Focus of this thesis

Previous studies have shown that cardiovascular disease rates are increased in patients treated for breast cancer in the past. The research presented in this thesis aimed to assess the incidence of various specific cardiovascular diseases for more contemporary breast cancer treatments, the onset of treatment-related cardiovascular disease risk, and the interaction between different treatments and with other cardiovascular disease risk factors. In this chapter, the main findings of our research will be summarized and discussed, followed by the strengths and limitations of our studies, the implications for clinical practice, and the recommendations for further research.

Main results

In Chapter 2 we present the results of a population-based cohort of over 10,000 patients treated for ductal carcinoma in situ (DCIS) in the Netherlands in the period 1989 to 2004. Treatment for DCIS consisted of surgery (either mastectomy or wide local excision) and in case of wide local excision this was frequently followed by tangential breast irradiation. Three treatment groups were distinguished, irrespective of type of surgery: patients not treated with radiotherapy, patients irradiated to the right breast, and patients irradiated to the left breast. Cardiovascular hospitalization and cardiovascular mortality rates were acquired through linkage and compared between the treatment groups and with the rates in the general population. After a median follow-up of ten years, no increased rates for cardiovascular mortality nor morbidity after radiotherapy for DCIS were observed when comparing surgery plus radiotherapy versus surgery only, nor when comparing radiotherapy for left- versus right-sided DCIS; e.g. the hazard ratio (HR) for any cardiovascular disease comparing left- versus right-sided radiotherapy was 0.94 (95% confidence interval (95% CI) 0.67-1.32). Compared to the general population, DCIS patients had a lower cardiovascular death rate (standardized mortality ratio 0.77; 95% CI 0.67-0.89), independent of treatment.

In Chapters 3 and 5 we studied the various specific cardiovascular disease rates after treatment for invasive breast cancer in two cohort studies. In Chapter 3 this was performed in a very large population-based study of 70,230 women. In this study, we compared cardiovascular hospitalization and cardiovascular mortality rates between treatment groups and with the rates in the general population. Treatment comparison groups were based on the available treatment data, i.e. type of surgery, radiotherapy yes/no, breast cancer laterality and chemotherapy yes/no. Just as for the DCIS patients in Chapter 2, we observed a slightly lower cardiovascular disease mortality ratio for invasive breast cancer patients compared with the general population (standardized mortality ratio 0.92, 95% CI 0.87-0.97).
CI 0.88-0.97). Only death due to valvular heart disease was more frequent (standardized mortality ratio 1.28, 95% CI 1.08-1.52). Patients treated with left-sided radiotherapy after mastectomy had a higher rate of any cardiovascular event compared to both patients treated with surgery alone (subdistribution hazard ratio [sHR] 1.23, 95% CI 1.11-1.36) and patients treated with right-sided radiotherapy (sHR 1.19, 95% CI 1.04-1.36). Increased event rates in patients treated with radiotherapy after mastectomy were found not only for ischemic heart disease, but also for valvular heart disease and congestive heart failure. The magnitude of the ischemic heart disease risk increase was more pronounced in patients aged younger than 50 years at breast cancer diagnosis (sHR 1.48, 95% CI 1.07-2.04 for left- vs. right-sided radiotherapy after mastectomy). Comparing left- versus right-sided radiotherapy after wide local excision, no increased rate for all cardiovascular events combined was observed, yet considering ischemic heart disease, a slight but statistically significant increased rate was found (sHR 1.14, 95% CI 1.01-1.28). For a subgroup of 20,398 patients, we managed to collect more detailed radiation therapy information, including radiation field. Analyses by radiation field showed an increased cardiovascular event rate for left-sided chest wall irradiation alone, left-sided breast irradiation alone, and internal mammary chain field irradiation, all compared to right-sided breast irradiation alone. Compared to patients not treated with chemotherapy, chemotherapy used in or after 1997 (i.e., anthracyline-based chemotherapy) increased the event rate of congestive heart failure (sHR 1.35, 95% CI 1.00-1.83).

Chapter 4 describes the linkage procedures that were used for the construction of the two population-based cohorts studied in Chapters 2 and 3, and the challenges that were addressed during this process.

