Department of Oncology-Pathology

Prognosis and predictive factors in human breast cancer during tumor progression

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ABSTRACT

In 2010, 1.6 million women contracted breast cancer globally, almost three times the number in 1980, making breast cancer the most common malignancy among women. In Sweden, approximately one out of nine women is expected to develop breast cancer during their lifetime. Traditionally, therapy decisions have been based on primary tumor predictive markers such as the estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) assuming these are unchanged in the relapse site.

The overall aim of this thesis was to investigate if prognostic and predictive factors such as ER, progesterone receptor (PR) and HER2 status change during breast cancer progression.

In our first cohort from Stockholm region consisting of patients with recurrent breast cancer, HER2 (n=151) status from both primary- and relapse tumor were assessed. We found a worse survival for patients with changed HER2 (n=15) status primary tumor and relapse compared to patients with a stable HER2 (n=35) positive disease.

In our second cohort from Stockholm region, consisting of breast cancer patients with biopsy (mostly by cytology) verified recurrences, ER (n=459), PR (n=430) and HER2 (n=104) status in both the primary tumor and the corresponding relapse were determined. The discordance of receptor status was 32.4%, 40.7% and 14.5%, respectively. Loss of ER in the relapse resulted in a statistically significantly increased risk of dying (HR 1.48; 95% CI, 1.08-2.05) compared with patients with stable ER-positive tumors.

A further population based cohort was established; inclusion of 2102 patients with a primary breast cancer diagnosis during the years 2000 through 2011 from the county of Värmland, at a mean follow-up time of 4.8 years. 1060 out of 2102 patients have had a biopsy taken after the initial breast cancer diagnosis demonstrating that 8.4% (n=177) of the patients had developed a recurrence, 4.4% (n=93) secondary cancers (colorectal-, lung-, skin cancer), 1.9% (n=40) cancer in situ (skin, breast) and 40.8% (n=857) were found to have benign lesions. For patients with recurrence, discordance in ER, PR and HER2 status between the primary- and metastatic tumor occurred in 14.2% (n=18), 39.6% (n=40) and 9.6% (n=7), respectively. Loss of ER or PR at relapse, resulted in statistically significantly increased risk of death (HR 3.62; 95% CI, 1.65-7.94) and (HR 2.34; 95% CI, 1.01-5.47) compared with patients with stable ER or PR positive tumors. The proportion patients with loss of ER was highest among the patients treated with adjuvant endocrine therapy.

In a cohort of patient with a primary ductal cancer *in situ* (DCIS), ER (n=112), PR (n=113) and HER2 (n=114) status from both the primary DCIS and the corresponding local events were assessed, revealing a conversion for ER, PR and HER2 status in 10-30% of instances. However, no general pattern for the conversion was seen, not even when stratified for either *in situ* or invasive relapse. Nevertheless, this study could not support the premise that HER2 overexpression had any major impact on tumor progression to invasive cancer.

In conclusion, the best approach of suspected breast cancer recurrence is to re-biopsy since this may change management of a substantial proportion of them.

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