BRCA 1-2 Ashkenazi mutations in Argentine patients at high risk of hereditary breast cancer

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Introduction

• BRCA 1 and BRCA 2 ashkenazi mutations (AM) are associated with increased risk of hereditary breast and ovarian cancer syndrome (HBOCS). (1,2,3,4)
• AM have been found in Hispanic populations with non direct Jewish ancestry. (5,6,7,8, 9, 10,11,12)
• There was no data about the frequency of AM in argentine patients (pts) with breast cancer at high risk of HBOCS.
• Genetic tests searching for the three founder AM were the only ones commercially available in our country by the time of the study design.
• The high costs of full gene sequencing made it unreacheable for most of the patients, in a country with high rates of breast cancer incidence.
• The purpose of this study was to evaluate the frequency of the three founder AM in BRCA 1 and 2 genes in a selected population of women with breast cancer at high risk of HBOCS.

Materials & Methods

• This was a prospective, observational study conducted by the Argentine Association of Clinical Oncology (AAOC) Collaborative Group.
• From september 2009 to may 2011, women with breast cancer diagnosis who fullfilled the inclusion criteria were included.
• Selection criteria:
- Accepted written informed consent.
- Age more than 18 years old.
- Confirmed histologic diagnosis of breast cancer.
- Genetic counseling consultation.
- HBOCS defined by one or more of the following:

a) 40 years or less at diagnosis of breast cancer.
b) 50 years or less at diagnosis but with at least one or more of the following characteristics:
bilateral breast cancer, one or more 1° or 2° relatives with breast cancer diagnosis at 50 years or younger, one or more 1° or 2° relatives with epithelial ovarian cancer diagnosis, breast cancer history in a male relative, personal history of ovarian cancer, Ashkenazi Jewish ancestry.

• Data about patient - tumor characteristics and family history were obtained.
• Direct DNA sequencing from a blood sample was performed at a central laboratory searching for the AM 185delAG- BRCA 1 exon 2; 5382insC- BRCA 1 exon 20 and 6174 delT- BRCA2 exon 11.
• The study was sponsored by the AAOC.

Results

•118 pts were screened
• 97 pts fullfilled inclusion criteria and were selected for genetic testing after genetic counseling consultation.
• Baseline patient characteristics are listed in Table 1.

Table 1. Patient – Tumor characteristics	n 97 (100%)
Sex	
Female	97 (100%)
Median age at diagnosis (years)	37 (r 23-50)
Age groups	
< 35 y	(29%)
35 – 40 y	(41%)
41 – 50 y	(30%)
Median tumor size (cm)	2 (0,2 – 10)
Histologic subtypes	
Ductal	80 (83%)
Lobulillar	10 (10%)
Ducto-Lobulillar	3 (3%)
Other	4 (4%)
Histologic Grade	
I	9 (10%)
II	33 (36%)
III	49 (54%)
IHQ	
Estrogen Receptor positive	62 (64%)
Progesterone Receptor positive	59 (61%)
Her 2 positive	25 (26%)
Triple Negative	14 (14%)
Disease Presentation	
Localized	77 (79%)
Locally Advanced	16 (17%)
Advanced	4 (4%)
Surgery	
Conservative	73 (75%)
Mastectomy	20 (21%)
Sentinel node biopsy	21 (22%)
Axillary Dissection	76 (78%)
Positive axillary lymph nodes	46 (48%)
Adjuvant therapies	
Chemotherapy	72 (77%)
Radiotherapy	75 (79%)
Hormone therapy	50 (53%)

Table 2. Selection criteria characteristics	n (%)
Age ≤ 40 years	68 (70%)
Ashkenazi ancestry	7 (7%)
1° relative with BOC diagnosis less than 50 y	31 (32%)
2° relative with BOC diagnosis less than 50 y	41 (42%)
Bilateral breast cancer at presentation	11 (11%)
Personal history of ovarian cancer	2 (2%)
Breast cancer in a Male family member	1 (1%)

• After performing direct DNA sequencing on the blood samples looking for the three founder AM the mutational analysis was negative in 99% of the patients (n 96).

• The only mutation found was the BRCA1 185delAG (heterozygous), in one patient (1% of the cohort).

• The patient was diagnosed at the age of 23, she had Ashkenazi ancestry and a family history of two second degree female relatives with diagnosis of breast cancer. One at the age of 48 and the other at the age of 49.

• In the Ashkenazi subgroup of patients (n 7) this finding represents a frequency of 14 %.

Conclusions

• The study results show the scarce or null effect of a panel with the three founder AM to confirm the diagnosis of hereditary breast cancer in a highly selected population of Argentine women with breast cancer diagnosis at high risk of hereditary breast ovarian cancer syndrome.

• This panel could be used as an initial and less expensive approach only for Ashkenazi patients with strong family history. (13)

• Full gene sequencing should be done in all patients at high risk of HBOCS, but this approach is not feasible to perform in the majority of patients in our country due to the elevated costs of this diagnostic test.

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