

## STELLINGEN

Behorende bij het proefschrift

A Genetic Basis for Luminal and Basal-Type Breast Cancer

1. The involvement of distinct biological pathways with genetic and epigenetic inactivation of *E-cadherin* challenges the paradigm that gene mutation and promoter methylation are two means to the same end in inactivating tumor suppressor genes (this thesis).
2. The non-causality of *E-cadherin* loss for the spindle cell morphology of breast cancer cell lines suggests that loss of *E-cadherin* is not a hallmark of epithelial to mesenchymal transition (this thesis).
3. Loss of *E-cadherin* protein expression is not a good marker to classify lobular breast cancers (this thesis). Analysis of p120ctn expression in routine diagnostics should be considered instead.
4.  $\alpha$ -Catenin is a putative new tumor suppressor gene (this thesis).
5. Luminal and basal-type breast cancers associate with distinct gene mutation profiles (this thesis).
6. It is the infrequently mutated gene "hills" and not the commonly mutated gene "mountains" that dominate the cancer genome landscape. The large number of "hills" actually reflects alterations in a much smaller number of cell signaling pathways (Wood *et al.*, *Science* 2007;318:1108-13).
7. A "promiscuous" polygenic model for breast cancer in which multiple common low-risk variants act multiplicatively explains a high breast cancer incidence in the population and suggests that the majority of breast cancers are, in fact, hereditary.
8. An alternative approach to the direct application of gene signatures is the translation of such profiles to protein expression characteristics, using immunohistochemistry on formalin-fixed paraffin-embedded tissue (Rakha *et al.*, *Histopathology* 2008;52:67-81).
9. The terms "lobular" and "ductal" used to designate the two major pathological subtypes of breast cancer are misleading, because they raise the misconception that the pathological subtypes of breast cancer are determined by their cell of origin instead of their cytological and architectural features.
10. The observation that shRNA suppression of PTEN in BT474 breast cancer cells induces resistance to trastuzumab (Berns *et al.*, *Cancer Cell* 2007;12:395-402) suggests that the K111N mutation in the p85 binding domain of PIK3CA is not relevant for trastuzumab resistance.
11. More can be less, if enough is enough (from "*This Much*" by Grace Tjon A Fat, songwriter)