Improving treatment outcomes in older patients with breast cancer

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TABLE OF CONTENTS

Chapter 1

General introduction and thesis outline

Breast cancer is the most commonly diagnosed malignancy among women, with every woman having a 1 in 7 lifetime risk of developing the disease [1]. The incidence of breast cancer increases with age and approximately 30 per cent of women is over the age of 70 years at the time of diagnosis [1, 2]. The proportion of older women with breast cancer is expected to rise due to the increasing breast cancer incidence and ageing of populations [1, 3]. Unfortunately, knowledge of the efficacy and side effects of treatment and other clinical outcomes in the older age group is limited. This is related to the fact that older women are often excluded in large randomised controlled trials [4]. In recent years, the view that patients are excluded from trials solely because of their older age seems to have changed [5]. However, the median age in breast cancer trials is still almost 8 years lower than the actual patient population [4]. But perhaps even more concerning than the age disparities is the fact that the enrolled older population is not representative of most older patients with breast cancer in terms of comorbidities, functional impairments, socioeconomic status, and tumour sizes [6, 7]. Studies investigating a representative older population are therefore urgently needed.

Differences between younger and older patients with breast cancer

Older women tend to develop breast cancers with a more favourable tumour biology than younger patients, as tumours in the older population are more often oestrogen receptor-positive, human epidermal growth receptor 2 (HER2)-negative and less proliferative [8, 9]. However, older patients are at higher risk to be diagnosed with larger tumour sizes and nodal involvement [10, 11]. The increased risk of advanced disease can be attributed to several factors, including reduced self-awareness and the upper age limit of 75 years for screening [12]. These variations in tumour characteristics are not the only difference between older and younger patients. With ageing, biological changes occur at multiple levels: fat mass increases while muscle tissue, bone density and organ functions decrease [13]. These changes may affect or coincide with increasing numbers of comorbidities and deterioration of functions, such as cognitive and physical functioning, resulting in reduced physical activity and decreased ability to carry out activities of daily living [14]. If patients are deficient in several of the geriatric domains, including physical function, somatic function, emotional function, nutrition, mobility, cognition, and social support, they are often referred to as ‘frail’. Frailty is used to describe a condition in which the patient’s resilience is compromised due to reduced physiologic reserve caused by the accumulation of ageing processes in organs and tissues [15]. Ageing may also be accompanied by life events, such as retirement, the loss of loved ones and relocation to senior housing, requiring psychological adaptations. All these processes differ between individuals and are not directly linked to calendar age, resulting in a heterogeneous older population with large variation in fitness, frailty, and resilience.

The European Society of Breast Cancer Specialists (EUSOMA) and International Society of Geriatric Oncology (SIOG) recommend using a geriatric screening tool for all patients aged 70 years and older to distinguish fit people from potentially frail ones [16]. For the potentially frail patients, a full geriatric assessment can provide an overview of individual general health and resilience and can be used to guide integrated geriatric and supportive care interventions [17, 18]. A geriatric assessment is a multidisciplinary evaluation of several health domains, including comorbidities, medication use, nutrition, cognition, functional status, mobility, and psychosocial status. This insight about frailty, concomitant diseases, and resilience also gives valuable information for treatment allocation itself.

Treatment of older patients with breast cancer

Treatment allocation in older patients presents unique challenges and depends on many factors. One of these challenges emerges from the fact that the risk of dying from causes other than breast cancer is higher in older patients than in younger ones, with more than 50% of patients older than 75 years dying of other causes [14]. Nevertheless, previous research showed that patients over the age of 75 are the only group in whom breast cancer-related survival is not improving [19]. This different trend in breast cancer-specific survival for the oldest age group suggests the potential for greater survival gains from treatment. Choosing the right treatment strategy for older adults, however, is further complicated by the fact that this age group is known to have higher risks of side effects and reduced treatment effectiveness when compared to their younger counterparts, especially if patients have concomitant diseases or are (pre-)frail [20-23]. Furthermore, most guidelines do not provide specific guidance for specific subgroups, such as older patients. As a result, physicians frequently deviate from guidelines, making older patients particularly vulnerable to the risks of both under- and overtreatment [24, 25]. Older patients themselves may also have other treatment priorities, such as maintenance of independence and quality of life instead of extension of life at all costs [26]. The benefits of treatment must therefore be carefully weighed against the risks and tailored to an individual. However, information on relevant outcome measures for older patients is often lacking [27].

THESIS OUTLINE

Overall, the main objective of this thesis is to gain further insight in relevant outcome measures for older patients after breast cancer treatment. The specific aims of this thesis are threefold. First, to improve breast cancer care for the older population by identifying patients who are likely to develop postoperative complications and side effects of therapy. Secondly, to investigate long-term effects of breast cancer treatment on quality of life and physical and psychological functioning. Third, to illustrate treatment patterns and survival of patients with HER2-overexpressing metastatic breast cancer in different age groups over time.

Climb Every Mountain (CLIMB) study

Data from the CLIMB study were used in chapters 2, 3, 4, 6, 7 and 8. The CLIMB study is a longitudinal multi-centre cohort study that included women aged 70 years and older diagnosed with non-metastatic (Tis-4, N0-3, M0) breast cancer from 9 sites across the Netherlands between 2013 and 2018. A geriatric assessment was conducted at diagnosis, after which patients were given the opportunity to participate for follow-up assessments. If patients did not want to participate in follow-up visits, information about tumour characteristics, treatment, complications and side effects were retrieved from medical records 15 and 27 months after diagnosis (Fig. 1). Patients participating in follow-up underwent multiple assessments and completed several questionnaires at 3, 9, 15, and 27 after diagnosis. At each follow-up visit, information on patient, tumour, and treatment characteristics, and their outcomes were retrieved by trained medical personnel from the medical records. The questionnaires were also sent to patients at 60 months after diagnosis and the vital status and date of death were obtained from medical records or the municipal Personal Records Databases at the same timepoint.

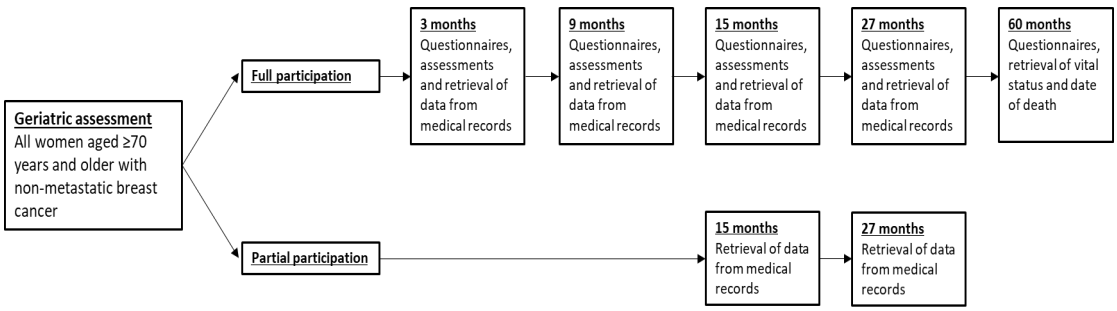

Fig. 1: Flowchart of the Climb Every Mountain study

Bridging the Age Gap in Breast Cancer (Age Gap) study

Data from the Age Gap study were used in chapters 2, 4 and 8. The Age Gap study is a longitudinal multi-centre cohort study that included women aged 70 years and older diagnosed with non-metastatic (Tis-3, N0-3, M0) breast cancer from 56 sites across the United Kingdom between 2013 and 2018. Participants could participate at three levels: full (including follow-up questionnaires), partial (no follow-up questionnaires), or by proxy (data collection only) (Fig. 2). A geriatric assessment was conducted at diagnosis for patients who participated fully or partially. Patients participating in follow-up completed several questionnaires at 6 weeks and 6, 12, 18 and 24 months after diagnosis. Regardless of the participation level, information on patient, tumour, and treatment characteristics, and their outcomes were retrieved by trained medical personnel from the medical records at each follow-up visit.

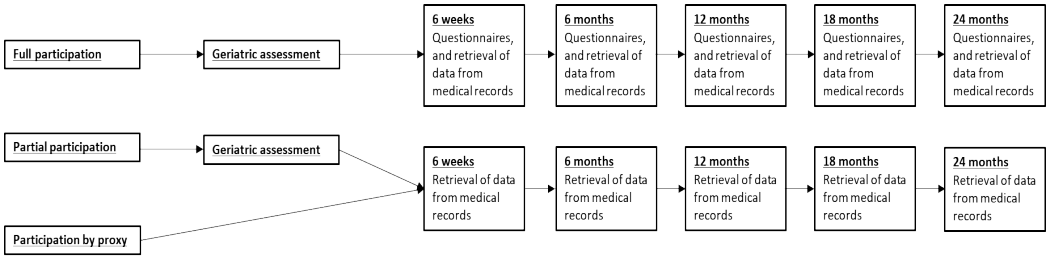

Fig. 2: Flowchart of the Bridging the Age Gap in Breast Cancer study

PART I: EVALUATION OF BREAST CANCER TREATMENT OUTCOMES IN OLDER WOMEN

Most knowledge about the effectiveness and side effects of treatment is based on trials conducted in younger and fit older patients. Since this is unlikely to change in the near future, knowledge of observational cohort studies is needed to tailor care for the older generation [27]. In **Chapters 2 and 3** the observational Climb Every Mountain cohort study including older patients aged 70 years and older with early-stage breast cancer is used to identify factors predictive of postoperative complications or side effects of adjuvant endocrine therapy, respectively. Both chapters also describe the impact of complications or side effects on an individual's quality of life and ability to perform activities of daily living.

Another way to get useful information about treatment strategies and its outcomes is to compare different countries. Previous research has shown that treatment allocation between the United Kingdom (UK) and the Netherlands differs, with UK patients generally receiving more systemic treatment [28]. **Chapter 4** compares the use of adjuvant endocrine therapy, side effects, and survival of older patients with breast cancer between the Netherlands and the UK.

Interesting information can also be obtained from national cancer registries. **Chapter 5** gives an overview of treatment allocation and survival outcomes of patients in different age groups diagnosed with synchronous HER2-overexpressing metastatic breast cancer between 2005 and 2021 in the Netherlands.

PART II: PATIENT REPORTED OUTCOME MEASURES IN OLDER WOMEN

The most frequently reported outcomes in cancer studies are cancer-related outcomes, such as recurrences, breast cancer-specific survival and overall survival. Although both outcomes are considered the gold standard in clinical trials, they may be less meaningful to older patients. In fact, a recent systematic review showed that older patients with cancer ranked quality of life as a higher priority than survival [29]. Quality of life is a multidimensional and dynamic concept of an individual's perception of their position in life [30]. Since this definition is rather broad and subjective, a recent qualitative study investigated the key determinants of quality of life in older patients [31]. The most commonly chosen determinants were those related to physical functioning and physical health. Psychological and cognitive functioning was also perceived as important. The goal of **Chapter 6** is to assess changes in physical activity and physical functioning in the first five years after breast cancer diagnosis and to investigate which factors affect these outcomes. **Chapter 7** presents psychological outcomes in older women with early-stage breast cancer in the first five years after diagnosis. Finally, because we previously found large differences in treatment allocation between the Netherlands and the UK with similar survival rates, **Chapter 8** compares the quality of life of older women with breast cancer between the Netherlands and the UK to better understand the impact of different treatment strategies on older patients with breast cancer.

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PART I:
EVALUATION OF BREAST CANCER TREATMENT OUTCOMES IN OLDER WOMEN

Chapter 2:

Predicting postoperative complications and their impact on quality of life and functional status in older patients with breast cancer.

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Abstract

Background
The percentage of older patients undergoing surgery for early-stage breast cancer has decreased over the past decade. This study aimed to develop a prediction model for postoperative complications to better inform patients about the benefits and risks of surgery, and to investigate the association between complications and functional status and quality of life (QoL).

Methods
Women aged at least 70 years who underwent surgery for Tis–3 N0 breast cancer were included between 2013 and 2018. The primary outcome was any postoperative complication within 30 days after surgery. Secondary outcomes included functional status and QoL during the first year after surgery, as assessed by the Groningen Activity Restriction Scale and the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-BR23 questionnaires. A prediction model was developed using multivariable logistic regression and validated externally using data from the British Bridging the Age Gap Study. Linear mixed models were used to assess QoL and functional status over time.

Results
The development and validation cohorts included 547 and 2727 women respectively. The prediction model consisted of five predictors (age, polypharmacy, BMI, and type of breast and axillary surgery) and performed well in internal (area under curve (AUC) 0.76, 95 per cent c.i. 0.72 to 0.80) and external (AUC 0.70, 0.68 to 0.72) validations. Functional status and QoL were not affected by postoperative complication after adjustment for confounders.

Conclusion
This validated prediction model can be used to counsel older patients with breast cancer about the postoperative phase. Postoperative complications did not affect functional status nor QoL within the first year after surgery even after adjustment for predefined confounders.

Introduction

Older women with breast cancer comprise a heterogeneous group with large differences in fitness and frailty. The relative efficacy and risk of complications from treatment, and impact on longer-term physical function and quality of life (QoL) may therefore vary widely. Consequently, it might not be appropriate to extrapolate the results of clinical trials based on younger and relatively healthy patients to older patients with breast cancer.

As a result, clinicians frequently deviate from standard treatment owing to patients' advanced age, co-morbidities, frailty or patients' preferences [1–3], leading to a lower proportion undergoing surgery and a higher proportion treated with primary endocrine therapy than among younger patients [4–6]. In the Netherlands, the percentage of patients aged 75 years or older with stage I–II breast cancer who did not undergo surgery increased significantly from 11.8 per cent in 2000 to 32.1 per cent in 2017 [7]. It is questionable whether withholding surgery is justified, as postoperative morbidity and mortality rates following breast cancer surgery are low [8, 9]. Survival is arguably the most important outcome in cancer treatment. It is also important to consider possible complications of treatment and their long-term impact on QoL, which may be relatively more important to older women [10]. Varying incidence rates of postoperative complications have been reported, ranging from 2 to 50 per cent [8, 9 , 11–14]. The most frequently reported complications are wound infections and seroma formation. Although these complications may be considered relatively innocuous, they might have a great impact on the functional status and QoL of those affected. These aspects have received limited attention but are significant in the breast cancer population [10, 15]. It is therefore important to identify patients at risk of developing postoperative complications, and to assess the impact of these complications on QoL and functional performance.

The objective of this study was to develop and validate a risk prediction model for postoperative complications in older patients with breast cancer using clinical and geriatric predictive factors, and to evaluate whether postoperative complications affect both functional status and QoL in the first year after surgery.

Methods

Design and study population of development cohort
Patients who underwent surgery were selected from the prospective and longitudinal CLIMB (Climb Every Mountain) cohort study. This study included patients aged 70 years and older with primary breast cancer (Tis–3 N0–3) between 2013 and 2018 in nine Dutch hospitals. Exclusion criteria were a previous breast cancer history, distant metastases, inability to read Dutch, and advanced dementia.

Data collection for development cohort
A geriatric assessment was conducted at diagnosis as standard care, which included a history of co-morbidities, use of medication, nutritional status (Malnutrition Universal Screening Tool) [16], cognition (Mini Mental State Examination, MMSE) [17], physical function (Timed Up and Go test) [18], and functional status (Groningen Activity Restriction Scale, GARS) [19]. The GARS is a validated questionnaire assessing 11 activities of daily living and seven instrumental activities of daily living. Patients were requested to indicate whether they could perform these activities, with or without assistance. Answers were given on a scale of 1–4, where 1 stands for being able to perform the actions independently and 4 indicates complete dependency. The total score ranges from 18 to 72, with higher scores indicating worse functional status. The GARS was categorized into four groups (below 19, no dependency; 19–28, some dependency; 29 or more, disabled; unknown, data missing) [20–22]. If less than 10 per cent of the answers were missing (only 1 question), the average mean score for the other answers was taken and recorded. If more than 10 per cent of answers in an independent questionnaire were missing, the score for the whole questionnaire was classified as unknown.

One week after the geriatric assessment, eligible women were asked to confirm whether they wanted to participate in the CLIMB study and written informed consent was obtained from all participants. The CLIMB study comprised three follow-up visits, 3, 6, and 12 months after diagnosis. At each follow-up, clinical data, including patient, tumour, treatment characteristics, and complications were retrieved from the medical records. The follow-up visits also included multiple assessments and completion of questionnaires, including cognition (MMSE), physical function (Timed Up and Go test), functional status (GARS), and QoL (Table S1). QoL was assessed by means of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and its breast cancer-specific module, QLQ-BR23 [23–25]. The optional questions in the breast cancer-specific module concerning sexual function, sexual enjoyment, and upset by hair loss were excluded from the total score, as these questions were answered by a limited number of women.

For the QLQ-C30 scores, the outcome was assessed as clinically relevant according to the findings of Musoro and colleagues [26]. For the QLQ-BR23 questionnaire, a difference of 10 points or more was considered clinically relevant [27]. To obtain as much information as possible on CLIMB cohort participants, including those not attending follow-up visits, information on tumour characteristics, treatment, and complications were retrieved from the medical records 1 year after diagnosis (Fig. S1).

Design and study population of validation cohort

Patients who underwent surgery were selected from the Bridging the Age Gap in Breast Cancer study. Extensive details of the procedures of this cohort have been published elsewhere [14, 28]. In short, this was a prospective, multicentre, observational cohort study of women aged 70 years or older with primary operable invasive breast cancer, diagnosed between 2013 and 2018 at 56 breast units in England and Wales. Similar data items were recorded, including QLQ-C30 scores (Table S1). The Age Gap cohort recruited women with dementia, but these were excluded from the present analyses to give a more comparable data set to the CLIMB cohort.

