Molecular mechanisms underlying BRCA1 deficiency may determine cancer in Benin

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ABSTRACT

Background: BRCA1 gene mutation or protein deficiency was well studied in black women from America, and Caribbean. However, this study was lacking among black women from west African countries including Benin. Study conducted on 50 breast cancer micro biopsy cell lysates gave us an overview of BRCA1 status in women with breast cancer in Benin.
Methods: Polymerase chain reaction (PCR) and immunoblotting were used to assess BRCA1 gene and protein profile on 50 breast cancer micro biopsy cell lysates collected in the University National hospital CNHU-HKM of Cotonou (Benin). BRCA1 gene deletion was assessed with primers targeting exon1 and exon2. Kaplan-Meier analysis was performed to determine median survival time according to BRCA1 profile.
Results: Overall, 78% of patients had lost the expression of BRCA1 protein while there was no gene deletion recorded. The analysis of Kaplan showed that the median survival rate was 20 months. The disparity between gene profile and protein status suggested an epigenetic regulation of BRCA1 gene expression among most black African women diagnosed with breast cancer in Benin.
Conclusion: Determination of molecular mechanism underlying BRCA1 malfunction or deficiency will be an excellent asset to better personalize targeted breast cancer therapy in Black African countries.

Key words: BRCA1, breast cancer, Black African women, Epigenetics, targeted therapy

INTRODUCTION

* BRCA1 is known as a tumor suppressor gene. Its protein plays crucial roles in genomic stability through various mechanisms comprising homologous double strand DNA break repair.
* BRCA1 gene mutation or protein deficiency linked to breast cancer was well studied in black women from America and Caribbean. However, this study was lacking among black women from west African countries including Benin where breast cancer ranked number 1 of all women cancers (Egue M. *et al*. 2018).
The implication of BRCA1 silencing or mutation needs to be investigated further.
Hypothesis: The determination of molecular mechanisms surrounding BRCA1 silencing may direct breast cancer therapy and prognosis in Benin.

Objectives:
- Evaluate BRCA1 gene and protein profile in 50 breast cancer DNA extract and cell lysates to have an overview of BRCA1 status among women with breast cancer in Benin.
- Determine the molecular mechanism underlying breast cancer among women in Benin to help clinicians delineate personalized targeted therapy accordingly.

METHODS

- Polymerase chain reaction (PCR) was used to assess BRCA1 gene status in 50 breast cancer micro biopsy DNA extracts. The presence of BRCA1 gene was assessed with primers targeting exon1 and exon 2
- Immunoblotting was used to assess BRCA1 protein on corresponding 50 breast cancer micro biopsy cell lysates from a reference hospital of Cotonou (Benin). In this study, the age range of women was 24-59 years. The study follows the guideline of Helsinki declaration.
- Kaplan-Meier analysis was performed to determine the median survival time according to BRCA1 protein profile

RESULTS

- We observed that 39/50 (78%) of breast cancer patients lost the expression of BRCA1 protein as shown by immunoblot (fig. 1). There was no gene deletion recorded on Exon 1 and Exon 2 which harbors BRCA1 gene transcription starting codon *ATG*.

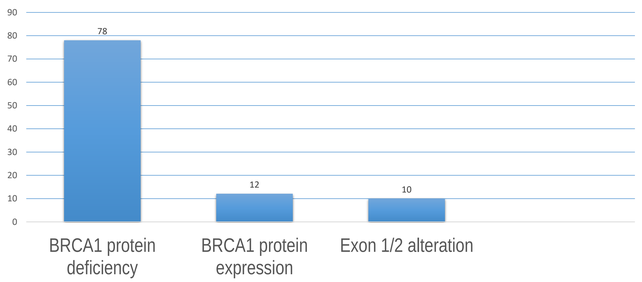
- Histogram in fig.2 displays the percentage of patients that lost BRCA1 expression while exon1/2 were amplified (78%); patients expressing BRCA1 protein (12%) and patient lacking BRCA1 protein associated with aberrant amplification of exon 1 or exon 2 (10 %)

BRCA1 analysis in cell lysates and DNA extracts

Immunoblot of BRCA1 protein

Figure 1: Immunoblot showing the absence of BRCA1 protein in most cell lysates. Sample numbers were scrambled

BRCA1 profile among women diagnosed with breast cancer in Benin



patient lacking BRCA1 protein associated with aberrant amplification profile of exon 1 or exon 2 (10 %).
Figure 2:: Histogram showing the percentage of patients that lost BRCA1 expression while exon1/2 were amplified (78%); patients expressing BRCA1 protein (12%) and

The Kaplan-Meier analysis indicated that the median survival rate in absence of BRCA1 protein was 20 months.

Switching from traditional broad therapy to personalized targeted therapy may expand median survival rate.
a- Epigenetic modifications could be reversed with:
- DNA Methyl Transferase (DNMT) inhibitors or
- Histone Deacetylase (HDAC) inhibitors,
b- women with breast cancer linked to germline or somatic BRCA mutations may benefit from treatment with the poly ADP ribose polymerase (PARP) inhibitor.
All of which will be inducing cancer cell apoptosis if the proper molecular modification is determined prior to therapy.

DISCUSSION

- The disparity between gene profile and protein status suggested an epigenetic regulation of BRCA1 gene expression among most Black African women (78%) diagnosed with breast cancer in Benin.

- The absence of exon amplification in 10% of breast cancer patients may either due to mutation at the primer hybridization site or exon deletion.

- Next generation sequencing (NGS) will be done for the 10% showing aberrant exon 1 or exon 2 amplification to document BRCA1 mutations that is linked to breast cancer among women in Benin.

Our main finding is that assessing BRCA1 protein profile will be more helpful than assessing only gene somatic or hereditary mutation.

CONCLUSIONS

The determination of molecular mechanisms underlying BRCA1 malfunction or deficiency will be an excellent asset in assisting clinicians to improved personalized targeted breast cancer therapy in African countries.

CURRENT COLLABORATIONS

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