



## Review Article

## BRCA1 and Ki-67 in breast cancer: A review

Minnu Sibby<sup>1</sup>, Bhavani Krishnamurthy<sup>1,\*</sup>, Nafeesa Banu<sup>1</sup>, Sowmya Srinivasan<sup>1</sup><sup>1</sup>Dept. of Pathology, Mahatma Gandhi Medical College and Research Institute- Sri Balaji Vidhyapeeth(Deemed-to-be University), Pondicherry, India

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## ABSTRACT

**Background and Objectives:** Breast cancer has become one of the leading cause of morbidity and mortality among female population both in developing and developed countries. Research also suggests the rising rate of breast cancer every year. Various advancements and research in this field has led to the discovery of both sporadic and genetic susceptibility prevailing in persons who develop this cancer. Even though various immunohistochemical(IHC) markers are being used in the workup of breast cancer, none of them is found to be totally effective in predicting the prognosis of the patient. It is known that BRCA mutations are associated with breast cancers and the protein expression of BRCA1 in breast cancer can be identified by IHC. Hence, the purpose of this review is to highlight the role of BRCA1 and KI-67 as diagnostic and prognostic IHC markers in breast cancer.

**Conclusion:** Breast cancer is one of the most leading causes of death in female population. BRCA1 and Ki-67 protein expression can be used to assess the grade of tumour and thereby predict the prognosis of the patient. Incorporating these markers along with existing hormone receptor workup can help in better approach in dealing with breast cancer.

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## 1. Introduction

When all cancers are considered in women, it is found that breast cancer is the second most common cause of mortality globally.<sup>1</sup> The incidence of the breast cancer has encouraged an exhaustive evaluation of the risk factors that contribute either directly or indirectly in its occurrence. Long lasting strong oestrogen exposure acts as a continuous source of stimulation especially in genetically susceptible individuals.<sup>2</sup>

## 2. Risk Factors

Research has proved beyond doubt that the occurrence of breast cancer is much higher in the developed high income countries as compared to the developing nations.<sup>3</sup> The relative risk of developing a second, 20 years after

initial diagnosis of breast cancer is 1.2 to 1.5.<sup>4</sup> Those females who have a first degree relative with a history of carcinoma of the breast is said to have a 2 to 3 times higher risk of developing breast cancer.<sup>5</sup> Early menarche and late menopause are implemented as risk factors in development of breast cancer<sup>5,6</sup> due to longer periods of exposure to estrogen. Breast is said to be immature and the cells of the breast in a resting phase, till the first lactation occurs. At this time the breast cells are more prone for various insults from environmental triggers to develop carcinoma of the breast. Therefore, age at first child birth and lactation are implicated as risk factors.<sup>3</sup> Nulliparity is another risk factor as there is hyper estrogenic stimulation in the absence of pregnancy.<sup>6</sup> Exposure to estrogen in the form of hormone replacement therapy also contributes to risk. Obesity also correlates with high risk of breast cancer. High fat intake is said to increase serum estrogen levels.<sup>6,7</sup>

\* Corresponding author.

E-mail address: [bhavanik@mgmcri.ac.in](mailto:bhavanik@mgmcri.ac.in) (B. Krishnamurthy).

### 3. Factors that affect Prognosis in Carcinoma of the Breast

The factors that predict the prognosis of carcinoma of the breast are categorized into major and minor prognostic factors.

#### 4. Major Prognostic Factors

In situ carcinomas are known to have a better prognosis than invasive carcinomas.<sup>8</sup> Those diseases with an advanced local stage either in the form of skin or chest wall involvement have a poor prognosis as compared to those without such involvement.<sup>9</sup> Prognosis also varies between histological types of breast cancer. Inflammatory carcinoma of the breast has a very poor prognosis as compared to the other variants. Rarer histological types are generally associated with good prognosis.<sup>10-12</sup> The presence of distant metastasis in any form at the time of presentation has an adverse effect on the prognosis, even though long term remission is possible to achieve in those who have tumours of hormone responsive breast cancers.<sup>11</sup> Also, the presence of metastasis to the axillary nodes is one of the important prognostic factors.<sup>12</sup> Size of the tumour is considered as the most important prognostic determinant in breast cancer.<sup>13</sup>

#### 5. Minor Prognostic Factors

Hormone receptors like ER and PR helps in assessing the prognosis in a patient with breast cancer.<sup>14</sup> ER or PR positive cases have a better prognosis than ER or PR negative status. Overexpression of HER-2/Neu is seen in about one fourth of all breast cancers and is related with a worse prognosis. Triple negative receptor status have the worst prognosis. Overexpression of HER-2/Neu is seen in about one fourth of all breast cancers and is related with a worse prognosis.<sup>14</sup> Higher grade tumours have a poorer prognosis.<sup>15</sup> The presence of invasion of the lymphatics and the blood vessels is also associated with poor prognosis.<sup>16</sup> Ki-67 is an index of the proliferative rate during the cell cycle and this index has an inverse relation to the prognosis. This antigen can be identified by monoclonal antibody using immunohistochemistry.<sup>17</sup>

