indicate that genomic alterations alone cannot explain acquired platinum resistance in many cases, and emerging evidence suggests epigenetic alterations may be critical. We wish to investigate epigenetic changes that may drive platinum resistance in HGSC by treating established HGSC cell lines and patient-derived cells with pulses of carboplatin and investigating the nature, kinetics and plasticity of platinum-induced epigenetic changes.

**Methodology** We will mimic, using an in vitro two-dimensional model, multiple cycles of platinum-based chemotherapy as used clinically. We will generate preliminary results from established cell lines and primary cultures. The primary cell cultures are collected from the ascites of patients with HGSC treated at Imperial College NHS Trust, London. Following validation (p53, PAX8 immunocytochemistry), carboplatin sensitivity is assessed (sulforhodamine B assay). Cells are then pulsed with four cycles of carboplatin (50μM for 6 hours) with a week of recovery between each cycle. Chemosensitivity of surviving cells is measured after each cycle. The cells are then harvested for downstream methylation (Illumina 850k array), transcriptomic (RNA sequencing) and chromatin accessibility (ATAC sequencing) assays. Cells are also imaged using STORM (Stochastic Optical Reconstruction Microscopy). Preliminary STORM data already indicate differences in chromatin structure and the distribution of specific histone modifications between paired sensitive and resistant HGSC cell lines.

**Results** We will receive the raw data within 8–12 weeks from now for the bioinformatic analysis. Differential gene expression analysis will uncover differently enriched pathways under the selective pressure of platinum-based chemotherapy.

**Conclusion** Understanding the epigenetic landscape of HGSC in real time using physiologically relevant models will allow us to identify possible therapeutic targets that could eventually prevent platinum resistance.

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**2022-RA-1251-ESGO**

**P-CADHERIN: A PROMISING PROGNOSTIC BIOMARKER FOR HOMOLOGOUS REPAIR PROFICIENT HIGH GRADE SEROUS OVARIAN CARCINOMA**

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Introduction/Background Consecutive OC series were characterized by high frequencies of BRCA1/2 and ATM mutations in BC patients, which were enriched by early-onset, family history-positive and receptor triple-negative disease, showed mutation rate varying from 4% to 14%. There were founder pathogenic alleles in Chechens and North Caucasus, with mutation rates varying from 4% to 33%.

**Methodology** Retrospective study using a convenience sample of archive human tissue (Fallopian tube epithelium (FTE), serous precursor lesions and chemo-naïf HGSOV), from a Portuguese cancer centre. In vitro and in silico validation performed using HGSOV cell lines (BG1 and OVCAR4 cell lines) and CCLE database, respectively. Protein expression evaluated using immunohistochemistry (H-scoring system) and western blot. Comparisons between groups were made using T-test and X², where appropriate. Survival analyses were estimated using Kaplan-Meier analysis and Log-rank test.

**Results** We included 321 samples (130 FTE, 53 precursor lesions and 138 HGSOV; 41.2% BRCA1/2 or RAD51D mutated) from 221 patients. All HGSOV co-expressed the 3 cadherins (28% with high co-expression scores). Expression pattern did not differ according to HR status. P-cadherin was significantly upregulated both in precursor lesions and HGSOV, when compared with FTE. CDH3 expression was positively correlated with CDH1, EpCAM and GRHL2 and inversely correlated with VIM, both in silico and in vitro. HGSOV with high cadherin co-expression and high P-cadherin expression were significantly associated with shorter OS in the HR proficient subgroup.

**Conclusion** Our results suggest that P-cadherin upregulation may be an early event in the serous carcinogenesis and a poor prognosis biomarker in HR proficient HGSOV. Functional assays are currently ongoing to unravel the biological mechanisms underlying P-cadherin role in this subgroup.

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**2022-RA-1342-ESGO**

**ETHNICITY-SPECIFIC SPECTRUM OF BRCA1, BRCA2 AND ATM PATHOGENIC VARIANTS IN OVARIAN AND BREAST CANCER PATIENTS FROM NORTH CAUCASUS**

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Introduction/Background North Caucasus hosts several large ethnic groups, which preserved their national identity through the course of history. These populations are likely to have a unique pattern of disease-predisposing alleles reflecting the genetic background of their ancestors.

**Methodology** This study involved ovarian cancer (OC) and breast cancer (BC) patients from Chechnya (n = 147), Kabardino-Balkaria (n = 139), North Ossetia (n = 83), Ingushetia (n = 88) and Dagestan (n = 137). The entire coding sequences of BRCA1, BRCA2 and ATM genes were analyzed by next-generation sequencing (NGS) in 180 OCs and 414 BCs.

**Results** Successive OC series were characterized by high frequency of BRCA1/2 mutations across all analyzed ethnic groups, ranging from 18% to 33%. BC patients, which were enriched by early-onset, family history-positive and receptor triple-negative disease, showed mutation rate varying from 4% to 14%. There were founder pathogenic alleles in Chechens (BRCA1 c.3629_3630delAG; 10 out of 20 BRCA1/2 mutations) and North Ossetians (BRCA2 c.6341delC; 6 out of 10
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 of 13 BRCA1/2 mutations; L1686X: 3 out of 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.

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 gynaecological 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 silencing 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.