Prognostic factors in breast cancer with focus on proliferation and non-linear effects

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Abstract

Breast cancer is the most common cancer today among women in the Western world. In Sweden in 2015, more than 8 000 women were diagnosed with breast cancer. For a large number of patients, the prognosis is good. The majority of the patients are cured by primary surgical treatment, and many of the recurring patients survive for long periods of time. Additional (adjuvant) treatment is administered to prevent recurrences, although many patients are already cured by the primary surgery, thereby leading to over-treatment. Despite adjuvant treatment, more than 1 400 patients die from breast cancer every year, demonstrating the need for tools to better tailor treatment. The most important and routinely used prognostic and treatment predictive factors are age at diagnosis, tumor size, spread to the lymph nodes, histological grade, hormone receptors, factors for proliferation and expression of a growth factor receptor (HER2).

The overall aim of this thesis was to investigate prognostic and predictive markers in breast cancer and to find ways to improve the use of established factors, with a focus on proliferation and non-linear effects. Factors for proliferation were studied in different breast cancer patient cohorts and with different methods.

In ***Study I***, we investigated whether an index, CAGE, based on cyclin A, histological grade, and estrogen receptor, could provide valuable prognostic information. CAGE was evaluated on tissue microarray slides, with samples from 219 premenopausal node-negative breast cancer patients. CAGE together with HER2 identified 53% of the patients as low risk with a 5-year distant disease-free survival of 95%. In ***Study II***, we investigated whether the results of ***Study I*** could be confirmed in independent and larger series, replacing cyclin A with the worldwide used Ki67, creating KiGE. In chemo-naïve N0/N1 patients, KiGE alone identified 57% of the patients as low risk, with a 5-year event-free survival of 92%.

In ***Study III***, we studied five factors for proliferation (mitotic activity index (MAI), phosphorylated histone H3 (PPH3), cyclin B1, cyclin A, and Ki67), separately and in combinations. Since all of the prognostic factors have pros and cons, our hypothesis was that combining factors would circumvent these issues. We demonstrated that a combination of MAI and cyclin A improved prognostication compared to use of the factors individually.

Although it is a well-known fact that information is lost when predictors are dichotomized (divided into two groups) or categorized into three groups, for clinical decision-making, this is often performed. In ***Study IV***, we investigated whether the prognostication could be improved by postponing dichotomization/categorization until the last step in the process. We concluded that dichotomization definitely leads to information loss and should be avoided. Categorization improved prognostication, whereas using non-linear transformations only moderately improved the predictions.

In conclusion, the studies included in this thesis demonstrated that several markers for proliferation could be used and that combinations seems to improve prognostication, compared to examining factors individually. With these combinations, it was possible to identify patients with a low risk of developing recurrence so that adjuvant chemotherapy might be avoided. Dividing prognostic factors in more groups than two gives better predictive performance, but keeping them continuous was only moderately better. However, by postponing categorization until the very last step of the prognostic modeling strategy, more possibilities for individual predictions were enabled.

Key words breast cancer, proliferation, prognosis, non-linear, validation

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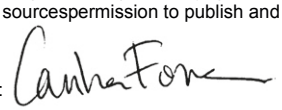
Signature:  Date: 2016-09-27