In Chapter 5 we present the results of our hospital-based cohort consisting of 14,645 women aged 61 years or younger at breast cancer diagnosis, treated at the Netherlands Cancer Institute, Amsterdam or the Erasmus MC – Cancer Institute, Rotterdam in the period 1970-2009. For this cohort, data on cardiovascular diseases were collected from patients’ medical charts and through questionnaires sent to the general practitioner of each patient. Additionally, information on the classic cardiovascular risk factors hypertension, hypercholesterolemia, diabetes and smoking at time of breast cancer diagnosis was collected. Cardiovascular disease rates were compared with general population rates and between treatment groups, taking into account radiation field and type of chemotherapy. Compared with the general population, patients treated with neither radiotherapy nor chemotherapy did not have an increased rate of myocardial infarction (standardized incidence ratio 0.8 95%CI 0.5-1.1) and had a lower heart failure rate (standardized incidence ratio 0.5 95%CI 0.4-0.8). For breast cancer patients treated with radiotherapy, the lowest typical whole mean heart doses were observed for those who received right-sided breast irradiation without irradiation of the
internal mammary chain (interquartile range of estimated whole mean heart doses 0.3-0.7 Gray). Compared to this group, patients irradiated to the left-breast only (also without irradiation of the internal mammary chain, interquartile range of estimated whole mean heart doses 1.5-4.8 Gray), had a cardiovascular event rate-ratio of 1.11 (95% CI 0.93-1.32). Internal mammary chain irradiation (including both left- and right-sided internal mammary chain irradiation; interquartile range of estimated whole mean heart doses 9-17 Gray) was associated with increases in cardiovascular disease rate overall, ischemic heart disease, heart failure, and valvular heart disease (range of HRs 1.6-2.4). Among women diagnosed before age 50 during the period 1987 through 1999, the cumulative incidence of ischemic heart disease twenty years after breast cancer treatment was 11.3% (95% CI 6.8-17.1) for patients who were irradiated to the internal mammary chain and had a cardiovascular risk factor (including smoking) at breast cancer diagnosis, compared to 6.4% (95% CI 4.5-8.7) for those who had a cardiovascular risk factor, but were not treated with internal mammary chain irradiation. Anthracycline-based chemotherapy was associated with a four-times increased heart failure rate (HR=4.18, 95% CI 3.07-5.69), emerging within five years and remaining increased until at least 10-15 years after treatment. The onset of ischemic heart disease was also studied in Chapter 5 and will be discussed later in this section, as will the results on classic cardiovascular risk factors (smoking, diabetes, hypertension, hypocholesteremica) and the joint effect with breast cancer treatment.

