

Summary

Breast cancer is by far the most frequent cancer among women in the Netherlands, with nearly 12,000 new female breast cancers diagnosed in 2006. Incidence rates have doubled since they became available in 1955, while breast cancer mortality remained almost unchanged. In view of this increased relative survival it has become exceedingly important to evaluate possible late adverse effects of treatment. Knowledge of long-term treatment effects may lead to modification of treatment regimens, techniques or indications in order to decrease the risk of adverse effects in future patients, while maintaining equal levels of therapeutic effectiveness. Of all late complications of treatment, cardiovascular disease and second malignancies are considered to be the most serious since they do not only cause substantial morbidity but also considerable mortality.

General aim of this thesis was to evaluate the long-term risks, both in terms of incidence and mortality, of second cancers, heart disease and cerebrovascular disease in survivors of breast cancer. Therefore, we conducted the Late Effects BC Study, a retrospective cohort study consisting of 7425 1-year survivors of breast cancer treated from the 1970s through the 1980s in two major cancer centers in the Netherlands.

Chapter 2 presents long-term cause-specific mortality among all 1-year survivors of the Late Effects BC Study. After a median follow-up of 13.8 years 4160 deaths were observed, of which 76% were due to breast cancer.

During follow-up, the relative risk of death from breast cancer declined, but even after more than 25 years since first treatment, patients still experienced a 6-fold increase of breast cancer mortality. Contrary to our expectations, overall cardiovascular mortality was not increased in our study population compared to the general population (standardized mortality ratio = 1.0). However, when we compared irradiated with non-irradiated patients within the cohort, adjusting for age and treatment period, radiotherapy was associated with a significant 1.7-fold increased risk of cardiovascular death. In absolute terms, irradiated patients experienced 19 excess deaths from cardiovascular disease per 10,000 patient-years. Postmastectomy radiotherapy showed a 2-fold increased cardiovascular mortality when applied before 1979, consistent with the literature on older radiation techniques, and then a decline in risk to a hazard ratio of 1.5 (95% CI: 0.9 - 2.7) when applied from 1979 on. For breast-conserving therapy irradiation administered in the latter period, we did not find an association with

increased risk of cardiovascular death (hazard ratio for breast conserving therapy vs. surgery only = 1.0; 95% CI: 0.5 - 1.9).

Second malignancies (excluding contralateral breast cancer) showed a slightly though significantly increased standardized mortality ratio of 1.16, corresponding with 5 excess deaths per 10,000 patient-years. Contralateral breast cancer contributed to only a small proportion (6%) of all breast cancer deaths, with 12 excess deaths per 10,000 patient-years.

In conclusion, patients irradiated after 1979 experience low (postmastectomy radiotherapy) or no (postlumpectomy radiotherapy) excess mortality from cardiovascular disease.

In **chapter 3** we report on the long-term risk of contralateral breast cancer in the 1-year survivors of the Late Effects BC Cohort, focusing on the effects of different radiation regimens, chemotherapy and family history of breast cancer.

Radiotherapy did not significantly increase the risk of contralateral breast cancer overall. However, the association with radiotherapy became stronger with younger age at breast cancer diagnosis (for age<35: hazard ratio = 1.78; 95% CI: 0.85 - 3.72; for age>45: hazard ratio = 1.09; 95% CI: 0.82 - 1.45). Furthermore, women treated before age 45 with postlumpectomy radiotherapy experienced 1.5-fold (95% CI: 1.11 - 2.09) increased risk of contralateral breast cancer compared with those who had postmastectomy radiotherapy. The dose-response relationship between radiation and risk of contralateral breast cancer became stronger when relating the radiation dose received by the medial portion of the breast to the development of contralateral breast cancer in the same area, supporting a role for radiation to induce malignancy in the contralateral breast. Our study is the first one examining the effects of combined exposure to radiotherapy and family history of breast cancer. For the subset of patients younger than 45, the joint effects of postlumpectomy radiotherapy and positive family history for breast cancer on risk of contralateral breast cancer were greater than expected when individual risks were summed (hazard ratio = 3.31; 95% CI: 1.96 - 5.60; *P* for departure from additivity = 0.045). Furthermore, we observed an association between adjuvant chemotherapy and decreased risk of contralateral breast cancer, but only in the first 5 years of follow-up; our data suggest that chemotherapy primarily affects contralateral breast cancer risk by eradicating pre-existing tumor cells in the contralateral breast.