#### 6. Ki-67 Protein

Ki-67 protein in man is encoded by the gene MK167. Ki-67 is considered as an indicator for proliferation of the cells. The coding gene for this protein is located on the long arm of chromosome 10. Ki-67 protein is exclusively expressed in those cells that are proliferating. This protein marker is not found in the cells when they are in their resting stage.<sup>15</sup> As it is the most consistent indicator of proliferation, which is an important feature of progression of tumours, measurement of this nuclear antigen by means of immunohistochemistry is practised routinely. High index of Ki-67 indicates poor

prognosis for the patient.<sup>17</sup> The antigen of Ki-67 is a nuclear protein and is needed for the synthesis of the RNA within the ribosome and hence it is associated with the proliferation of cells.<sup>15,17</sup>

The value of Ki-67 labelling index as a marker of prognostic significance and for recurrence of tumour is thus been proved beyond doubt by various studies that have been done in breast cancer.<sup>18</sup> The guidelines of the ASCO (American Society Of Clinical Oncology) do not have Ki-67 as a mandatory marker. But, with newer modalities, advent of new genetic tests has emphasized the role of proliferative genes, including Ki-67, as prognostic and predictive markers.<sup>19</sup> "International Ki-67 in Breast Cancer Working Group," approved the assessment of Ki-67 by IHC as the method that was preferred in order to determine, decide and monitor the proliferation of cancer cells in specimens. The most commonly used method to detect Ki-67 positivity is by staining with MIB-1 antibody. Ki-67 score is defined as the percentage of total number of tumour cells with nuclear staining.<sup>20</sup> A high Ki-67 is associated with tumours that have a higher grade, larger size, involvement of the lymph node, basal phenotype, and ER, PR negative with HER-2 positive hormone status.<sup>20</sup> Khanna et al<sup>21</sup> and Kaur et al.<sup>22</sup> observed that higher Ki-67 index was associated with higher grade of tumour which was seen to have poor prognosis. Han et al.<sup>23</sup> suggested that high Ki-67 expression was more common in triple negative breast cancers which are high grade tumours with poor prognosis.

### 7. Molecular Classification

Based on hormone receptor status, breast cancers are divided into four different groups.

#### 7.1. Luminal type A

These types of cancers, are positive for HR (ER and PR) and negative for HER2/Neu. They are found to have low Ki-67 index.<sup>24</sup> These tumours are more responsive to hormone therapy than hormone receptor-negative tumours. They have an overall tumour grade of 1 or 2.<sup>24,25</sup>

#### 7.2. Luminal Type B

These tumours are mostly triple positive with estrogen receptor positive, progesterone receptor positive and human epidermal growth factor receptor 2/neu positive or negative. They are found to have high Ki-67 index and they have a poor disease free survival and disease recurrence. These cancers are considered aggressive and fast growing than luminal A with a higher tumour grade. They are treated with antibodies against HER2/Neu receptors (Herceptin) blocking their action.<sup>26,27</sup>

### 7.3. Basal-like

These tumours have triple negative phenotype with estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2/Neu negative status. They are referred to as basal-like because the tumour cells have features similar to those of the outer (basal) cells surrounding the mammary ducts. Cancers in this category are associated with high Ki-67 index with most of them associated with BRCA-1 gene. Although these cancers respond fairly well to chemotherapy, they tend to recur.<sup>28,29</sup>

### 7.4. Triple negative phenotype

Triple negative phenotype (TNP) breast cancers can be further sub classified into two categories by adding epidermal growth factor receptor (EGFR) and cytokeratin 5/6 (CK-5/6) immunostaining information. The two subcategories are core basal and 5 negative phenotype (5-NP). The core basal group in addition to TNP is positive for EGFR and CK-5/6. While as the 5-NP group, which as the name suggests is TNP and also EGFR and CK-5/6 negative.<sup>30-32</sup>

## 8. Role of Genetics in Breast Cancer

### 8.1. BRCA gene

BRCA refers to "Breast Cancer gene and normally in every individual both BRCA1 and BRCA2 genes are present and are tumour suppressor genes.<sup>33</sup> Their presence is needed as they repair and modify the DNA breaks that cause malignancy and unrestrained expansion of cancer. The BRCA1 gene gives the directions for construction of a protein that plays as tumour suppressor.<sup>34,35</sup> Its gene is encoded by a factor that inhibits the expansion of the cells. The factor in addition is concerned with the control of the cell cycle regulation like gene transcription regulation, DNA damage repair, apoptosis, other important cellular processes and maintaining gene stability. It is the mutation of BRCA1 gene that is responsible for the 35%-40% of familial breast and ovarian cancers.<sup>36</sup> In the nucleus of many types of normal cells, the BRCA1 protein interacts with several other proteins to mend breaks in DNA. These breaks can be caused by natural and medical radiation or other environmental exposures, and they also occur when chromosomes exchange genetic material in preparation for cell division. By helping to repair DNA, BRCA1 protein plays a critical role in maintaining the stability of a cell's genetic information.<sup>36</sup>

