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# Long-term side effects of Radiotherapy in Breast Cancer
## -studies in ischemic heart disease and lung cancer

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## Abstract
Adjuvant radiotherapy (RT) in breast cancer (BC) is well established and significantly reduces local recurrences and BC mortality. Still, it usually involves some accidental irradiation to the heart and lungs, which can lead to long-term side effects, mainly ischemic heart disease (IHD) and lung cancer (LC). The overall aim with this thesis was to study IHD and radiation-induced LC in women receiving RT from the early 1990s until recently.

**Paper I** was a reproducibility study with the aim to examine the inter-observer variation in delineation of the coronary arteries (CAs) at RT planning (n=32). The CAs were delineated in the patients' CT-scans by three oncologists independently. The main finding was a median distance between the centers of the delineated arteries of 1-4 mm for the left main coronary artery (LMCA) and the left anterior descending artery (LAD). The intraclass correlation coefficient (ICC) was derived to quantify the variance in estimated doses. The ICC for mean doses varied from 0.76 to 0.98 for LMCA-LAD. In conclusion, the study showed high consistency in contouring the CAs in the patients' planning CTs, in particular the LMCA-LAD. In **paper II**, the aim was to examine the relationship between radiation dose to the CAs and subsequent coronary stenosis that required a coronary intervention at this location (n=182). The CAs were delineated and divided into segments in the patients' planning-CTs, and doses were recalculated based on the dose distribution of the original RT plans. Segment-wise analyses were performed to assess the risk of developing a coronary stenosis that required an intervention at a certain radiation dose. Segments receiving radiation doses < 1 Gray (Gy) were used as reference. The main finding was a five-fold increase in risk of a clinically relevant coronary stenosis in the mid LAD at mean doses over 20 Gy, compared to doses of 0-1 Gy (odds ratio 5.23; 95 % CI (confidence interval) 2.01-13.6). There were too few events to calculate increase in risk per Gy, still, the result of this study supports that the dose to the LAD should be considered at RT planning and kept as low as possible.

In **paper III** and **IV**, the BcBaSe cohort was used to examine risk of IHD, and radiation-induced LC after adjuvant RT for BC. The BCBaSe consists of 68089 women diagnosed with BC and 340352 age-matched women without BC diagnosis. In **paper III** Cox regression analyses were performed to estimate risk of IHD, by comparing women with BC to women without BC diagnosis, and by comparing left-sided BC to right-sided BC. Kaplan-Meier analysis was performed to assess cumulative incidence of IHD. Women with BC had lower risk of IHD compared to women without BC diagnosis at follow-up (hazard ratio (HR) 0.91; 95 % CI 0.88-0.95). Women irradiated for left-sided BC had a higher risk of IHD compared to women irradiated for right-sided BC (HR 1.18; 95 % CI 1.06-1.31). The cumulative IHD incidence was increased in women receiving left-sided RT compared to right-sided RT, starting from the first years after RT and sustained with longer follow-up. In **paper IV** Kaplan-Meier analyses were performed to assess cumulative incidence of LC and LC-specific survival. Cox regression analyses were performed to estimate risk of LC after adjuvant RT for BC, comparing women with BC to women without BC diagnosis. Women with BC receiving RT had a higher cumulative incidence of LC compared both to women with BC not receiving RT and women without BC. This became apparent 5 years after RT and increased with longer follow-up. Women with BC receiving RT had a higher risk of LC compared to women without BC diagnosis (HR 2.35; 95 % CI 1.54-3.59). LC-specific survival was significantly higher in women with a prior BC compared to women without a prior BC diagnosis. The results of **paper III** and **paper IV** emphasize the importance of further develop and implementing RT techniques and regimens that lower the cardiac and lung doses.

## Keywords
Breast cancer, Radiotherapy, Side effects, Ischemic heart disease, lung cancer

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