Coming of age : treatment and outcomes in older patients with breast cancer

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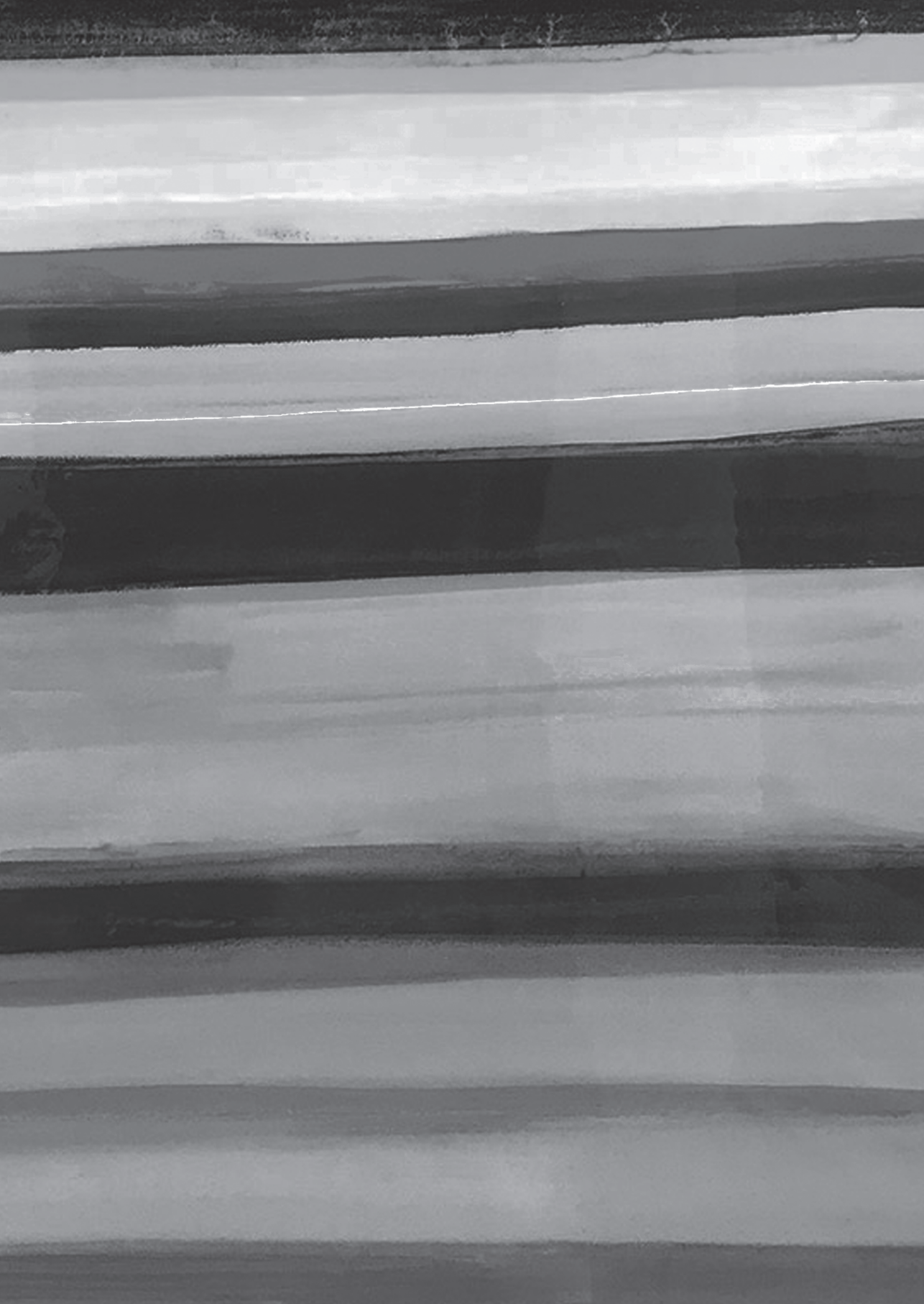

CHAPTER 1

General introduction and outline of this thesis

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INTRODUCTION

Patients with breast cancer are getting older

Populations around the world are rapidly ageing. In high-income countries, increasing longevity is mainly due to rising life expectancy among people aged 60 years and older.[1] Ageing of a population increases the exposure to age-related diseases, such as cancer.[1] In high-income countries, cancer is now surpassing cardiovascular disease as the leading cause of death and it is expected to become the leading cause of morbidity and mortality worldwide in the coming decades.[2] For this reason, we can expect an exponentially growing number of older patients diagnosed with cancer that will pose serious challenges to our health care system and resources.

