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Risks Related to Breast Cancer

- Advancing Age
- Early Menarche
- Lack of Exercise
- Alcohol
- Hormone Replacement Therapy
- Overweight
- Gender
- Late Menopause
- Close Relative Age at First Birth
- Benign Breast Disease
- Ionizing Radiation
- Chemicals - Work - Home - Garden - Recreation
- Education & Income
- Genetics
When to Suspect a Hereditary Cancer Syndrome

- Cancer in 2 or more close relatives (on same side of family)
- **Early age at diagnosis**
  - Multiple primary tumors
  - Bilateral or multiple rare cancers
  - Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
Finding Mutations is Difficult and Expensive

- BRCA1: 22 coding exons, > 5,500 bp

- BRCA2: 26 coding exons, > 11,000 bp
BRCA1- and BRCA2-Associated Cancers: Lifetime Risk

Breast cancer 50%-85% (often early age at onset)

Second primary breast cancer 40%-60%

Ovarian cancer 15%-45%

- Absolute risk likely to be higher than 10%
  - Prostate cancer
- Absolute risk 10% or lower
  - Male breast cancer
  - Fallopian tube cancer
  - Pancreatic cancer
How Much Breast and Ovarian Cancer Is Hereditary? Is it different in Latin America?

Breast Cancer
- Sporadic: ~5%
- Family clusters: 15% - 20%
- Hereditary

Ovarian Cancer
- Sporadic: ~10%
- Family clusters
- Hereditary
Mexico-U.S. Migration

Source: www.saludmigrante.salud.gob.mx/
International Cancer Genetics Community Research Network

Hereditary Cancer Research Registry; City of Hope IRB # 96144; supported by Award Number RC4A153828 (PI: J.Weitzel) from the NCI and the Office of the Director, NIH
### BRCA Mutations in 746 High Risk Hispanic Families

#### Mutation Status and Cancer History of Probands

<table>
<thead>
<tr>
<th></th>
<th>Mutation Status</th>
<th>Carriers</th>
<th>Non-Carriers</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>189 (25)</td>
<td>523 (70)</td>
<td>34 (5)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. (%) N=746</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>187</td>
<td>520</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>169</td>
<td>449</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>No. with breast cancer</td>
<td>144</td>
<td>419</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>No. with ovarian cancer</td>
<td>17</td>
<td>21</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No. with breast and ovarian cancer</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Average age at first breast cancer diagnosis</td>
<td>40</td>
<td>40.8</td>
<td>39.5</td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>20</td>
<td>74</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
BRCA1 mutations observed in Hispanic cohorts in TX and CA

Weitzel, et al. CEBP 2005
Vogel, et al. JCO 2007
John, et al. JAMA 2007
## Grandparental Origins for Recurrent Mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>No. of observations</th>
<th>Country of Origin</th>
<th>States in Mexico</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>185delAG</td>
<td>18</td>
<td>Mexico (16) Spain (2)</td>
<td>Chiapas Durango Jalisco Michoacan Distrito Federal</td>
</tr>
<tr>
<td></td>
<td>Exon9-12del</td>
<td>13</td>
<td>Mexico</td>
<td>Chihuahua (2) Durango Jalisco Puebla Tamaulipas Veracruz</td>
</tr>
<tr>
<td></td>
<td>R71G</td>
<td>9</td>
<td>Mexico (7) Spain (2)</td>
<td>Michoacan (2) Sonora</td>
</tr>
<tr>
<td></td>
<td>R1443X</td>
<td>6</td>
<td>Mexico (4) Colombia (1) Peru (1)</td>
<td>Oaxaca</td>
</tr>
<tr>
<td></td>
<td>Q1200X</td>
<td>5</td>
<td>Mexico</td>
<td>Aguascalientes Colima Michoacan</td>
</tr>
<tr>
<td></td>
<td>917delTT</td>
<td>5</td>
<td>El Salvador (4) Guatemala (1)</td>
<td></td>
</tr>
</tbody>
</table>
Ancestry Informative Markers

185delAG Carriers

Mean EUR and AMI Ancestry

<table>
<thead>
<tr>
<th></th>
<th>Ex9-12del</th>
<th>185delAG</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUR</td>
<td>36%</td>
<td>50%</td>
<td>0.03</td>
</tr>
<tr>
<td>AMI</td>
<td>43%</td>
<td>30%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*P-value for Student’s T-test
The **BRCA1** 185delAG mutation is prevalent in Latinos, and shares the Jewish founder haplotype

