including 1,832 consecutive patients treated between 2007 and 2008 to replicate our findings in the first dataset.

Results: A U-shaped relationship (previously observed in two European populations) between age and LN status failed to be replicated in our dataset of Chinese patients. Instead, we observed a linear rather than piecewise relationship. Moreover, the interaction between age and LN involvement was not modified by tumor size. After multivariate adjustment, the linear relationship was still present. The odds of LN involvement decreased by 1.5% for each year increase in age (OR 0.985, 95% CI 0.979–0.991, P < 0.001). Breast cancer subtypes were also associated with LN status. Proportions of basal-like and ERBB2+ subtypes decreased with increasing age. The observations in the first dataset were successfully replicated in a second independent dataset.

Conclusion: We confirmed a straightforward but not piecewise relationship between age and LN status in Chinese patients. The different pattern between Chinese and European elderly patients should be considered when making clinical decisions.

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The change of tumour size between diagnosis and surgical treatment in breast cancer patients

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Background: Sometimes, patients who were diagnosed with breast cancer have to wait for surgery because of referral to and delay in tertiary care centers. These waiting time raise concerns for tumor progression. We evaluated the change in tumor size between diagnosis and surgical treatment by ultrasonography (US), and its correlation with upgrade of cancer stage, mastectomy rate, and prognosis. We also evaluated the clinical significance of tumor growth rate (TGR) determined by US in patients.

Materials and Methods: We identified 919 patients who were diagnosed invasive breast cancer from January 2002 to August 2009 in Seoul National University Hospital and who underwent US study at the time of first visit of our institute and at one day before surgery. We compared the change of ultrasonographic tumor size during these intervals. We excluded the patients who underwent neoadjuvant chemotherapy and had size difference of more than 1 cm between the final pathology and the last US before surgery. Disease free survival (DFS) was estimated using the Kaplan-Meier method.

Results: The median time duration from the first imaging study at our center to surgery was 27.5 days (range 8 to 92). The correlation coefficient between the last US and pathologic maximal tumor dimension was 0.906 (p < 0.0001). The median TGR (the change of tumor size in US/day) was 0.0083 cm/day. In a multivariate analysis, larger tumor size at the first imaging (p < 0.001), higher tumor grade (p = 0.01), ER negativity (p = 0.027), lymph node metastasis (p < 0.001), and perivascular invasion (p = 0.016) were significant predictors of higher TGR. There was a weak linear correlation between the time interval and change of tumor size (Pearson r = 0.114; p = 0.001). However, the time interval did not significantly affect the upgrade of T stage (p = 0.345) and mastectomy rate (p = 0.195). There was no difference in DFS between the patients with longer interval time (⩾28 days) and with shorter interval time (<28 days) (p = 0.918). Patients with higher TGR showed significantly worse DFS than patients with lower TGR (p = 0.039).

Conclusion: There was no evidence that longer interval time between diagnosis and surgical treatment leads to upstage, more mastectomy, or worse DFS. High tumor growth rate was a significant indicator for worse prognosis.

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HER-2 and Ki-67 co-expression gives more prognostic information in breast cancer

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Introduction: HER-2 and Ki-67 have been extensively investigated on long term outcome of breast cancer. Immunohistochemical positivity of the HER-2 and Ki-67 in breast cancer cells were found associated with worse outcome in most of these studies. We investigated together effect of these markers on breast cancer outcome in this study.

Methods: A 10-year retrospective review was performed using the Breast Cancer Registry data at Akdeniz University Hospital, a tertiary care facility in Antalya, Turkey. A total of 736 patients with invasive breast cancer that underwent surgery between January 1999 and January 2009 were enrolled. The expression of HER-2 and Ki-67 in the tumor was assayed by immunohistochemistry in 406 patients. We accepted cutoff value for Ki-67 >15% and for HER-2 >30%++. Disease free survival (DFS) and overall survival (OS) were analyzed for the relation between conventional prognostic factors, HER-2, Ki-67, HER-2 and Ki-67 co-expression and clinical outcome. Patients follow-up time was median 58 months (range 4 to 128 months). A statistical analysis was performed by log rank test for univariate analysis and cox regression for multivariate analysis with SPSS 13.0 program and p < 0.05 was accepted significant.