Breast cancer is the leading contributor to cancer incidence and the second cause of cancer death among all cancers in women living in high income countries.[3] Breast cancer is often perceived as a disease that affects young women. However, the majority of women diagnosed with breast cancer is older than 65 as the probability of developing breast cancer increases with age. Among women aged between 50-59 years, one out of 44 will develop breast cancer during that age interval while among women aged over 70 years, it rises to one out of 15 women that will develop breast cancer.[4] With the ageing of the population, the number of women diagnosed with breast cancer will sharply increase in the coming decades. In the United States, it is estimated that the absolute number of women aged between 70 and 84 years diagnosed with invasive oestrogen positive breast cancer will rise by 4.0% per year (Figure 1).[5]

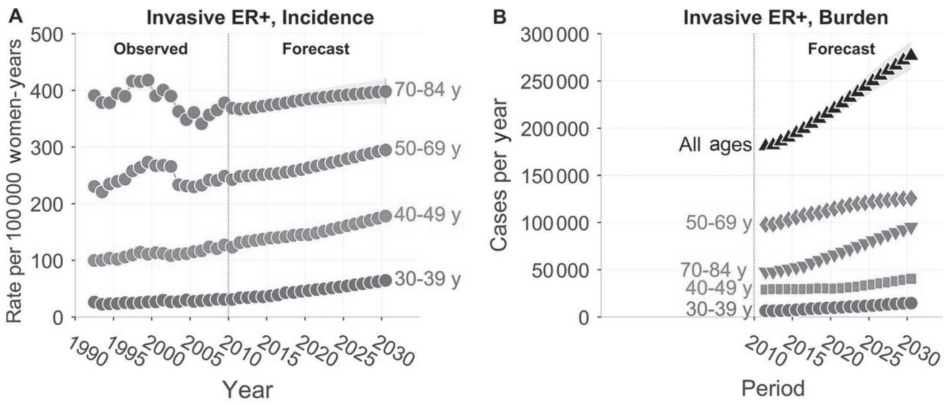

Figure 1. Observed and projected incidence of invasive and in situ estrogen receptor (ER)–positive breast tumours in Surveillance, Epidemiology, and End Results (SEER) 13 and corresponding forecasts of cancer burden in the entire United States. A) Observed and projected incidence of invasive ER+ tumours per 100 000 woman-years in SEER 13. B) Predicted burden of invasive ER+ tumours in the United States (number of newly diagnosed cases per year) by age group and overall. Adapted from Rosenberg et al.[5]

Old versus young

Older patients are more likely to present with estrogen and progesterone receptor positive tumours. Among patients aged 80-84 years, 85% is diagnosed with oestrogen receptor positive cancer compared to 60% among patients aged 30-34.[5] The proportion of patients presenting with Human epidermal growth receptor (HER2) receptor positive breast cancer decreases from 22% among patients younger than 40 years to 10% in patients aged 70 years and older.[6] Tumour size at diagnosis increases with age and this is most pronounced after the age of 80. Above the age of 70 years the proportion of patients with positive lymph nodes rises significantly.[7-9] Among postmenopausal patients, tumour grade does not appear to change with increasing age.[6] Although breast cancer survival significantly improved over the last three decades for younger patients, such an improvement was not observed among older patients.[7] This has led to an increasing gap in survival outcomes between younger and older patients.

There are many other aspects than breast cancer itself that distinguish older patients from young patients. In older patients, breast cancer occurs on the background of ageing. Due to the ageing process, there is a large variety in older individuals with respect to concomitant diseases, physical and cognitive functioning and physiological reserve. As a result, life expectancy among older patients varies considerably and does not merely depend on breast cancer prognosis. Ageing influences treatment decisions in several ways. In patients with a short life expectancy, the benefit of treatment might be limited as the patient is not expected to be alive long enough to experience that benefit. Moreover, comorbidities or polypharmacy can limit the efficacy of treatment or increase the risk of complications or toxicity related with treatment.[10] For these reasons, it is challenging for a clinician to estimate the potential benefits and harms of treatment strategies for an individual older patient.

Moreover, patient preferences for treatment might vary between younger and older patients. For the majority of older patients maintaining or increasing quality of life becomes more important than increasing length of life.[11] The burden of frequent hospital visits associated with radiotherapy and the risk of a second surgery are treatment-related aspects that withhold some older patients to undergo breast-conserving surgery.[12] Although a majority of patients would accept adjuvant chemotherapy, older patients are less willing to trade of cognitive or physical capacity for survival benefit.[13,14]

Research in older patients with breast cancer

Most international or national clinical guidelines on the treatment of breast cancer do not provide specific guidance for the treatment of older patients. Dutch guidelines do provide specific recommendations for the administration of chemotherapy in older patient. They state that 'chemotherapy should not be given to patients aged over 70 years, unless the

patient is considered very fit'.[15] There is no further elaboration on the concept 'very fit' nor is there any evidence to underline this statement. Instead, they argue evidence for the effectiveness of chemotherapy among patients aged over 70 years is not available and for this reason it should not be given. In 2012, the International Organization for Geriatric Oncology (SIOG) published an updated guideline with recommendations for the management of older patients with breast cancer.[6] Unfortunately, the common thread throughout the guideline was the inability to provide evidence based recommendations for this population.

