Name of the Candidate: KAPIL DEV

Supervisor: Dr. M. Ejaz Hussain, Director & *Professor*, Centre for Physiotherapy & Rehabilitation Sciences, Jamia Millia Islamia, New Delhi.

Co-Supervisor: Dr. A. K. Mandal**,** *Professor,* Department of Pathology, M.A.M.C., New Delhi.

Centre: Centre for Physiotherapy & Rehabilitation Sciences, Jamia Millia Islamia, New Delhi

Title: "Immunohistochemical and molecular studies of apoptotic regulators (Bcl-2, Bax) and Her -2/neu oncogene in Breast cancer".

ABSTRACT

The present retrospective study was conducted in the Department of Pathology, Maulana Azad Medical College, New Delhi and Centre for Physiotherapy and Rehabilitation Sciences, Jamia Millia Islamia, New Delhi. All the diagnosed cases of carcinoma of breast which came to the Department of Surgery at Lok Nayak Jai Prakash Hospital, New Delhi for treatment were selected. Here all the specimens were processed and paraffin blocks were prepared for histological examination. The required tissue sample for the presents study was retrieved from those paraffin blocks, which were prepared from Primary breast tumor site only those cases, which were diagnosed as infiltrating ductal carcinoma, not otherwise specified (IDC, NOS) were included in the study. Finally a total of 165 cases were selected, which fulfill all the relevant selection criteria. Tissue sample from these cases were used for the Immunohistochemical and molecular studies of apoptotic regulators (Bcl-2 and Bax) and proto-oncogene Her-2/*neu*. For comparision 150 pre malignant lesions cases of the breast tissue were used as control for both Immunohistochemical stain as well as for molecular study. The study was conducted to find the association between apoptotic regulators (Bcl-2, Bax) and oncogene Her-2/neu with breast carcinoma in Indian population. All the cases were evaluated for immunohistochemical expression of apoptotic regulators (Bcl-2, Bax) and oncogene Her-2/ neu as well as their mutational status /polymorphism of these genes by RFLP. Cases in our study had age range between 18 years and 73 years. The mean and median age of breast cancer was 48.69 years and 48 years respectively with peak prevalence rate in the age group of 45 years to 60 years. Over all expression of apoptotic regulators (Bcl-2, Bax) and oncogene Her-2/new was 58.78%, 29.09% and 46.66% respectively. Bcl-2 was found

to inversely correlate with histological differentiation of cancer while Her-2/neu was positively correlated with grade. Bax on the other have showed variable expression. The age wise expression was also random. Further the expression of these genes was correlated with each other. The two apoptotic regulator (Bcl-2 and Bax) were inversely correlated, which support the mechanism of cell cycle regulation by these apoptotic regulators forming Bcl-2 and Bax heterodimer. Few studies have even proposed greater role for Bax than Bcl-2 in cell cycle regulation and hence, an important prognostic marker for breast carcinoma. Bcl-2 was inversely correlated with Her-2/neu expression while Bax showed linear correlation with Her-2/neu expression. Bcl-2 and Her-2/neu correlation was statistically significant while Bax and Her-2/neu correlation was insignificant. Correlation of apoptotic regulators (Bcl-2 and Bax) and oncogene Her2/neu give the possibility for role of Bcl-2 in breast cancer therapy. However, it will require bigger study on large number of cases at molecular level. Analysis of SNP polymorphism in *HER2/neu* showed significant association between particular type of genotype and breast cancer. Genotypes like Val (G) allele genotype (AG+GG), Ile/ Val (AG) and Val/Val (GG) showed significant difference between case and control group, thus, predicting significant implication in pathophysiology of break carcinoma risk. On the other hand, analysis of mutation/polymorphism in *BCL2* and *BAX* gene did not yield significant difference in case and control groups. Various genotypes of HER2, BCL2 and BAX were noted for their prevalence in different histological grades as well as correlated with immunohistochemical expression of these regulator proteins. However, because of small sample size no conclusive and significant correlation could be found. Thus, if we have to study the exact risk of breast carcinoma in Indian population we need to know prevalence of various genotypes of main culprit genes involved in breast carcinoma in our population. The contribution of genetic polymorphisms to the risk of breast cancer may be dependent on the population being studied, as well as on several environmental and diet factors that influence that population. Based on the present study findings, we suggest that each population has to evaluate its own genetic profile for cancer risk that may help us to understand the geographic and racial differences reported for breast cancer incidence and mortality.