Apparently young patients with a strong family history of breast cancer are more susceptible to radiation-induced breast cancer than patients without affected relatives. This finding should be taken into account when advising breast-conserving therapy in young breast cancer patients, particularly in mutation carriers, and warrants further research.

Next we studied treatment-specific incidence of cardiovascular disease in the 4414 10-year survivors of the Late Effects BC Study (**chapter 4**). After a median follow-up of almost 18 years, 942 cardiovascular events were observed (standardized incidence ratio = 1.30; 95% CI: 1.22 - 1.38; corresponding to 62.9 excess cases per 10,000 patient-years). Breast irradiation

only was not associated with increased risk of cardiovascular disease. However, radiotherapy to either the left or right side of the internal mammary chain was associated with increased cardiovascular disease risk for the treatment period 1970–1979 (for myocardial infarction, hazard ratio = 2.55; 95% CI: 1.55 - 4.19; $P < .001$; for congestive heart failure, hazard ratio = 1.72; 95% CI: 1.22 - 2.41; $P = .002$) compared with no radiotherapy. Among patients who received internal mammary chain-radiotherapy after 1979, risk of myocardial infarction declined over time toward unity, whereas the risks of congestive heart failure (hazard ratio = 2.66; 95% CI: 1.27 - 5.61; $P = .01$) and valvular dysfunction (hazard ratio = 3.17; 95% CI: 1.90 - 5.29; $P < .001$) remained increased. Patients who underwent radiotherapy plus adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) after 1979 had a higher risk of congestive heart failure than patients who were treated with radiotherapy only (hazard ratio = 1.85; 95% CI: 1.25 - 2.73; $P = .002$). Smoking and radiotherapy together were associated with a more than additive effect on risk of myocardial infarction (hazard ratio = 3.04; 95% CI: 2.03 - 4.55; P for departure from additivity = .039). In conclusion, radiotherapy as administered from the 1980s onwards is associated with an increased risk of cardiovascular disease. Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease. Our finding of increased risk of congestive heart failure after adjuvant non-anthracycline containing chemotherapy warrants further research.

In **chapter 5** we describe treatment-specific risk of cerebrovascular events (stroke and transient ischemic attack) in all 10-year survivors of the Late Effects BC Study ($n = 4414$), accounting for cerebrovascular risk factors. Overall the risk of stroke was decreased by 25% in comparison with the general female population. Patients irradiated at the supraclavicular area and/or internal mammary chain did not experience a higher risk of stroke (hazard ratio = 1.0; 95% CI: 0.7 - 1.6) or TIA (hazard ratio = 1.4; 95% CI: 0.9 - 2.5) in comparison with patients who did not receive radiotherapy or were irradiated on fields other than supraclavicular area or internal mammary chain. Significantly increased risks of stroke were found in women who had received hormonal treatment (tamoxifen), and in women who had hypertension or hypercholesterolemia, with hazard ratios of 1.9, 2.1, and 1.6, respectively. From these data we may conclude that long-term survivors of breast cancer experience no increased risk of cerebrovascular events compared with the general population. Hormonal treatment is associated with an increased risk of stroke, while radiation fields including the carotid artery do not increase the risk of stroke compared with other fields.

