Improved breast cancer survival rates have led to a growing population of breast cancer survivors, who are at risk of developing a new cancer in the contralateral breast. The current literature is inconclusive as to whether occurrence of contralateral breast cancer (CBC) per se will affect breast cancer survival, and how specific characteristics such as age and time interval between first and second tumour influence the survival. As breast cancer survivors potentially are faced with a worse prognosis if diagnosed with CBC, it is important to identify preventive therapy. Previous studies have suggested that common medications such as statins may protect against CBC, but the evidence is sparse. Established systemic breast cancer treatments, such as tamoxifen and chemotherapy, protect against CBC, however, few studies have examined how long the protective effects persist after end of treatment and whether the beneficial effects differ by patient and tumor characteristics of the first breast cancer. Other important questions concern whether the protective effect of tamoxifen during active treatment and afterwards is dependent on how long patients have been treated, and whether long-term use of tamoxifen will increase the risk of estrogen receptor (ER)-negative CBC.

The main objectives of the studies included in this thesis were to investigate the mortality after a CBC diagnosis and to identify preventive therapy against CBC. We examined these issues in two cohort studies based on Danish nationwide registries and in a multi-centre case-control study. The register-based cohort studies included patients diagnosed with breast cancer from the Danish Breast Cancer Group database while the case-control study was nested in the same database and seven population-based cancer registries in the United States and Canada. The cohort studies comprised 68,466 breast cancer patients diagnosed during 1978–2012 (paper 1) of whom 52,723 were diagnosed during 1996–2012 (paper 2). Patients who subsequently developed a new breast cancer in the contralateral breast were identified in a previously established database (N=3,004 in paper 1 and N=1,382 in paper 2). Cox regression analyses were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer-specific death associated with a CBC diagnosis (paper 1) and for CBC associated with statin use according to the National Prescription Registry (paper 2), with adjustment for potential confounding factors selected à priori from information available in the Danish registries. The case-control study (paper 3) comprised 1,521 cases with CBC and 2,212 age- and calendar-year-matched controls with unilateral breast cancer (UBC) diagnosed with a first breast cancer before age 55 years during 1985–2008. We obtained detailed information on treatment from medical records, while information on family history of breast cancer and other known breast cancer risk factors was obtained during telephone interviews. Multivariable conditional logistic regression models were used to estimate rate ratios (RRs) and 95% CIs for CBC associated with tamoxifen use and chemotherapy, with adjustment for potential confounding factors selected à priori.

Breast cancer-specific mortality rates were markedly higher after a CBC diagnosis compared with a UBC diagnosis (HR=2.48, 95% CI=2.31–2.66). Among patients diagnosed with CBC before age 70 years, we found increased breast cancer-specific mortality associated with a short interval
between diagnoses (<5 years) compared with a long interval (≥5 years) (age <50 years: HR=1.35; 95% CI=0.95–1.92 and age 50–69 years: HR=1.43; 95% CI=1.18–1.75). Post-diagnosis statin use was associated with a slightly reduced risk of CBC (HR=0.88; 95% CI=0.73–1.05). The inverse association was most pronounced for long-term use (HR=0.64; 95% CI=0.43–0.96), although the HR for long-term consistent use and high-intensity use approached unity. Among patients diagnosed with ER-negative disease, statin use was associated with a reduced risk of CBC (HR=0.67; 95% CI=0.45–1.00). Tamoxifen was associated with a decreased RR of CBC (ever versus never use: RR=0.76; 95% CI=0.63–0.92). The RR of CBC was reduced for current users of tamoxifen (RR=0.73; 95% CI=0.55–0.97) and for past users within 3 years of last use (RR=0.73; 95% CI=0.53–1.00). The strongest CBC risk reduction was observed for current users treated with tamoxifen for 4.5 years or longer (RR=0.44; 95% CI=0.27–0.73). There was no evidence of an increased risk of ER-negative CBC associated with long-term use of tamoxifen (RR=0.93; 95% CI=0.50–1.74). Use of chemotherapy (ever versus never) was associated with a reduced RR of CBC (RR=0.71; 95% CI=0.59–0.85) that seemed to persist up to 10 years after first breast cancer diagnosis (RR=0.73; 95% CI=0.56–0.95). RRs of CBC associated with tamoxifen and chemotherapy were largely independent of patient and tumor characteristics.

In conclusion, the results of this thesis showed a markedly higher breast cancer-specific mortality associated with the occurrence of CBC compared with UBC. We found higher breast cancer-specific mortality after CBC associated with a short interval between diagnoses among patients diagnosed with CBC before age 70 years. There was some indication that statins reduce the risk of CBC among breast cancer patients, especially patients diagnosed with ER-negative disease, but additional studies are needed to confirm the findings. Lastly, this thesis provides further evidence that treatment with tamoxifen and chemotherapy reduce the risk of CBC. This risk reduction appeared to persist for some time following completion of treatment. The largest CBC risk reduction was associated with long-term active treatment with tamoxifen.

Our results concerning mortality after CBC underscore the importance of developing risk prediction models to help clinicians identify the patients at high risk of a CBC who would benefit most from preventive therapy at the time of the first breast cancer diagnosis. The finding of a reduced CBC risk among statin users diagnosed with ER-negative breast cancer suggests that there may be other benefits of statins after a breast cancer diagnosis in addition to previous findings of reduced recurrences and mortality. Pilot trials are currently ongoing that will provide more evidence on the clinical benefits of statins in breast cancer. The observed CBC risk reductions associated with tamoxifen and chemotherapy supplement the findings from clinical trials and provide evidence of protection in ‘real world’ settings with varying levels of treatment durations and time since treatment stop. Our finding of a stronger CBC risk reduction among women actively being treated for a long period suggests that the recent recommendations that tamoxifen should be used for ten years is also beneficial in relation to CBC risk.