Results: There were 65 (16%) distant recurrences and 50 (12%) death due to cancer in study period. Tumor size T status (P < 0.001, P < 0.001), axillary lymph node metastasis (P < 0.001, P < 0.001), axillary node status (P < 0.001, P < 0.001), pathologic stage (P < 0.001, P < 0.001), nuclear grade (P < 0.001, P < 0.001), histological grade (P = 0.001, P < 0.001), estrogen receptor status (P = 0.007, P < 0.001), HER-2 expression (P < 0.001, P < 0.001), Ki-67 expression (P = 0.015, P = 0.036), HER-2 and Ki-67 co-expression (P < 0.001, P = 0.001) were found influence of the DFS and OS by univariate analysis. Tumor size T status (P = 0.035, P < 0.001), axillary node status (P < 0.001, P < 0.001) and HER-2 and Ki-67 co-expression (P < 0.001, P = 0.003) were found independent risk factors for distance recurrence and death due to cancer by cox regression analysis (P value for DFS and OS given respectively). Estrogen receptor status (P = 0.012) were found independent risk factors for death due to cancer and axillary lymph node metastasis (P = 0.005), pathologic stage (P = 0.001), nuclear grade (P = 0.035) were found independent risk factors for distance recurrence. Five years DFS and OS were found 93%, 97% and 69%, 74% for two markers negative and two markers positive patient respectively (Table).

Conclusion: In addition to other conventional pathological factors, tumor growth and proliferation markers, such as HER-2 and Ki-67 predict outcome breast cancer patients. If these two markers are evaluated together, co-expression of both markers influences DFS and OS independent of conventional factors. In conclusion, if HER-2 and Ki-67 expressions assessed together may be gives more prognostic information in breast cancer.

HER-2	Ki-67	DFS (%±Std. Error)	OS (%±Std. Error)
negative	negative	93±3	97±2
negative	positive	88±3	92±3
positive	negative	82±5	88±4
positive	positive	69±5	74±5

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Accumulation of p53 determined by immunohistochemistry as a prognostic marker in node negative breast cancer; analysis according to St Gallen consensus and intrinsic subtypes

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Background: The purpose of the current study was to evaluate the prognostic impact of p53 accumulation by immunohistochemistry (IHC) in node-negative breast cancer and to determine the usefulness of p53 expression in subgroups according to St Gallen consensus and intrinsic subtypes.

Methods: A total 845 consecutive patients with LNN-BC that underwent surgery at the National Cancer Center, Korea between 2001 and 2005 were enrolled. We retrospectively reviewed the clinicopathologic characteristics and disease recurrence. The expression of p53 was assayed using immunohistochemistry (cut-off value: 10%, median value).

Results: The median age was 48 years (range: 25−85) and median follow-up period was 66.0 months (range: 9–101). Univariate analysis determined that tumor size, estrogen !!!receptor (ER), progesterone receptor (PgR), p53 (cut-off value: 10%), and Ki-67 (cut-off value: 15%) were significant for disease free survival (DFS). Of these factors, PgR negativity (HR 3.57, 95% CI 1.26–10.09, P = 0.01) and p53 positivity (HR 3.17, 95% CI 1.51–6.65, P =0.002) were identified as independent prognostic factors for DFS based on multivariate analysis. After then, we divided total patients into 4 intrinsic subtypes by expression of ER, PgR and HER2 and two risk groups (low-, intermediate-risk) by St Gallen consensus, and compared the DFS according to p53 expression in each subgroup. In luminal A, triple-negative subtypes and intermediate risk group, there were significant differences in the DFS rates. (5-yr DFS rate, luminal A; 97.2% for p53(−) vs 93.8% for p53(+); P = 0.03, triple-negative subgroups; 94.1%

for p53(−) vs 78.7% for p53(+); P = 0.002, intermediate-risk group; 96.5% for p53(−) vs 90.7% for p53(+); P = 0.003).