Classification of variables

Patients were assigned to three groups according to age (70–74, 75–79, 80 years or more). Tumour size was classified as 0–2 cm, larger than 2 cm or unknown. If the pathological size was missing, the clinical size was used. Nodal status was classified as either no positive nodes (N0) or at least one positive node (N+). If the pathological lymph node status was not recorded, the clinical stage was used. Breast surgery was categorized as breast-conserving surgery, mastectomy or unknown. If patients initially underwent breast-conserving surgery and a later mastectomy, the most extensive procedure was used in the analyses. Axillary surgery was classified as sentinel node biopsy, axillary lymph node dissection (ALND) or unknown. Patients who underwent sentinel node biopsy first followed by a later completion ALND were classified as having had the latter. Any co-existing diseases were registered according to the Charlson Co-morbidity Index (CCI), without adjustment for age [29–31]. Breast cancer was not included, because this index quantifies the presence of co-existing diseases at breast cancer diagnosis. BMI was subdivided into four groups (less than 20.0, 20.0–24.9, 25.0 kg/m2 or more, unknown). Polypharmacy was defined as taking five or more types of medication, and documented as yes, no or unknown [32].

Outcome

The primary outcome was any postoperative complication, defined as any complication occurring within 30 days after surgery requiring treatment measures not applied routinely after surgery. Secondary outcomes were QoL and functional status after 3, 6, and 12 months in patients with and without postoperative complications.

Statistical analysis

The χ2 test and Fisher's exact test were used to assess differences between patients who participated in the CLIMB and Age Gap cohorts. Predetermined potential risk factors were examined in univariable logistic regression analyses to calculate odds ratios (ORs) with 95 per cent confidence intervals and P values for the association between risk factors as independent variables and postoperative complications as the dependent variable. These predictors for the univariable model were based on earlier research, and consisted of age, nodal status, tumour size, type of (axillary) surgery, CCI score, BMI, polypharmacy, Malnutrition Universal Screening Tool score, the Timed Up and Go test, and functional status (GARS) [11–13, 33–38]. A prediction model was built by using multivariable logistic regression analysis that included the statistically significant outcomes of the univariable logistic regression analyses, in combination with variables identified in previous studies. A receiver operating characteristic (ROC) curve was used to test internal validity of the prediction model, by calculating the area under the curve (AUC). After selecting the model with the highest AUC, points were attributed to each predictor by creating a Kattan-style nomogram [39]. For internal validation, bootstrapping was performed 1000 times to avoid overfitting of the model. External validation was also undertaken with construction of a ROC curve and calibration plots. Calibration was performed by creating three equally large groups, consisting of patients with a low, medium or high probability of developing a postoperative complication.

Functional status and QoL were assessed by plotting graphs of mean scores at each time point with corresponding standard deviations (SD) for patients with and without postoperative complications. Multivariable linear mixed models were used to assess whether this changed significantly over time. An advantage of linear mixed models is that they also include incomplete patient sets, by assuming that the data are missing at random [40]. Functional status and QoL were both analysed separately as dependent variables with postoperative complications as independent categorical variable and time after surgery (3, 6, and 12 months) as independent continuous variable. All predefined confounders were added to the model as fixed variables. These predefined confounders were age, nodal status, tumour size, polypharmacy, co-morbidities, and BMI [15, 41–46]. Any interaction between postoperative complications and time was tested to assess whether complications were time-dependent. For sensitivity analysis, QoL and functional status were analysed with inclusion of only seromas as postoperative complication. All analyses were performed in SPSS® version 25.0 (IBM, Armonk, New York, USA) and Stata® SE version 16.0 (StataCorp, College Station, Texas, USA). For all analyses, the threshold for a two-sided, statistically significant P value was 0.050.

Results

The present study included a total of 547 women from the CLIMB cohort and 2727 women from the Age Gap cohort with breast cancer (Tis–3 N0–3), who underwent surgery and for whom outcome data were available (Fig. S1).

Table 1: Patient characteristics in the two cohorts

	CLIMB	Age Gap	p-value*
Age (years)			<0.001
70-74	270 (49.4)	1145 (42.0)	
75-79	120 (21.9)	863 (31.6)	
≥ 80	157 (28.7)	719 (26.4)	
Nodal status			<0.001
N0	436 (79.7)	2298 (84.3)	
N+	88 (16.1)	428 (15.7)	
Unknown	23 (4.2)	1 (0.0)	
Tumour size (cm)			<0.001
0-2	348 (63.6)	1650 (60.5)	
> 2	193 (35.3)	1077 (39.5)	
Unknown	6 (1.1)	0 (0.0)	
Breast surgery			0.059
Breast conserving	307 (56.1)	1649 (60.5)	
Mastectomy	240 (43.9)	1078 (39.5)	
Axillary surgery			<0.001
None	34 (6.2)	85 (3.2)	
Sentinel node procedure	408 (74.6)	2133 (78.2)	
Axillary lymph node dissection	99 (18.1)	508 (18.6)	
Unknown	6 (1.1)	1 (0.0)	
Charlson Comorbidity Index			<0.001
0	293 (53.6)	1411 (51.7)	
1	133 (24.3)	452 (16.6)	
≥ 2	121 (22.1)	864 (31.7)	
BMI (kg/m2)			<0.001
20-24.9	173 (31.6)	676 (24.8)	
≥ 25	352 (64.4)	1557 (57.1)	
< 20	20 (3.6)	88 (3.2)	
Unknown	2 (0.4)	406 (14.9)	
Polypharmacy			<0.001
No	305 (55.8)	1571 (57.6)	
Yes	219 (40.0)	1156 (42.4)	
Unknown	23 (4.2)	0 (0.0)	
Functional status (GARS)			
< 19	230 (42.0)		
19 - 28	234 (42.8)		
≥ 29	73 (13.4)		
Unknown	10 (1.8)		

Values in parentheses are percentages. GARS, Groningen Activity Restriction Scale.
*$\chi 2$ or Fisher's exact test.

Patient and tumour characteristics of the development (CLIMB) and validation (Age Gap) cohorts are shown in Table 1. Almost three-quarters of the patients ranged in age from 70 to 79 years (71.3 and 73.6 per cent in CLIMB and Age Gap cohorts respectively). The majority of patients had lymph node-negative disease (79.7 and 84.3 per cent). Most patients underwent breast-conserving therapy (56.1 and 60.5 per cent), and had a sentinel node procedure (74.6 and 78.2 per cent). Almost half of all patients had a CCI score of 1 or higher (46.4 and 48.3 per cent).

Postoperative complications

A total of 285 complications occurred in 224 patients (41.0 per cent) in the CLIMB population, and 1205 complications in 984 patients (36.1 per cent) in the Age Gap cohort (Table 2). Some patients had more than one complication (57 and 190 patients respectively). The most frequent complications were seromas (26.3 per cent in both cohorts), wound infections (9.5 and 5.8 per cent), and haematomas (9.0 and 6.2 per cent). In the CLIMB cohort, two patients (0.4 per cent) died within 1 week after surgery, whereas no patient in the Age Gap cohort died within 30 days after surgery.

Table 2: Postoperative complications that required treatment in first 30 days in both cohorts

	CLIMB	Age Gap	p-value*
All complications	285 (52.1)	1205 (44.2)	0.001
Patients with at least one complication	224 (41.0)	984 (36.1)	0.031
Wound infection	52 (9.5)	158 (5.8)	0.002
Haemorrhage	17 (3.1)	28 (1.0)	0.001
Seroma	144 (26.3)	718 (26.3)	0.983
Hematoma	49 (9.0)	169 (6.2)	0.018
Lymphedema	14 (2.6)	13 (0.5)	<0.001
Death	2 (0.4)	0 (0.0)	0.074
Necrosis	0 (0.0)	17 (0.6)	0.095
Wound, non-infectious	5 (0.9)	42 (1.5)	0.263
Somnolence	0 (0.0)	32 (1.2)	0.007
Allergic reaction	0 (0.0)	4 (0.1)	1.000
Arrythmia	0 (0.0)	12 (0.4)	0.237
Embolism, infarction, stroke	2 (0.4)	10 (0.4)	1.000
Atelectasis	0 (0.0)	1 (0.0)	1.000

Values in parentheses are percentages. *$\chi 2$ or Fisher's exact test.

Age, nodal status, tumour size, type of breast surgery, type of axillary surgery, and the Timed Up and Go test were statistically significantly associated with postoperative complications in a univariable logistic regression model (Table S2). In the multivariable logistic regression model, the effect of nodal status, tumour size, and the Timed Up and Go test disappeared, and so these variables were omitted from the final model. The final model included five predictors: polypharmacy, BMI, type of axillary surgery, type of breast surgery, and age.

In the final model, the type of breast surgery was strongly correlated with postoperative complications. Mastectomies had higher rates of postoperative complications than breast-conserving surgery (OR 5.27, 95 per cent c.i. 3.50 to 7.93; P < 0.001) (Table 3 and Fig. S2). Patients aged 80 years or more had significantly higher rates of complications than those aged between 70 and 74 years (OR 1.70, 1.06 to 2.72; P = 0.029).

Table 3: Multivariable logistic regression analysis of association between patient characteristics and occurrence of postoperative complications in the CLIMB and Age Gap cohorts

	CLIMB			Age Gap		
	No. of patients	Odds ratio*	p-value	No. of patients	Odds ratio*	p-value
Age			0.086			0.313
70-74	270 (49.4)	1.00 (reference)		1145 (42.0)	1.00 (reference)	
75-79	120 (21.9)	1.13 (0.68 - 1.89)		863 (31.6)	0.92 (0.75 - 1.12)	
≥ 80	157 (28.7)	1.70 (1.06 - 2.72)		719 (26.4)	1.08 (0.88 - 1.34)	
Most extensive surgery			<0.001			<0.001
Breast conserving	307 (56.1)	1.00 (reference)		1649 (60.5)	1.00 (reference)	
Mastectomy	240 (43.9)	5.27 (3.50 - 7.93)		1078 (39.5)	3.35 (2.81 - 4.00)	
Most extensive axillary surgery			<0.001			<0.001
No axillary surgery	34 (6.2)	1.00 (reference)		85 (3.2)	1.00 (reference)	
Sentinel node procedure	408 (74.6)	0.48 (0.22 - 1.05)		2133 (78.2)	1.23 (0.75 - 1.99)	
Axillary lymph node dissection	99 (18.1)	2.20 (0.91 - 5.32)		508 (18.6)	2.29 (1.37 - 3.81)	
Unknown	6 (1.1)	1.51 (0.23 - 10.12)		1 (0.0)	†	
Body Mass Index (BMI)			0.766			0.924
20-24.9	173 (31.6)	1.00 (reference)		676 (24.8)	1.00 (reference)	
≥ 25	352 (64.4)	1.25 (0.81 - 1.92)		1557 (57.1)	0.95 (0.77 - 1.16)	
< 20	20 (3.6)	0.96 (0.33 - 2.81)		88 (3.2)	0.88 (0.54 - 1.44)	
Unknown	2 (0.4)	†		406 (14.9)	0.93 (0.69 - 1.25)	
Polypharmacy			0.613			0.183
No	305 (55.8)	1.00 (reference)		1571 (57.6)	1.00 (reference)	
Yes	219 (40.0)	1.17 (0.77 - 1.76)		1156 (42.4)	1.13 (0.95 - 1.35)	
Unknown	23 (4.2)	0.74 (0.25 - 2.19)		0 (0.0)	†	

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Could not be calculated because of the small numbers.

Validation

The AUC for the development cohort was 0.76 (95 per cent c.i. 0.72 to 0.80) after bootstrapping, compared with 0.70 (0.68 to 0.72) for the external validation cohort. In both cohorts, the risk of postoperative complications increased with increasing risk score (14.8 versus 20.4 per cent in low-risk group, 43.3 versus 32.7 per cent in medium-risk group, and 67.2 versus 56.4 per cent in high-risk group in development and validation cohorts respectively; P < 0.001) (Fig. 1).

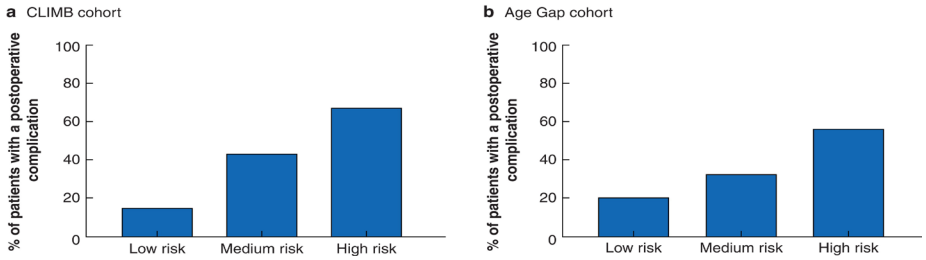


Fig. 1: Calibration of prediction tool in the development (CLIMB) and validation (Age Gap) cohorts **a** CLIMB cohort and b Age Gap cohort. **a,b** P < 0.001 (chi-square test).

Functional status and quality of life

For analyses of QoL and functional status, only participants who were enrolled for the follow-up questionnaires and who did not withdraw consent before the first follow-up (320 patients) were included from the CLIMB cohort. The response rate was 92.8 per cent (297 of 320 patients) after 3 months, 85.6 per cent (255 of 298) after 6 months, and 89.5 per cent (248 of 277) after 12 months (Fig. S1).

Patients with postoperative complications had statistically significantly higher mean GARS scores than those without any complication, indicating worse functional status (b=1.96, 95 per cent c.i. 0.64 to 3.28; P = 0.004) (Table S3 and Fig. 2a). This effect was, however, very small and no longer significant when adjusted for predefined confounders (b=0.51, −0.68 to 1.71; P = 0.402). No statistically significant interaction was found between time and postoperative complications with regard to functional status (b=−0.11, −0.32 to 0.10; P = 0.291), indicating that changes in functional status did not differ over time between patients with or without a postoperative complication. The association between postoperative complications and effect on functional status was also analysed separately for seromas. Again, no statistically significant or clinically relevant difference was found in functional status after adjustment for predefined confounders (results not shown).

There was no statistically significant difference in QoL between patients with or without postoperative complications in either the generic (b=−1.43, −5.19 to 2.32; P = 0.453) or breast cancer-specific questionnaire (b=−2.59, −6.56 to 1.38; P = 0.200) (Table S3 and Fig. 2b,c). Body image scores were significantly lower among patients with a postoperative complication after correction for predefined confounders (b=−4.98, −9.07 to −0.89; P = 0.017). This impact on body image was probably explained by the type of surgery performed, as the effect disappeared when corrected for type of surgery. Moreover, a difference of 4.98 points on the body image scale is small and therefore not clinically relevant [27]. None of the other subscale scores showed any statistically significant differences. Seromas did not affect QoL in the first year after surgery (results not shown).

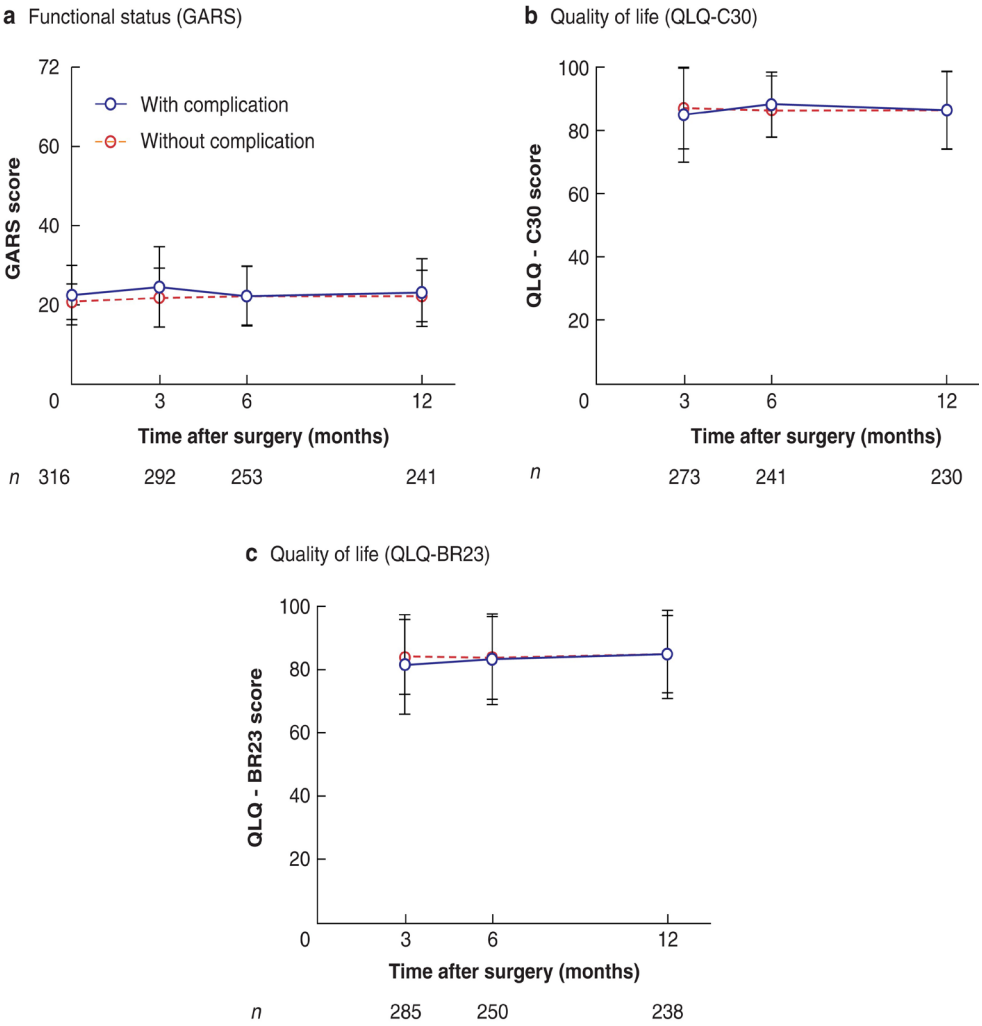


Fig. 2: Functional status and quality of life over time in CLIMB cohort
a Functional status (Groningen Activity Restriction Scale, GARS), **b**, quality of life assessed using the EORTC QLQ-C30 and c its breast-specific module QLQ-BR23. A higher GARS score denotes a worse functional status, whereas a higher QLQ score indicates better quality of life. Values are mean(s.d.).

