Summary (Abstract)

Cancer is now the leading cause of death in economically developer countries, with epidemiological indicators rising steadily on a global scale. This is mainly a result of socio-economic and demographic developments, particularly ageing populations or changes in lifestyle in some populations. Meanwhile, as absolute incidence and mortality rates are rising, the prevalence of cancer is also increasing, representing a heavy social and economic burden. Cancer research has received a great deal of attention from the scientific community, with molecular genetics in particular making the greatest recent progress. Thanks to modern methods of genome analysis, so-called genomics and other 'omics' disciplines, many biomarkers have been discovered, leading to better diagnosis, prognosis and more effective treatment with reduced incidence of adverse effects. However, there is still a long way to go in order to make the idea of personalised oncology, i. e., a precise therapeutic approach tailored to the individual patient, a reality.

This paper examines three types of solid tumours. Firstly, breast cancer, which has the highest incidence worldwide in women, even overall. The next is colorectal cancer, which is the second and third most common cancer in women and men, respectively, and more common in the Czech Republic compared to the rest of the world. The last type studied is ovarian cancer, which, although not being a particularly common type of tumor, has a very poor prognosis and problematic treatment, especially due to the high frequency of resistance to chemotherapy. The objectives of this work include molecular characterization of patients with the aforementioned tumors and their tumor tissue with the aim of discovering novel genomic biomarkers with the potential to improve prognosis or predict response to treatment.

A panel of 113 genes involved in oxysterol signaling was analyzed in breast cancer using massively parallel DNA sequencing. Oxysterols are a large group of oxidized cholesterol derivatives that have been shown to modulate tumor behavior, particularly in breast cancer, but whose roles in cancer have been genomically unexplored. Somatic variants (variants gained by tumors) have been associated with shorter survival in patients, namely in the *CYP46A1* gene, nine functionally related genes, and a panel of twenty genes individually associated with progesterone receptor expression. This study was then expanded to include data on the expression of oxysterol signaling genes (RNA sequencing) and miRNAs at the transcriptome-wide level (microarray) and was conducted as a multi-omic integration study, the main outcome of which was an interaction network comprehensively mapping the correlations between oxysterol gene mRNAs and regulatory miRNAs. In particular, the *ESR1-CH25H-INSIG1-ABCA9* gene axis and the seven miRNAs linking them provide a promising basis for future focused functional studies.

Since a biomarker of resistance to chemotherapy is not yet known for ovarian cancer, a study comparing the genome-wide mutational profiles of patients resistant and sensitive to platinum derivatives, frequently used chemotherapeutic agents, was performed. Significantly

higher mutational burden in the *TP53* gene was found in the tumors of sensitive patients, simultaneously with lower mutational burden in several genes of the Hippo signaling pathway. The frequency of somatic mutations in DNA repair pathway genes by homologous recombination allowed successful prediction of patients' sensitivity to treatment, while the combination of somatic and germline variants further refined the prediction. Minor differences between patients divided by resistance, disease subtype, or survival were then observed in the mutation rates of the *PABPC1*, *PABPC3*, and *TFAM* genes, mutational signatures, and overall mutational burden.

A comprehensive comparison of whole-exome mutation profiles was also performed in a unique group of paired samples of primary colorectal cancers and their synchronous liver metastases. Metastases are much less studied in the literature compared to primary tumors, although they are key for disease lethality. The known association of mutations in the *KRAS* gene in primary tumors with shorter time to relapse was confirmed, but in addition, potential negative prognostic factors were found in metastases in the *ATM*, *DNAH11* and *MUC5AC* genes, and in the SBS24 mutational signature.

The application of genomic methods in breast, ovarian and colorectal cancer cohorts has identified novel putative, or confirmed candidate, prognostic and predictive biomarkers with the potential to improve the effectiveness of therapy for these diseases.