Clinical and molecular aspects of hereditary breast cancer diagnosis and management: PALB2 and RECQL epidemiology in Latvia, Manchester scoring system and contralateral breast cancer risk reduction

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Here we are going to present three small studies covering different aspects of hereditary breast cancer management.

Large-scale case control studies revealed a number of moderate risk - low frequency breast cancer alleles of the *PALB2* and *RECQL* genes. Some of them reported as founder variants of Central and Eastern Europe. Based on highly similar founder variant spectra of the *BRCA1* in Poland and Latvia, we decided to test frequency of other common variants of moderate breast cancer risk - c.509_510delGA (rs515726124) and c.172_175delTTGT (rs180177143) of the *PALB2* gene and c.1667_1667+3delAGTA variant of the *RECQL* gene in breast cancer case-control series from Latvia to gain better understanding of the role of genes in susceptibility to breast cancer and their clinical significance. The calculated frequency for c.509_510delGA of the *PALB2* gene in the case group is 0.35% and 0.00% in the control group, with respective relative risk (RR) 7.18 (CI 95% 0.37 − 138.75; $p = 0.19$). As for *PALB2* c.172_175delTTGT variant, the frequency in the case group of our study is 0.04%. In the control group of our study non heterozygous carriers were detected, which lead to calculated RR = 1.50 (CI 95% 0.06 − 36.83; *p*-value = 0.80). There were no carriers of the *RECQL* variant c.1667_1667+3delAGTA identified in our case group and 2 heterozygotes were identified in the control group. The calculated RR = 0.26 (CI 95% 0.01 − 5.33; *p*-value = 0.38).Acquired results on the *PALB2* gene variants are able to supplement evidence on the allele frequency in the breast cancer patients. Based on our results we cannot confirm contribution of the *RECQL* variant c.1667_1667+3delAGTA allele to the breast cancer development.

Recent availability of commercial complete BRCA1/2 testing in BRCA1 founder (c.4035delA, c.5266dupC) population like Latvia and relatively high non-founder BRCA1/2 mutations frequency has raised question about the selection criteria for this service, if BRCA1 founder mutations are negative. Wide variety of reasons contributes to low diagnostic accuracy of family cancer history criteria alone in our population. Aim of the study is to evaluate the diagnostic value of Manchester scoring system (MSS). MSS was calculated in 1006 unselected breast cancer cases. 57/1006 (5.7%) MSS positive cases were identified. 24/57 MSS positive cases were BRCA1 founder positive, but 33/57 – negative. From the other hand there are 36/1006 (3.6%) BRCA1 founder mutation carriers in our cohort. 24/36 has positive MSS and 12/36 negative MSS. Our conclusion is that MSS has higher diagnostic accuracy in comparison to family cancer history alone and 3.3% of unselected MSS positive and BRCA1 founder mutation negative breast cancer cases should undergo complete BRCA1/2 testing as probability of finding pathogenic mutation is more than 10%.

BRCA1 positive breast cancer cases has more frequently contralateral breast cancer (CBC) events. The most effective prevention strategy is contralateral risk reductive mastectomy (CRRM). Since 2009 22 CRRMs have been performed in BRCA1 positive unilateral breast cancer cases. Control group consist of 21 BRCA1 positive unilateral breast cancer case without CRRM. Median follow-up since treatment of primary breast cancer is 4.29 +/- 0.78 years. There are 5/21 (24%) cases of CBC in the control group, but no CBC events 0/22 (0%) in CRRM group. Our conclusion is that BRCA1 positive breast cancer patients have high frequency of CBC events and CRRM is effective method to reduce CBC events in BRCA1 positive breast cancer cases.