MOLECULAR STUDIES ON THE *BRCA1* GENE IN BREAST CANCER

Scholor
Suresh Hedau

Supervisor
Prof. Syed Akhtar Husain
Department of Biosciences
Jamia Millia Islamia
New Delhi-25

Co-Supervisor
Dr. B.C. Das,
Sr. Deputy Director & Chief
Divison of Molecular Oncology
Institute of Cytology & Preventive Oncology (ICMR)
Maulana Azad Medical College Campus,
New Delhi-110002

In India, breast cancer is the second most common cancer in women after the cancer of the uterine cervix except in Mumbai and Delhi where it is the leading cancer. The development of breast carcinoma has been associated with several well-recognized epidemiological risk factors such as early menarche and late menopause, family history, dietary, environmental factor and genetic factors. Of several genes that have been implicated in the genetics of breast cancer, mutations in breast cancer susceptibility genes,*BRCA1* and *BRCA2* have been shown to account for more than 80% of hereditary breast and ovarian cancers. Also, *p53* tumor suppressor gene that controls cellular growth and differentiation known to be mutated in more than 50% of human cancers including breast cancer. We have carried out a study on *BRCA1* and *p53* gene mutations in both sporadic as well as familial breast cancer patients from India where breast cancer is fast emerging as a major cancer among premenopausal urban women. The expression of the *BRCA1*gene at both RNA and protein level has been studied in sporadic breast cancer and correlated with the methylation status of the *BRCA1* gene promoter.

A total of 129 untreated primary breast cancer patients comprising 105 sporadic and 24 familial breast cancer cases including 35 age-matched healthy controls were examined for the presence of *BRCA1* and *p53* gene mutation using PCR-SSCP and direct DNA sequencing. The frequently mutated exons such as 2, 5, 11, 13 and 20 of the *BRCA1* gene and exons 5 and 7 of *p53* gene were analyzed in sporadic breast cancer while all 22 coding exons of *BRCA1* gene were analyzed in familial breast cancer patients. Few of the common*BRCA1* gene mutation in different populations are *185delAG* in exon 2 and *5382insC* in exon 20 commonly found in Ashkenazi Jewish; similarly *2803delAA* in exon 11 in Dutch population and *Cys61Gly* in exon 5 in American

population. We identified six patients (25%) with *BRCA1* mutation of which three were found to be of novel type one in exon 16 (57655insG) and two in exon 7 (Lys110Thr) (Ser114Pro) out of 24 familial breast cancer patients studied from two different geographic regions/populations of India. Two sisters from single family (12.5%) out of a 8 families from Goa with Portuguese colonial origin showed presence of founder Ashkenazi Jewish *BRCA1* mutation (185delAG) while from New Delhi, four (25%) of 16 breast cancer families showed *BRCA1* mutations; a frame shift protein truncating (57655insG), a transition nonsense (Gln1395Stop) and two amino acid substitutions (Lys110Thr) and (Ser114Pro). Only one (4%) *p53* mutation (Val97Ile) in its exon 4 along with *BRCA1* mutation (57655insG) could be detected. None of the 105 sporadic breast cancer patients revealed any protein truncating or deleterious *BRCA1* gene mutation. Interestingly, three (2.85%) *p53* mutation in its exon 5 were detected in sporadic breast cancer patients. Although three novel *BRCA1* mutations including a founder Ashkenazi Jewish *BRCA1* mutation were recorded in Indian women with familial breast cancer, the overall prevalence of *BRCA1* gene mutations in Indian women with a family history of breast cancer appears to be low.

Low expression of *BRCA1* mRNA transcripts (51%) and protein (50%) was observed in sporadic breast carcinoma and this could be due to an aberrant cytosine methylation in the promoter region of the *BRCA1* gene. But only 20% of the cases showed hypermethylation of the *BRCA1* gene. In majority of the cases where hypermethylation of *BRCA1* promoter is absent or reduced *BRCA1* mRNA and protein expression might be attributed to modifications at transcriptional or post translation level.

It is therefore appears that neither *BRCA1* mutation nor *p53* mutation or their level of expression play major role in at least sporadic breast carcinogenesis, if not in familial breast carcinogenesis.