

Meeting abstract

Primary prevention of breast cancer in high-risk women by monitoring epigenetic changes in nipple aspirates

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Breast cancer is the leading cause of cancer death in women in the Western world. In the Netherlands, the incidence is about 12,000 per year, which means that eventually every 9th woman will get breast cancer. The most well-established breast cancer risk factor is the presence of a germline mutation in the BRCA1 or BRCA2 genes, which indicates a life time risk of 45–80% to get breast cancer.

Regular screening by clinical breast examination, mammography and/or Magnetic Resonance Imaging (MRI) is offered to these high-risk women, but one out of four breast tumors are missed by these screening modalities. The most effective form of primary prevention for high-risk women is bilateral mastectomy, which gives a considerable breast cancer risk reduction. As this procedure is highly mutilating, many women opt out and those who decide to undergo prophylactic surgery prefer to postpone it as much as possible. This bears a significant risk of developing invasive breast cancer in the meanwhile. In contrast, the procedure has to be seen as over-treatment in the 15%–55% of BRCA carriers that would never have developed breast cancer. Up to now no procedures are available that accurately predict who of these high-risk women will and who will not develop breast cancer nor, at what age the cancer will occur.

A new primary prevention modality for these high-risk women could very well be found in the analysis of nipple fluid. Nipple fluid, that contains breast epithelial cells, free DNA and proteins secreted by them, is produced in

small amounts in the breast ducts of non-lactating women and can be collected in a non-invasive way by vacuum-aspiration. We were the first to prove that intranasal administration of oxytocin enables harvesting nipple fluid in almost all women.

We have set up a clinical trial for genetic monitoring of nipple aspirates as a primary prevention tool for women at high risk of breast cancer. To this end, we once yearly harvest nipple fluid in patients with a hereditary predisposition for breast cancer. In this nipple fluid, we assess promoter methylation of a selected set of tumor suppressor genes known to be involved in breast carcinogenesis. Such epigenetic changes are non-specific, frequent and early changes that are ideally suited for early detection of breast cancer and its precursors. Patients will be monitored until preventive or therapeutic surgery, and epigenetic changes in nipple fluid will be correlated to histopathological findings in the resection specimens. This will allow us to establish in retrospect a specific pattern of epigenetic changes that points to a progression from benign to malignant and therefore indicate the time point for prophylactic surgery in high-risk women. On the other hand, should this pattern never occur, prophylactic surgery could be completely avoided.

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