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Prognostic factors for BRCA 1-associated familial breast cancer from Russian population

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Background: It has been demonstrated that cancer arising in carriers of mutation in *BRCA1/2* genes differs from sporadic breast cancer (BC) of age-matched control.
Material and methods: 195 breast and/or ovarian cancer patients with strong cancer history from cancer genetics registry of N.N. Blochin Cancer Researc Center RAMS, Moscow were screened for germline mutations in *BRCA1/2* genes using CSGE and direct sequencing.
Results: 57 *BRCA 1/2* mutation carriers have been detected. High frequency of 5382insC mutation (76.4% from all mutations revealed) was shown. A multivariant analysis was performed, it includes 32 cases of *BRCA1*-linked BC. Control groups consisted of 57 patients with sporadic BC selected by age and disease stage. Mean age in the groups studied was 39 years old in familial cancer patient and 41 years old in control. Mean menarhe age was 13.3 years old in *BRCA* carriers and 13.7 years old in sporadic cancer patients. In 4 patients with pathological *BRCA* genotype (12.2%) BC developed during pregnancy. Histopathologic characteristics of *BRCA*-associated BC were: 1) infiltrated ductal carcinoma – 89.8%/87.7%; 2) high grade – 58.2%/29.2%; 3) prominent lymphocyte complete clinical response to primary chemotherapy (anthracyclin-based treatment) followed by surgery – 98.1%/38.2% compared with the control group ($p < 0.05$). Mouse mammary tumor virus MMTV)-related sequences were found by specific PCR using primers for gp52-coding area for the *env* MMTV gene in 39% of sporadic BC patients and in 42% of familial BC patients, while these sequences were detected in about 57% of BC patients during pregnancy or shortly after delivery. MMTV-related retroviral agent might be considered as BC risk factor, especially in familial and gestational BC cases.

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Cyclin E is an important prognostic factor in Japanese breast cancers

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Breast cancer is one of the most common female tumors not only in western countries but in Japan. It was reported that cyclin E is strongly correlated with disease-specific survival in patients with breast cancer. However, this relationship between cyclin E and survival was elucidated only in Caucasian people. It is very important to investigate whether cyclin E is a prognostic factor also in Japanese breast cancers.
Patients and methods: The material for this study was obtained from 79 consecutive patients admitted to Hokkaido University Hospital. Total RNA was prepared using Blood RNA extraction kit. Real Time RT-PCR was performed for detection of cyclin E expression using the Light cycler OCR detection system. Stastified analyses were performed by the use of Stat View 5.0 software.
Results: The median observation period was 98 months and the median age at diagnosis was 51 years old. The clinical stages of the breast cancers according to the TNM classification (UICC), were identified 14 Stage 1, 51 Stage 2, 11 Stage 3, 3 Stage 4. At the time of data analysis during follow-up, 20 patients had distant meastases, and 13 patients died. We compared with cyclin E mRNA expression in breast cancer specimen and clinicopathological variables related to relapse or survival. Cyclin E expression was not correlated with menopausal status, clinical stage, steroid hormone receptor status, and nodal status. Cyclin E expression was strongly associated with p53 status ($p = 0.0001$). In univariate analysis, age, vessel invasion, estrogen receptor status and histological grade were not associated with both relapse free survival(RFS) and over all survival(OS). Progesterone receptor status was associated with both RFL ($P = 0.0377$) and OS ($P = 0.0188$). Nodal status (negative vs positive) was strongly associated with both RFS ($P = 0.0027$) and OS ($P = 0.0280$). p53 status was not associated with RFS ($P = 0.6569$) but associated with OS ($P = 0.0458$). Cyclin E expression was significantly correlated with both RFS ($P = 0.0399$, RR = 2.523, 95%CI: 1.043–6.101) and OS ($P = 0.0049$, RR = 6.394, 95%CI: 1.757–23.275). Multivariate analysis showed significant correlation between cyclin E expression and both RFS ($P = 0.0113$, RR = 0.158, 95%CI: 0.038–0.659) and OS ($P = 0.0455$, RR=0.197, 95%CI:0.040–0.968), independently of nodal status and p53 status.
Conclusion: Cyclin E is a prognostic factor in Japanese breast cancers as well as in Caucasian breast cancers.

