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Novel hyper methylated miRNA genes and its potential targets in breast cancer

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Epigenetic mechanisms including DNA methylation and interaction between miRNAs and mRNAs are the most dynamic mechanisms of genes deregulation in cancer. The aim of the study was to identify novel miRNA genes, regulated by DNA methylation, and target genes involved in the apoptosis, in breast cancer (BC). We used 58 paired (tumor/normal) BC samples, methylation-specific PCR, and quantitative PCR. Algorithms *of miR*Walk 2.0 database and the IBM SPSS statistics base 20 software package were used. We observed hyper methylation of 9 miRNA genes, and for the first time – *of MIR-127, -132, -1258* and *-193a*, and hypo-methylation *of MIR-191*. Using qPCR, we established a strong correlation between promoter methylation and expression levels for 10 miRNA genes, demonstrating the functional importance of altered methylation patterns. A strong association between hyper methylation *of MIR*-127 and *MIR-125b-1* and BC progression, particularly metastasis was found. The negative correlations were revealed between expression level alterations of 3 genes and 6 potential regulatory miRNAs for the following pairs: *BCL2* – miR-124-3p, -212-3p, -24.2-5p; *DAPK1–miR-127*-5p, miR-9; *RASSF1 (A)*–miR-375 (Rs=-0.43 - -0.32, $p \leq 0.01$, $p \leq 0.05$). The results of transfection of MCF7 cell line with miR-124-3p duplex oligonucleotide analogues strengthened the hypothesis on the direct or indirect interaction of this miRNA with mRNA of the *BCL2* gene. Thus, novel hyper methylated miRNA genes and potential interactions of *DAPK1*, *BCL2*, and *RASSF1 (A)* mRNAs with a number *of miR*NAs were identified that could be useful as markers and potential targets in combined BC therapy.

Biography

Eleonora A Braga has completed her PhD at Lomonosov Moscow State University, Bioorganic Chemistry Department. She has taken part in Russian Human Genome Project and HUGO. She was an Invited Principle Investigator at Karolinska Institute (Stockholm, Sweden, 1999-2000). She has completed her full Dr. of Biology Sc. at Engelhardt Institute of Molecular Biology in 2007. She is a head of Laboratory of Pathogenomics and Transcriptomics at Institute of General Pathology and Pathophysiology, Moscow, Russia. She has published more than 70 papers in reputed Journals.

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Role of PI3K/AKT-signaling pathway in triple-negative breast cancer

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Breast cancer accounts for 23% of all new tumor cases and it is the most common cancer among women worldwide. A high percentage (15-25% of all breast cancer cases) is characterized as triple-negative breast cancer (TNBC). Although triple-negative cancers are sensitive to chemotherapy, survival of patients with these tumors is poor. Lack of effective therapies, younger age at onset and early metastatic spread have contributed to the poor prognosis and outcomes associated with TNBC. The phosphatidylinositol 3-kinase (PI3K)/ AKT-pathway plays a critical role in malignant transformation of tumors and their subsequent growth, proliferation and metastasis as well as in activation of pathways that result in immune-escape mechanisms. Therefore, the PI3K/AKT pathway is considered an attractive candidate for therapeutic interventions. We used a modified FATAL assay as an *in-vitro* system to investigate the interaction between TNBC cell lines and natural killer (NK)-cells. Furthermore we explored the ability of PI3K/AKT inhibition with AEZS-126 to selectively target TNBC cell proliferation and survival. In parallel we analyzed mechanisms of cytotoxicity related to PI3K/AKT inhibition. Our results show that TNBC cells (MDA-MB468, HCC1806, HCC1937) can stimulate the NK-cell immune response significantly stronger than estrogen-receptor (ER)-positive breast cancer cells (MCF-7). These findings could explain the increased presence of immunosuppressive Tregs infiltrate in human specimens of TNBC compared to ER-positive breast cancer tissue. AEZS-126 showed good anti-tumor activity in *in-vitro* models of TNBC as well as in MCF-7 cells. Main mechanism of cytotoxicity seems to be programmed cell death, which could be abrogated by co-incubation with z-VAD-fmk in MCF-7 and MDA-MB468 cells. In HCC1806 cells, addition of necrostatin-1 has only slightly protective effects, but in HCC1937 cells, the addition of necrostatin-1 has the same protective effect as co-incubation with z-VAD-fmk, and this observation argues for cell death caused by apoptosis and necroptosis in this cell line.