Conclusions: This study demonstrates that p53 accumulation based on IHC has prognostic impact in LNN-BC, and it gives the additional prognostic information for intrinsic phenotypes and the St Gallen consensus.

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Nuclear p53 protein and cell cytosol LDH expression as prognostic indicators to monitor FEC treatment in triple negative breast cancer

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Background: The p53 tumor suppressor is involved in the control of cell growth and programmed cell death. p53 mutations are most commonly seen in human cancer, with some estimate 25% of primary breast carcinomas. Approximately 10−17% of triple negative (lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) invasive breast cancer is significantly associated with mutant p53 overexpression. This type of cancer displays more aggressive clinical behaviour, distinctive metastatic patterns and poorer prognosis when compared with other breast cancer subtypes. 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) are usually combined to treat as the neo-adjuvant or adjuvant chemotherapy for breast cancer. Lactate dehydrogenase (LDH) is a stable cytoplasmic enzyme that is present in all cells. It is rapidly released into the cell-culture supernatant upon damage of the plasma membrane. In this study breast cancer cells were treated with single and combination use of FEC followed by the measurement of the level of nuclear p53 protein, cytosol LDH and DNA synthesis in 5-bromo-2'-deoxyuridine (BRDU).

Material and Methods: High levels of mutant p53 breast cancer cell line MDA-MB-231 was selected. The cells were cultured in flasks and 96 well plates with L-15 medium in assigned control, 0.6ug/mL 5-Fluorouracil, 0.5ug/mL Epirubicin, 0.6ug/mL Cyclophosphamide and FEC combination groups, respectively for 24 hours. At the harvest day, the cultured medium and cell homogenates of different groups were quantified by a photometric enzyme immunoassay, ELISA kit. The LDH released from damaged cells and DNA synthesis labelled with BRDU were measured by the nonradioactive colorimetric immunoassay.

Results: All four test groups demonstrated a statistically significant difference from control group and the most significant result was from the FEC group.

Group	p53 (pg/ml)	LDH (OD)	BRDU (OD)
Control	1.89±:0.04	1.35±:0.10	1.27±:0.15
5-Fluorouracil	*0.71±:0.001	*1.93±:0.07	*0.94±:0.03
Epirubicin	*0.65±:0.006	*1.87±:0.02	*0.86±:0.02
Cyclophosphamide	*0.8±:0.001	*2.12±:0.02	*1.14±:0.02
FEC	*0.32±:0.001	*2.44±:008	*0.57±:0.03

Values are mean±:SD (standard deviation); OD: Optical Density. *p < 0.05.

Conclusion: FEC regimen suppresses cell proliferation, nuclear p53 mutations and LDH. These three indicators may predict how triple-negative breast cancer patients would respond to various chemodrugs or regimens.

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New recurrence prediction model for breast cancer by data mining

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Background: Many studies were published to predict recurrence of breast cancer. The most frequently used methods to predict recurrence are the statistical technique of regression. However, Cox regression does not allow non-linear relations between the independent and dependent variables and low accuracy. A new technique based on machine learning has recently been proposed as a supplement or alternative to Cox regression. Our study aims to develop more accurate prediction model for recurrence of breast cancer.

Material and Methods: Data from 1480 patient with breast cancer from the department of surgery of Ajou university hospital were collected and recorded during the period 1994–2007 years. This study used 631 patients to be excluded in case of other cancer, man, and metastasis to other organ, stage IV, and follow up period under 5 years. Eight among 64 variables were selected with Pearson chi-square test. To obtain a reliable estimate of model accuracy applied the holdout method that divided into 438 patients for training and 193 patients for testing. Since Cox regression is the most popular algorithm to build a predictive model for time-to-event data, this study compared accuracy of two algorithms; Cox regression and Support Vector Machine (SVM).