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Association between HER-2/neu and nodal status in premenopausal and postmenopausal patients with breast carcinoma

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Background: Her-2/neu protein is a member of the epidermal growth factor family of receptors which, upon activation, contributes positively to the growth and dissemination of neoplasia. Over-expression of this protein has been shown to be a valuable prognostic factor in breast cancer. We studied the prevalence of Her-2/neu over-expression in Iranian breast cancer patients and assessed its correlation with other prognostic factors.
Material and methods: Records of two hundred and four patients (101 premenopausal and 103 postmenopausal) with invasive ductal carcinoma of the breast were reviewed for menopausal status, tumor size, lymph node involvement, grade, HER-2/neu, ER, PR and P53 expression.
Results: The mean age of the patients was 41.5 ± 7.2 years in premenopausal and 60.1 ± 8.2 years in postmenopausal group. Most of the patients were in stage II in both groups (60% in premenopausal and 58%in postmenopausal group). In premenopausal patients, ER, PR, P53 and HER-2/neu were positive in 68%, 60%, 49% and 58% respectively. In postmenopausal patients, ER, PR, P53 and HER-2/neu were positive in 74%, 68%, 44% and 55% respectively. There was no association between HER-2/neu and menopausal status. We found a statistically significant association between HER-2/neu and nodal status in premenopausal patients ($p = 0.007$). There was no significant association of HER-2/neu and other tumor markers or nodal status in postmenopausal patients.
Conclusions: The findings suggest that there is no difference in HER-2/neu expression in premenopausal and postmenopausal patients. HER-2/neu expression is associated with lymph node involvement and more advanced disease in premenopausal patients.

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Prognostic relevance of HER2 expression and gene amplification in estrogen receptor-positive lymph-node negative breast cancer patients

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Background: Breast cancer patients with tumors positive for estrogen/progesterone receptors (ER/PR) are though to have good prognosis. There are few data concerning the prognostic relevance of HER2 alterations in association with ER/PR status In lymph-node negative breast carcinomas (LNNBC).
Patients and methods: We immunohistochemically analyzed HER2, ER and PR expression in a series of 230 LNNBC. Gene status was studied by Chromogenic in situ Hybridization (CISH) (Zymed) in 150 cases randomly selected. Discordant cases were further analyzed by Fluorescence in situ Hybridization (FISH) (DAKO pharmaDxTM). IHC, CISH/FISH, as well as clinico-pathological features and survival data were correlated.
Results: HER2 overexpression (2+, 3+) was seen in 27.8% cases (64/230), and amplification in 18% (27/150). ER and PR were positive ($\geqslant$10% of cells) in 73.7% (162/220) and 67% (147/219) tumors, respectively. A negative correlation was observed between HER2 overexpression and ER (24/58; 41.4%; $p = 0.009$), as well as for PR (28/72; 39%; $p = 0.015$). On the other hand, non amplified cases were positive for RE (92/103; 89.3%; $p = 0.021$) or RP (83/93; 89%; $p = 0.06$). HER2 overexpression and amplification were also more frequently seen in large tumors (>2 cm), high grade, with necrosis and lymph-vascular invasion (LVI) (all $p \leqslant 0.05$). Shorter disease free- and overall survival (DFS and OS) (Kaplan-Meier; log lank) were noticed for patients with tumors grade 3, LVI, and HER2 amplification ($p < 0.05$). Lower rate of recurrence was associated with absence of necrosis ($p = 0.01$) positive-ER ($p = 0.05$); or PR ($p = 0.06$), and better OS when lack of HER2 protein overexpression ($p = 0.005$). Patients with ER-negative/HER2-positive tumors had a trend to shorter DFS than those with ER-negative/HER2-negative (63.6% vs 77.5%, respectively; $p = 0.09$). OS was significantly poorer (79% vs 87%; respectively), as well as for the group with ER-positive/HER2-positive tumors (81.6%) compared to those with ER-positive/HER2-negative (94%) ($p = 0.013$). The results with ER and the levels of amplification yielded only nearly statistical significance ($p = 0.10$).
Conclusions: Those patients with LNNBC and HER2 overexpression/amplification, have a higer risk of recurrence and death independently of ER status and may benefit of a specific treatment with trastuzumab.