Biography

J C Hahne is currently working for The institute of Cancer Research, Russia. He has several publications in the reputed journals.

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Soft silicone film prevents radiation-induced moist desquamation

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Aim: We previously showed that soft silicone dressings used in a management setting decreased the severity of radiation-induced acute skin reactions in breast cancer patients by 40% but did not affect moist desquamation rates. Here we investigated whether the prophylactic use of a transparent soft silicone film would decrease moist desquamation rates.

Method: Datasets of 78 breast cancer patients receiving radiation therapy, recruited between October 2012 and April 2013 in one department, were analyzed. Patient acted as their own controls to circumvent potentially confounding treatment and patient related factors. Lateral and medial halves of the skin areas to be irradiated were randomized to silicone film or aqueous cream; the film was applied by the radiation therapist and stayed in place for 1 or 2 weeks, aqueous cream was applied by the patient twice a day. Skin dose was determined by thermo luminescent dosimeters. Skin reaction severity was assessed using RISRAS and RTOG scales.

Results/Discussion: RISRAS analysis showed that the silicone film reduced overall skin reaction severity by 92% ($p<0.0001$). All patients developed some form of reaction in cream-treated skin which progressed to moist desquamation in 26% of patients (RTOG grades I: 28%; IIA: 46%; IIB: 18%; III: 8%). Only 44% of patients had a skin reaction under the film, which did not progress to moist desquamation in any of the patients (RTOG grades I: 36%; IIA: 8%).

Conclusion: Soft silicone film completely prevented moist desquamation from developing and reduced skin reaction severity by 92% when used prophylactically in this cohort.

Biography

Herst has been employed by the University of Otago since 2001 and divides her time between undergraduate and postgraduate teaching, preclinical and clinical research. She has been a committee member of the Health and Disability Ethics Committee (HDEC) since 2012. Herst has been a visiting scientist at the Malaghan Institute since completion of her PhD in 2006. There, she conducts research into drug resistance of highly aggressive cancer cells in collaboration with Professor Mike Berridge. Her most recent research, in close collaboration with Dr McConnell at the University of Victoria, Wellington. She has conducted randomized controlled clinical trials in NZ hospitals that investigate management of radiation-induced side effects since 2008. To date 5 trials (3 skin trials, one cystitis trial and one oral mucositis trial) have been completed, analysed and published

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Epistemology of indigenous healing practice: A micro sociological perspective

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Every year, countless women will be diagnosed and treated for breast cancer, most of whom will require surgery. A clean margin around the cancer site is the only prognostic factor that a surgeon can control in order to reduce local recurrence. Having an accurate method of assessing margin status is imperative not only for better oncologic outcomes for the patient, but also to prevent unnecessary additional surgeries for re-excision, additional emotional distress for patients, delays in subsequent adjuvant therapy for breast cancer, and associated additional health care costs. There are two commonly used techniques that surgeons use to orient breast specimens for the pathologists: Intra-operative labeling of the margins with sutures and intra-operative inking of the margins. Using a creative, a novel 3D technique, we demonstrate the results of the world's first prospective clinical trial that evaluates the accuracy of both techniques on the same lumpectomy specimen, in a blinded fashion, using with the aim of identifying the most accurate method of specimen orientation. The results of this trial are practice-changing with significant implications for patient safety and health care costs. This study will form the foundation for unifying breast cancer surgeons and pathologists on best practices for accurate specimen orientation and improved patient outcomes. Findings from the study can be extrapolated to the pathological assessment of other surgical resect able cancer types in which margin status is a quality indicator. At the end of the presentation, the audience should: 1) Understand the pitfalls of commonly used specimen orientation techniques 2) understand the importance of accurate specimen orientation and 3) work together with the breast pathologists and surgeons to identify best practices for specimen orientation for cancers.

