Göteborg, 2019

Tumour evolution and novel biomarkers in breast cancer

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson Hörsal, Academicum, Medicinaregatan 3, fredagen den 24 maj 2019, klockan 9:00

av **Jana Biermann**

Fakultetsopponent:

Dr. Nick Tobin

Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten:

I. **Biermann J**, Nemes S, Parris TZ, Engqvist H, Werner Rönnerman E, Forssell-Aronsson E, Steineck G, Karlsson P, Helou K. A novel 18-marker panel predicting clinical outcome in breast cancer.
Cancer Epidemiology, Biomarkers & Prevention (2017)
DOI: 10.1158/1055-9965.EPI-17-0606

II. **Biermann J**, Parris TZ, Nemes S, Danielsson A, Engqvist H, Werner Rönnerman E, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K. Clonal relatedness in tumour pairs of breast cancer patients.
Breast Cancer Research (2018)
DOI: 10.1186/s13058-018-1022-y

III. **Biermann J**, Langen B, Nemes S, Holmberg E, Parris TZ, Werner Rönnerman E, Engqvist H, Kovács A, Helou K, Karlsson P. Radiation-induced genomic instability in breast carcinomas of the Swedish haemangioma cohort.
Genes, Chromosomes and Cancer (2019)
DOI: 10.1002/gcc.22757

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

Göteborg, 2019

Tumour evolution and novel biomarkers in breast cancer

Jana Biermann

Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Abstract

Several gene signatures have been proposed in the past two decades to improve outcome prediction for breast cancer patients and to guide treatment decisions. Current treatment guidelines, however, primarily focus on established clinicopathological features. In **Paper I**, we identified a novel 18-marker gene expression signature predicting breast cancer-specific survival. The 18-marker signature was validated in three independent cohorts and showed increased predictive power over the clinically validated Oncotype Dx signature.

Despite increasing survival rates, about 6-23% of patients suffer from recurrences within five years of initial diagnosis indicating treatment failure. It is highly important to differentiate between clonally related recurrences and independent primary tumours due to potentially differing prognoses and treatment regimes. Currently, there is no consensus on how to define clonal relatedness between multiple tumours in the same patient. In **Paper II**, we identified the Similarity Index (SI) as the most reliable tool to classify tumour clonality.

The mammary gland is known to be highly sensitive to radiation, especially at a young age. In the years from 1920-1965, a total of 17,200 female Swedish infants were treated with ionizing radiation for skin haemangioma, resulting in an increased risk of developing breast cancer. In **Paper III**, we analysed breast tumours for genomic instability, which can be induced by ionizing radiation. Patients with higher absorbed doses to the breast exhibited increased genomic instability compared to patients exposed to lower absorbed doses. These results strongly suggest radiation-induced genomic instability as a biological link between ionizing radiation exposure at a young age and the increased breast cancer risk in subsequent decades.

In conclusion, this work highlights the importance of complementing established clinicopathological features with molecular biology and statistical models to improve breast cancer risk assessment and personalize treatment strategies.

Keywords: breast cancer, gene signature, molecular biomarkers, tumour clonality, genomic instability, Swedish haemangioma cohort

ISBN: 978-91-7833-440-7 (PRINT) http://hdl.handle.net/2077/59802
ISBN: 978-91-7833-441-4 (PDF)