act by either suppressing the local estrogen formation or by competitively inhibiting receptor binding. Nevertheless, little is known about the local expression of aromatase and sulfotransferase, which are key modulators of intratumoral estrogen levels.

We have performed immunohistochemostry to investigate the expression of aromatase and sulfotransferase in 42 samples obtained directly from malignant breast tumors, and compared it to biopsies obtained from uninvolved tissue in the vicinity of the front and to distant breast tissue. We found that aromatase was equally detectable in both tumor epithelial and stroma, but was mostly confined to the epithelium in non-malignant tissues ($p = 0.00008$, Fisher's Exact Test). Also, aromatase protein expressin was significantly more common in tumoral stroma when compared to peritumoral and distant breast stroma ($p = 0.00005$, and $p < 0.00001$, respectively). By contrast, sulfotransferase protein was only detectable in epithelial tissues, regardless of the location within the diseased breast. Epithelial sulfotransferase was, however, correlated with epithelial aromatase ($r = 0.35461$, $p = 0.0009$, Spearman's Rho test) and with the epithelial ER status ($r = 0.29313$, $p = 0.005$).

Taken together, we have demonstrated a differential aromatase and sulfotransferase protein expression pattern that is dependent of the spacial relation to a malignant breast tumor. Our results indicate a net increase in intratumoral active estrogen levels through increased stromal aromatization, while physiological local inactivation by sulfotransferase activity remains essentially unchanged.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Predictive and prognostic factors

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Prognostic factors and impact of contralateral cancer on survival of hereditary breast cancer

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Introduction: A high incidence of contralateral breast cancer (CBC) has been reported in BRCA1 mutation carriers and high risk familial patients. Data are scarce on the influence of hereditary CBC on survival, while 10- 25% of new familial patients opt for a risk-reducing contralateral mastectomy. Here we assess differences in CBC incidence, ipsilateral recurrence (ILR) and breast cancer specific survival (BCSS) in 3 risk groups and which factors influence prognosis.

Methods: We assessed tumour characteristics, CBC incidence, ILR and BCSS in 223 BRCA1 mutation carriers with invasive BC and 311 BC patients with $\geqslant 3$ breast and/or ovarian cancers in the family but no BRCA1/2 gene mutation (non-BRCA1/2). They were matched to 759 sporadic controls for year and age at detection.

Results: Median follow-up was 5.4 yrs. Tumours were $\leqslant$ T1 in 50% of the BRCA1, 60% of non-BRCA1/2 and 45% of sporadic patients ($p = 0.02$), node-negative in 66%, 53% and 48% respectively ($p < 0.001$), grade 1 or 2 in 8%, 30% and 26% respectively ($p < 0.001$). Risk-reducing contralateral mastectomy was performed in 23%, 11% and 1% respectively ($p < 0.001$.

After correction for the selection bias of offering DNA-testing with preference to patients with CBC and longer living patients, by exclusion of the patients with a DNA test performed 2 years or more after their diagnosis, 10 years metachronous CBC incidence was 25% in 170 unselected-BRCA1 patients, 6% in 238 unselected-non-BRCA1/2 patients and 5% in the sporadic patients ($p < 0.001$).

After correction for age, stage, grade, estrogen receptor and adjuvant therapy there was no significant difference in BCS survival between the 3 groups (unselected-BRCA1 vs. sporadic HR 1.1; p0.6) (unselected-non-BRCA1/2 vs. sporadic HR 0.9; p0.7), nor did ILR differ (multivariate HR 0.81 for BRCA1 vs. sporadic $p = 0.6$; HR 1.5 for non-BRCA1/2 vs. sporadic $p = 0.2$).