Discussion

In the present study, 41.0 per cent of older patients with breast cancer developed a postoperative complication within 30 days after surgery. A prediction tool was designed for complication risk, with good internal and external validity. Postoperative complications did not affect functional status or QoL in the first year after surgery after adjustment for predefined confounders.

The number of older patients with breast cancer who undergo surgery varies widely between European countries [47]. A recent study [7] showed that the number of patients with stage I–II breast cancer aged over 75 years receiving surgery decreased, and the percentage of those who received endocrine therapy (either neoadjuvant or adjuvant or as primary treatment) increased between 2000 and 2017. Moreover, breast cancer-specific and overall survival is worse for patients receiving primary endocrine therapy compared with those undergoing surgery followed by adjuvant endocrine therapy [28, 48]. The reason for this recent change in treatment strategy is unknown, but might be based on fear of postoperative complications, and loss of independence and QoL [49]. The probable survival benefit for operated patients, combined with the present findings that postoperative complications do not affect QoL or functional status in the first year after diagnosis, might not justify this decrease in patients receiving surgical treatment.

The present results have shown that postoperative complications do not have a clinically relevant impact on QoL and functional status over time. In contrast, a previous study [43] of nearly 6000 nursing home residents in the USA noted a functional decline in 58 per cent of women 1 year after breast cancer surgery. One could argue, however, that nursing home residents may naturally exhibit a decline in functional status, regardless of interventions, and were probably older and more frail than the average patient in the CLIMB and Age Gap cohorts [50]. Earlier research from Wyld and co-workers [28], using data from over 2000 UK women aged over 70 years in the Age Gap study, found that breast cancer surgery was associated with a small functional decline in the first 6 weeks after surgery, which did not recover even after 2 years. This difference might, however, be explained by the fact that only one question was asked concerning the ability to perform usual activities, whereas the present study used a complete questionnaire (GARS) designed to measure functional status. Regarding QoL, the same study showed a decline in mean global health status between baseline and 6 weeks after surgery that did not recover within 24 months [28]. Musoro et al. [26] however, have questioned the clinical significance of this finding.

In another study [51] of more than 6000 women who underwent mastectomy, one-third above 65 years of age, a statistically significant difference was found between women with and without complications in terms of physical well-being, emotional well-being, and breast area appearance score. These differences were, however, mostly considered clinically insignificant.

The high incidence of postoperative complications in the present study concurs with earlier reports [8, 11–13]. Results from the Age Gap study [14] showed that only 19 per cent of operations resulted in a postoperative complication. However, in contrast to the present study, seromas were not taken into account. Consistent with previous studies [8, 11, 13], type of surgery was found to be a predictor of development of postoperative complications. Several studies [8, 11–13, 35, 36] have investigated the effect of age, co-morbidities, polypharmacy, BMI or functional status on complication rates, but the results are very inconsistent. No statistically significant association between these factors and the incidence of postoperative complications was found here, possibly because of a smaller sample size.

As for many other decisions in medicine, it is important to inform every patient about possible treatment outcomes to improve the shared decision-making process. Previous Research [49, 52] has shown that surgeons seem to underestimate patients' desire for information about the risk of complications. The prediction tool presented could therefore be used to calculate the individual risk of postoperative complications after breast cancer surgery to create awareness of possible consequences, such as more hospital visits and additional treatment measures.

The strengths of this study include its prospective design with highly detailed information regarding older patients with breast cancer at baseline and during follow-up, with a high response rates (85.6–92.8 per cent). The study also has limitations. The aim was to target all women aged 70 years and older with breast cancer, but patients who discontinued from the study had more polypharmacy, and worse functional status and physical functioning than those for whom follow-up data were available. This form of selection bias was also observed in the completed questionnaires during follow-up. Furthermore, owing to differences in assessments at baseline and during follow-up, QoL was not assessed at baseline. Therefore, any changes in QoL between baseline and postoperative time points could not be determined. It is therefore difficult to draw conclusions about complications and QoL. To further improve treatment strategies for older patients with breast cancer, future research should focus more on QoL and functional status, after both primary endocrine therapy and surgery.

Supplementary data

Supplemental Table 1: Data collection at follow-up for the CLIMB and Age Gap cohort

	Baseline		**1.5month**		**3 months**		**6 months**		**12 months**		**18 months**		**24 months**	
	CLIMB	Age Gap	CLIMB	Age Gap	CLIMB	Age Gap	CLIMB	Age Gap	CLIMB	Age Gap	CLIMB	Age Gap	CLIMB	Age Gap
Comorbidities	x	x												x
Medications	x	x												
ADL/IADL	x	x			x		x		x				x	
MMSE	x	x			x		x		x				x	
Timed Up & Go test	x				x		x		x				x	
Nutrition (MUST)	x													
Nutrition (aPG-SGA)		x												
ECOG-PS		x												
EQ-5D-5L		x		x				x		x		x		x
EORTC-QLQ C30/BR23		x		x	x		x	x	x	x		x	x	x
Decision style		x												
RECIST if PET		x		x				x		x		x		x
ISCOPE					x		x		x				x	
Cantril Ladder					x		x		x				x	
Geriatric Depression Scale					x		x		x				x	
Starkstein Apathy Scale					x		x		x				x	
De Jong Gierveld Loneliness Scale					x		x		x				x	
Questionnaire for physical activity					x				x				x	
Tumour details		x			x		x		x				x	
Treatment details		x		x	x		x	x	x	x		x	x	x
Adverse events		x		x	x		x	x	x	x		x	x	x

x indicated that these data are collected at this time point

ADL – Activity of Daily Living; IADL – Instrumental Activities of Daily Living; MMSE – Mini Mental State Examination; MUST – Malnutrition Universal Screening Tool; aPG-SGA – abridged Patient-Generated Subjective Global Assessment; ECOG-PS – Eastern Cooperative Oncology Group Performance Status; EQ-5D-5L – European Quality of Life Five Dimension Five Level Scale; EORTC-QLQ-C30/BR23 – European Organization for Research and Treatment for Cancer Core Quality of Life Questionnaire and its breast-specific module; RECIST – Response Evaluation Criteria in Solid Tumours; PET – Primary Endocrine Therapy; ISCOPE – Integrated Systematic Care for Older People

Supplemental Table 2: Association between patient characteristics and the occurrence of postoperative complications in the CLIMB cohort, univariate logistic regression analysis

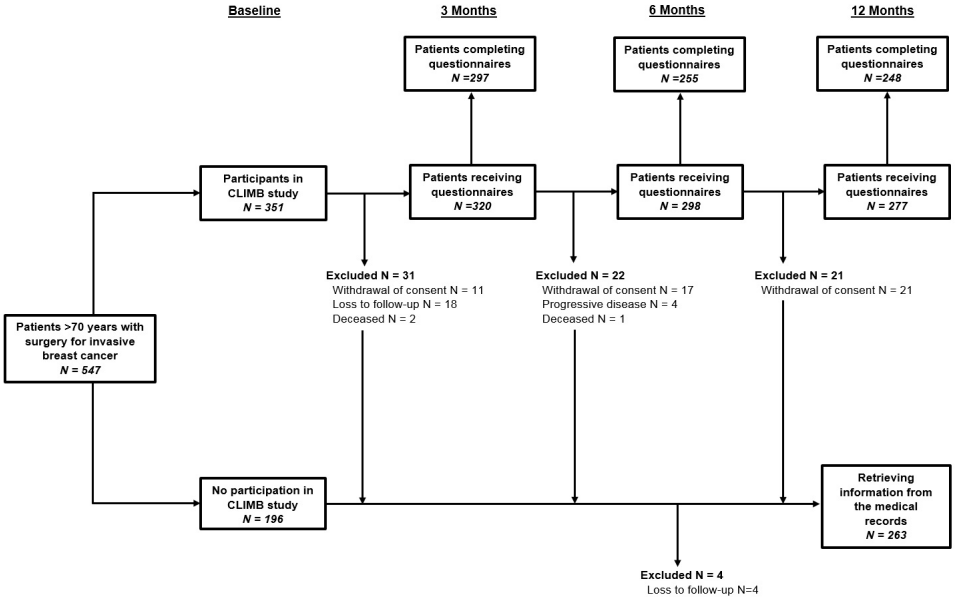
	N (%)	OR	95% CI	p-value
Age				<0.001
70-74	270 (49.4)	Ref		
75-79	120 (21.9)	1.16	0.74 - 1.82	
≥ 80	157 (28.7)	2.41	1.61 - 3.60	
Nodal stage				0.005
N0	436 (79.7)	Ref		
N+	88 (16.1)	2.14	1.35 - 3.40	
Unknown	23 (4.2)	0.87	0.36 - 2.09	
Tumour size				<0.001
0-2 cm	348 (63.6)	Ref		
> 2 cm	193 (35.3)	2.28	1.59 - 3.26	
Unknown	6 (1.1)	0.98	0.18 - 5.40	
Most extensive breast surgery				<0.001
Breast conserving	307 (56.1)	Ref		
Mastectomy	240 (43.9)	5.85	4.02 - 8.49	
Most extensive axillary surgery				<0.001
No axillary surgery	34 (6.2)	Ref		
Sentinel node procedure	408 (74.6)	0.73	0.36 - 1.49	
Axillary lymph node dissection	99 (18.1)	3.29	1.47 - 7.36	
Unknown	6 (1.1)	1.43	0.25 - 8.14	
Charlson Comorbidity Index (CCI)				0.574
0	293 (53.6)	Ref		
1	133 (24.3)	1.18	0.78 - 1.79	
≥ 2	121 (22.1)	1.22	0.80 - 1.88	
Body Mass Index (BMI)				0.963
20-24.9	173 (31.6)	Ref		
≥ 25	352 (64.4)	1.00	0.69 - 1.44	
< 20	20 (3.6)	0.77	0.29 - 2.04	
Unknown	2 (0.4)	*	*	
Polypharmacy				0.242
No	305 (55.8)	Ref		
Yes	219 (40.0)	1.33	0.93 - 1.89	
Unknown	23 (4.2)	0.86	0.35 - 2.08	
Nutritional status (MUST)				0.710
Low risk	450 (82.4)	Ref		
Medium risk	28 (5.1)	0.81	0.37 - 1.80	
High risk	13 (2.4)	1.71	0.57 - 5.17	
Unknown	55 (10.1)	1.13	0.64 -2.00	
Physical functioning (TUG)				0.038
≤ 12 s	328 (59.9)	Ref		
> 12 s	108 (19.8)	1.73	1.11 - 2.68	
Unknown	111 (20.3)	0.98	0.63 - 1.52	
Functional status (GARS)				0.146
< 19	230 (42.0)	Ref		
19 - 28	234 (42.8)	0.96	0.66 - 1.39	
≥29	73 (13.4)	1.75	1.03 - 2.98	
Unknown	10 (1.8)	1.02	0.28 - 3.71	

*Could not be calculated because of the small numbers. MUST – Malnutrition Universal Screening Tool; TUG – Timed Up & Go test; GARS – Groningen Activity Restriction Scale

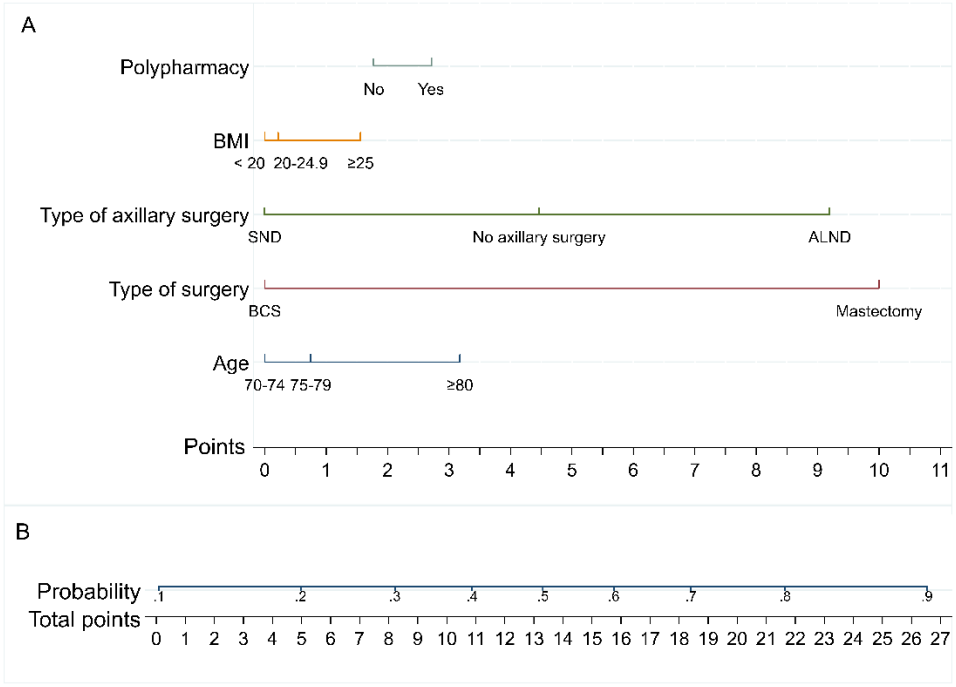
Supplemental Table 3: Association between postoperative complications and functional status and quality of life over time in the CLIMB cohort, adjusted and unadjusted for predefined confounders

		Unadjusted			Adjusted*		
		b	95% CI	p-value	b	95% CI	p-value
Functional status	**Postoperative complication**						
	No	Ref			Ref		
	Yes	1.96	0.64 - 3.28	0.004	0.51	-0.68 - 1.71	0.402
	Follow-up moment	0.11	-0.01 - 0.24	0.074	0.12	0.01 - 0.23	0.040
	Complication x follow-up moment	-0.11	-0.32 - 0.10	0.291	-0.04	-0.22 - 0.14	0.669
General quality of life	**Postoperative complication**						
	No	Ref			Ref		
	Yes	-1.43	-5.19 - 2.32	0.453	1.20	-2.32 - 4.71	0.504
	Follow-up moment	-0.05	-0.36 - 0.25	0.730	-0.01	-0.29 - 0.27	0.920
	Complication x follow-up moment	0.19	-0.31 - 0.68	0.457	0.04	-0.41 - 0.50	0.854
Breast cancer specific quality of life	**Postoperative complication**						
	No	Ref			Ref		
	Yes	-2.59	-6.56 - 1.38	0.200	-0.98	-4.69 - 2.73	0.604
	Follow-up moment	0.12	-0.20 - 0.44	0.466	0.12	-0.18 - 0.41	0.444
	Complication x follow-up moment	0.23	-0.29 - 0.75	0.387	0.16	-0.33 - 0.64	0.527

*Adjusted for age, nodal stage, tumour size, Charlson Comorbidity Index, Body Mass Index and polypharmacy



Supplemental Fig. 1: Flowchart



Supplemental Fig. 2: Nomogram

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Chapter 3

Discontinuation of adjuvant endocrine therapy and impact on quality of life and functional status in older patients with breast cancer

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Breast Cancer Research and Treatment

Abstract

Purpose

Side effects are the main reason for discontinuation of adjuvant endocrine therapy in older adults. The aim of this study was to examine geriatric predictors of treatment discontinuation of adjuvant endocrine therapy within the first 2 years after initiation, and to study the association between early discontinuation and functional status and quality of life (QoL).

Methods

Patients aged ≥ 70 years with stage I–III breast cancer who received adjuvant endocrine therapy were included. The primary endpoint was discontinuation of endocrine therapy within 2 years. Risk factors for discontinuation were assessed using univariate logistic regression models. Linear mixed models were used to assess QoL and functional status over time.

Results

Overall, 258 patients were included, of whom 36% discontinued therapy within 2 years after initiation. No geriatric predictive factors for treatment discontinuation were found. Tumour stage was inversely associated with early discontinuation. Patients who discontinued had a worse breast cancer-specific QoL (b = − 4.37; 95% CI − 7.96 to − 0.78; p = 0.017) over the first 2 years, in particular on the future perspective subscale (b = − 11.10; 95% CI − 18.80 to − 3.40; p = 0.005), which did not recover after discontinuation. Treatment discontinuation was not associated with functional improvement.

Conclusion

A large proportion of older patients discontinue adjuvant endocrine treatment within 2 years after initiation, but geriatric characteristics are not predictive of early discontinuation of treatment. Discontinuation of adjuvant endocrine therapy did not positively affect QoL and functional status, which implies that the observed poorer QoL in this group is probably not caused by adverse effects of endocrine therapy.