In Chapters 3 and 5, cardiovascular disease rates after radiotherapy were compared between different radiation fields (e.g. breast, chest wall, internal mammary chain). Because the radiation dose to the heart does not only depend on radiation field but also on other radiotherapy determinants, including differences in beam energy, field borders, and angle, one would ideally take into account more detailed, individual radiotherapy data. Because this is not feasible in large cohort studies such as ours, in which most of the patients were treated before CT-planning for radiotherapy was used, we performed two matched case-control studies nested in our hospital-based cohort of breast cancer survivors. An important advantage of case-control studies is efficiency; data collection on the detailed information required, such as individual radiotherapy data, is confined to patients with the event of interest (cases) and a (matched) sample of non-cases (controls). These studies are described in Chapters 6 and 7, with heart failure and myocardial infarction, respectively, as cardiovascular events of interest. Methods for both of these case-control studies were very similar. For all included cases and controls, medical charts were abstracted to obtain cumulative chemotherapy doses and detailed information on radiotherapy, including target definition, field borders, total dose and dose per fraction, beam energy and the use of shielding, wedges and bolus. Radiation regimens were reconstructed by Prof. S.C. Darby and colleagues from the University of Oxford, by using a CT-planning scan of a representative patient to estimate typical whole mean heart dose, mean ventricle dose, and dose-volume...
parameters. The heart failure case-control study in Chapter 6 included 102 cases. These cases had been diagnosed with congestive heart failure or cardiomyopathy as first heart disease after breast cancer, and were each matched to three controls taking into account age and date of breast cancer diagnosis. Case inclusion was based on the definition of heart failure as an ejection fraction decreased to less than 50% or a ≥10% drop from baseline from first ejection fraction measurement. Median whole mean heart dose was 6.8 Gray in cases (interquartile range 0.8-13.7 Gray) and 3.9 Gray in controls (interquartile range 0.9-13.4). Whole mean heart dose was not associated with heart failure rate overall, nor in patients treated without anthracyclines; excess rate ratio (ERR) 1% per Gray (95%CI 2%-10%), and 0% per Gray (95% CI -3%-8%), respectively. However, exposure of ≥10% of the heart to ≥25 Gray in addition to anthracycline-treatment was associated with increased heart failure rates; compared to patients in whom less than 10% of the heart received 25 Gray, the rate ratio was 5.7 (95% CI 1.5-21.7) for patients of whom ≥10% of the heart received ≥25 Gray and 11.0 (95% CI 2.4-51.6) for those of whom ≥20% received ≥25 Gray. After anthracycline-treatment, we observed a strong dose-dependent increase of heart failure rate, with a rate ratio of 8.8 for patients receiving a cumulative dose of more than 240 mg/m² (95%CI 4.6-16.7) compared to no chemotherapy. Among patients additionally treated with trastuzumab, the rate ratio was 17.5 (95%CI 5.0-61.3) compared to no chemotherapy. Exposure to aromatase inhibitors, but not to tamoxifen alone, was associated with an increased heart failure rate (RR 4.0 95%CI 1.0-16.3). In the myocardial infarction case-control study, a total of 183 patients were identified with myocardial infarction as first heart disease after breast cancer. These cases were each matched to one control based on age and date of breast cancer diagnosis. (Chapter 7) Median whole mean heart dose was 9.5 Gray (range: 0.3-35.2 Gray). Myocardial infarction rate increased linearly with increasing whole mean heart dose, with an ERR of 6.5% per Gray (95%CI 1.3%-16.3%). Patients receiving ≥20 Gray whole mean heart dose had a 3.4-fold (95%CI: 1.3-6.1) higher myocardial infarction rate than unirradiated patients. ERRs were higher for younger women, but the difference was not statistically significant; the ERR for patients aged younger than 45 years at breast cancer diagnosis was 24.6%/Gray, versus 2.5%/Gray for patients aged 50 years or older, p_{interaction}=0.07. ERR by time since breast cancer treatment were also estimated and will be discussed in the next paragraph. Endocrine therapy and chemotherapy (with or without anthracyclines) were not associated with increased myocardial infarction rate and neither the use of chemotherapy nor the presence of cardiovascular risk factors significantly confounded the association between whole mean heart dose and myocardial infarction rate.

The onset of increased ischemic heart disease rates after breast cancer treatment was studied in several chapters of this thesis. In the hospital-based cohort (Chapter 5) no significant increases in ischemic heart disease were observed in the first ten years after breast cancer treatment, neither for left-sided breast irradiation nor for internal mammary
chair irradiation (both compared to right-sided breast irradiation), and the proportional increase in the ischemic heart disease risk after internal mammary chain irradiation was greatest in the period more than twenty years after treatment. In the population-based cohort (Chapter 3), we, consistently, found no increased rates of hospitalization for ischemic heart disease in the first ten years after treatment. Power, however, was limited for this endpoint. Looking at the rates of hospitalization for any cardiovascular event by time since breast cancer treatment, increased rates were observed directly after treatment for patients irradiated to the internal mammary chain in addition to chest wall irradiation, but not for patients irradiated to the internal mammary chain only or in addition to breast irradiation. In Chapter 7, ERRs for myocardial infarction were estimated by time since breast cancer treatment, and tended to increase with longer follow-up (ERR for 0-9 years: 0.1% per Gray, ERR 10-14 years: 7.2% per Gray, ERR ≥15 years: 15.1% per Gray), but these differences were not statistically significant ($p_{interaction}$: 0.26).