Results: The results of the univariate analysis used to determine the correlation between clinicopathologic variables and recurrence of breast cancer and showed a significant association between recurrence of breast cancer and variables such as histological grade ($p < 0.001$), local invasion of tumor ($p < 0.001$), HER2 ($p < 0.05$), number of tumor ($p < 0.001$), tumor size ($p < 0.001$), lymphovascular invasion ($p < 0.001$), estrogen receptor ($p < 0.05$) and number of metastatic lymph node ($p < 0.001$). For both model (Cox regression and SVM), a recurrence probability for each patient in the test set was calculated. The predictive accuracy of two models was computed using the area under Receiver Operation Curve (ROC) curve (AUC). SVM: AUC=0.842) was higher AUC than Cox regression (AUC=0.648). As compared by Adjuvant! Online software program, The AUC and accuracy of purposed model (0.842, 80.3%) was slightly higher than the adjuvant! online (0.7, 70.5%).

Conclusions: This study predicted recurrence of breast cancer which is as important as early detection of breast cancer. A parallelism of adequate treatment and follow-up by recurrence prediction prevent the recurrence of breast cancer. This study compared accuracy of models; Cox regression and SVM. SVM showed higher AUC than Cox regression. Our new model can predict more accurately recurrence of breast cancer than previous models.

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Ki-67 as a long-term prognostic factor in lobular breast cancer

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Background: Ki-67 has recently been introduced in the St Gallen consensus as an important prognostic factor in breast cancer. The aim of the present study was to specifically investigate the prognostic bearing of Ki-67 in a subgroup of lobular breast cancer.

Material and Methods: This population-based non-screening material consists of 212 patients (pts) with lobular breast cancer diagnosed between 1980 and 1991. The median follow-up time was 12 years and for those still living, 20 years (range 0.6−30 years). Clinical stage was recorded. The expression of Ki-67 in the tumour was assayed by immunohistochemistry (Mib-1 antibody).

Results: With this long follow-up time, 72 pts (34%) have died of breast cancer, 73 pts (34%) have died of other causes and 67 pts (32%) are alive. Among those alive there were five with local recurrences, one with regional recurrence and one with distant recurrence. At diagnosis the clinical stage was stage I in 90 pts (42%), stage II in 70 pts (33%), stage III in 41 pts (19%), stage IV in 7 pts (3.3%) and stage was undefined in 4 pts (1.9%). Ki-67 expression was categorized into four groups: 0 (0%), 1 (1−10%), 2 (11−30%) and 3 (>30%). A logrank test for trend shows that the null hypothesis of equal overall survival for these four groups could be rejected in favour of the trend alternative (p = 0.037). High Ki-67 expression gives negative impact on survival.

Conclusions: Ki-67 expression seems to give long time prognostic information in lobular breast cancer and might thus be a useful tool in the adjuvant decision making.

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Body mass index is associated with breast cancer of large size and positive lymph nodes in pre-menopausal but not post-menopausal women

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Background: Obesity is known to be a risk factor for breast cancer. While many studies suggested that overweight would be associated with higher risk of breast cancer with higher grade tumours, greater tumour burdens and poorer prognosis, the association between body mass index (BMI) and breast cancer outcome is controversial. There is recent suggestion that the prognostic outlook of Chinese breast cancers might be somewhat different from those in the Western population. Western studies have shown that body mass index may affect important biological mechanisms related with breast cancer prognosis but there is limited data with regard to the impact of BMI upon breast cancer features in the Hong Kong Chinese population.

Methods: We conducted a preliminary retrospective study on 166 Hong Kong Chinese primary breast cancer patients seen as new cases during