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The pathological profile of Saudi females with palpable breast lumps: knowledge that guides practice

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While the incidence of breast cancer (BCa) shows less geographic variability than many other malignancies such as prostate cancer, the biologic behavior is, however, different. Many local studies have documented the earlier age of onset in Arab females and a more advanced stage at the time of diagnosis. Therefore, we planned to determine the spectrum of pathologies of palpable breast lumps in Saudi females and their significance in different age groups. This knowledge is crucial for modifications in the current screening programs, which is adopted from the international guidelines. All needle biopsies for the complaint of breast mass felt by the female patients were retrospectively included over 4 years. Fisher exact test was used to determine the age of significant cancer risk. Out of 140 cases met the inclusion criteria, 110 were BCa. The median age of BCa was 46 years. There was 68% positivity for BCa in cases belong to females below 40 years, and 75% in patients aged younger than 50 years. The age of 40 year-old show significant cancer risk. The results showed that almost 4 out of 5 females with palpable breast lumps subjected to needle biopsy had BCa. Although this risk is higher with increased age, BCa is a disease of young in the population under study. Review of the current preventive and management measures is critically needed in our nation. Besides, it is advisable to customize the screening age for each country.

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Locoregional surgery in metastatic breast cancer

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Background: A current guidelines do not recommend locoregional surgery for metastatic breast cancer at presentation despite some studies suggesting a survival benefits. We aimed to assess outcomes in patients with metastatic breast cancer who underwent surgery.

Methods: In a cohort study of all metastatic breast cancer diagnosed at single institution between 2000 and 2012, we assessed patient survival in the context of demographics, clinical and histopathology characteristics, metastatic burden, and type of surgery performed.

Results: 678 patients with metastatic breast cancer were included, 412 (60.77%) underwent surgery for primary tumor, with a median follow-up of 41 months. Patients in the surgery group had longer survival (3.1 vs. 1.9 years, P<0.0001). The surgery group had longer survival (41 versus 27months, p<0.0029). The 5 year survival rate for surgery group was 34% compared with 14% for the nonsurgery group. A multivariate analysis revealed surgery (p=0.0003), large tumor size (p=0.0195), ER positive (p<0.0001), and metastasis at presentation (p=0.0032) were prognostic variables.

Conclusions: Locoregional surgery does confer a survival advantage in stage iv breast cancer.

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MicroRNAs expression profiles as novel biomarkers for the diagnosis, prognosis of breast cancer

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MicroRNAs (miRNAs) are short, non-coding RNA molecules of 19-25 nt, involved in a wide array of physiological and pathological processes by modulating the expression of their cognate target genes through cleaving mRNA molecules or inhibiting their translation. In cancer, microRNAs can act as oncogenes or tumor suppressor genes. Oncogenic miRNAs may be amplified, resulting in increased expression of the oncomir. Tumor-suppressive miRNAs could reside in chromosome fragile sites characterized by deletions or mutations, leading to reduced levels of these miRNAs. Some miRNAs are emerging as a novel class of potential biomarkers for early breast cancer (BC) diagnosis, prognosis, and prediction of therapeutic outcomes. MiRNAs are of interest as easily accessible, affordable, non-invasive tools for the management of patients with BC. MicroRNA expression signature appears to provide a better characterization of cancer subtypes than gene expression profiling and may represent a new classification system for breast cancer. Abnormal microRNA expression patterns are closely related to specific tumor stages, lymph node, steps of the metastasis cascade, poor survival, disease outcomes and responses to specific therapies in many types of cancer. MicroRNA profiling has been assessed to differentiate patients with BC as responding or not responding to therapies. MicroRNA deregulation in the development of BC in several tissues and lineages, have correlated miRNA profiles with mRNA subtypes. In this review, the potential value of these microRNAs as diagnostic and prognostic markers, and the possible development of microRNA-based therapies will be assessed.