Indeed, evidence to guide treatment of these patients remains scarce. Clinical trials often have inclusion criteria that, either directly or indirectly, preclude older patients from participating.[16,17] Furthermore, older patients who do participate in breast cancer trials may not be representative for the general older population due to selection of fitter older patients with a higher socio-economic status and with good cognitive function. These differences impair the external validity of a clinical trial and limit the extrapolation of outcomes to the wider older population with breast cancer.[18]

Moreover, it is questionable whether current trials provide endpoints that are adequate and relevant for older patients. Most clinical trials assess cancer-related outcomes, such as disease-free survival, recurrence-free survival or progression-free survival as their main endpoints.[16] First, the validity of these endpoints might be problematic among older patients. With increasing age, the risk of dying due to other causes than breast cancer, so called competing mortality, increases.[19,20] As a result, competing mortality influences cancer-related endpoints and this is not adequately addressed in the analyses of current clinical trials.[21] Furthermore, defining cause of death is challenging in older patients because some cancer treatments might influence non-cancer related deaths. Misclassification of cause of death is more likely to occur among older patients.[22] Most importantly, we should ask ourselves if cancer-related endpoints fit to the needs and desires of older patients. As described above, maintaining quality of life becomes an important aspect of treatment decisions. For older patients, side effects of therapy might outweigh the potential survival benefit.

Over the last decade, it was increasingly acknowledged that the lack of evidence based medicine in the growing older population with breast cancer should be addressed as this may contribute to survival differences between younger and older patients. International organizations such as the American Society for Clinical Oncology (ASCO), the European CanCer Organization (ECCO), the European Organiasation for Research and Treatment (EORTC) and the SIOG have urged researchers to include older patients in clinical trials and to design trials that are specifically focused on older patients.[6,21,23] Despite the encouragement of these important international organizations to include older patients in clinical trials, only 4% of the current clinical trials in breast cancer is focused on older patients.[16]

As current clinical trials will not improve evidence based medicine for the older population in the forthcoming years, alternative research methods should be considered. Although randomized clinical trials are considered the gold standard in evidence based medicine, observational studies could be a reasonable alternative when the adequate methodological methods are used.[24] Patients included in observational studies are more representative of the general population and thereby improve the external validity of research findings.

OUTLINE

The aim of this thesis is to better define which older patients will benefit from treatment and to improve our understanding of the impact of breast cancer treatment on both breast cancer related and non-breast cancer related outcomes. In **Part I,** we investigate the association with various treatment strategies on breast cancer related and non-breast cancer related outcomes. **Part II** discusses the long term prognosis of breast cancer among younger and older patients in the presence of competing causes of death. **Part III** elaborates on several methods for performing and evaluating research in the older population.

Part I: Evaluating treatment of older patients with breast cancer

The lack of evidence to guide treatment decisions and the heterogeneity among the older population has led to deviation from standard guidelines among older patients.[19] This might be justified for frail older patients who have a high chance of dying due to other courses or who are at a high risk of adverse events of treatment. In these patients, treatment according to guidelines might lead to overtreatment. On the other hand, some patients might not have received treatment while they would have gained benefit from this treatment. In this case, deviation from guidelines to withhold treatment may contribute to undertreatment. In **Chapter 2,** we use population-based data from European cancer registries to study variation in treatment strategies between countries in older patients with non-metastatic breast cancer and we assess whether country specific treatment strategies are associated with variation in relative survival between these countries. Older patients are often diagnosed with hormone receptor positive breast cancer. In this subgroup, several types of adjuvant endocrine treatment strategies are available.[25] In **Chapter 3**, we evaluate long-term outcomes of two types of endocrine treatment strategies in postmenopausal patients included in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial. **Chapter 4** evaluates the influence of age on physical functioning at time of diagnosis, one and two years after start of endocrine therapy among a subset of patients included in the TEAM trial.

Part II: Breast cancer prognosis in the presence of competing mortality

As life expectancy is increasing, older patients remain at risk of dying of breast cancer over a long time period. At the same time, the risk of dying from other causes than breast cancer

increases substantially with advancing age.[26] Survival estimates that take these competing causes of death into account are essential for individual decision making to balance between benefits and toxicities of cancer therapy.[27] As breast cancer can recur until 20 years after initial diagnosis,[28] it is relevant to investigate how breast cancer mortality and other cause mortality compete over a longer time period. In **Chapter 5**, the impact of age at diagnosis on long-term breast cancer mortality and other cause mortality is assessed using competing risk analysis. Moreover, comorbidities influence other cause mortality and possibly influence breast cancer mortality.[7,19,29] In **Chapter 6**, we study the impact of comorbidities and age at diagnosis on breast cancer mortality and other cause mortality.

Part III: From research setting to clinical practice: improving methodology in studies in older patients

In the world of research, we became accustomed with measurements and outcomes from a biomedical perspective. These measurements and outcomes may be disconnected from the experience and relevance in clinical practice and the patient itself. As a consequence, findings from clinical trials are often not reproducible in clinical practice, especially among older patients. In **Chapter 7**, we investigate how the construct of successful ageing has been defined and changed over the last century and how the definition of successful ageing influences our research methodology in the field of geriatrics and gerontology. In **Chapter 8**, we describe how the use of absolute risks instead of relative risks improves our understanding of impact of risk factors in clinical practice and how the use of absolute risks leads to different findings among older patients. In **Chapter 9**, we propose a new endpoint for clinical studies that will enable researchers to adequately include the patients experience in the evaluation of effectiveness of treatment among older patients.

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