Introduction

Breast cancer is the most frequently diagnosed malignancy amongst women, with more than 30% of all patients being over 70 years of age at the time of diagnosis [1]. Adjuvant endocrine therapy is a significant part of treatment in patients with high-risk hormone receptor-positive breast cancer because of its beneficial effect on recurrence rates and breast cancer-specific survival [2, 3]. However, whilst the number of patients above 75 years of age receiving endocrine therapy has increased between the years 2000 and 2017, their relative survival rate has not improved [4]. This lack of survival gain might be due to a limited effect of adjuvant endocrine therapy on low-risk earlystage breast cancer in older patients [4, 5]. Another reason might be the higher impact of competing causes of death in older patients [5]. Therefore, other outcomes, such as the impact of therapy on quality of life and functional status merit further exploration [6].

Moreover, despite the recommended minimum of 5 continuous years of adjuvant endocrine therapy, studies show a substantial discontinuation rate within this period of about 40% and ranging from 8 to 73% of patients [7–15]. The main reason for discontinuation is the occurrence of side effects, with a higher proportion of discontinuation in older patients than in younger ones [8, 11–13, 16]. Studies on older patients with breast cancer treated with chemotherapy show a correlation between specific geriatric conditions and toxicity [17, 18]. There is only little information about specific geriatric factors that might contribute to a higher discontinuation rate of endocrine therapy amongst older patients [7]. Therefore, the objective of this study was to investigate adjuvant endocrine therapy discontinuation in older patients with breast cancer, and to analyse geriatric predictive factors for early discontinuation. Another aim was to evaluate whether early discontinuation is associated with changes in functional status and quality of life over time.

Methods

Climb Every Mountain study (UL-2011-5263). This is a prospective, multicentre observational study. Details of this cohort have been extensively described in previous publications [19, 20]. Briefly, patients were recruited from nine Dutch hospitals between 2013 and 2018 and included women aged ≥ 70 years with primary breast cancer. For this study, patients with hormone receptor-positive breast cancer (ER and/or PR > 10%), stage I–III, who were treated with surgery and adjuvant endocrine therapy were selected. Exclusion criteria were a previous history of breast cancer, distant metastases, the inability to read Dutch and advanced dementia.

At baseline, patients underwent a geriatric assessment as part of standard care and follow-up was performed at three, six, twelve and twenty-four months after diagnosis. To obtain as much information as possible on all patients who participated in the CLIMB, including the patients who did not attend for follow-up, information about the tumour characteristics, type of treatment and complications was retrospectively retrieved from the medical records of all patients one year after diagnosis (Supplemental Fig. A). Written informed consent was obtained from all participants and the study was approved by the medical ethics committee of the Leiden University Medical Center.

Questionnaires

The baseline geriatric assessment included a history of comorbidities prior to breast cancer diagnosis [Charlson comorbidity index (CCI)] [21], use of medication, nutritional status [Malnutrition universal screening tool (MUST)] [22], cognition [Mini mental state examination (MMSE)] [23], physical function [Timed up and go test (TUG)] [24], and functional status using ADL and IADL [Groningen activity restriction scale (GARS)] [25]. At follow-up, clinical data including patient, tumour and treatment characteristics with the associated side effects were retrieved from medical records. Tumour stage was classified according to the eighth edition of TNM criteria from the cancer staging manual of the American Joint Committee on Cancer [26].

Follow-up at 3, 6, 12 and 24 months after diagnosis consisted of multiple assessments and questionnaires, including cognition (MMSE), physical function (TUG), functional status (GARS), quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23) [27, 28], the Cantril Ladder for overall patient satisfaction [29]; depression [30]; apathy [31] and loneliness [32]. For breast cancer-specific quality of life, optional questions regarding sexual function, sexual enjoyment and upset by hair loss were excluded from the total score, since these questions were answered by a limited number of patients (Supplemental Fig. B). For the EORTC QLQ-C30, the outcome was assessed as clinically relevant according to the findings from Musoro et al. [33]. For the EORTC QLQ-BR23, a difference of ≥ 10 points was considered to be clinically relevant [34]. The questionnaires from the first follow-up (i.e. three months post-diagnosis) were considered to be the baseline for the analyses of quality of life and the other functional domains, because most patients start adjuvant endocrine therapy around that time.

Outcome

Discontinuation of the initiated adjuvant endocrine therapy due to toxicity or patient preferences within two years after initiation was defined as the primary outcome for the present study. The golden standard for adjuvant endocrine therapy in postmenopausal women is 2–3 years of tamoxifen followed by 2–3 years of an aromatase inhibitor or 5 years of an aromatase inhibitor [35].

The second choice is 5 years of tamoxifen monotherapy. Therefore, early discontinuation was defined as discontinuation of the initial adjuvant endocrine therapy within two years after start. Changes in quality of life, functional status, life satisfaction, depression, apathy and loneliness over time were assessed as the secondary outcome.

Statistical analyses

All analyses were performed in IBM SPSS Statistics version 25.0. For all statistical analyses, the threshold for a two sided, statistically significant p-value was 0.05. All analyses were planned in advance to avoid post hoc analyses. Logistic regression analysis was used to assess predictive factors for discontinuation. We also analysed 'frailty', which was defined as impairments in two or more domains: cognition (MMSE < 24), physical function (timed up and go > 12 s), somatic (Charlson comorbidity index ≥ 2 or polypharmacy) or nutrition (high risk on the malnutrition universal screening tool). Patients with a GARS score of ≥ 29 were also considered frail [36].

Linear mixed models were performed to assess longitudinal changes in quality of life, functional status, life satisfaction, depression, apathy and loneliness and whether there were differences in these scores between patients who discontinued therapy and who did not. All outcome measures were seperately analysed as dependent variable with discontinuation and time as fixed parameters. Predefined confounders were also added as fixed parameters to assess the independent effect of adverse events of adjuvant endocrine therapy on these outcome measures. These confounders included age, tumour stage, BMI, Charlson comorbidity index, polypharmacy and type of surgery. Results were presented as beta coefficients (b), 95% confidence intervals (CI) and p-values.

Results

Overall, we included 258 patients with hormone receptor-positive breast cancer, stage I–III, who underwent surgery and started on adjuvant endocrine therapy. General characteristics, tumour characteristics and therapies are shown in Table 1. Median age was 74 years old. A fifth of all patients had a Charlson comorbidity index of 2 or higher (17%) prior to breast cancer diagnosis. A total of 95 patients (37%) were ADL/IADL independent and 91 patients (35%) were classified as frail. Most patients had stage I or II disease (84%). Very few patients received chemotherapy either in the neoadjuvant (2%) or adjuvant setting (7%). One hundred twenty-nine patients (50%) started with tamoxifen and 124 patients (48%) with an aromatase inhibitor and it was not specified in 5 patients (2%).

Table 1: Patient-, tumour- and treatment characteristics at baseline

	N	%
Age		
70-74	130	50.4
75-79	59	22.9
≥ 80	69	26.7
Charlson Comorbidity Index (CCI)		
0	146	56.6
1	67	26.0
≥ 2	45	17.4
BMI		
20-24.9	80	31.0
< 20	10	3.9
≥ 25	167	64.7
Unknown	1	0.4
Polypharmacy		
No	155	60.1
Yes	93	36.0
Unknown	10	3.9
Nutritional status (MUST)		
Low risk	224	86.8
Medium risk	9	3.5
High risk	8	3.1
Unknown	17	6.6
Functional status (GARS)		
< 19: no dependency	95	36.8
19 - 28: some dependency	126	48.8
≥29: disabled	35	13.6
Unknown	2	0.8
Cognition (MMSE)		
Normal cognition (≥ 24)	233	90.3
Cognitive impairment (<24)	9	3.5
Unknown	16	6.2
Physical function (TUG)		
≤ 12 s	164	63.6
> 12 s	50	19.4
Unknown	44	17.0
Current living situation		
Independent	243	94.2
Assisted living	14	5.4
Unknown	1	0.4
Stage		
I	101	39.1
II	116	45.0
III	31	12.0
Unknown	10	3.9
Grade		
I	33	12.8
II	142	55.0
III	75	29.1
Unknown	8	3.1
Hormone receptor status		
ER+/PR+	185	71.7
ER+/PR-	72	27.9
ER-/PR+	1	0.4

Table 1: Continued

	N	%
HER2		
Negative	201	77.9
Positive	27	10.5
Unknown	30	11.6
Neoadjuvant treatment		
No neoadjuvant treatment	211	81.8
Chemotherapy (CT)	6	2.3
Endocrine therapy (ET)	21	8.1
Combination of ET and CT	0	0.0
Unknown	20	7.8
Most extensive surgery		
Breast conserving	121	46.9
Mastectomy	137	53.1
Most extensive axillary surgery		
No axillary surgery	6	2.3
Sentinel node procedure	183	70.9
Axillary lymph node dissection	66	25.6
Unknown	3	1.2
Adjuvant systemic treatment		
Endocrine therapy (ET)	241	93.4
Combination of ET and CT	17	6.6
Adjuvant radiotherapy		
No	120	46.5
Yes	138	53.5
Adjuvant herceptin (trastuzumab)		
No	251	97.3
Yes	7	2.7

Abbreviations: BMI – Body Mass Index; MUST – Malnutrition Universal Screening Tool; GARS – Groningen Activity Restriction Scale; MMSE – Mini Mental State Examination; TUG – Timed Up and Go test; ER – Estrogen Receptor; PR – Progesterone Receptor; HER2 – Human Epidermal growth factor Receptor 2

Of patients with adjuvant endocrine therapy, 193 patients (75%) had at least one side effect (Table 2). The most reported side effects were musculoskeletal symptoms in 37% of patients, followed by hot flushes (34%) and fatigue (23%). Some patients experienced severe side effects, such as a thromboembolism (2%), cardiovascular symptoms (2%) or an allergic reaction (2%). In total, 94 patients (36%) discontinued the initiated adjuvant endocrine therapy within 2 years, of which 97% for reasons other than recurrence of breast cancer (Table 2). Half of the patients who discontinued treatment, did so within the first six months and 75% within the first year (Fig. 1). As for the discontinuation rates, there was no statistically significant difference between aromatase inhibitors or tamoxifen.

Table 2: Side effects and reason for discontinuation of adjuvant endocrine therapy within 2 years after initiation

	N	%
Total number of side effects	434	-
Thromboembolism	5	1.9
Cardiovascular	5	1.9
Allergic reaction	4	1.6
Musculoskeletal	96	37.2
Hot flashes	88	34.1
Fatigue	60	23.3
Psychological	40	15.5
Gastrointestinal	26	10.1
Hair loss and thinning	17	6.6
Vaginal dryness or discharge	13	5.0
Dizziness/balance problems	11	4.3
Dermatological	9	3.5
Other	52	20.2
At least 1 side effect	193	74.8
Discontinuation of endocrine therapy		
No	164	63.6
Yes	94	36.4
Reasons for early discontinuation		
Recurrence	3	3.2
Toxicity	56	59.6
Not specified	35	37.2

None of the geriatric characteristics or frailty status predicted who would discontinue adjuvant endocrine therapy within two years (Table 3). Patients with a higher tumour stage, however, were less likely to discontinue treatment (stage II: OR 0.42, 95% CI 0.24–0.74, stage III: OR 0.25, 95% CI 0.09–0.65, p = 0.001, compared to stage I).

One hundred sixty-five patients (64%) participated in the follow-up questionnaires (Supplemental Fig. A). After adjustment for predefined confounders, patients who discontinued endocrine therapy within two years had a longitudinal clinically relevant reduction in breast cancer-specific quality of life in the first 24 months post-diagnosis (b = − 4.37; 95% CI − 7.96 to − 0.78; p = 0.017, Fig. 2), in particular on the future perspective subscale (b = − 11.10; 95% CI − 18.80 to − 3.40; p = 0.005, Fig. 3). These patients also showed worse scores on the fatigue subscale (b = 7.06; 95% CI 0.78–13.34; p = 0.028, Fig. 3). As for the functional status, life satisfaction, depression, apathy and loneliness, there was no statistical difference between patients who discontinued therapy and those who continued (Fig. 2).

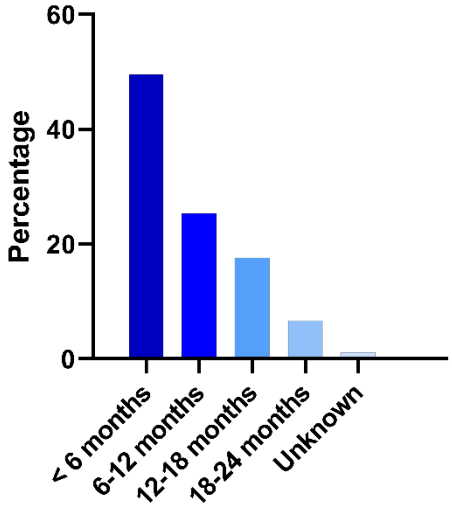


Fig. 1: Period of discontinuation of adjuvant endocrine therapy after start

Table 3: Association between patient-, tumour-, and treatment characteristics and early discontinuation of adjuvant endocrine therapy <2 years because of toxicity or non-specified reasons, univariate logistic regression analysis

	N patients (%), total	N patients (%), discontinued**	OR	95% CI	p-value
Age					0.371
70-74	130 (50.4)	47 (51.6)	Ref		
75-79	59 (22.9)	24 (26.4)	1.21	0.64 - 2.28	
≥ 80	69 (26.7)	20 (22.0)	0.72	0.38 - 1.36	
Charlson Comorbidity Index (CCI)					0.560
0	146 (56.6)	49 (53.8)	Ref		
1	67 (26.0)	23 (25.3)	1.04	0.56 - 1.91	
≥ 2	45 (17.4)	19 (20.9)	1.45	0.73 - 2.87	
BMI					0.794
20-24.9	80 (31.0)	29 (31.9)	Ref		
< 20	10 (3.9)	2 (2.2)	0.44	0.09 - 2.21	
≥ 25	167 (64.7)	60 (65.9)	0.99	0.57 - 1.72	
Unknown	1 (0.4)	0 (0.0)	*	*	
Polypharmacy					0.600
No	155 (60.1)	56 (61.5)	Ref		
Yes	93 (36.0)	33 (36.3)	0.97	0.57 - 1.66	
Unknown	10 (3.9)	2 (2.2)	0.44	0.09 - 2.15	
Nutritional status (MUST)					0.941
Low risk	224 (86.8)	80 (87.9)	Ref		
Medium risk	9 (3.5)	3 (3.3)	0.90	0.22 - 3.70	
High risk	8 (3.1)	2 (2.2)	0.60	0.12 - 3.04	
Unknown	17 (6.6)	6 (6.6)	0.98	0.35 - 2.75	
Functional status (GARS)					0.992
< 19: no dependency	95 (36.8)	33 (36.3)	Ref		
19 – 28: some dependency	126 (48.8)	46 (50.5)	1.08	0.62 - 1.89	
≥ 29: disabled	35 (13.6)	12 (13.2)	0.98	0.43 - 2.22	
Unknown	2 (0.8)	0 (0.0)	*	*	

Table 3: Continued

	N patients (%), total	N patients (%), discontinued**	OR	95% CI	p-value
Cognition (MMSE)					0.764
Normal cognition (≥ 24)	233 (90.3)	81 (89.0)	Ref		
Cognitive impairment (< 24)	9 (3.5)	3 (3.3)	0.94	0.23 - 3.85	
Unknown	16 (6.2)	7 (7.7)	1.46	0.52 - 4.06	
Physical function (TUG)					0.030
≤ 12 s	164 (63.6)	66 (72.5)	Ref		
> 12 s	50 (19.4)	17 (18.7)	0.77	0.39 - 1.49	
Unknown	44 (17.0)	8 (8.8)	0.33	0.14 - 0.76	
Stage					0.001
I	101 (39.1)	50 (54.9)	Ref		
II	116 (45.0)	34 (37.4)	0.42	0.24 - 0.74	
III	31 (12.0)	6 (6.6)	0.25	0.09 - 0.65	
Unknown	10 (3.9)	1 (1.1)	0.11	0.01 - 0.93	
Grade					0.412
I	33 (12.8)	9 (9.9)	Ref		
II	142 (55.0)	53 (58.2)	1.59	0.69 - 3.67	
III	75 (29.1)	28 (30.8)	1.59	0.65 - 3.90	
Unknown	8 (3.1)	1 (1.1)	0.38	0.04 - 3.55	
Neoadjuvant treatment					0.466
No neoadjuvant treatment	211 (81.8)	78 (85.7)	Ref		
Chemotherapy (CT)	6 (2.3)	2 (2.2)	0.85	0.15 - 4.76	
Endocrine therapy (ET)	21 (8.1)	4 (4.4)	0.40	0.13 - 1.24	
Unknown	20 (7.8)	7 (7.7)	0.92	0.35 - 2.40	
Most extensive surgery					0.165
Breast conserving	121 (46.9)	48 (52.7)	Ref		
Mastectomy	137 (53.1)	43 (47.3)	0.70	0.42 - 1.16	
Adjuvant systemic treatment					0.129
Endocrine therapy (ET)	241 (93.4)	88 (96.7)	Ref		
Combination of ET and CT	17 (6.6)	3 (3.3)	0.37	0.10 - 1.33	
Frailty					0.746
No	167 (64.7)	74 (81.3)	Ref		
Yes	91 (35.3)	17 (18.7)	0.90	0.47 - 1.72	

