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BRCA1 and BRCA2 analysis in breast cancer families from Sardinia: identification of two BRCA2 founder mutations with their clinical and pathological implications

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Background: Genetically homogeneous Sardinian population can be helpful in defining the molecular basis of cancer. To evaluate the incidence of disease-causing mutations in breast cancer (BC) families from Sardinia we screened the two major BC susceptibility genes, BRCA1 and BRCA2, and correlated the presence of mutations with clinicopathological parameters.

Patients and Methods: Fifty BC families with at least three affected members, apparently unrelated and originated from the northern-central part of Sardinia were selected. Mutation screening was performed on DNA from blood samples (informed consent was obtained for each family member) by a combination of different techniques: haplotype analysis, DHPLC-based analysis, and, mostly, nucleotide sequencing.

Results: No mutation was found in BRCA1 gene. Two founder BRCA2 mutations, 8765delAG and I3412V, were detected in 7 and 1 (14% and 2%, respectively) families; considering the total number of BC cases per family, all BRCA2 mutations were registered in the 15 (53%) families with >5 BC cases. Frequency of these mutations were then investigated in unselected BC patients from the same area of Sardinia: 8765delAG was found in 7/498 (1.4%) cases [all positive patients belonged to BC families (6 of them showing >5 BC cases)], whereas none of the 61 BC cases analyzed presented the I3412V mutation. Altogether, 14 families with BRCA2 mutations were identified. Pathological (grading, proliferation rate, estrogen receptor status) as well as clinical (DFS and OS) parameters are being evaluated in these two groups (BRCA2+ and non-BRCA1/2 families).

Conclusion: Although families studied here showed a clear predisposition to BC, majority of them have remained negative for mutations in BRCA1/2, suggesting that other mechanisms or genes are involved. However, BRCA2 mutations seem to be strongly correlated to breast cancer development among Sardinian families with high recurrence of cases.

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Somatic BRCA1 tumorigenesis in sporadic breast and ovarian cancer

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Purpose: Over 80% of BRCA-associated breast/ovarian cancers in Hungary are due to five founder mutations (Ramus et al., 1997a,b; Van der Looij et al., 2000a). Despite the presence of allele loss (LOH) at the BRCA1 locus, somatic mutations are rarely observed in sporadic breast tumors. We have investigated whether large somatic BRCA1 deletions occur in these tumors and have thus far been missed by conventional PCR-based mutation screening. Further, we investigated whether in addition to LOH, also microsatellite instability (MSI) is associated with BRCA1 in these tumors.

Methods: A total of 122 breast and 41 ovarian tumors were analyzed for somatic BRCA1 mutations by HDA/SSCP (exons 2, 5, 20) or Southern Analysis (exons 6-24). Tumors were assayed for genome wide MSI (10 markers) and for LOH at the BRCA1 locus (6 markers).

Results: For the first time we report the presence of somatic BRCA1 mutations in sporadic breast tumors (1%) due to large genomic rearrangements. Specific BRCA1 mutations were detected in 12% of ovarian and 2% of breast tumors, all of germ-line origin. LOH was detected in 49% of BRCA1 negative and 40% of BRCA1-positive tumors. MSI was found in 14% of ovarian tumors all of which were BRCA1-negative.

Conclusion: we conclude that i) a significant fraction of sporadic Hungarian breast/ovarian cancer patients carry inherited founder BRCA1 mutations; ii) a small portion of sporadic breast tumors are due to somatic BRCA1 genomic instabilities (Van der Looij et al., 2000b); iii) MSI detected in ovarian tumors is not BRCA1-associated and may reflect inactivation of DNA mismatch repair genes (Van der Looij et al., 2001).

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Distinct role of the cyp19 del3(TTTA)7 allele in the susceptibility to premenopausal and postmenopausal breast cancer

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Purpose: The CYP19 gene encodes for the enzyme called aromatase, which plays a key role in the conversion of androgens to estrogens. CYP19 intron 4 (TTTA)n polymorphism has been reported to be associated with breast cancer (BC) risk, although conflicting evidence has also been published.

Methods: Here we employed a non-traditional, highly demonstrative design of molecular epidemiological study, where the comparison of BC cases and healthy middle-aged female donors was supplemented by the analysis of the groups with extreme characteristics of either BC risk (bilateral breast cancer (biBC) patients) or cancer tolerance (tumor-free elderly women aged more than 75 years).

Results: None of the (TTTA)n polymorphic variants was overrepresented among the affected women as compared to any of the control groups. However, a 3 bp deletion/insertion CYP19 polymorphism, which is located in the same intron approximately 50 bp upstream to the (TTTA)n repeat, was evidently associated with the menopausal status in both BC and biBC cohorts. In particular, the del3(TTTA)7 allele occurred significantly more frequently in premenopausal than in postmenopausal BC patients (65/172 (37.8%) vs. 67/310 (21.6%); P = 0.0001; OR = 2.20 (1.46; 3.32)), while the perimenopausal cases demonstrated an intermediate value (9/34 (26.5%)). In the biBC cohort, women who developed both tumors in premenopausal period had significantly higher prevalence of the del3(TTTA)7 than patients with postmenopausal onset of the bilateral disease (16/46 (34.8%) vs. 8/50 (16.0%); P = 0.035; OR = 2.80 (1.08; 7.23)); those biBC patients, whose tumors diagnoses were separated by the cessation of menses, displayed intermediate occurrence of the del3(TTTA)7 allele (7/32 (21.9%)). Moreover, the overrepresentation of this allele in premenopausal patients and its underrepresentation in postmenopausal BC remained statistically significant when the cases were compared to the age-adjusted non-affected controls.

Conclusions: The del3(TTTA)7 appears to be related with the increased risk of premenopausal breast cancer but may protect against the postmenopausal disease. Similar tendencies in del3(TTTA)7 allele distribution in BC and biBC patients suggest that its association with the menopausal status of the patients is truly non-random and thus deserves further detailed investigation.

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BRCA1, BRCA2 and TP53 mutations among breast cancer families from upper silesia in poland

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Purpose: Current genetic testing for mutations in breast cancer susceptibility genes BRCA1 and BRCA2 are the basis for estimating disease risk for women with a strong family history of breast and ovarian cancer. There is also a need for data regarding BRCA1, BRCA2 and TP53 mutation frequencies among carcinoma cases not specifically ascertained on the basis of extreme family history profiles.

Method: We screened BRCA1, BRCA2 and TP53 mutations in population of patients from Upper Silesia in Poland. We analysed the BRCA1, BRCA2