DCIS of the breast - aspects on treatment and prognosis

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Aulan, Sundsvalls Sjukhus, plan 1, hiss 8, fredagen den 5 oktober, kl. 13:00.
Avhandlingen kommer att försvaras på engelska.

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Abstract
Breast cancer is the most common cancer form and a leading cause of death in women worldwide. Ductal breast carcinoma in situ (DCIS) is characterized by a proliferation of malignant cells confined within the mammary ducts and is a potential precursor of invasive breast cancer. The risk of a DCIS to develop into invasive cancer over a 10-year period range from 30% to 50%. In the past 25 years, concomitant with the implementation of screening mammography, the incidence of DCIS has increased dramatically and presently almost 1 000 women are diagnosed with DCIS each year in Sweden. The increased incidence poses concerns of overtreatment and current research aim at identifying clinical or pathological markers that can reliably distinguish hazardous from harmless DCIS. The overall aim of this thesis was to explore the prognostic significance of clinical and tumour biological characteristics of DCIS and to assess the benefits and harms of adjuvant treatment.

We analysed trends in incidence, treatment and outcome over a 20-year period in Uppsala-Örebro healthcare region between 1992 and 2012 (paper I). Information was obtained from the regional breast cancer register. The major finding was a trend towards more intensified treatment over time without any notable improvement of outcome. Relative survival was >97% after 10 years with no significant variation over time. These results may reflect adequate treatment selection, but may also indicate a significant overtreatment.

In paper II and III, a nested case-control study was conducted from a cohort of 6 964 women with primary DCIS to identify characteristics in DCIS associated with subsequent breast cancer death. Ninety-six women who later died from breast cancer were compared to 318 controls selected by incidence density sampling. Detection mode, tumour size, focality, and margin status affected the risk of breast cancer death. More extensive treatment was not associated with lower risk, which may be due to confounding by indication, or indicate that some DCIS have an inherent potential for metastatic spread. In paper III, to further explore the association of tumour biology and breast cancer related death, archival tumour blocks were collected for histopathological re-evaluation and immunohistochemical analysis (IHC) of biomarkers. Intense periductal lymphocytic infiltration (LI) was associated with increased risk of breast cancer death. Progesterone Receptor (PR) negativity in combination with LI; PR negativity, LI and presence of comedonecrosis; and the combination of PR negativity, LI, comedonecrosis and HER2 positivity were all independently associated with increased risk of breast cancer related death in multivariate analyses, stepwise adjusting for age, tumour size and treatment.

In paper IV, we studied the risk of ischemic heart disease (IHD) after treatment for DCIS. Postoperative radiotherapy (RT) in DCIS reduces recurrence rates by half but confers no benefits in terms of survival. It is thus of major importance to consider long-term adverse effects. Left-sided breast irradiation may involve exposure of the heart to ionising radiation with an associated risk of subsequent cardiovascular disease. The cumulative incidence of IHD was analysed in a population-based cohort of 6 270 women with DCIS compared to 31 257 women without a history of breast cancer. After a median follow-up of 8 years, there was no increased risk of IHD for women with DCIS versus the comparison cohort. The risk was lower for women with DCIS allocated to RT compared to non-irradiated women and to the comparison cohort, probably due to patient selection. Comparison of RT by laterality did not show any over-risk for irradiation of the left breast. These results are reassuring, but longer follow-up may be warranted considering the continuously increasing use of RT in DCIS management.

Keywords
DCIS, screening, breast conserving surgery, postoperative radiotherapy, mastectomy, breast cancer death, periductal lymphocytic infiltration, biomarkers, ischemic heart disease