Hereditary Breast Cancer

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Introduction

- Breast cancer, with a 12.5% lifetime risk in general population, is the most frequent cancer in women. About 5-10% of breast cancers are thought to be hereditary whereas the remaining 90% is sporadic.
- Most inherited cases of breast cancer are associated with two abnormal genes: *BRCA1* (BReast CAncer gene one) and *BRCA2* (BReast CAncer gene two) but these only make up 25% of hereditary breast cancers while the remaining 75% is due to moderate and low penetrance and unknown genes.
- Because of the lack of awareness of this pathology, it does not have a standard and harmless treatment to fight it so the research of novel therapies and the improvement of actual strategies would suppose a highly breakthrough in the disease.

Objectives

The aim of this divulgative work is to create an informative website intended for hereditary breast cancer patients and their relatives where the following objectives are reflected:

- Explanation of what hereditary breast cancer is, focusing on *BRCA* genes.
- Provide a description of *BRCA* mutation carriers' features.
- Provide the highlights of genetic counselling
- Exposure the current available treatments
- Show the novel therapies

Materials And Methods

It was undertaken a critical review of journal articles published between 2001 and 2013, identified by searches in MEDLINE and PubMed using the following search terms: *BRCA1, BRCA2*, hereditary breast cancer, hereditary ovarian cancer, genetic counsellors, risk assessment, genetic susceptibility, medical outcomes and treatment. References of retrieved articles were undertaken.

Genetic Causes

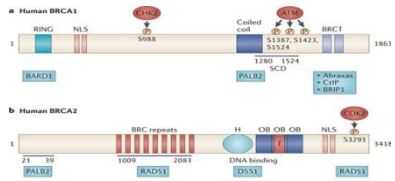


Figure 1. The main high penetrance susceptibility genes: *BRCA1* and *BRCA2* (Rohini Roy *et al*., 2012).

Table 1. Summary of known breast cancer predisposition genes (Adapted from Turnbull C and Rahman N, 2008)

Penetrance	Gene/Locus	Carrier Frequency	Cancers
High penetrance	BRCA1	0.1%	Breast and ovarian
	BRCA2	0.1%	Breast and ovarian
	TP53	Rare	Sarcomas, adrenal and brain
Uncertain penetrance	PTEN	Rare	Thyroid and endometrium
	STK11	Rare	Gastrointestinal
	CDH1	Rare	Gastric
	ATM	0.4%	
Intermediate penetrance	CHEK2	0.4%	
	BRIP1	0.1%	
	PALB2	Rare	
	RAD51	Rare	
Low penetrance	10q26 16q12q35, 8q24, 5p12	24–50%	

Genetic Counselling

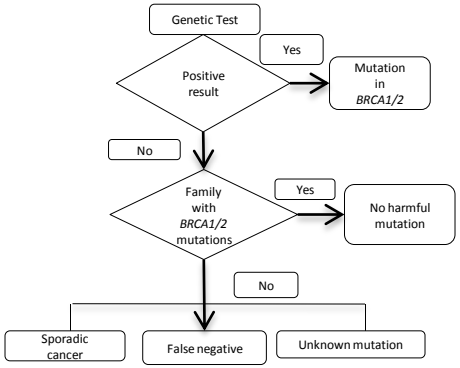


Figure 2- Genetic counseling algorithm (Berliner JL *et al*., 2007)

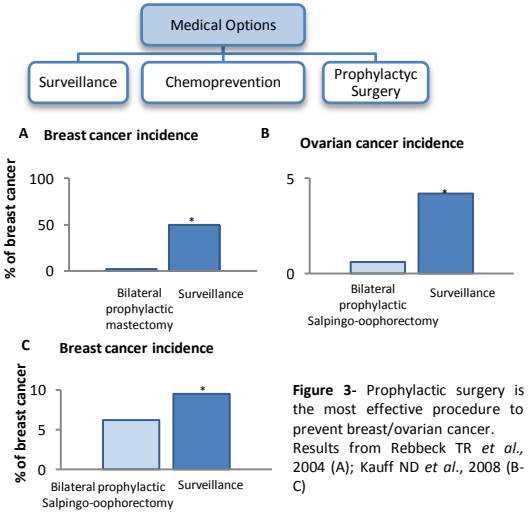
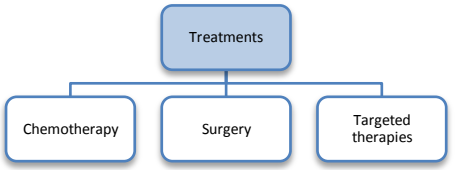


Figure 3- Prophylactic surgery is the most effective procedure to prevent breast/ovarian cancer. Results from Rebbeck TR *et al*., 2004 (A); Kauff ND *et al*., 2008 (B-C)

Treatment



One of the novel targeted therapies is tumor synthetic lethal strategy of Poly(ADP-Ribose) Polymerase (PARP) inhibitors

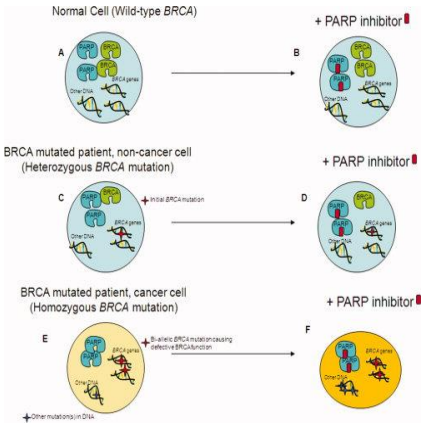


Figure 4- Hypothesis for the tumor synthetic lethal strategy of Poly(ADP-Ribose) Polymerase (PARP) inhibitors in *BRCA1/2* mutation carriers (Yap TA *et al*., 2011)

Conclusions

Breast cancer:
- Is the most common cancer in women with 230,000 women diagnosed in the US in 2012
- Its origin is:
  - 90% sporadic
  - 10-5% hereditary

Genetic causes:
- 25% due to *BRCA1/2* mutations
- 5% is caused by other high susceptibility genes
- 5% is composed by moderate susceptibility genes
- 14% is formed by low susceptibility genes
- 51% remains unknown

Genetic counselling is a useful procedure to:
- Give the chance to perform a genetic testing
- Assess patient about cancer risk
- Give patients medical options to prevent cancer
- The most useful and effective procedure to prevent breast/ovarian cancer is the prophylactic surgery of these organs

Treatment:
- Tumor-specific synthetic lethal strategy with PARP inhibitors is showing considerable potential for delivering selective tumor cell kill while sparing normal cells
- Nowadays is being tested in clinical trials