*Could not be calculated because of the small numbers

**Discontinuation of adjuvant endocrine therapy for reasons other than recurrence

Abbreviations: OR – Odds Ratio; 95% CI – 95% Confidence Interval; BMI – Body Mass Index; MUST – Malnutrition Universal Screening Tool; GARS – Groningen Activity Restriction Scale; MMSE – Mini Mental State Examination; TUG – Timed Up and Go test

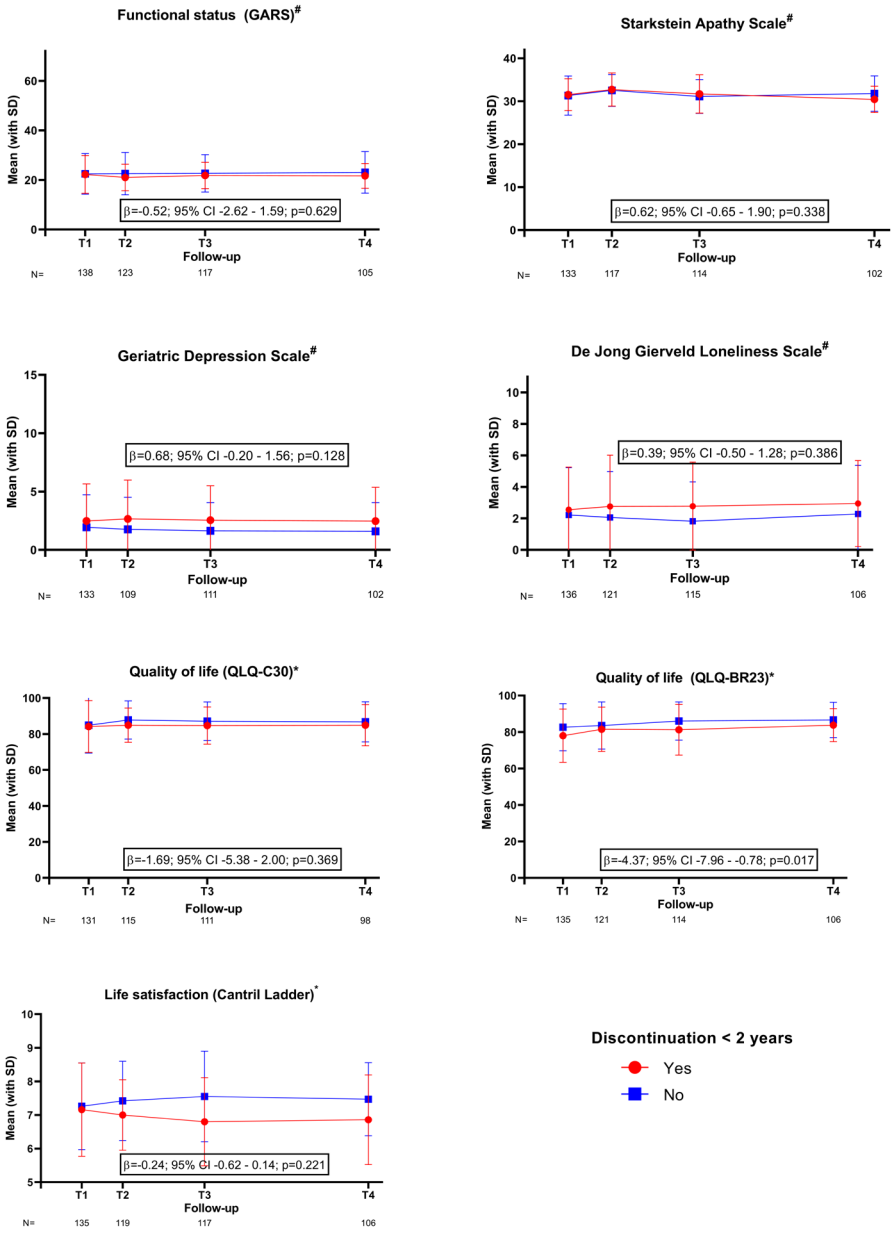


Fig. 2: Functional status, apathy, depression, loneliness, general quality of life, breast cancer-specific quality of life and life satisfaction over time, after adjustment for age, tumour stage, BMI, Charlson Comorbidity Index, polypharmacy, and type of surgery

#A higher score indicates a worse outcome; *A higher score indicates a better outcome.

Adjusted for age, tumour stage, BMI, Charlson Comorbidity Index, polypharmacy, and type of surgery.

T1 – baseline, 3 months after diagnosis, start adjuvant endocrine therapy; T2 – 6 months after diagnosis; T3 – 12 months after diagnosis; T4 – 24 months after diagnosis

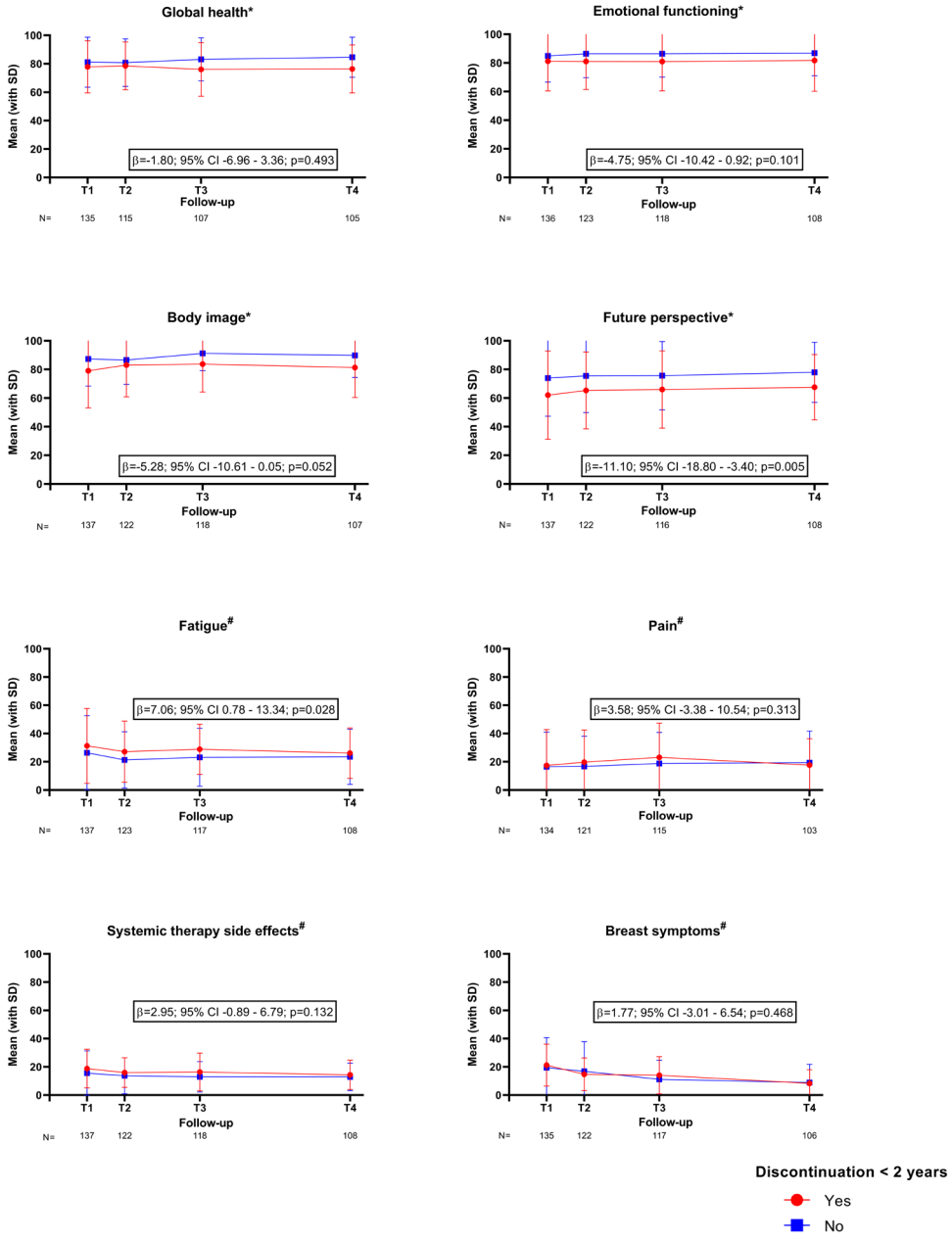


Fig. 3: Selection of subscales from the EORTC QLQ-C30 and QLQ-BR23 quality of life questionnaires, after adjustment for age, tumour stage, BMI, Charlson Comorbidity Index, polypharmacy, and type of surgery
#A higher score indicates a worse outcome; *A higher score indicates a better outcome.
Adjusted for age, tumour stage, BMI, Charlson Comorbidity Index, polypharmacy, and type of surgery.
T1 – baseline, 3 months after diagnosis, start adjuvant endocrine therapy; T2 – 6 months after diagnosis; T3 – 12 months after diagnosis; T4 – 24 months after diagnosis

Discussion

During the first two years of treatment, a relatively high proportion of older patients discontinued the initiated adjuvant endocrine therapy, with the majority of patients stopping within the first six months. A higher tumour stage was inversely associated with discontinuation. No geriatric predictive factors for treatment discontinuation were found. Regarding the quality of life, patients who discontinued treatment for other reasons than recurrence or death had clinically relevant worse scores on future perspective and fatigue subscales, but these did not recover after discontinuation, suggesting that this lower score is not related to possible side effects of endocrine treatment itself. Other domains were not statistically significantly different in patients who discontinued adjuvant endocrine therapy compared to those who did continue therapy in the first two years after diagnosis.

This study was not able to find any geriatric factors that were associated with early adjuvant endocrine therapy discontinuation. Previous studies showed that cognition, frailty status and poor sleep quality were associated with poor adherence to adjuvant endocrine therapy [10, 11]. Cognition was also tested in this study, but the small number of patients with cognitive impairment included, prevents reliable determination of an association. In this study, patients with unfavourable tumour characteristics were less likely to discontinue treatment. Other studies have also explored the association between tumour stage and discontinuation of adjuvant endocrine therapy, but the results have been inconsistent [7, 10–12]. A study of Bluethmann et al. including 1000 patients aged ≥ 65 years with stage I–IIIa breast cancer, showed that patients with a higher stage had a lower hazard ratio compared to stage I for early and late discontinuation of adjuvant endocrine therapy. However, Kidwell et al. with 500 postmenopausal patients of 35–89 years of age (median age 59) with stage 0–III breast cancer, did not find an association between stage and early discontinuation of adjuvant endocrine therapy [10]. It might be possible that this relation is only evident in older patients.

Moreover, the association between discontinuation and tumour stage may implicate that motivation and oncologist's recommendations play a major role in continuation of treatment. This hypothesis is supported by the results of Fink et al. showing that patients with neutral or negative beliefs about risks and benefits of therapy were more likely to discontinue treatment early [14]. Furthermore, a study by Sheppard et al. although tested in a limited number of patients, showed that less optimistic patients were more likely to discontinue therapy than those who were more optimistic [12].

This seems to be in line with other studies showing that optimism is related to improved health outcomes, with optimists being better at taking health conductive action because of a greater sense of projecting oneself into the future and making a judgement that things will be good [37]. This assumption concurs with the current study in which patients that continued therapy had a better score on the future perspective scale. Similar results were seen for the fatigue subscale and breast cancer-specific quality of life. A previous study found a similar worse breast cancer-specific quality of life in patients who discontinue therapy compared to those who continue therapy both at baseline and during follow-up in patients of all age groups [38]. The role of medication beliefs and illness perceptions (i.e. views, ideas, cognitions and emotions a patient has about the disease) is currently being investigated in the ADHERE trial (NL8541).

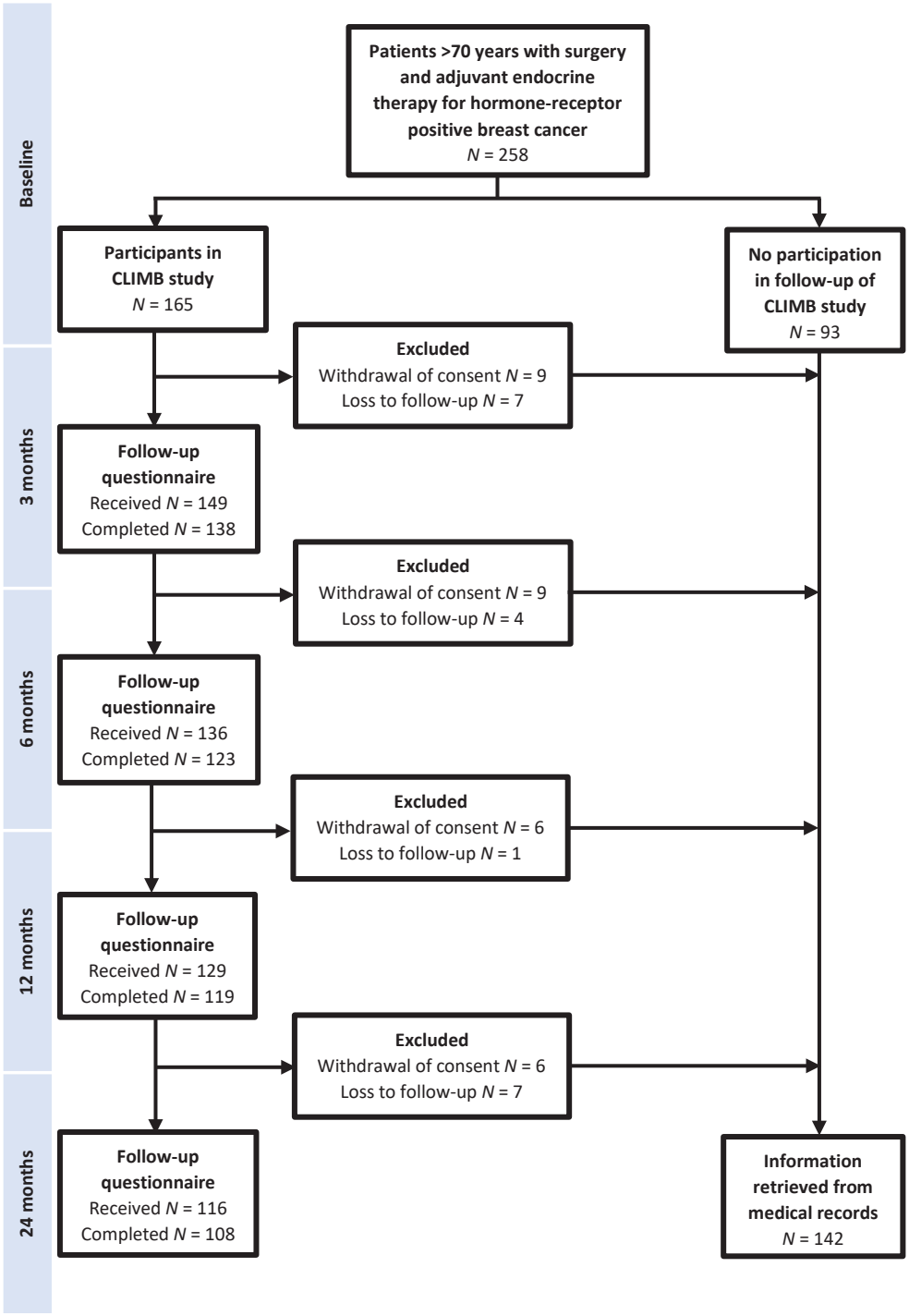
This aspect underlines the importance of the role of the physician in explaining about the balance of benefits and risks of therapy and that incorporating interventions into clinical practice to promote treatment continuation is critical for sustaining. An important consideration of this risk benefit ratio in older patients is that the beneficial effect of adjuvant treatment might differ from younger patients due to competing risk of mortality [39]. Interestingly, a study investigating persuasion in decision-making about adjuvant higher tumour stages oncologists were more likely to steer towards intensifying adjuvant chemotherapy [40]. However, tumour stage did not affect persuasive behaviours of oncologists for endocrine therapy. Nevertheless, the current study shows that in the occurrence of side effects patients with higher tumour stages are more likely to continue adjuvant endocrine therapy, which is probably due to motivational interviewing. Therefore, motivational interviewing in this group of patients might improve persistence of adjuvant endocrine therapy.

Strengths of this study include the prospective design with detailed information about a large number of older patients on baseline and follow-up. There are also several limitations to our study. First, this study was not primarily designed to collect detailed information about treatment discontinuation. However, it was a planned analysis in which the reason for discontinuation was extracted from medical records, which did not always contain specific reasons. Moreover, the questionnaires were only completed at prespecified time points, making it more difficult to determine the direct effect of treatment discontinuation on certain outcome measures. However, in the current study, we showed that even after discontinuation patients still had a statistically significant worse quality of life, which implies that this worse quality of life is not due to endocrine therapy. Another disadvantage of retrieving information from medical records in the first two years is that it might result in underrepresentation of discontinuation rates.

