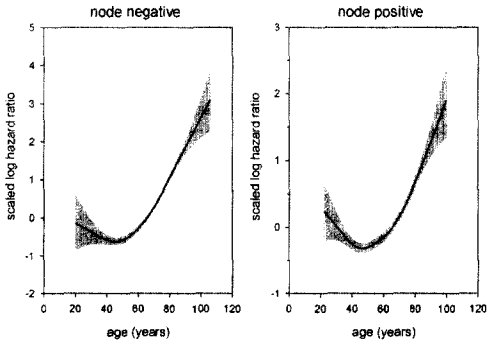
was assessed. The age covariate was then iteratively fitted with parametric functions until the linearity condition of the PH model was satisfied. Finally, the parametric function of age found in N0 was verified in a PH model applied to node-positive (N+) cases.

Results: The analysis by martingale residuals was performed on 58,139 N0 cases. Age was significantly non-linear in PH models. The graph of functional form showed a U-shape of the effect of age on mortality (Fig1). An appropriate transform was obtained with the function: Age + |Age-50|$^{1.5}$. Modeling based on 25,665 N+ cases found a similar U-shape functional form. The transform applied to a PH model based on N+ cases improved the model, but the linearity condition of PH was satisfied only by using Age+|Age-50|$^{1.8}$.



Discussion: The U-shape functional form indicate an abnormal age pattern in which younger patients experienced the same mortality as much older patients, e.g. patients aged 20 had the same relative mortality risk as patients aged 60-65. The modeling suggests that the age pattern has two components: a linear log hazard ratio which represents the normal aging process, and a non-linear component which might represent the disease related age process. The non-linear component is more intense the farther away from the peri-menopause period as expressed by the absolute difference |Age-50|, and more intense in N+ than in N0 as expressed by the larger 1.8 exponent. We hypothesize that efficacy of cancer treatment might be detected by a change in the non-linear component. The modeling approach might represent in that case a powerful measurement of treatment effects.

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Genomic DNA amplification of decoy receptor 3 (DcR3) correlates with lymphatic invasion and lymphnode metastasis in breast cancer.

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Background: Decoy receptor 3 (DcR3) shows inhibitory effect to Fas-mediated apoptosis (Nature 1998; 396 (6712): 699-703). We have reported positive relationship between DcR3 mRNA expression and the gene amplification in breast cancer tissues (The 23rd Annual San Antonio Breast Cancer Symposium; abstract#380), suggesting that breast cancer, in some part, express DcR3 under the gene amplification to evade the apoptotic mechanism. In the present study, we examined the relationship between DcR3 genomic amplification and clinicopathologic factors to clarify its effect(s) in human breast cancer.

Materials & Methods: One hundred patients who underwent operations for primary breast cancer at Niigata University Hospital between 1996 and 2000 were selected for the present study. Genomic DNA of 100 breast cancer tissues and 14 normal breast tissues was extracted respectively from paraffin embedded sections of surgical specimens by microdissection under light microscope. Real-time quantitative PCR was performed to measure genomic amplification of DcR3 by standardizing with b-globin gene. The results were expressed as DcR3/b-globin ratio (D/b), and compared with clinicopathologic factors, disease free survival (DFS) and overall survival (OS) of patients. D/b of both cancer tissues and normal tissues were also compared, and genomic amplification in cancer tissue was defined as D/b > 1.55; greater than mean + 2SD of normal breast samples. Statistical analysis was performed by Mann-Whitney U-test and Breslow- Graham-Wilcoxon test, and the statistical significance was defined as $P < 0.05$.

Results: D/b was significantly higher in cancer tissues compared to normal tissues ($p<0.0001$). In cancer tissue, D/b was significantly higher in the lymphatic invasion positive group compared to negative group ($p=0.0056$), and was also significantly higher in the lymphnode metastasis positive group compared to negative group ($p=0.0396$). There was no significant association between D/b and other clinicopathologic factors, such as age, tumor size, venous invasion or hormone receptor status. The DFS was significantly lower in the genomic amplification positive group compared to negative group ($p=0.0397$), however, the OS showed no statistical difference with or without genomic amplification.

Conclusion: These results suggest that DcR3 gene amplification in breast cancer might be involved in both lymphatic invasion and lymphnode metastasis of cancer cells, and might decrease DFS.

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Abnormalities of erbB oncogenes in locally advanced breast cancer

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Background: The *erbB* family of protooncogenes (*erbB-1, erbB-2, erbB-3, erbB-4*) and receptors encoded by them play an important role in normal cell growth and in neoplastic transformation. Literature data indicate that some abnormalities of *erbB* oncogene family (amplification, deletion) have special importance in breast cancer development, correlate with tumor aggressiveness and with worse clinical outcome. Therefore, these abnormalities may be potentially useful for determining prognosis and for optimizing breast cancer treatment.

Aim of the study: This study was designed to determine gene dosages of *erbB* oncogene family in breast cancer. The relationship of these abnormalities with (CA)n dinucleotides polymorphism and with loss of heterozygosity (LOH) in *erbB1* was examined. Molecular parameters were analyzed in relation to clinical and pathological features of the tumors and to chemotherapy response.

Matherials and methods: Study subjects included 32 chemotherapy naive patients (pts) with primary inoperable locally advanced breast cancer (any T,N_2, any N,T_4). All pts were managed with induction chemotherapy. Tumor (incisional or core needle biopsy) and blood samples were taken prior to treatment and frozen immediately for further analysis. Chemotherapy regimens included ET (docetaxel 100 mg/m^2, epirubicin 90 mg/m^2; 6 pts), FEC (5-Fu 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2; 8 pts) and FAC (5-Fu 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2; 18 pts). Tumor measurement was performed after each cycle and at the completion of induction chemotherapy. Double differential PCR (ddPCR) was used for detection of *erbB* oncogene family abnormalities (gene amplification/deletion). Microsatellite polymorphism of *erbB-1* was examined by PCR with fluorescently labeled primers, followed by capillary electrophoresis and quantitative analysis of PCR product with GeneScan system, using automated sequencer ABI PRISM 310.

Results: Amplifications of *erbB-1, erbB-2, erbB-3, erbB-4* (defined as AGCN value >1.6) were detected in 5.9%, 26.5%, 2.9% and 2.9% of examined cases, respectively. Deletions, defined as AGCN value <0.4 occurred only in *erbB-1* and was found in 26.5% of all cases. There was a polymorphic simple sequence repeat region of 12-20 CA repeats detected in the first intron of *erbB-1*. Homozygotes comprised 31% of the examined group. The majority of the homozygous pts revealed 14/14 CA repeat combination. LOH (most frequently affecting shorter allele) was determined in breast cancer heterozygotes and occurred in 50% of cases. Correlation between these findings and clinical outcomes in extended group of 50 pts will be presented at the meeting.

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New sequence variants, recurrent BRCA1/BRCA2 mutations and new aberrations in BRCA1 promoter region in breast and ovarian cancer cases from Upper Silesia in Poland.

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Purpose: Germline mutations within BRCA1 and BRCA2 are responsible for a significant fraction of hereditary breast and ovarian cancer cases. BRCA