# GENE EXPRESSION PROFILES IN HEREDITARY BREAST CANCER

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Breast cancer is one of the most common types of cancer affecting women. The majority of breast cancers are sporadic cases with multifactorial etiology. Only 5-10% of patients show familial aggregation of breast tumors, which can be associated with mutations in *BRCA1* and *BRCA2* genes, and rarely may arise due to mutations in other genes (e.g. in *CHEK2, TP53, ATM, or PTEN*) [1, 2]. Oncogenic pathways that lead to cancer may be different for sporadic and hereditary breast cancer. Moreover, it was shown that BRCA1-, BRCA2-mutated cancers differ from each other and from sporadic tumors in their morphological and immunophenotypic characteristics. More often patients with BRCA1-associated tumors are characterized by high grade, high proliferation index, pushing tumor margins, and distinct lymphocyte infiltration; these tumors are negative for estrogen and progesterone receptors, express cell markers characteristic of the basal epithelial cells, and cluster within "basal-like" group in gene expression profile studies [2, 3**].**

The question of molecular differences between hereditary BRCA1- and BRCA2-linked and sporadic tumors has been addressed by many studies in the nineties [3]. However, only a few studies have aimed to identify gene signatures of BRCA1-, BRCA2-mutated, BRCAx and sporadic breast cancers. One of the first studies of gene expression profile of BRCA1/2-mutated and sporadic tumors was performed by Hedenfalk and colleagues (2001) [4]. They evaluated a set of genes whose differential expression best distinguished among these three types of tumors was proposed. Among them genes related to apoptosis, DNA repair, and estrogen and progesterone receptors. The paper of Hedenfalk et al raised enormous interest, other studies could not confirm these results and allowed to suggest that difference between BRCA1-mutated breast cancers and sporadic ones is very small [5, 6, 7, 8].

Thus, Jazaeri et al (2002) analyzed hereditary and sporadic ovarian cancers and showed that BRCA1 and BRCA2 tumors had distinct molecular phenotype, while sporadic cancers were placed

by unsupervised method between these two tumor groups, i.e. some sporadic tumors were similar to BRCA1-linked ones and other were similar to BRCA2-linked tumors [5]. Palacios and colleagues (2005) showed similar data from analysis of phenotypic features of BRCA1, BRCA2-mutated breast cancers and sporadic ones based on a tissue microarray study with 37 immunohistochemical markers [6]. Initially, the authors found that BRCA1- and BRCA2-mutated tumors were divided into two groups by hierarchical clustering. The first group showed similar ER-positive phenotype, including higher expression of progesterone receptor, BCL2 and the cell cycle proteins. The second one consisted of the most of ER-negative carcinomas and expressed basal cell markers (P-cadherin and CK5/6). Within the ER-positive group, BRCA2-mutated tumors were co-clustered with sporadic ones. ER-negative tumors were divided into two subgroups, e.g. BRCA1-mutated carcinomas and sporadic tumors with overexpression of HER2 [6].

Later, the small molecular difference between BRCA1-mutated and sporadic tumors has been also indicated by Kote-Jarai and colleagues (2006) [7]. These investigators have shown that the gene expression profile of BRCA1 carriers can be distinguished from the gene expression profile of both BRCA2 mutation carriers and control ones only after induced DNA damage. Authors analyzed gene expression profiles of short-term primary fibroblast cultures that were obtained from skin biopsies from BRCA1- and BRCA2-mutation carriers, and they compared this with the profile of controls, all of which had had breast cancer previously. Cells cultures were irradiated to induce DNA damage and the expression profiles of all samples were analyzed before and after irradiation [7]. Without induced DNA damage, the expression profiling was not able to discriminate the groups.

Similar data were obtained by Vuillaume and colleagues (2009). Investigators compared gene expression profiles in peripheral blood cells of BRCA1 mutation carriers who belong to high-rick breast cancer families with gene expression profiles of BRCA1 and BRCA2 mutation non-carriers. The set of differentially expressed genes (genes related to transcription and translation functions, immune-response, cell-cycle and DNA repair) did not allow

to discriminate all BRCA1 mutation carrier samples from non-carrier samples [8].

It is well known that BRCA1 is a member of complex and versatile protein network involved in multiple functions, so there is no surprise that in all studies mentioned above, genes associated with BRCA1 network were present among genes differentiating BRCA1-mutated from other tumors. Though breast cancers developing in BRCA1 mutation carriers exhibit only minor differences in their gene expression profile as compared to both BRCA2-mutated and sporadic cancers and are much less prominent than the differences related to the presence of estrogen receptors or to the histotype of cancer.

REFERENCES:

1. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer / W. D Foulkes [et al]// J.Natl.Cancer Inst. – 2003. Vol 95, №12 - P. 1482-1485.

2. BRCA1 and BRCA2: 1994 and beyond / S. A. Narod [et al]// Nat.Rev.Cancer.- 2004.- Vol 4, №9 – P.665-676.

3. Van de Vijver, M. J. Gene-expression profiling and the future of adjuvant therapy / M. J van de Vijver// Oncologist. – 2005. –Vol. 10 Suppl 2. - P.30-34.

4. Gene-expression profiles in hereditary breast cancer/ Hedenfalk, I. [et al]//N.Engl.J.Med. – 2001. – Vol.344, №8. – P.539-548.

5. Gene expression profiles of BRCA1-linked, BRCA2-linked, and sporadic ovarian cancers /Jazaeri, A. A. [et al]. J.Natl.Cancer Inst. – 2002. – Vol94, №13. – P.990-1000.

6. Phenotypic characterization of BRCA1 and BRCA2 tumors based in a tissue microarray study with 37 immunohistochemical markers/ [Palacios, J. et al]// Breast Cancer Res.Treat. -2005. –Vol. 90, № 1 - P.5-14.

7. Accurate prediction of BRCA1 and BRCA2 heterozygous genotype using expression profiling after induced DNA damage/ Kote-Jarai, Z., L. [et al]// Clin.Cancer Res – 2006. – vol.12, № 13. – P. 896.-901.

8. Use of gene expression profiles of peripheral blood lymphocytes to distinguish BRCA1 mutation carriers in high risk breast cancer families/ M.L.Viullaume [et al]// Cancer informatics. – 2009. - №7.- P.41-56