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Breast cancer: Prevalence and public education in the Kingdom of Saudi Arabia

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Breast cancer is a leading cause of death amongst women worldwide. Advanced diagnostic and therapeutic techniques may reduce the mortality rate due to breast cancer. The major problem is that patients arrive for diagnosis at a late stage, when the disease has already spread. Early checking of the breast conditions, especially for women with history of breast cancer in the family is vital. Breast self-examinations and breast screening programs may help detecting cancer at early stages, and thus reduce the need for aggressive therapies. Public awareness and education plays a key role. Early diagnosis of breast cancer may save the lives of many women. This requires public education and awareness and outreach for rural areas. The Eastern province is playing a leading role to reach and educate women and have programs such as Pink Eastern province, so it won't be discovered later in addition to mobile screening facilities that are provided to women in areas of accumulation such as malls; with a goal to reduce the mortality rate from breast cancer. Regular visits and public lectures in schools and religious areas could also facilitate in educating women about that. Women should understand that breast cancer is not a curse, nor is it the end of the world as many might think. This is also an important issue to address during the awareness programs. A team of volunteers from different disciplines, educational levels and geographic areas are collaborating to reach the goals for a pink Eastern province with the help and support of the health authorities. Some of the activities carried out in different regions in the eastern province will be presented.

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Colored computer aided diagnosis system for breast mammography

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Breast Cancer is the most common and life threatening cancer among women. Mammography is a key screening tool for breast abnormalities detection. It is an effective way that has demonstrated the ability to detect breast cancer at early stages, because it allows identification of tumor before being palpable. Radiologists may miss the breast abnormality due to the textural variation of breast tissues intensity in mammogram. So, radiologists may result in false-positive or false-negative results. Efforts in developing the Computer Aided Detection/Diagnosis (CAD) systems for mammogram analysis improve the diagnostic accuracy by radiologists. This study developed an algorithm to read mammograms automatically with colors. It proposed the use of discrete wavelet decomposition technique using Symlet wavelet as a feature extraction, and the linear discriminant analysis (LDA) as a classifier in order to discriminate the extracted features to find out this detection. The algorithm achieved 98.8% accuracy, 95.0% sensitivity in breast tissue classification. This accuracy has been verified with the ground truth given in the mini-MIAS database. So, this algorithm will help radiologists for a true diagnosis and decrease the number of the missing cancerous regions or unnecessary biopsies which are very stressful for women, it can help in early detection of breast cancer, and following treatment can significantly improve the chance of survival for patients with breast cancer. So, it will save women lives.

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A novel handheld diffuse optical breast cancer imaging probe

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Diffuse optical spectroscopy (DOS) and diffuse optical imaging (DOI) are relatively new methods for breast cancer diagnosis which are noninvasive and nonionizing techniques. In the present study, we have introduced a novel handheld diffuse optical breast scanning (DOB-Scan) probe to measure optical properties of breast tissue and create functional and compositional cross-sectional images of the breast. Four near-infrared wavelengths light emitting diodes (LED), encapsulated in a package (eLED), are used to illuminate the breast tissue. A linear charge coupled device (CCD) measures the intensity of the scattered photons at different radial destinations from the illumination source on the surface of the breast tissue. The proposed method replaces fiber optic based illumination techniques, which increases the complexity, size and cost of a potential probe, by multi-wavelengths eLED which acts as a pencil beam source in such a scattering media like the breast tissue. Although the introduced technique miniaturizes the probe, this study points to the reliability and accuracy of this technique in breast imaging. The average scattering coefficient of the medium and localized concentration variations in oxyhemoglobin and deoxyhemoglobin can be measured utilizing the probe. In order to evaluate the performance of DOB-scan probe, a series of tissue-like materials, containing of Intralipid®, Black ink, Delrin®, and PierceTM have been used. We have received ethical approvals to test the DOB-scan probe on patients who are known with breast cancer and we are currently testing the DOB-scan probe on real subjects.