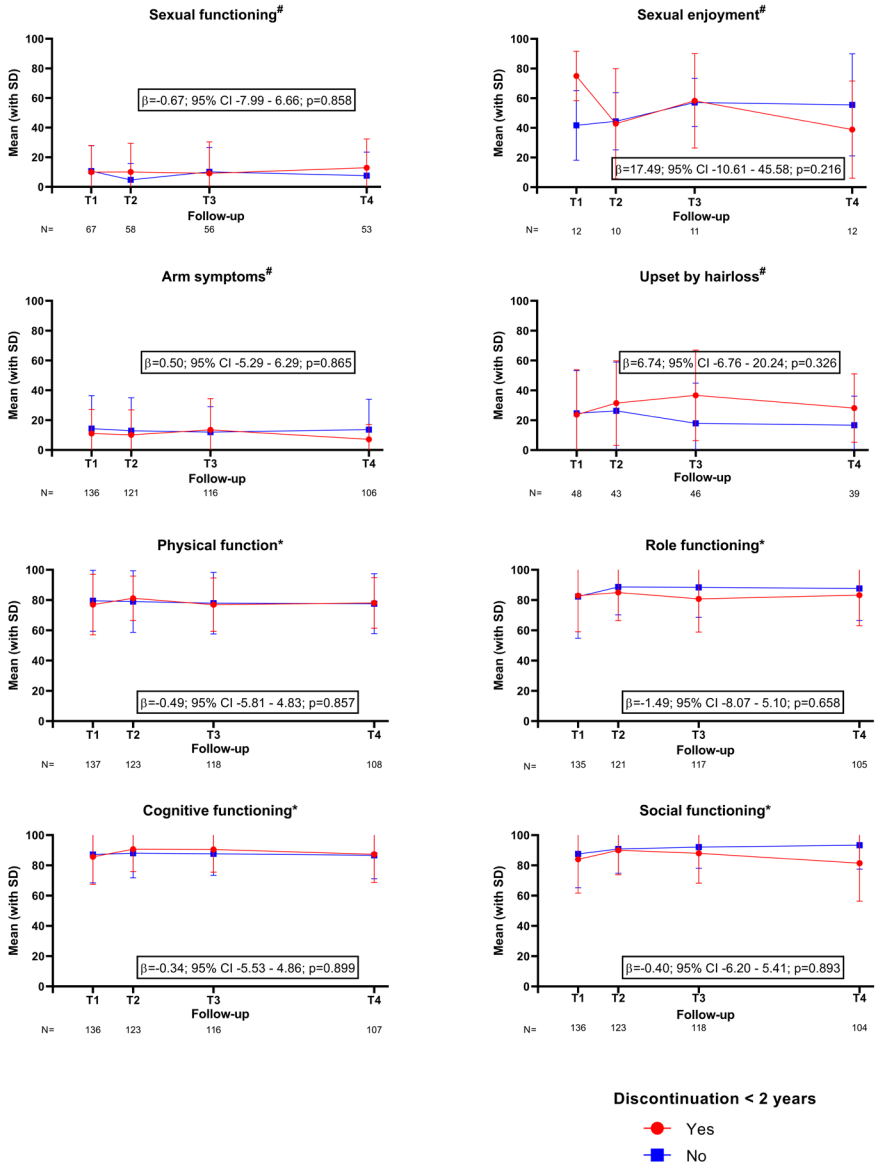
However, the reported rate of the current study is in line with previous research and this study showed that most patients discontinued therapy within the first six months after initiation [9–13]. Of note, in the study by Hershman et al. the incidence of treatment discontinuation of aromatase inhibitors progressively increased from year 1 to year 4 in patients of all age groups, whilst discontinuation rates of tamoxifen decreased over time [13]. In the current study, we did not find such a difference between early discontinuation of aromatase inhibitors and tamoxifen. This difference might be explained by the fact that Hershman et al. deducted discontinuation rates from prescriptions, in which they had to make several assumptions. They were also unable to determine the reason of discontinuation.

In conclusion, this study illustrates that a large proportion of older patients with breast cancer discontinues adjuvant endocrine therapy within the first two years after initiation. None of the geriatric factors that we explored predicted the rate of early discontinuation. A higher tumour stage was inversely associated with discontinuation. Patients who discontinue early had a worse breast cancer-specific quality of life and worse scores on fatigue and future perspective subscales. Following their discontinuation of adjuvant therapy, these scores did not improve, which implies that the poorer quality of life is probably not caused by adverse effects of endocrine therapy. Future studies should investigate strategies to motivate patients to continue adjuvant endocrine therapy, especially when the benefits outweigh the risks.

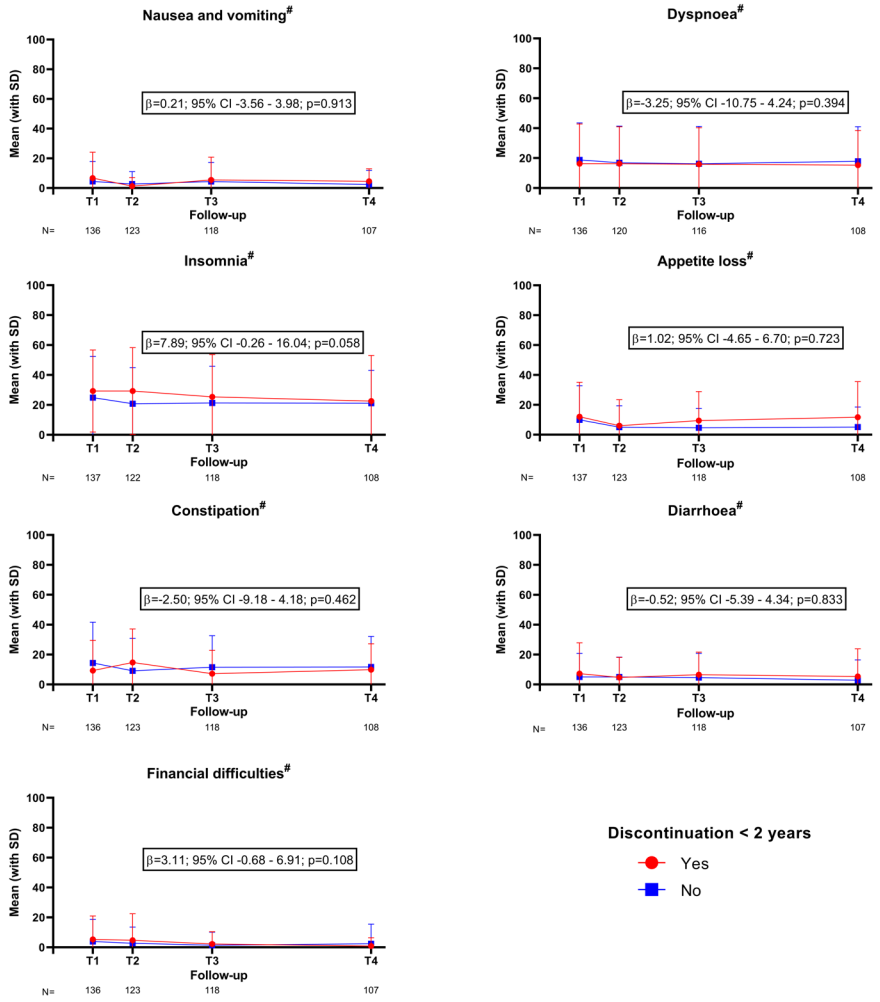
Supplementary data



Supplemental Fig. A: Flowchart



Supplemental Fig. B: Other subscales from the EORTC QLQ-C30 and QLQ-BR23 questionnaires
#A higher score indicates a worse outcome; *A higher score indicates a better outcome.
Adjusted for age, tumour stage, BMI, Charlson Comorbidity Index, polypharmacy, and type of surgery.
T1 – baseline, 3 months after diagnosis, start adjuvant endocrine therapy; T2 – 6 months after diagnosis; T3 – 12 months after diagnosis; T4 – 24 months after diagnosis



Supplemental Fig. C: Other subscales from the EORTC QLQ-C30 and QLQ-BR23 quality of life questionnaires

#A higher score indicates a worse outcome; *A higher score indicates a better outcome.

Adjusted for age, tumour stage, BMI, Charlson Comorbidity Index, polypharmacy, and type of surgery.

T1 – baseline, 3 months after diagnosis, start adjuvant endocrine therapy; T2 – 6 months after diagnosis; T3 – 12 months after diagnosis; T4 – 24 months after diagnosis

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Chapter 4

Adjuvant endocrine therapy in older women with breast cancer: a comparison of practice and outcomes between the United Kingdom and the Netherlands

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Concept

Abstract

Introduction

Allocation of adjuvant endocrine therapy for breast cancer varies between the UK and the Netherlands. In the UK all women with oestrogen receptor-positive (ER+) breast cancer are offered endocrine therapy whereas in the Netherlands a selective approach is applied for women with low-risk disease. This study compares the use of, and outcomes from, adjuvant endocrine therapy between the UK and the Netherlands.

Methods

Women aged ≥70 years with ER+ early breast cancer were prospectively recruited into two separate cohort studies: the UK Age Gap and Dutch CLIMB studies. Differences in the allocation of endocrine therapy, overall survival, side effects, early treatment discontinuation and quality of life were assessed. Sensitivity survival analyses were performed for women in whom adjuvant endocrine therapy may be omitted according to Dutch guidelines (low risk disease defined as lymph node-negative disease grade I and <2cm in size, or grade II/III and <1cm in size) and in whom adjuvant endocrine therapy should be prescribed according to both the British and Dutch guidelines (i.e., medium- and high-risk disease).

Results

In total, 2399 British and 458 Dutch women were included. Endocrine therapy was prescribed in 2247/2399 (94%) of UK women compared to 254/458 (56%) of Dutch women. Fewer UK women discontinued therapy early (538/2247,24%) compared to Dutch women (89/254,35%). In the Age Gap study, 91% of patients with low-risk disease and 94% of patients with medium- or high-risk disease received adjuvant endocrine therapy, compared with 24% and 76%, respectively, in the CLIMB study. Overall survival did not differ between the two countries (HR1.22, 95%CI 0.96–1.54, p=0.105), but British women with medium- and high-risk disease had a better survival than Dutch women (HR1.38, 95%CI 1.06–1.78, p=0.016). Small quality of life differences were found in favour of Dutch women.

Conclusion

While the allocation of adjuvant endocrine therapy differed between the UK and the Netherlands, overall survival was similar. However, women with medium- and high-risk breast cancer had a better overall survival in the UK but at the expense of slightly worse quality of life. This emphasizes the importance of a stratified approach to endocrine therapy in both countries.

Introduction

Adjuvant endocrine therapy has been standard of care for oestrogen receptor-positive (ER+) breast cancer since the late 1960s [1]. Endocrine therapy reduces systemic and local recurrence rates and improves breast cancer-specific survival, with aromatase inhibitors or a sequential treatment with tamoxifen and aromatase inhibitors being more effective than tamoxifen monotherapy [2-4]. There are, however, important differences within Europe in the selection of patients for adjuvant treatment. For example, the National Institute for Health and Care Excellence (NICE) guideline in the United Kingdom (UK) recommends 5 years of aromatase inhibitor for every postmenopausal woman with ER+ invasive breast cancer [5]. In contrast, the Dutch guideline recommends aromatase inhibitors or a combination of 2-3 year tamoxifen followed by an aromatase inhibitor in postmenopausal women with ER-positive and/or progesterone receptor (PR)-positive breast cancer [6]. The Dutch guideline further specifies that endocrine therapy is not required for women with lymph node-negative disease and grade I tumours that are smaller than 2 centimetres or grade II and III tumours smaller than 1 centimetre. Neither guideline specifies strategies for adjuvant endocrine therapy in older women.

Older women are more likely to experience side effects and are more likely to discontinue treatment prematurely than their younger counterparts [7]. Moreover, the benefit from therapy for older women may differ from younger women, due to competing risks of mortality. Competing mortality risks generally increase with age and for this reason data specific to this age group should be used when drafting guidelines [8]. However, older women are frequently underrepresented in randomised controlled trials, requiring the use of other study designs to evaluate the effectiveness of therapy in this population [9-12]. Confounding can be a problem in non-randomized studies, since the treatment choice invariably depends on the patient's functionality and disease characteristics. Whilst no method can fully account for this, one approach to mitigating the bias associated with treatment selection is to compare outcomes between countries with different treatment policies but otherwise similar patient groups [13].

The aim of the current study was therefore to compare the use of adjuvant endocrine therapy, side effects, quality of life and survival in older women with hormone receptor-positive, non-metastatic breast cancer between the UK and the Netherlands.

Methods

Women aged 70 years and older who had been diagnosed with hormone receptor-positive, early-stage (TNM stages: T1-3, N0-2, M0) breast cancer were included from two cohort studies: the British Bridging the Age Gap in Breast Cancer study (Age Gap) and the Dutch Climb Every Mountain study (CLIMB). Women were recruited from 56 hospitals in England/Wales and 9 hospitals in the Western part of the Netherlands between 2013 and 2018. Only women with hormone receptor-positive disease who underwent surgery were included in the current analyses. The Age Gap study received ethics and research governance approval (IRAS: 115550). Approval for the CLIMB study was obtained from the medical ethics committee of the Leiden University Medical Centre (CCMO: NL43463.058.13). All women gave written informed consent.

Data collection

Both cohort studies have been extensively described in previous papers [14-17]. In short, a baseline geriatric assessment was performed in both cohort studies, consisting of the following: age, comorbidity according to the Charlson Comorbidity Index (CCI) without age adjustment and breast cancer diagnosis, medication use, Body Mass Index (BMI), activities of daily living (ADL), and cognition, using the Mini Mental State Examination (MMSE). Polypharmacy was defined as five or more daily medications at the time of diagnosis. ADL was assessed differently in both studies: the Age Gap study used the Barthel questionnaire, while the CLIMB study used the Groningen Activity Restriction Scale (GARS). To compare baseline levels of ADL between the two cohorts, the GARS questionnaire was converted into the Barthel score. The CLIMB study did not contain sufficient data about bladder and bowel incontinence, and these two questions from the Barthel were therefore excluded for analyses in both cohorts. The same cut-off values were used as before (i.e., 0-31 points: very/fully dependent, 32-63 points: partially/minimally dependent, 64-80 points: independent, or unknown if data was missing) [16]. If one or more answers to questions within a questionnaire were missing, the total ADL score was categorised as unknown. For the MMSE questionnaire, the maximum score was assigned to a single item if less than 10% of the total questionnaire was missing. If more than 10% of the items were missing, the total MMSE score was categorised as unknown.

Clinical data including patient, tumour and treatment characteristics were recorded at baseline. Information on endocrine therapy discontinuation or switching of therapy and side effects were recorded. Nodal status was classified as either no positive nodes (lymph node-negative) or at least one positive node (lymph node-positive). If the pathological lymph node status was not recorded, the clinical stage was used. The most extensive type of breast surgery and axillary surgery was recorded.

In the Age Gap study, follow-up was registered at 1.5, 6, 12, 18 and 24 months after diagnosis, and in the CLIMB study this took place at 3, 9, 15 and 27 months. In both studies, participants could participate at two levels: full or partial (which meant participation without quality of life questionnaires). Regardless of participation level, clinical data, including patient, tumour, treatment characteristics, and side effects were recorded at each follow-up visit. For fully participating women, the follow-up visits also included the completion of multiple questionnaires, including quality of life questionnaires. Quality of life was recorded using the validated European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and its breast cancer-specific module, QLQ-BR23 [18, 19]. For the Age Gap study, survival outcomes were obtained directly via follow-up to 24 months and after this follow-up time, through the UK cancer registry. For the CLIMB study, survival outcomes were also obtained directly from follow-up data until 27 months after diagnosis, followed by information from the Personal Records Database (BRP) or medical records. Overall survival was defined as the time in years from baseline assessment until death or censored at the date last known to be alive.

Statistical analyses

The chi-square test and Fisher's exact test were used to assess baseline differences between women who participated in the Age Gap and CLIMB studies. The same tests were used to analyse differences between the two studies in the use of adjuvant endocrine therapy, side effects/rates of early discontinuation and compliance with clinical guidelines. The reverse Kaplan-Meier estimator was used to calculate median follow-up in both countries. Median overall survival with interquartile ranges (IQR) were estimated for both studies using the Kaplan-Meier method and the log-rank test was used to compare these outcomes. Cox proportional hazard models were also used to calculate and compare the overall survival between the two countries. Multivariable analyses were performed with adjustment for clinically relevant confounders, which were predefined as tumour grade, tumour size, lymph node-status, age, comorbidity, polypharmacy, BMI, cognition (MMSE) and ADL (Barthel). Sensitivity survival analyses were performed for women with low-risk disease in whom adjuvant endocrine therapy may be omitted according to Dutch guidelines (lymph node-negative disease grade I and <2cm in size, or grade II/III and <1cm in size) and in whom adjuvant endocrine therapy should be prescribed according to both the British and Dutch guidelines (i.e, medium- and high-risk disease). The Cox proportional hazard models were adjusted for age, comorbidity, polypharmacy, BMI, cognition (MMSE) and ADL (Barthel). Quality of life differences were assessed only in women who participated fully and thereby intended to complete quality of life forms during follow-up. Linear mixed models were estimated to assess longitudinal differences in quality of life subdomains between the two cohorts and to assess whether the slopes changed over time.

All subscales were separately analysed as dependent variables, with a random intercept and time as a fixed parameter. An interaction term between time and study (i.e., Age Gap or CLIMB) was added to assess differences in longitudinal trajectories between both countries. Linear mixed models were adjusted for the following potential confounders measured at baseline: age, tumour grade, tumour size, nodal status, CCI, polypharmacy, BMI, MMSE, and functional status (ADL). The statistical tests were performed in SPSS version 29.0 (IBM, Armonk, New York, USA). All analyses were two-sided and P-values less than 0.050 were considered statistically significant.

