Summary

This thesis consists of three parts. The ***first part*** of this thesis was designed to investigate differences in treatment between different countries and different Dutch regions, the so-called "patterns of care" studies. Optimal curative treatment for early breast cancer consists out of locoregional therapy (surgery with or without radiotherapy) with or without systemic therapy (endocrine therapy, chemotherapy, and/or targeted therapy). International and national guidelines have been developed to enable optimal implementation of up to date evidence and expert-opinion based therapy for early breast cancer patients.

We compared the locoregional and systemic therapy in patients included in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial in **chapter two and three**. Differences were found in locoregional treatment between the different participating TEAM countries (Belgium, Germany, France, Greece, Ireland, Japan, the Netherlands, United Kingdom and the United States of America (USA)). Country appeared to be an independent predictive factor for type of surgery besides age at diagnosis, tumour stage and year of surgery. French patients had the greatest chance of breast conserving surgery and American patients the lowest chance. In addition, radiotherapy was not always given as part of breast-conserving therapy, ranging from 86% in the USA to 100% in France.

In the Netherlands, the implementation of guidelines is facilitated by the different comprehensive Cancer Centres (CCCs). We observed that patients in one CCC had a higher chance to receive breast conserving surgery compared to patients in another CCC. Besides, the rates of the sentinel lymph node procedure varied between the CCCs as well as the percentage of postoperative chemotherapy given. In conclusion, despite (inter)national consensus guidelines, there are major differences in therapy for postmenopausal early breast cancer patients between countries and within the Netherlands.

Endocrine therapy improves disease free survival and overall survival in the adjuvant setting in postmenopausal hormone sensitive breast cancer patients. However, all treatments have risks and side effects. Therefore, the ***second part*** of this thesis has been performed in the context of the TEAM trial.

Chapter four provides an introduction and an overview of the various so-called "switch studies" in postmenopausal women with hormone sensitive early breast cancer. A switch means sequential therapy of tamoxifen followed by an aromatase inhibitor (AI). The TEAM trial is one of these trials. The rationale for the sequential strategy is to improve efficacy of the treatment and to minimise the impact of adverse events observed with either treatment alone. The other chapters of part two, chapter five to eight, describe several substudies of the TEAM trial concerning side effects and the impact on quality of life of endocrine therapy.

For years, tamoxifen was the golden standard for patients with hormone sensitive early breast cancer. Therefore, the tolerability of tamoxifen is well defined and tamoxifen use has been associated with gynaecological symptoms, thromboembolic effects on one hand and positive effects on bone metabolism on the other hand. AIs were introduced in the last decennia of the twentieth century in patients with early breast cancer and they have been generally well tolerated. They have been associated with musculoskeletal adverse events.

Chapter five is dedicated to the bone metabolism of patients included in the TEAM trial in Belgium, Germany, the Netherlands and the USA. In TEAM patients using exemestane, the bone mineral density decreased and an increase was seen in bone turnover markers. In contrast, the opposite was observed for patients using tamoxifen: an increase in bone mineral density and a decrease in bone turnover markers. These results are generally consistent with results of other AI-studies.

In **chapter six** the effect of exemestane (as well as tamoxifen) on breast density was explored. Breast density is one of the strongest independent risk factors for developing breast cancer: women with over 75% of their breasts composed of dense fibroglandular tissue have a four to six times higher risk of developing breast cancer as compared to women with lower breast density percentages. In

our TEAM population of postmenopausal early breast cancer patients, breast density scores did not substantially change over time for patients using exemestane or tamoxifen, and there was not a difference between both therapies. Consequently, breast density was not a predictive marker for efficacy of adjuvant endocrine therapy.

Side effects of endocrine therapy can influence quality of life. In **chapter seven**, the quality of life of patients using tamoxifen was compared to the quality of life of patients using exemestane. A total of 742 Dutch TEAM patients were invited to complete questionnaire concerning quality of life at one and two years after start of endocrine therapy. Overall quality of life and most functioning scales improved over time. The only clinically relevant, and statistically significant difference between both treatment types concerned insomnia: exemestane-treated patients reported more insomnia than tamoxifen-treated patients.

In the last chapter of the second part, **chapter eight**, the association between physical activity, body weight and quality of life was examined in Dutch TEAM patients using lifestyle and quality of life questionnaires. It appeared that patients who maintained their high prediagnosis physical activity level and a healthy body weight, had a better quality of life after the diagnosis of breast cancer compared to patients who did not. Therefore, we recommend physicians to advise and support their patients in staying physically active and maintaining a healthy body weight after a breast cancer diagnosis.

In the ***third and last part*** of this thesis, several prognostic factors were explored in a consecutive series of early breast cancer patients who received a primary surgical resection (with or without radiotherapy) in the Leiden University Medical Centre between 1985 and 1994. Patients with a prior history of cancer (other than basal cell carcinoma or *in situ carcinoma*) were excluded. Age at diagnosis, TNM stage, locoregional and systemic therapy, locoregional/distant recurrence, second primary and death were recorded. Of all these tumours, oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) were determined and all tumours were classified and graded by one pathologist.

The influence of COX2 is described in **chapter nine**. COX2 is overexpressed in most human epithelial cancer and had been linked to various aspects of cancer progression. In our population, we examined COX2-expression by immunohistochemistry. COX2 was prognostic for disease free survival and overall survival in univariate analysis. However, COX2 did not remain independent in multivariable analysis. In patients with hormone receptor positive tumours, COX2 expression had a negative influence on outcome and this effect disappeared when endocrine therapy was administered, while it remained statistically significant when endocrine therapy was omitted. Our results suggest that COX2 plays a role in hormonal pathways.

In **chapter ten**, we investigated the prognostic value of the factors SNAIL, SLUG, and TWIST, as well as E-cadherin as N-cadherin in the process of epithelial mesenchymal transition (EMT). There is evidence that EMT plays a critical role in the development of invasiveness and metastatic potential of cancer. E-cadherin, which maintains cell-cell contacts, is thought to be a suppressor of invasion in carcinoma. Loss of E-cadherin and increased N-cadherin expression is a hallmark of EMT and subsequent invasion. In the above described consecutive series, the level of SNAIL and TWIST expression were associated with a worse patient relapse free period, specifically in patients with ER-positive tumours. Co-expression of SNAIL-TWIST was associated with low E-cadherin and high N-cadherin expression, especially in oestrogen-positive tumours. This suggests that, through interactions with the ER, SNAIL and TWIST may regulate E- and N-cadherin expression, and thereby inducing EMT.

Finally, the findings of the above mentioned chapters and their implications are discussed in **chapter eleven**.