

BRCA1/2 mutations). Interestingly, Chechen BRCA1 c.3629_3630delAG allele was not observed among patients of Ingush ethnicity, despite these nations are believed to have common Nakh (Vainakh) roots. In Ingush patients, there were two recurrent alleles in the BRCA2 gene (c.5351dupA: 5 out 13 BRCA1/2 mutations; L1686X: 3 out 13 mutations). BRCA2 Q3299X mutation was repeatedly observed across several ethnic groups. OC patients from Kabardino-Balkaria had unusually high frequency of germ-line ATM truncating alleles (3/49, 6%); all 3 ATM mutations were represented by distinct ATM pathogenic variants.

Conclusion Genetic analysis of non-selected ovarian cancer patients is highly efficient in revealing ethnicity-specific BRCA1/2 mutations. Contribution of BRCA1/2 pathogenic alleles in OC and BC morbidity is high across various ethnic groups. Founder BRCA1/2 alleles are characteristic for some but not all North Caucasus nations.

2022-RA-1360-ESGO CIRCULATORY HMGB-1 AS A PLAUSIBLE DIAGNOSTIC MARKER IN LIQUID BIOPSY OF CERVICAL CANCER

¹Alpana Sharma, ¹Nidhi Gupta, ¹Rehan Khan, ²Manoj Sharma. ¹Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, India; ²Department of Radiation Oncology, Delhi State Cancer Institute, Delhi, India

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Introduction/Background Cervical cancer (CaCx) is one of the common malignancies in women worldwide. Autophagy is a significant hallmark of cancer wherein high mobility group box 1 (HMGB-1) plays a crucial role. Aberrant expression of HMGB-1 is associated with tumor development, progression and poor prognosis. There are no reports available studying HMGB-1, autophagy related molecule in context to clinical significance in cancer cervix. Thus, we aim to investigate the association between HMGB-1 and its associated molecules (RAGE, p53 & p62) in CaCx. We have also evaluated the clinical significance of serum HMGB-1 in CaCx diagnosis.

Methodology 50 subjects including 20 CaCx patients, 20 healthy women and 10 controls having gynecological disorder other than malignancy were recruited. Circulatory levels of HMGB-1 were measured by ELISA. mRNA and protein levels of HMGB-1 and its associated molecules were quantitated using Q-PCR and western blotting respectively in tissues of study subjects. The data obtained were then validated *in vitro* by siRNA-based silencing of HMGB-1. Data was statistically analyzed and ROC curve was plotted.

Results Circulatory levels of HMGB-1 were significantly higher in patients as compared to controls. mRNA and protein expression of HMGB-1 were significantly higher in tumor tissues. The levels of RAGE, p53 and p62 were also significantly altered than their expression in controls at mRNA and protein levels. ROC curve analysis showed better sensitivity and specificity for HMGB-1 for non-invasive diagnosis of CaCx in liquid biopsy. Furthermore, siRNA-mediated targeting of HMGB-1 significantly altered expression of associated molecules, thus, validating the patients' data.

Conclusion HMGB-1 level could be a useful marker for evaluating disease and diagnosis in non-invasive liquid biopsy. Autophagy mediated HMGB-1/RAGE pathway might play a significant role in pathogenesis of CaCx. Validation in larger patient cohort might exploit HMGB-1 as a novel non-invasive diagnostic marker for CaCx in liquid biopsy in future.

2022-RA-1446-ESGO COMPREHENSIVE ASSESSMENT OF GENE MUTATIONS REVEALED OVERLAPPING DEPENDENCIES FOR PARPI AND CHEMOTHERAPY RESPONSE IN OVARIAN CANCER

¹Alessandra Tozzi, ²Muriel Disler, ²Ricardo Coelho, ²Flavio Lombardo, ²Andre Fedier, ²Monica Nunez Lopez, ²Florian Freuler, ²Francis Jacob, ¹Viola Heinzelmann-Schwarz. ¹Hospital for Women, University Hospital of Basel, Basel, Switzerland; ²Ovarian Cancer Research, Department of Biomedicine, Basel, Switzerland

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Introduction/Background PARP inhibitors (PARPi) have revolutionized the therapeutic landscape of epithelial ovarian cancer (EOC) prolonging the progression-free survival, especially in BRCA1/2 mutations carriers or in patients with defects in homologous recombination (HR) repair. However, it remains uncertain which PARPi to apply and how to select responders using clinical and molecular characteristics, especially in forefront therapy when platinum sensitivity is still unknown.

Methodology We selected 33 promising genes that showed a prediction of enhanced PARPi sensitivity after a systematic literature review and the exploration of publicly available CRISPR-Cas9 library screens and Genomics of Drug Sensitivity in Cancer data. We performed functional assessment in six constitutively Cas9 expressing OC cell lines and subsequent examined our set of genes using a CRISPR-Cas9 mutagenesis assay with various PARPi and carboplatin.

Results Our functional screen identified ten novel potential PARPi response biomarkers, with different impact on cell fitness and drug response. ATM was the only gene that produced an enhanced olaparib sensitivity in all the cell lines. Acquired olaparib sensitivity was also observed for MUS81, NBN, RAD51B/C, RNASEH2A, PALB2, XRCC1, and XRCC3 in at least 3 cell lines. CDK12 was identified as an essential gene in all the cell lines tested without altering the response to Olaparib. Since the best clinical biomarker of PARPi sensitivity remains the sensitivity to chemotherapy, we next compared dropout rates of top candidate genes under different PARPi (olaparib, niraparib, talazoparib) and carboplatin. Interestingly, we observed almost identical results, independently of tested gene and drug compound. This confirming the strong correlation of cancer cell response to DNA damaging drugs.

Conclusion Our data show various overlapping gene dependencies suggesting a general mechanism-of-action of PARPi and chemotherapy. Genetic screen of the identified set of genes correlated with PARPi sensitivity may allow a better stratification of patients with increase benefit to this treatment.

2022-RA-1449-ESGO THE PROGNOSTIC VALUE OF SERUM CA125 AND HE4 IN ENDOMETRIAL CANCERS STRATIFIED BY MOLECULAR SUBGROUP

^{1,2}Chloe Evelyn Barr, ¹Louise Wan, ¹Nomondary Quille, ³Matthew Brown, ³Katarzyna Kedzierska, ^{3,4}David Church, ^{1,2}Richard Edmondson, ^{1,2}Emma Jane Crosbie. ¹University of Manchester, Manchester, UK; ²Manchester University NHS Foundation Trust, Manchester, UK; ³University of Oxford, Oxford, UK; ⁴Oxford University Hospitals NHS Foundation Trust, Oxford, UK

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Introduction/Background Endometrial cancer is the commonest gynaecological malignancy. Molecular classification informs