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Nucleostemin immunohistochemical expression is associated with more aggressive phenotypes of invasive breast cancer

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Cancer stem cells (CSCs) are postulated to play significant role in the pathogenesis and progression of breast cancer, among several other cancers, and might contribute to resistance to chemotherapy and/or radiotherapy. Nucleostemin (NS) is thought to be a key molecule for stemness, and the clinical impact of NS immunoreactivity in breast cancer can indicate its actual role and future therapeutic potentials. In the current study, NS immunohistochemistry was performed on purchased TMA sections of 102 patients in addition to a series of 50 archival specimens of invasive breast cancer diagnosed in Al Baraha Hospital, Dubai, UAE. Ns expression was predominantly exhibited in patients <50 years (p=0.047), in infiltrating duct carcinoma, tumors >2 cm (74.8%) (P=0.0005), those with lymph node metastasis (79%) (p=0.018) and stage III tumors (83%) (p=0.0004). Notably, NS expression was significantly correlated to ER negative (75%) and P53 positive (78%) status. Moreover, HER2 – enriched tumors significantly displayed the highest NS expression, followed by TNBC, Luminal B and Luminal A (80%, 73%, 60% and 51% respectively) (p=0.048). In conclusion, the significant correlation between NS expression and the more aggressive clinicopathological attributes of invasive breast cancer implies that NS may be a potential target for CSC-associated breast cancer management.

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Promoter region polymorphisms in *IL-6* and *IL-10* genes can lead to pathogenesis of breast cancer

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This study investigated polymorphisms in the promoter regions of *IL-6* (-174 G>C) and IL-10 (-1082 G>A) genes through a case-control study. Features like the expression of estrogen and progesterone receptors, involvement of the lymph node, tumor morphology and tumor grades were observed, for the patient group. For the *IL-6*-174G>C polymorphism, there was significantly higher frequency of C/C genotype in the patients. Further, the C/C genotype was significantly more prevalent among the patients who had lymph node involvement. For the IL-10-1082G>A polymorphism, there was no difference in the distribution of genotypes among the patients and control subjects.

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Cardiac toxicity after radiotherapy for breast cancer: a cardiovascular update

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Radiotherapy (RT) in the treatment of breast cancer uses ionizing radiation to kill malignant cells. Radiation treatment following breast cancer surgery-breast conserving surgery (BCS) or mastectomy-is associated with significant improvement in locoregional control. However, the beneficial effects of RT in reducing breast cancer death and recurrence are offset by the increased risk of cardiac toxicity. Radiation-induced cardiac toxicity is a well-documented sequela of radiation treatment that can occur immediately, or manifest months or years after completion of radiation therapy. The damaging effects to any structure of the heart, including the pericardium, vasculature, myocardium, valves, and conduction system depends on total dose of radiation received by the heart, volume of the heart exposed, and radiation technique used. Another factor that potentiates the risk of cardiac toxicity is whether patients are receiving RT for left-sided breast cancer vs. those receiving RT for right-sided tumors. The damaging effects include: acute and chronic pericarditis, pericardial effusion, constrictive pericarditis, coronary artery disease, cardiomyopathy, valvular heart disease, conduction system abnormalities, etc. Techniques to limit radiation exposure such as image-guided therapy; 3-dimensional treatment planning; respiratory gating; and intensity modulated RT, enables the selection of the most optimum treatment method when planning and administering RT. However, understanding patients' risk of an event and stratifying patients according to cardiovascular risk for these events would be useful in identifying those patients most likely to benefit from management plans, as well as strategies to reduce cardiotoxicity.