In **chapter 6** we address the risk of cardiovascular disease following postlumpectomy irradiation restricted to tangential fields. We assessed the incidence of cardiovascular disease in 1601 patients with T1-2N0 breast cancer treated with breast tangentials in five different hospitals between 1980 and 1993. Patients treated with radiation fields other than breast tangentials and those treated with adjuvant chemotherapy were excluded. For patients with

left-sided breast cancer maximum heart distance was measured on the simulator films as a proxy for irradiated heart volume. Median follow-up was 16 years. The incidence of cardiovascular disease was 11.6% in patients with right-sided breast cancer versus 16.0% in left-sided cases. The hazard ratio associated with left-sided versus right-sided breast cancer was 1.38 (95% CI: 1.05 - 1.81) for cardiovascular disease overall, 1.35 (95% CI: 0.93 - 1.98) for ischemic heart disease, and 1.53 (95% CI: 1.09 - 2.15) for other heart disease. The risk of cardiovascular disease did not significantly increase with increasing maximum heart distance. In conclusion, patients irradiated for left-sided breast cancer with tangential fields have a higher incidence of cardiovascular disease compared with right-sided cancer. However, the risk does not seem to increase with larger irradiated heart volumes.

Finally, the general discussion in **chapter 7** considers some important issues related to the design and results of the Late Effects BC Study that have not been evaluated in the separate studies. In particular, we explained the approach of active follow-up and the specific new findings of our studies obtained through this approach. Furthermore we described mechanisms underlying cardiotoxicity of radiotherapy and chemotherapy. Results from the various Late Effects BC studies that seemed inconsistent with each other were discussed, as well as some limitations of studies on late adverse effects. We evaluated the impact of several adverse outcomes by comparing the absolute excess risks of the various events. The absolute excess risks for cardiac events were 70 per 10,000 irradiated patients per year, for lung cancer and esophageal cancer 5.8 and 1.3, respectively, and for contralateral breast cancer 13 per 10,000 irradiated patients per year. Clearly, the impact of radiotherapy on the occurrence of cardiovascular disease was higher than on second malignancies. Chemotherapy (CMF) in addition to radiotherapy seemed to further increase the risk of congestive heart failure compared with treatment with radiotherapy alone. The impact of chemotherapy on solid tumor risk was negligible apart from a temporarily protective effect on risk of contralateral breast cancer. Next we discussed clinical implications. With respect to cardiovascular disease, we made a distinction between patients treated in the past and future patients. Our advice to women who have been treated with older radiotherapy methods, with potential harmful effects on the heart, would be to control and/or treat any existing cardiovascular risk factors: high blood pressure, diabetes mellitus, hypercholesterolemia, and to stop smoking. As for the patients of tomorrow, we expect that with the introduction of Intensity Modulated Radiotherapy and Image Guided Radiotherapy, normal tissues will be spared more effectively. Whether these improvements in techniques will prevent all late cardiac toxicity, cannot be evaluated before another 15 - 20 years. For the time being, we recommend heart sparing techniques in the radiotherapeutic treatment of breast cancer. With respect to contralateral breast cancer, clinicians should be aware that the median time to contralateral breast cancer is 7.7 years, stressing the importance of surveillance for at least 10 years after the primary breast cancer diagnosis. Furthermore, in particular young patients from breast cancer families should be

informed about the increased risk of developing a contralateral breast cancer after whole breast irradiation with tangential fields. Recommendations for future research were presented: prospective studies will be needed to define the most radiosensitive part of the heart, and to establish a threshold dose for increased risk of cardiovascular disease. Our finding of increased risk of heart failure after CMF in combination with radiotherapy needs reaffirmation in other studies; moreover, the long-term toxicity profile of current cancer therapeutics, like anthracyclines and trastuzumab, should be evaluated as well. Further study is needed to evaluate the susceptibility to radiation-induced breast cancer in BRCA1/2 mutation carriers; possibly also other gene mutations are involved from non-BRCA1/2 breast cancer families. Our final remarks concern the privacy law in medicine (WGBO) that was introduced in 1995, allowing destruction of medical records after a period of 10 years. Obviously this action obstructs the evaluation of late effects of medical treatments in The Netherlands. The WGBO should be adapted along the lines proposed by the committee of the Health Council. Until the necessary changes in the law have been made, further destruction of medical data must be prevented.