Independent prognostic factors for BCS survival in the total BRCA1, non-BRCA1/2 and sporadic group were tumour size (HR T2 vs. T1: 2.3; $p < 0.001$) nodal status (HR+ vs. HR−: 3.2; $p < 0.001$), age (HR 0.98 per year increase; $p = 0.009$), adjuvant therapy (HR 0.5; $p < 0.001$), and positive estrogen receptor (HR 0.6; $p < 0.001$) Metachronous CBC was associated with favourable BCSS,using follow-up from first diagnosis HR 0.6;p0.01, reflecting longevity before CBC. After CBC, BCSS was comparable (H 1.1; $p = 0.7$)

Conclusion: After correction for selection bias, stage and treatment factors we found no significant difference in BCS survival between both hereditary groups and sporadic breast cancer patients. Stage at detection of the first BC and adjuvant therapy are also in hereditary patients key determinants of prognosis, whereas the occurrence of metachronous contralateral breast cancer is not. We will discuss the impact of CBC and risk-reducing contralateral mastectomy. Decisions on breast-conserving treatment can be made on the same grounds in hereditary and sporadic patients.

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Expression of the HOXB13-to-IL17BR-gene ratio in oestrogen receptor positive primary breast carcinomas: Relation with tumour aggressiveness and response to tamoxifen

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Using a genome-wide screening, Ma et al. [(1)] identified the HOXB13-to-IL17BR expression ratio to predict clinical outcome of breast cancer patients treated with adjuvant tamoxifen. However, in the adjuvant setting this ratio may predict both a tumour's response to tamoxifen and its intrinsic aggressiveness. Therefore, we evaluated the two-gene expression ratio in retrospectively collected frozen specimens from 917 oestrogen receptor (ER) positive primary breast tumours. Using a quantitative RT-PCR assay we have assessed: 1) the relation with tumour aggressiveness and 2) the association with response to first-line tamoxifen monotherapy. Patients who received adjuvant systemic therapy were excluded in this study.

To investigate the relation with tumour aggressiveness, 619 tumours were analysed from 468 lymph node-negative and 151 node-positive patients of whom 332 patients showed a recurrence. The association with therapy response was determined in 193 tumours from patients treated with first-line tamoxifen for advanced disease. Expression levels were compared to housekeeper genes and correlated with clinical outcome. The hazard ratio (HR) and 95% confidence interval (95% CI) were calculated and all statistical tests were two-sided.

As continuous variable, the two-gene ratio had a statistically significant correlation in univariate analysis with disease-free survival (DFS) and progression-free survival (PFS), irrespective of lymph-node status. When dichotomised, high expression levels of HOXB13-to-IL17BR ratio showed a strong association with a shorter DFS for both node-negative (HR = 1.52 [95% CI: 1.16–1.99]; P = 0.002) as well as node-positive patients (HR = 1.66 [95% CI: 1.14–2.44]; P = 0.009). In addition, a shorter PFS for patients treated with first-line tamoxifen (HR = 3.43 [95% CI: 2.18–5.40]; P < 0.0001) was observed.

In conclusion, these results indicate that the HOXB13-to-IL17BR ratio is able to identify 1) patients at risk for earlier recurrence as well as 2) patients who fail to respond to first-line tamoxifen monotherapy for advanced disease. As a consequence, these patients may benefit more from other treatment modalities.

References

[1] Ma XJ, Wang Z, Ryan PD, Isakoff SJ, Barmettler A, Fuller A, et al. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell 2004; 5: 607–616.

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Risk of second non breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving treatment

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Purpose: *BRCA1* and *BRCA2* germline mutations are associated with a strong risk of breast and ovarian cancer. The increased risk of other cancers is not clearly established. We investigated whether mutation status influenced the rate of second non breast malignancies (SNBM).

Patients and Methods: *BRCA1* and *BRCA2* genes were screened for germline mutations in 131 patients with a family history of breast and/or ovarian cancer, treated with breast conserving surgery and radiotherapy. The 131 patients with familial history were matched to 261 patients without, according to age at diagnosis and year of treatment. The follow-up of controls was at least equal to the time-interval between diagnosis and genetic testing in familial cases. SNBM free interval was calculated from the