### 8.2. BRCA protein

The BRCA protein is also known as the breast cancer type 1 susceptibility protein. This protein is responsible for repairing of the damaged DNA. BRCA1 encodes a protein of 220 k Da consisting of 1863 amino acids; whereas

BRCA2 produces a 384 k Da protein that has 3418 amino acids.<sup>37</sup> In order to maintain and perform its function of repairing the DNA and during embryogenesis, the BRCA1 protein interacts with various cell controlling mechanisms and tumour suppressor genes so that it can perform optimally. It is shown that many malignancies that have a germ line breaker 1 mutation are associated with a loss of heterozygosity at these two locations in the chromosomes, suggesting that loss of this wild-type BRCA1 is associated with malignancy.<sup>38</sup> Somatic mutations have not yet been described. But it is suggested that loss of heterozygosity, reduced levels of BRCA1 with reduced levels of BRCA1 protein expression, reduced methylation of BRCA1 protein in the region of the promoters, are all involved in sporadic malignancies of the breast. Hence, there is enough evidence to state that even in the sporadic variety of breast carcinoma, BRCA proteins are involved. The protein that is associated with BRCA1 gene is located exclusively in the nucleus of both normal and abnormal breast tissue. Various researches that have been done, have suggested that there is reduced expression of ER and total loss of this BRCA protein in both sporadic and familial breast cancers when evaluated by IHC.<sup>39</sup> Human BRCA1 protein contains different domains like RING finger, C3HC4 and BRCA1 C Terminus (BRCT) domain. This protein also contains nuclear localization signal and nuclear export signal. These domains encode approximately 27% of BRCA1 protein. There are six known isoforms of BRCA1, with isoforms 1 and 2 comprising 1863 amino acids each. In the nucleus of many types of normal cells, the BRCA1 protein interacts with RAD51 during repair of DNA double-strand breaks. These breaks can be caused by natural radiation or other exposures, but also occur when chromosomes exchange genetic material. BRCA2 protein, which has a function similar to that of BRCA1, also interacts with the RAD51 protein. BRCA1 is also involved in another type of DNA repair, termed mismatch repair. BRCA1 interacts with the DNA mismatch repair protein MSH2.<sup>40</sup> It is approximated that 1 per 450 or 0.25% of individuals who develop breast cancer tend to carry the mutated gene. People with BRCA gene mutation are more likely to develop breast cancer, and mostly at a younger age. The carrier of the mutated gene can also pass a gene mutation down to his or her offspring.<sup>38-40</sup>

Concerning BRCA1 protein, different types of staining have been described: nuclear, cytoplasmic, or both. The use of monoclonal antibodies after antigen exposure in a microwave, demonstrates a predominantly nuclear labelling. This localization is consistent with the role of BRCA1 in the maintenance of genome integrity, cell cycle control, apoptosis, and DNA repair. A minute proportion of individuals carry mutated BRCA1 or BRCA2 gene. Mahmoud Abeer M et al<sup>41</sup> showed that reduced BRCA1 protein expression was associated with poor prognosis. However, Kush Juneja et al<sup>42</sup> quoted that there is no

association of BRCA1 expression with tumour grade or prognosis. Mavaddat et al<sup>43</sup> observed in a large data set of 4,325 BRCA1 mutation carriers that 78% of the tumours were ER negative and overexpression of HER2 was shown in approximately 10% of the cases and 69% were triple negative and showed poor prognosis.

## 9. Conclusion

In this pragmatic review we focussed on the application of Ki-67 and BRCA1 as diagnostic and prognostic markers in the management of breast cancer. It is crucial to diagnose breast cancer not only on the basis of morphology but also with the help of adjunct markers in view of the different treatment regimens. Precise diagnosis requires application of ancillary techniques such as IHC and molecular diagnosis. Nevertheless, morphology remains the cornerstone in the diagnosis and is helpful in selecting optional immunohistochemical markers and molecular techniques. Breast cancer patients have better disease free survival and fewer relapse rates after the advent of specific IHC panel of markers. Hence panel of markers such as BRCA1 and Ki-67 along with molecular profiling can contribute to better approach of breast cancer patients.

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None.

## 11. Conflict of Interest

The authors declare that there is no conflict of interest.

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### Author biography

**Minnu Sibby**, PG Student

**Bhavani Krishnamurthy**, Professor

**Nafeesa Banu**, Associate Professor

**Sowmya Srinivasan**, Professor & HOD

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