Interaction between treatments in the pathogenesis of cardiovascular disease was assessed in Chapters 5, 6, and 7. Because nowadays both internal mammary chain irradiation and anthracycline-based chemotherapy are often recommended for women with e.g. poor prognostic features such as nodal involvement, it is important to assess such interaction. In Chapter 5, we studied the interaction between these treatments on both the additive and multiplicative scale for the endpoints any cardiovascular event, ischemic heart disease, heart failure, and valvular heart disease. Interaction on either scale could be neither rejected nor confirmed for all endpoints, although for heart failure the combined effect of internal mammary chain irradiation and anthracycline-based chemotherapy seemed more than additive ($p=0.06$). A more than nine-fold increased risk of heart failure was observed among patients treated with both internal mammary chain irradiation and anthracycline-based chemotherapy (HR 9.23 95%CI 6.01-14.18), whereas the separate HRs were 2.14 (95%CI 1.55-2.96) and 5.10 (95%CI 3.12-8.34), respectively, all compared to patients treated with neither internal mammary chain irradiation nor anthracycline-based chemotherapy. In Chapter 6, heart failure risk was also studied by anthracycline-based chemotherapy and radiotherapy, now not by radiation field, but in more detail, by whole mean heart dose and dose-volume parameters. In this study cases were mainly diagnosed with heart failure with reduced ejection fraction (HFrEF), and for these patients we observed that, although radiotherapy in addition to anthracycline-based chemotherapy seemed to increase the heart failure rate more than anthracycline-based chemotherapy alone (RR 12.4 95%CI 4.0-39.2 vs. RR 6.3 95% CI 3.0-13.2), radiotherapy itself did not increase the rate of heart failure in the overall analysis (RR 1.1 95%CI 0.59-1.9).

For the patients in our hospital-based cohort (Chapter 5), information on classic cardiac risk factors hypertension, diabetes, hypercholesterolemia, and smoking at time of breast
cancer diagnosis was collected. This allowed us to study the joint effects of classic cardiac risk factors and radiotherapy. The classic risk factors themselves were associated with increased rates of ischemic heart disease and heart failure. Radiation-related cardiovascular disease, however, was not significantly modified in the presence of classic risk factors. This means that although there is no significantly increase in relative risk of radiation-related cardiovascular disease, there is an increase in the absolute radiotherapy-associated rate due to differences in background risk caused by the classic risk factors themselves. This absence of effect modification by classic cardiac risk factors for the association between radiotherapy and myocardial infarction was confirmed in Chapter 7; in which we showed that the excess rate ratio per Gray for women with and without classic cardiac risk factors at breast cancer diagnosis were similar (p_{interaction}>0.50).

Our and previous studies have shown increased incidence rates of acute coronary syndromes. Because mouse models indicate that the mechanistic pathways behind radiation-induced atherosclerosis might differ from age-related atherosclerosis, it is conceivable that also the outcome of acute coronary syndromes subsequent to radiotherapy is different. Therefore, in Chapter 8, we studied whether radiotherapy influences the prognosis of acute coronary syndromes. From our hospital-based cohort, we selected all patients who suffered from acute coronary syndromes after being treated with radiotherapy, which came to a total of 398 patients. Highest heart doses in breast cancer radiotherapy are mainly caused by internal mammary chain irradiation. Hence, patients were compared based on treatment with internal mammary chain irradiation (yes/no). Ten-year cumulative incidence of cardiac death was 35% for internal mammary chain irradiated patients (95% CI 29%-41%) compared to 24% (95%CI 17%-31%) for patients without internal mammary chain irradiation (p=0.04). After correction for confounders, internal mammary chain irradiation remained associated with a higher cardiac death rate compared to no internal mammary chain irradiation (HR=1.7, 95%CI 1.1-2.5). Irradiation to the internal mammary chain was particularly associated with an increased rate of fatal acute coronary syndromes (HR 2.2 95% CI 1.2-3.9). Although further studies are needed, our results suggest that radiotherapy may not only increase the risk of acute coronary syndrome, but may also worsen acute coronary syndromes prognosis.

General discussion

A comparison with literature

In line with previously published studies, our research shows quite strongly increased heart failure rates after treatment with anthracycline-based chemotherapy. Our estimates of the proportional increase in both our cohort study (HR=4.18, Chapter 5) and in the heart failure case-control study (RR=4.1 for patients treated with a cumulative anthracycline dose of