- Possible descendents of Spanish Jews who converted to Christianity to avoid persecution

Large deletion mutation seen in 18 independent Mexican families (high risk clinic=13; population-based=5) “Mexican Founder Mutation”

- Estimated by haplotype analysis to have arisen ~74 generations/1,480 yrs ago
- Speculation – Amerindian or mestizo origin

Among 746 Latinas tested in high risk clinic consortium: **BRCA1** 185delAG (n=18), ex9-12del (n=13), **BRCA2** 3492insT (n=10) account for 22% (41/189) of all carriers; recurrent mutations (n>4) cover 54%.

J.N. Weitzel; manuscript in preparation
Founder Mutations
### BRCA: Selected Examples of Founder Mutations

<table>
<thead>
<tr>
<th>Population</th>
<th>BRCA1 Mutations</th>
<th>BRCA2 Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>185delAG, 5382insC</td>
<td>6174delT</td>
</tr>
<tr>
<td>Icelandic</td>
<td></td>
<td>999del5</td>
</tr>
<tr>
<td>British</td>
<td>6-kb duplication of exon 13, 4184del4</td>
<td>6503delTT</td>
</tr>
<tr>
<td>Dutch (Netherlands)</td>
<td>2804delAA, Large deletions of exons 13 &amp; 22</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>1081delG</td>
<td></td>
</tr>
<tr>
<td>Russian</td>
<td>5382insC, 4153delA</td>
<td></td>
</tr>
<tr>
<td>African A.</td>
<td>1832del5, 5296del4</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>185delAG, deletion exons 9-12, 3492insT</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Management of BRCA Mutation-Positive Patient

Cancer Screening & Prevention Program

Positive BRCA1 or BRCA2 test result

Possible testing for other adult relatives

- Prophylactic surgery
- Lifestyle change
- Increased surveillance
- Chemo-prevention
City of Hope Cancer Screening & Prevention Program
Patient Characteristics and BRCA Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Probands N=79</th>
<th>At-risk relatives N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age at time of visit (years)</td>
<td>40.3 (range 22-61)</td>
<td>35.7 (range 22-54)</td>
</tr>
<tr>
<td>Cancer status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaffected (%)</td>
<td>16 (20.3%)</td>
<td>15 (83.3%)</td>
</tr>
<tr>
<td>Affected with BC and/or OC</td>
<td>63 (79.7%)</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>breast cancer (%)</td>
<td>49 (77.7%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>bilateral breast cancer (%)</td>
<td>11 (17.5%)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>ovarian cancer (%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Average age at first BC diagnosis</td>
<td>38.6 (range 23-61)</td>
<td>38.0 (range 29-49)</td>
</tr>
<tr>
<td>BRCA Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Tested (%)</td>
<td>17 (21.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Tested (%)</td>
<td>62 (78.4%)</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>Positive (%)</td>
<td>17 (27.4%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>42 (67.8%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>VUS (%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary

• To date, this is the largest study of high-risk Hispanic families in the United States and the first to demonstrate the high prevalence, age and likely ancestral origin of the \( BRCA1 \) ex9-12del mutation in this population

• \( BRCA1 \) ex9-12del has never been observed in Spain or South America and is estimated to have arisen approximately 1,500 years ago, predating the Spanish Inquisition which is believed to be the origin of \( BRCA1 \) 185delAG in Mexicans

• Furthermore, history cites the integration of the Mayans and Toltecs around this time period around Puebla, the same region of origin reported by some of the ex9-12del carriers.

• Our admixture analyses support this observation showing a higher proportion of Ameridian ancestry and a lower proportion of European ancestry among ex9-12del compared to 185delAG carriers.

• Therefore, ex9-12del appears to be not only one of the most frequent population-specific large rearrangement mutations in the world, but also the first reported Mexican founder mutation.
Overall, the identification of several recurrent mutations suggests that a panel for such mutations for ancestry-informed genetic screening, especially among the Hispanic population, could be cost effective.

Currently, the sensitivity of a Hispanic-specific BRCA mutation panel is being evaluated.

Going forward, given the high proportion of BRCA mutation carriers, future breast cancer epidemiology studies may need to take into account BRCA status when investigating Hispanic populations.
Hereditary Breast Cancer and Novel Hispanic *BRCA* Mutations Project

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