Results

Study differences

The British Age Gap study included 2399 women and the Dutch CLIMB study included 458 women who underwent surgery for hormone receptor-positive breast cancer (Table 1). Median ages were 76 (IQR: 72-80) in the Age Gap study and 75 (IQR: 72-80) in the CLIMB study. Compared to the CLIMB study, more women in the Age Gap study had a tumour of >2cm (52% compared to 32%) and lymph node-positive disease (30% compared to 24%). The CLIMB study included more grade I and grade III tumours. Women in the Age Gap study more often had higher comorbidity scores than women in the CLIMB study: 31% of women in the Age Gap study had a CCI ≥ 2 compared to 20% in the CLIMB study. More women in the Age Gap study were treated with adjuvant chemotherapy when compared to women in the CLIMB study (11% vs. 4% of women).

Differences in the use of adjuvant endocrine therapy

Ninety-four per cent of women in the Age Gap study had adjuvant endocrine therapy, compared to 56% of women in the CLIMB study (Table 1). Women in the CLIMB study who did not receive adjuvant endocrine therapy were more likely to have smaller, lower grade tumours and no lymph node metastases (Table 2). The age, number of comorbidities, cognition and dependency in ADL did not differ between women receiving or not receiving adjuvant endocrine therapy in either study. Moreover, in the Age Gap study, the lymph node status did not appear to affect the choice of adjuvant endocrine therapy (Supplemental Table 1). In the CLIMB study, however, patients with lymph node-negative disease receiving breast conserving surgery or radiotherapy were less likely to also receive adjuvant endocrine therapy, whereas this was not the case in lymph node-positive disease (Supplemental Table 1). More women were treated according to national guidelines in the Age Gap study (94%) than in the CLIMB study (76%) (Supplemental Table 2). Those women not treated according to the Dutch guideline were generally older, had more grade 2 tumours, had higher comorbidity scores, and were generally more dependent in their ADL.

Table 1: Women with hormone receptor-positive breast cancer who underwent surgery

	Age Gap (N = 2399)	Climb (N = 458)	P-value
Age			
70-74	1018 (42.4)	225 (49.1)	0.002
75-79	761 (31.7)	105 (22.9)	
80-84	435 (18.1)	88 (19.2)	
≥ 85	185 (7.7)	40 (8.7)	
Grade			
I	411 (17.1)	131 (28.6)	<0.001
II	1566 (65.3)	217 (47.4)	
III	415 (17.3)	101 (22.1)	
Unknown	7 (0.3)	9 (2.0)	
Histopathology			
Ductal	1672 (69.7)	338 (73.8)	<0.001
Lobular	383 (16.0)	90 (19.7)	
Other	341 (14.2)	22 (4.8)	
Unknown	3 (0.1)	8 (1.7)	
Tumour size			
0-1 cm	279 (11.6)	174 (38.0)	<0.001
1-2 cm	875 (36.5)	134 (29.3)	
2-5 cm	1091 (45.5)	127 (27.7)	
> 5 cm	154 (6.4)	20 (4.4)	
Unknown	0 (0.0)	3 (0.6)	
Nodal status			
Node-negative	1670 (69.6)	332 (72.5)	<0.001
Node-positive	729 (30.4)	109 (23.8)	
Unknown	0 (0.0)	17 (3.7)	
HER2-status			
Negative	2037 (84.9)	361 (78.8)	<0.001
Positive	255 (10.6)	34 (7.4)	
Unknown	107 (4.5)	63 (13.8)	
Charlson Comorbidity Index (CCI)			
0	1258 (52.4)	258 (56.3)	<0.001
1	393 (16.4)	107 (23.4)	
2	489 (20.4)	55 (12.0)	
≥ 3	259 (10.8)	38 (8.3)	
Polypharmacy			
No	1401 (58.4)	263 (57.4)	<0.001
Yes	998 (41.6)	179 (39.1)	
Unknown	0 (0.0)	16 (3.5)	
BMI			
< 18.5	19 (0.8)	4 (0.9)	<0.001
18.5-25	629 (26.3)	160 (34.9)	
25-30	776 (32.5)	186 (40.6)	
> 30	613 (25.7)	107 (23.4)	
Unknown	352 (14.7)	1 (0.2)	
Mental status (MMSE)			
Normal (≥ 24)	1623 (67.7)	417 (91.0)	<0.001
Impaired (< 24)	57 (2.4)	14 (3.1)	
Unknown	719 (29.9)	27 (5.9)	
Functional status (Barthel)*			
Independent	2146 (89.5)	409 (89.3)	<0.001
Partially or minimally dependent	43 (1.8)	31 (6.8)	
Very or fully dependent	1 (0.0)	6 (1.3)	
Unknown	209 (8.7)	12 (2.6)	

Table 1: Continued

	Age Gap (N = 2399)	Climb (N = 458)	P-value
Most extensive breast surgery			
Breast conserving	1487 (62.0)	260 (56.8)	0.018
Mastectomy	897 (37.4)	198 (43.2)	
Unknown	15 (0.6)	0 (0.0)	
Most extensive axillary surgery			
No axillary surgery	68 (2.8)	21 (4.6)	0.065
Sentinel lymph node procedure	1900 (79.1)	346 (75.5)	
Axillary lymph node dissection	416 (17.3)	85 (18.6)	
Unknown	15 (0.6)	6 (1.3)	
Neo-adjuvant systemic treatment			
None	2258 (94.1)	430 (93.9)	0.979
Chemotherapy (CT)	41 (1.7)	8 (1.7)	
Endocrine therapy (ET)	100 (4.2)	20 (4.4)	
Adjuvant endocrine therapy			
No	152 (6.3)	204 (44.5)	<0.001
Yes	2247 (93.7)	254 (55.5)	
Adjuvant chemotherapy			
No	2142 (89.3)	440 (96.1)	<0.001
Yes	257 (10.7)	18 (3.9)	
Adjuvant radiotherapy			
No	871 (36.3)	197 (43.0)	0.007
Yes	1528 (63.7)	261 (57.0)	

Table 2: Differences in the use of adjuvant endocrine therapy within cohort studies

	Age Gap			CLIMB		
	Yes *N=2247 (94%)*	No *N=152 (6%)*	p-value	Yes *N=254 (56%)*	No *N=204 (44%)*	p-value
Age						
70-74	952 (93.5)	66 (6.5)	0.755	131 (58.2)	94 (41.8)	0.142
75-79	718 (94.3)	43 (5.7)		55 (52.4)	50 (47.6)	
80-84	406 (93.3)	29 (6.7)		52 (59.1)	36 (40.9)	
≥ 85	171 (92.4)	14 (7.6)		16 (40.0)	24 (60.0)	
Grade						
I	380 (92.5)	31 (7.5)	<0.001	33 (25.2)	98 (74.8)	<0.001
II	1485 (94.8)	81 (5.2)		141 (65.0)	76 (35.0)	
III	379 (91.3)	36 (8.7)		73 (72.3)	28 (27.7)	
Unknown	3 (42.9)	4 (57.1)		7 (77.8)	2 (22.2)	
Histopathology						
Ductal	1565 (93.6)	107 (6.4)	0.337	179 (53.0)	159 (47.0)	0.122
Lobular	365 (95.3)	18 (4.7)		60 (66.7)	30 (33.3)	
Other	314 (92.1)	27 (7.9)		11 (50.0)	11 (50.0)	
Unknown	3 (100.0)	0 (0.0)		4 (50.0)	4 (50.0)	
Tumour size						
0-1 cm	253 (90.7)	26 (9.3)	0.575	59 (33.9)	115 (66.1)	<0.001
1-2 cm	822 (93.9)	53 (6.1)		78 (58.2)	56 (41.8)	
2-5 cm	1026 (94.0)	65 (6.0)		99 (78.0)	28 (22.0)	
>5 cm	146 (94.8)	8 (5.2)		16 (80.0)	4 (20.0)	
Unknown	0 (0.0)	0 (0.0)		2 (66.7)	1 (33.3)	
Nodal status						
Node-negative	1561 (93.5)	109 (6.5)	0.561	154 (46.4)	178 (53.6)	<0.001
Node-positive	686 (94.1)	43 (5.9)		91 (83.5)	18 (16.5)	
Unknown	0 (0.0)	0 (0.0)		9 (52.9)	8 (47.1)	

Table 2: Continued

	Age Gap			CLIMB		
	Yes *N=2247 (94%)*	No *N=152 (6%)*	p-value	Yes *N=254 (56%)*	No *N=204 (44%)*	p-value
HER2-status						
Negative	1918 (94.2)	119 (5.8)	0.044	198 (54.8)	163 (45.2)	0.021
Positive	230 (90.2)	25 (9.8)		26 (76.5)	8 (23.5)	
Unknown	99 (92.5)	8 (7.5)		30 (47.6)	33 (52.4)	
Charlson Comorbidity Index (CCI)						
0	1181 (93.9)	77 (6.1)	0.310	141 (54.7)	117 (45.3)	0.186
1	360 (91.6)	33 (8.4)		68 (63.6)	39 (36.4)	
2	462 (94.5)	27 (5.5)		27 (49.1)	28 (50.9)	
≥ 3	244 (94.2)	15 (5.8)		18 (47.4)	20 (52.6)	
Polypharmacy						
No	1300 (92.8)	101 (7.2)	0.038	151 (57.4)	112 (42.6)	0.445
Yes	947 (94.9)	51 (5.1)		93 (52.0)	86 (48.0)	
Unknown	0 (0.0)	0 (0.0)		10 (62.5)	6 (37.5)	
BMI						
<18.5	15 (78.9)	4 (21.1)	0.008	4 (100.0)	0 (0.0)	0.081
18.5-25	578 (91.9)	51 (8.1)		85 (53.1)	75 (46.9)	
25-30	728 (93.8)	48 (6.2)		96 (51.6)	90 (48.4)	
>30	580 (94.6)	33 (5.4)		68 (63.6)	39 (36.4)	
Unknown	337 (95.7)	15 (4.3)		1 (100.0)	0 (0.0)	
Mental status (MMSE)						
Normal (≥24)	1511 (93.1)	112 (6.9)	0.217	229 (54.9)	188 (45.1)	0.723
Impaired (<24)	53 (93.0)	4 (7.0)		9 (64.3)	5 (35.7)	
Unknown	683 (95.0)	36 (5.0)		16 (59.3)	11 (40.7)	
Functional status (Barthel)*						
Independent	2002 (93.3)	144 (6.7)	0.044	224 (54.8)	185 (45.2)	0.554
Partially or minimally dependent	39 (90.7)	4 (9.3)		18 (58.1)	13 (41.9)	
Very or fully dependent	1 (100.0)	0 (0.0)		5 (83.3)	1 (16.7)	
Unknown	205 (98.1)	4 (1.9)		7 (58.3)	5 (41.7)	
Most extensive breast surgery						
Breast conserving	1405 (62.5)	82 (53.9)	0.015	121 (47.6)	139 (68.1)	<0.001
Mastectomy	830 (36.9)	67 (44.1)		133 (52.4)	65 (31.9)	
Unknown	12 (0.6)	3 (2.0)		0 (0.0)	0 (0.0)	
Most extensive axillary surgery						
No axillary surgery	63 (2.8)	5 (3.3)	0.080	7 (2.8)	14 (6.9)	0.003
Sentinel lymph node procedure	1788 (79.6)	112 (73.7)		183 (72.0)	163 (79.9)	
Axillary lymph node dissection	384 (17.1)	32 (21.0)		61 (24.0)	24 (11.8)	
Unknown	12 (0.5)	3 (2.0)		3 (1.2)	3 (1.5)	
Neo-adjuvant systemic treatment						
None	2124 (94.5)	134 (88.2)	0.005	233 (91.7)	197 (96.6)	0.100
Chemotherapy (CT)	36 (1.6)	5 (3.3)		6 (2.4)	2 (1.0)	
Endocrine therapy (ET)	87 (3.9)	12 (8.5)		15 (5.9)	5 (2.5)	
Adjuvant chemotherapy						
No	2021 (89.9)	121 (79.6)	<0.001	237 (93.3)	203 (99.5)	<0.001
Yes	226 (10.1)	31 (20.4)		17 (6.7)	1 (0.5)	
Adjuvant radiotherapy						
No	771 (34.3)	100 (65.8)	<0.001	121 (47.6)	76 (37.3)	0.026
Yes	1476 (65.7)	52 (34.2)		133 (52.4)	128 (62.7)	

*Without the questions on bladder and bowel incontinence. ER - oestrogen receptor; PR - progesterone receptor; HER2 - human epidermal growth factor receptor 2; CCI - Charlson Comorbidity Index; BMI - body mass index; MMSE - mini-mental state examination; CT - chemotherapy; ET - endocrine therapy

Type of adjuvant endocrine therapy, early discontinuation and side effects

Of the 2247 women that were treated with adjuvant endocrine therapy in the Age Gap study, 89% started with an aromatase inhibitor, 11% with tamoxifen, and it was unknown in 1 woman. Of the 254 women who were treated with adjuvant endocrine therapy in the CLIMB study, 49% started with an aromatase inhibitor, 49% with tamoxifen, and it was unknown in 2% of women. In the Age Gap study, 24% switched or discontinued adjuvant endocrine therapy within two years, of whom 36% were on tamoxifen and 22.6% on an aromatase inhibitor. In the CLIMB study, a higher proportion of women (35%) switched or discontinued therapy within two years after initiation: of whom 37% were on tamoxifen and 33% on an aromatase inhibitor.

Hot flushes and joint pain were the most frequently reported side effects in both studies (28% and 33% of women in the Age Gap study versus 35% and 37% of women in the CLIMB study, respectively) (Table 3). The Age Gap study found statistically significant differences between the reported side effects from tamoxifen and aromatase inhibitors: asthenia/somnolence, musculoskeletal complaints and diarrhoea were all less common in tamoxifen users. These differences were not observed in the CLIMB study, in which aromatase inhibitors were associated with dizziness and tamoxifen with vaginal complaints.

Table 3: Side effects according to type of treatment in the Age Gap study and the CLIMB study

	Age Gap				**CLIMB**			
	Number of events	Tamoxifen	AI	p-value*	Total	Tamoxifen	AI	p-value*
Hot flushes	618 (27.5)	83 (32.5)	535 (26.9)	0.056	88 (34.6)	49 (39.5)	35 (28.0)	0.055
Musculoskeletal	731 (32.5)	44 (17.3)	687 (34.5)	<0.001	95 (37.4)	45 (36.3)	47 (37.6)	0.830
Asthenia/ somnolence	390 (17.4)	31 (12.2)	359 (18.0)	0.020	59 (23.2)	29 (23.4)	29 (23.2)	0.972
Vaginal dryness/ discharge	88 (3.9)	10 (3.9)	78 (3.9)	0.998	13 (5.1)	11 (8.9)	2 (1.6)	0.010
Hair thinning	291 (13.0)	25 (9.8)	266 (13.4)	0.111	17 (6.7)	9 (7.3)	8 (6.4)	0.788
Dermatological	114 (5.1)	13 (5.1)	101 (5.1)	0.986	9 (3.5)	5 (4.0)	4 (3.2)	0.725
Nausea	185 (8.2)	24 (9.4)	161 (8.1)	0.469	NA	NA	NA	
Diarrhoea	108 (4.8)	5 (2.0)	103 (5.2)	0.024	NA	NA	NA	
Headache	188 (8.4)	18 (7.1)	170 (8.5)	0.422	NA	NA	NA	
Vomiting	37 (1.6)	5 (2.0)	32 (1.6)	0.676	NA	NA	NA	
Loss of bone density	13 (0.6)	0 (0.0)	13 (0.7)	0.196	8 (3.1)	7 (5.6)	1 (0.8)	0.030
Other	81 (3.6)	19 (7.5)	62 (3.1)	<0.001	50 (19.7)	32 (25.8)	17 (13.6)	0.015
Allergic reaction	NA	NA	NA		4 (1.6)	2 (1.6)	2 (1.6)	0.994
GI problems	NA	NA	NA		24 (9.4)	16 (12.9)	7 (5.6)	0.047
Thromboembolism	NA	NA	NA		5 (2.0)	4 (3.2)	1 (0.8)	0.172
Cardiovascular	NA	NA	NA		5 (2.0)	2 (1.6)	3 (2.4)	0.658
Psychological	NA	NA	NA		38 (15.0)	18 (14.5)	20 (16.0)	0.745
Dizziness	NA	NA	NA		11 (4.3)	2 (1.6)	9 (7.2)	0.032

* without women of whom the type of adjuvant endocrine therapy was unknown.
Values in parentheses are percentages. NA – Not Assessed; AI – Aromatase Inhibitor

Recurrences and survival

Seventy women (3%) in the Age Gap study had a recurrence in the first 2 years after diagnosis, versus 18 women (4%) in the CLIMB study. Median follow-up in the Age Gap study was 4.6 years (IQR 4.5-4.7) and in the CLIMB study: 5.3 years (IQR 5.2-5.4). Overall survival between the two countries was not statistically significantly different in the univariate analyses (log-rank test: p = 0.105; univariate HR: 1.22, 95% CI 0.96 – 1.54, p = 0.105), but after adjustments, a statistically significant difference was observed (adjusted HR: 1.33, 95% CI 1.01 – 1.74, p = 0.041) (Fig. 1) with a 5-year overall survival of 84% in the Age Gap study and 83% in the CLIMB study.

