUT01 and MUT05, 3 (60%) of the women were over the age of 40 years and 2 (40%) were under the age of 40 years. Approximately 3 (60%) of the women who possessed one of the most prevalent mutations (MUT01, MUT05) had a positive family history of cancer, while 2 (40%) had no family history of cancer. Across all other mutations (MUT02, MUT03, MUT04, MUT06, MUT07, MUT08), 2 (33%) of the women who possessed one of the above mutations were over

the age of 40 years and 4 (67%) were under the age of 40 years. Of these 6 women who possess one of the aforementioned mutations, 3 (50%) have a positive family history of cancer and 3 (50%) do not have a family history of cancer.

Discussion

The risk of developing breast cancer can increase up to two-fold when there is a positive family history present.¹ Therefore, some individuals will tend to be more predisposed to developing breast cancer and other cancers simply because of their ancestry, among other factors.¹ Increasing age can also increase a woman's risk of developing breast cancer simply because of hormonal changes that occur during menopause.⁷ In fact, breast tissue exposure to estrogens, which occurs, for example, during menopause when women undergo hormone replacement therapy, has also been found to increase the risk of breast cancer.⁷ Though estrogens are not considered mutagenic, they are believed to alter the rate at which epithelial cells in the breast tissue proliferate, differentiate and atrophy.⁷ Thus, both a positive family history and increasing age can pose a significant risk for women who present with either or both.

A total of 11 women from a study population of 91 women (12.1%) were found to have BRCA 1 or BRCA2 mutations. Additionally, of those 11 women, approximately 6 (54.5%) had a positive family history of cancer. There appears to be a correlation between possessing a BRCA1/BRCA2 mutation and having a positive family history of cancer. In this case, approximately 55% of the women who presented with a mutation in either the BRCA1/BRCA2 gene had a positive family history of cancer. Thus, it is possible that family history has a strong influence on the presence of mutations on the BRCA genes of women who have a family history of cancer. This is consistent with the findings of a study performed by Weitzel *et al* that sought

to determine the prevalence of BRCA mutations in a Hispanic population attending a high risk clinic.⁸ Their findings suggested that the overall prevalence of BRCA mutations in this population was approximately 30.9%.⁸ In addition, a study performed by Ricker *et al.*, in which they sought to determine whether establishing a genetic assessment clinic would benefit a population of underserved Hispanic women, found that approximately 23.5% of women who were found to have a BRCA mutation also had a positive family history of cancer.⁹ The percentage of women who were found to have a BRCA mutation (12.1%) in this study was lower than the expected value (30.9%), while the percentage of those women with both a BRCA mutation and a positive family history was higher (55%) than the expected value (23.5%). Still, the results obtained in this study are consistent with the notion that family history is positively correlated with the presence of a BRCA mutation in populations of Hispanic women.

It is also interesting to note that a great deal of the BRCA gene mutations found within this study population were of Mexican ancestry. In particular, among those mutations found in women who had a positive family history of cancer, 4 out of the 5 BRCA mutations had Mexican or Spanish ancestry. Given this and the fact that all women who participated in this study were of Mexican descent, it can further be concluded family history does indeed play a critical role in determining whether the cause for a women's breast cancer is the result of genetics.

A more accurate assessment of family history, however, is necessary in order to capture its significance in relation to BRCA mutations. Although family history is, in fact, an important determinant of breast cancer risk, it can be obscured when factors such as limited family structure introduce limitations. In the ELLA Study, family history is currently assessed through the use of a risk factor questionnaire that includes questions such as "Are you adopted?" and "Have any of your immediate family members ever been diagnosed with cancer?". The

participant then proceeds to provide details on the type of cancer each affected family member had, their relationship to that family member and which side of their family that relative is from. As of now, there are no questions about limited family structure. It may be beneficial to include questions regarding limited family structure, which is defined as having less than 2 second degree relatives with cancer. If an individual has a limited family dynamic, it may be difficult for them to report an accurate family history.

Conclusions/Future Directions

Family history was found to be significant for BRCA mutation carriers. Over half of those women who possessed a BRCA mutation also had a positive family history of cancer. Clearly, family history is an important component in assessing a woman's risk for developing breast cancer but in order to effectively document family history, certain changes in the way family history is currently evaluated need to be made. This could involve modifying the family history section of the ELLA Study risk factor questionnaire to include questions regarding family structure and a resampling of ELLA participants with a BRCA mutation in order to test this new questionnaire. This will determine if family history has been underestimated in this population of women of Mexican descent. Nonetheless, family history has proven to be an important factor in the assessment of breast cancer risk and the potential resampling of ELLA Study cases could provide additional insight into its relationship to BRCA mutation status.

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