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Commentary

Methylation of *BRCA1* promoter in sporadic breast cancer

The major risk for the development of breast cancer is related to hormonal and genetic factor[1]. The germline mutation is mostly responsible for hereditary breast carcinomas while hormonal factors for sporadic breast carcinomas (SBCs). Oestrogen plays an important role in breast tumour development due to its direct carcinogenetic effect and is also responsible for cellular DNA damage and mutations.

Breast cancer is the most commonly diagnosed malignancy worldwide[2] and a leading causes of cancer death among women[3]. In clinical practice, early diagnosis of breast cancer has a significant role. Currently, various techniques are employed for a breast lump evaluation including sonomammography, fine needle aspiration cytology (FNAC), core biopsy, xeroradiography, thermography, frozen sections, hormonal study, immunohistochemistry (IHC) and molecular diagnosis. For the early detection of breast cancer and its disease progression, there is a requirement of a reliable biomarker.

Various genetic and epigenetic changes in tumour suppressor genes and oncogenes are thought to be responsible for the development of breast cancer. To detect and target such epigenetic changes, various diagnostic methods are required which will be helpful to treat and prevent breast cancers.

Two such breast cancer susceptibility genes are noted by linkage studies, the breast cancer gene 1 (*BRCA1*) located on chromosome 17g12-21 and *BRCA2*, located on 13q12-13. The *BRCA1* is a multifunctional protein involved in DNA repair, control of cell cycle checkpoints, protein ubiquitination and chromatin remodelling. Any changes or mutations in this gene can lead to an increased risk of developing breast, ovarian or prostate cancer. It is a classic tumour suppressor gene that plays a significant role in hereditary breast cancers. It is observed that *BRCA1* gene mutation is commonly associated with familial hereditary breast cancer, however, it is rarely found in SBC[4]. Also reported frequency of *BRCA1* gene mutation is relatively less in men.

About 5-10 per cent of cases of hereditary breast cancer are due to *BRCA1* or *BRCA2* germline mutations. It is responsible for 40-80 per cent lifetime risk of developing breast cancer[5]. With a history of familial *BRCA1* or *BRCA2* gene mutation, there are reportedly 50 per cent chances of having the same gene mutation[6]. The reported incidence is about one in every 500 women in the United States with a mutation in either her *BRCA1* or *BRCA2* gene.

Inactivation of *BRCA1* by promoter hypermethylation is associated with reduced gene copy number and chromosome 17 aneusomy[6]. There is decreased expression of *BRCA1* gene as well as protein in breast cancer as compared to normal mammary epithelial cells. In about 19 per cent of SBCs, both nuclear and cytoplasmic BRCA1 protein loss has been observed[7].

A biomarker for the diagnosis of breast cancer is to study the differences in DNA methylation pattern. The differences between BRCA 1 mRNA expression and promoter methylation are done by quantitative PCR and bisulfite sequencing PCR technics. Methylation within the promoter regions of tumour-suppressor genes typically causes their silencing[8]. It is observed that the multiple factors are involved in the initiation and progression of breast tumours.

The epigenetic alterations of the genome such as DNA promoter methylation and chromatin remodelling play an important role in the early phase of tumourigenesis. The promoter methylation assays serve as pre-screening tests and have been widely employed for breast cancer detection, prognosis as well as in treatment.

Methylation-specific multiplex ligation-dependent probe amplification assay is a recently developed technique for the molecular diagnosis of several genetic diseases and cancers for the detection of abnormal DNA methylation. It is a PCR-based technique that requires minimal amount of DNA, which can be derived from paraffin tissue blocks.

In cancer development of various organs such as ovary, prostate, lung, urogenital and gastric, the breast promoter hypermethylation plays an important role[9]. The hypermethylation of cytosine phosphate guanine sites in the promoter region lead to down regulation of tumour-suppressor genes[10]. This is currently recognized to be a means of providing a silencing alternative to mutation or allelic loss in the cancer progression. The high frequency of hypermethylation in the promoter regions of *BRCA1* and *BRCA2* is observed from 5.2 to 65.2 per cent of cases in SBCs[11]. This difference is related to the selection criterion of control groups, study cohort, mutation detection techniques, detection methods for methylation, sample materials and also geographic variability.

The study by Li *et al*[3] suggested that the absence of BRCA1 transcript is associated with promoter methylation in SBC. Numerous studies have demonstrated the aberrant hypermethylation of *BRCA1* promoter in sporadic breast tumours[12,13]. BRCA1 protein expression correlates with tumour mitotic rate, consistent with normal cell-cycle regulation of the *BRCA1* gene. The *BRCA*1 hypermethylation exhibited a higher percentage of the smaller size primary tumour (T1 and T2, tumour size ≤5 cm) compared to the *BRCA1* non-methylation (58.1 *vs*. 49.1%)[3]. *BRCA1* promoter methylation, its relationship to gene expression profiles and immunohistochemical status are also studied in breast cancer. Khan *et al*[14] in their study published in this issue of *Ind J Med Res* have made efforts to analyze and understand the possible roles of *BRCA1* promoter methylation and its IHC correlation in SBC.

Matros *et al*[15], stated that there might be different BRCA1 promoter methylation levels and patterns in sporadic and hereditary breast cancer. They noted a subgroup of ER-positive high grade tumours that have a significantly greater number of *BRCA1* methylated tumours.

Zhang and Long[16] showed that *BRCA1* promoter methylation was higher in cases of breast cancers. There was an association of *BRCA1* methylation with various factors such as higher tumour grades, oestrogen receptor (ER) negative, progesterone receptor (PR) negative and triple-negative breast cancer (TNBC). While other studies did not find a significant association between *BRCA1* hypermethylation and ER/PR status[16,17].

Khan *et al*[14] recommend that females with SBC especially TNBC, must be advised BRCA1 IHC scoring to identify the cases which may benefit from the above chemotherapy. Multiple reasons have been stated behind the differential IHC expression and molecular results. The molecular alterations could either be methylation silencing, deletion or point mutation. *BRCA1*-mutated tumours have a specific pattern of genomic alteration that can be observed in patients with *BRCA1*-gene methylation and some other TNBC. TNBC is regarded as important because of the aggressive clinical behaviour, poor prognosis and lack of targeted therapy thus UNBC remains an important challenge in today's clinical practice[18,19]. *BRCAl* promoter hypermethylation is associated with a good prognosis and chemosensitivity in TNBC. When treating breast cancer patients with chemotherapy *BRCA1* methylation is an important predictive factor to look for chemosensitivity and response to treatment.

BRCA1 loss identification in SBC can make it an ideal patient for poly adenosine diphosphate ribose polymerase (PARP) inhibitors or cisplatin-based therapy like hereditary ones[14]. In future, there should be standard protocol for the diagnosis of breast cancer, specific detection methods of methylation and an approach to novel-targeted therapy. In breast cancer, aberrant epigenetic modifications are potentially reversible, so it can be used as targeted therapy.

To conclude that the *BRCA1* promoter methylation will be a useful predictive or diagnostic biomarker for patients with breast cancer and it has clinical significance in evaluation. *BRCA1* promoter methylation was found to be associated with an increased risk of breast cancer by Khan *et al*[14], however, large-scale research in this area is required to extrapolate their findings.

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