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MiR-10b, miR-133a, miR-155 and miR-639 as non-invasive potential biomarkers in breast cancer

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Background: Among women, the second leading cause of death worldwide is the breast cancer (BC). MicroRNAs (miRNAs) expression participates in breast cancer.

Objectives: The purpose of this study is to investigate the expression of miRNA-10b, miR-133a, miR-155 and miR-639 in breast cancer and study their correlation with clinicopathological features and tumor suppressor protein (p53) concentration.

Material & Methods: The four miRNAs levels were measured in serum using quantitative real-time PCR (QRT-PCR) and (p53) concentration by enzyme-linked immunosorbent assays (ELISA) in women with breast cancer (n=60) and healthy controls (n=80).

Results: In this study miRNA-10b, miRNA-155, and miRNA-639 were overexpressed while miR-133a had down expression in the serum of breast cancer patients compared to control serum. P53 had no significant correlation with any of the studied miRNAs. A significant association was observed between miR-10b and human epidermal growth factor-2 (HER-2) (P=0.046), miR-155 with lymph node involvement (P=0.05), and between miR-133a and tumor grade (P=0.039).

Conclusion: These miRNAs have a significant signature in the pathogenesis of breast cancer and can be used as non-invasive molecular biomarkers for breast cancer detection.

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Cancer stem cells as new targets for tumor treatment

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Cancer stem cells (CSCs) are a small population of tumorigenic cancer cells which are considered as beginners for cancers. We conducted a systematic review article by surfing the PubMed and Scopus data bases, and found 16 articles from 2000 to 2017. Few articles are published about CSCs in oral squamous cell carcinoma, but similar to other tumors, these cells are able to self-renew and differentiate by cell division. Studies showed that they play role in metastasis, therapies resistance and recurrences through expression of different markers. Rapid tumor growth and weak prognosis have been related to the presence of CSCs. Helen H. Yu et al. noted three subpopulations in SCC. One CSC group exists in the tumor nests, the second group in the stroma between tumoral nests, and the third group in the endothelium of stromal vessels. Some studies focused on the mediators and cytokines produced by CSCs. Kelsey A. et al. showed that IL-6 is secreted by the third subpopulation named above, and induces the effect of Cisplatin, therefore increases the tumorigenic potential of head and neck CSCs. Moreover high serum levels of this cytokine have been correlated with patient's poor survival. It is assumed that discovering the characteristics of CSCs in tumors would be a goal for better, more precise and targeted cancer treatments.

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Immunohistochemical analysis of *p53* protein expression in Indian female breast cancer cases: Correlation with clinico-pathological variables

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Breast cancer has been defined as the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012. We did *p53* protein expression study through immunohistochemistry in 105 cases breast cancer cases from India. The study was attempted to improve the prognostic and predictive value of *p53* in breast cancer. Prior informed consent and ethical approval was obtained form Rajiv Gandhi Cancer Hospital and Research Centre, New Delhi, India. All patients and normal controls were subjected immunohistochemistry using *p53* gene antibody to check the expression level of *p53* protein in paraffin embedded tissue slides of 4mm thickness. All non-neoplastic cases showed no expression for *p53*. In the tumor samples, immunohistochemical scoring was done as low or no expression (+), moderate expression (++) and high expression (+++). So, out of 105 cases studied, 26 cases (26/105, 24.80%) had low (+) or no expression of *p53* protein, 50 cases (50/105, 47.60%) had moderate (++) expression and 29 cases (29/105, 27.60%) had high (+++) expression of *p53* protein. In our study sample, we were not able to find any significant association between *p53* gene expression and the clinico pathological variables like age, nodal status, tumor stage, menopausal status, ER status, HER 2 status and histological grade. Our study did provide the information on the evaluation of *p53* significance in cancer cases from India and larger population based study will be needed to show the presence or absence of the biomarker property of *p53* in breast cancer.

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