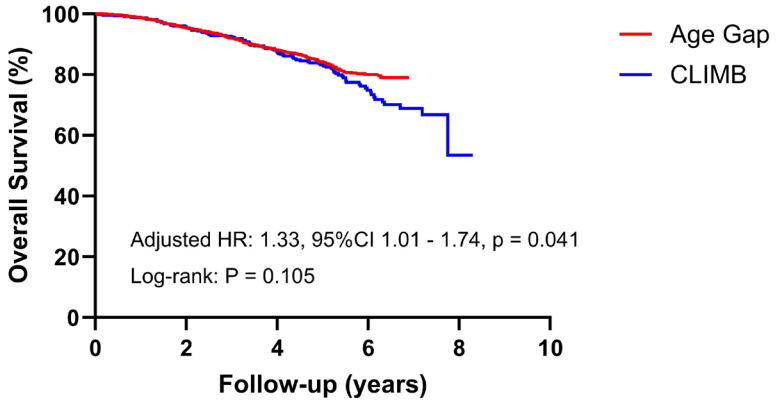


Fig. 1: Kaplan-Meier curves with the log-rank test and multivariate Cox proportional hazard regression for overall survival of British (Age Gap) and Dutch (CLIMB) women with non-metastatic hormone receptor-positive breast cancer who underwent surgery*

Adjusted for tumour grade, tumour size, lymph node-status, age, comorbidity, polypharmacy, BMI, cognition (MMSE) and Activities of Daily Living (Barthel)

* 2247 (93.7%) women in the Age Gap study and 254 (55.5%) women in the CLIMB study received adjuvant endocrine therapy

For women in whom adjuvant endocrine therapy could be omitted according to the Dutch guideline (lymph node-negative disease grade I and <2cm in size, or grade II/III and <1cm in size) a statistically significant difference in overall survival was found in favour of women in the Age Gap study (log-rank test: p = 0.041, univariate HR: 1.95, 95% CI 1.02 – 3.72, p = 0.045). After adjustment for the predefined confounders age, comorbidity, polypharmacy, BMI, cognition and ADL, this was no longer statistically significant, although the hazard ratio remained above 1 (adjusted HR: 1.97, 95% CI 0.86 – 4.56, p = 0.112) (Fig. 2a). In this group of women, 91% in the Age Gap study and 24% in the CLIMB study received adjuvant endocrine therapy. Adjuvant chemotherapy was prescribed to 1% of women in the Age Gap study and 0% of women in the CLIMB study, and 65% versus 67% of women received adjuvant radiotherapy in the Age Gap and CLIMB studies, respectively.

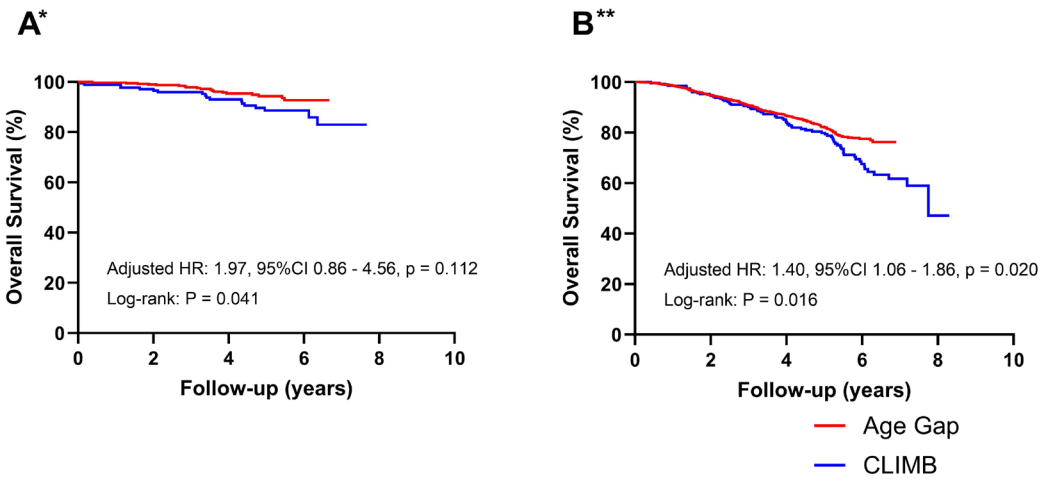


Fig. 2: Kaplan-Meier curves with the log-rank test and multivariate Cox proportional hazard regression for overall survival of British (Age Gap) and Dutch (CLIMB) women with non-metastatic hormone receptor-positive breast cancer who underwent surgery (A) in whom adjuvant endocrine therapy can be omitted according to the Dutch guideline (lymph node-negative disease grade I and <2cm in size, or grade II/III and <1cm in size) (B) in whom adjuvant endocrine therapy should be prescribed according to both guidelines. Adjusted for age, comorbidity, polypharmacy, BMI, cognition (MMSE) and Activities of Daily Living (Barthel)
* 358 (91.1%) women in the Age Gap study and 43 (24.2%) women in the CLIMB study received adjuvant endocrine therapy.
** 1889 (94.2%) women in the Age Gap study and 211 (75.6%) women in the CLIMB study received adjuvant endocrine therapy.

In women with higher risk disease, in whom adjuvant endocrine therapy is recommended in Dutch as well as British guidelines, a statistically significant overall survival difference was found in favour of women in the Age Gap study (log-rank test: p = 0.016, univariate HR: 1.38, 95% CI 1.06 – 1.78, p = 0.016), which persisted after adjustment for confounders (adjusted HR: 1.40, 95% CI 1.06 – 1.86, p = 0.020) (Fig. 2b). Of these women, 94% received adjuvant endocrine therapy in the Age Gap study compared to 76% women in the CLIMB study. Adjuvant chemotherapy was administered in 13% of women in the Age Gap study and in 7% in the CLIMB study. Women in the Age Gap study also more frequently received adjuvant radiotherapy than women in the CLIMB study (Age Gap: 63% of women, CLIMB: 51% of women), but women in the CLIMB study more often had a mastectomy (Age Gap: 42% of women, CLIMB: 57% of women).

Quality of life

For the quality of life analyses, only women who participated fully and thereby received quality of life forms during follow-up were included, which were 1825 (76%) women in the Age Gap study and 285 (59%) women in the CLIMB study.

After adjustment for relevant predefined confounders, small, but clinically relevant, general quality of life differences were found between both countries across the entire study period (Supplemental Fig. 1, Supplemental Fig. 2, Supplemental Table 3). The biggest difference in quality of life subscale between both countries over time was observed on the global health score (difference for the global health status subscale over entire study period: β = 9.96; 95% CI = 7.94 – 11.98; p < 0.001), followed by the role functioning subscale (difference for the role function subscale: β = 8.76; 95% CI = 6.15 – 11.37; p < 0.001), both in favour of Dutch women.

For the breast cancer-specific quality of life questionnaire, women from the CLIMB study were less upset by hair loss and had a lower score on the sexual enjoyment subscale (Supplemental Fig. 3, Supplemental Table 4). However, as these questions were optional, and numbers for the analyses were small.

Discussion

This study showed that almost all older women with non-metastatic hormone receptor-positive breast cancer in the UK were treated with adjuvant endocrine therapy, while in the Netherlands just over half of all women received adjuvant endocrine therapy. Side effects from endocrine therapy were common in both countries, but the proportion of women who discontinued therapy within the first 2 years after initiation was larger in the Netherlands. Quality of life outcomes were slightly better in the Netherlands, whereas overall survival for the entire cohort was statistically significantly better in the UK. Of note, absolute survival differences were minimal.

Strikingly, a previous EURECCA study that included all women aged 70 years and older with non-metastatic breast cancer between 2000 and 2013 from five nationwide registries, showed a worse relative survival in all tumour stages in British women than in Dutch women [20]. One reason for this disparate finding may be that in the current study overall survival was compared between the two countries, which is also affected by causes other than breast cancer, especially in the older population [21]. However, life expectancies are largely comparable between the two nations [22]. Importantly, the contradictory results could also be attributed to selection bias inherent in cohort studies, as well as the fact that more older and less fit women with hormone receptor-positive breast cancer were excluded from the British cohort for the analyses, due to the exclusion of patients who received primary endocrine therapy [23]. However, it has previously been shown that the survival of patients receiving primary endocrine therapy was comparable between both countries [16].

Although the relative benefit of adjuvant endocrine therapy is independent of tumour size, several studies have suggested that adjuvant endocrine therapy can safely be omitted in women with low-risk tumours [24, 25]. A Danish population-based cohort study of approximately 5.900 women found that women aged 60-74 years of age with tumours up to 10 mm who did not receive adjuvant endocrine therapy had similar mortality rates to the general population [26]. This is in line with the Stockholm tamoxifen randomised clinical trial (STO-3), in which postmenopausal women aged 45-74 years with lymph node-negative breast cancer and tumours <30mm of size were randomised between 2 or 5 years of tamoxifen or no adjuvant endocrine therapy and in whom no 25-year breast cancer-specific survival benefit was found from endocrine therapy in women with the smallest tumours (T1a/b) [27].

Although not statistically significant after adjusting for confounders, in the present study British women in whom adjuvant endocrine therapy can be omitted according to the Dutch guideline had better overall survival than women in the CLIMB study (of whom 24% received adjuvant endocrine therapy). While more difficult to explain than in the higher risk tumours, this may relate to the difference in prescription rates and the type of adjuvant endocrine therapy, but possibly also with higher discontinuation rates in the CLIMB study in patients who started this therapy. However, a study by van de Water and colleagues showed that, in contrast to women below 65 years of age, women aged 65 years and older who discontinued therapy had a similar breast cancer-specific survival to those who were treated according to the guideline [7]. This may imply that some older women derive no benefit from adjuvant endocrine therapy, or that 2-3 years of therapy may be good enough in some older women. This is currently being studied in the LESS study in France [28]. Longer follow-up is needed before robust conclusions can be drawn from the current study in women with low-risk disease, also because the numbers were small and the statistical significance disappeared after adjustment for confounders.

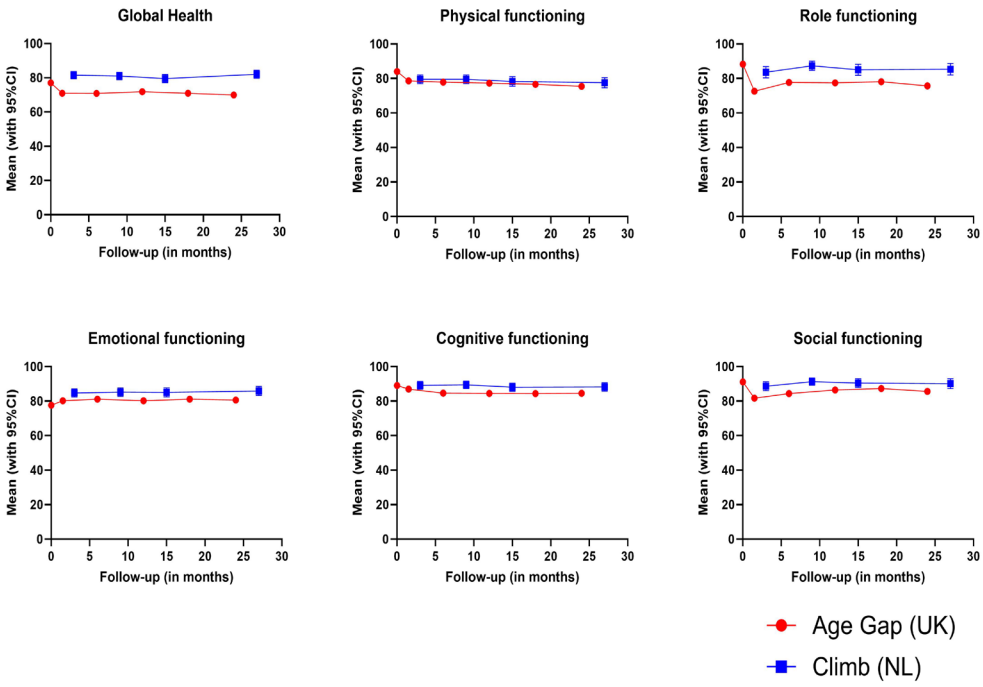
The risk of death due to other causes than breast cancer increases with age [21]. Full treatment of all women with ER+ disease may result in overtreatment of some older patients, especially in those who are frail [21]. Interestingly, in the present study, age, the number of comorbidities, cognition and dependency in activities of daily living did, in both countries, not differ between women receiving adjuvant endocrine therapy and those not. This implies the need for better individual risk evaluation of breast cancer- and competing risk mortality and potential benefit and risk of treatment in every woman. This treatment decision can be assisted by decision-support tools, such as the PORTRET tool, or by gene-expression signatures [29-31]. However, further research is needed to determine the benefit of gene expression signatures in older women [32].

In the Age Gap and CLIMB studies, respectively, 24% and 35% of women discontinued adjuvant endocrine therapy within 2 years after initiation. The frequently observed musculoskeletal complaints and asthenia/somnolence in women with aromatase inhibitors and vaginal symptoms with tamoxifen are in line with previous studies [4, 33, 34]. The type of endocrine therapy should be based on the individual's comorbidities, recurrence risks and side effects. Several trials are currently investigating alternatives for women who had to discontinue adjuvant endocrine therapy due to side effects or other reasons [35, 36]. Of note, symptoms such as musculoskeletal symptoms, dizziness, fatigue and headache are frequently attributed to therapy, but it is important to keep in mind that these symptoms are also common among healthy people [37, 38].

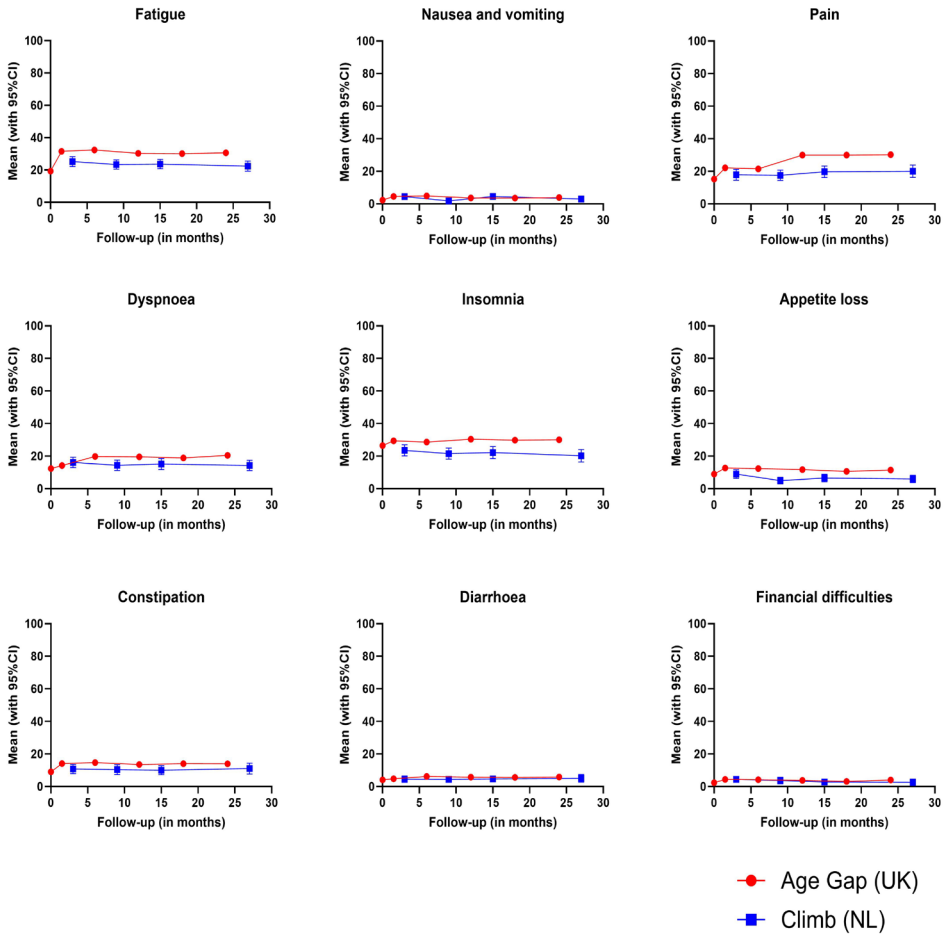
The study has limitations. The survival analyses are limited by the relatively short follow-up, which is particularly relevant in ER+ breast cancer. Moreover, as the cause of death was not collected in the Netherlands, we were unable to calculate breast cancer-specific survival rates. It is therefore difficult to conclude that the observed survival difference is completely attributable to breast cancer and its differences in treatment allocation. A further limitation is that recurrences were only collected until two years after diagnosis, while the risk of late recurrences in hormone receptor-positive tumours is substantial [24, 39]. Also, the study is subject to selection bias relative to the general populations of older women as both cohort studies were generally younger and fitter than the general older population with breast cancer in each country, limiting the generalisability of the results [23].

In conclusion, the allocation of adjuvant endocrine therapy for older women with non-metastatic hormone receptor-positive breast cancer differed between the UK and the Netherlands. Although absolute differences were minimal, overall survival was statistically significantly better in the UK than in the Netherlands, especially for women with medium- and high-risk breast cancer. Although other factors might have played a role in the survival difference between the two studies, increased prescription of endocrine therapy may improve survival of Dutch women. Future studies should investigate long-term survival differences and the incorporation of tools such as gene arrays and risk algorithms, on how best to identify and treat older women at risk for recurrences and those who could safely forego adjuvant endocrine therapy.

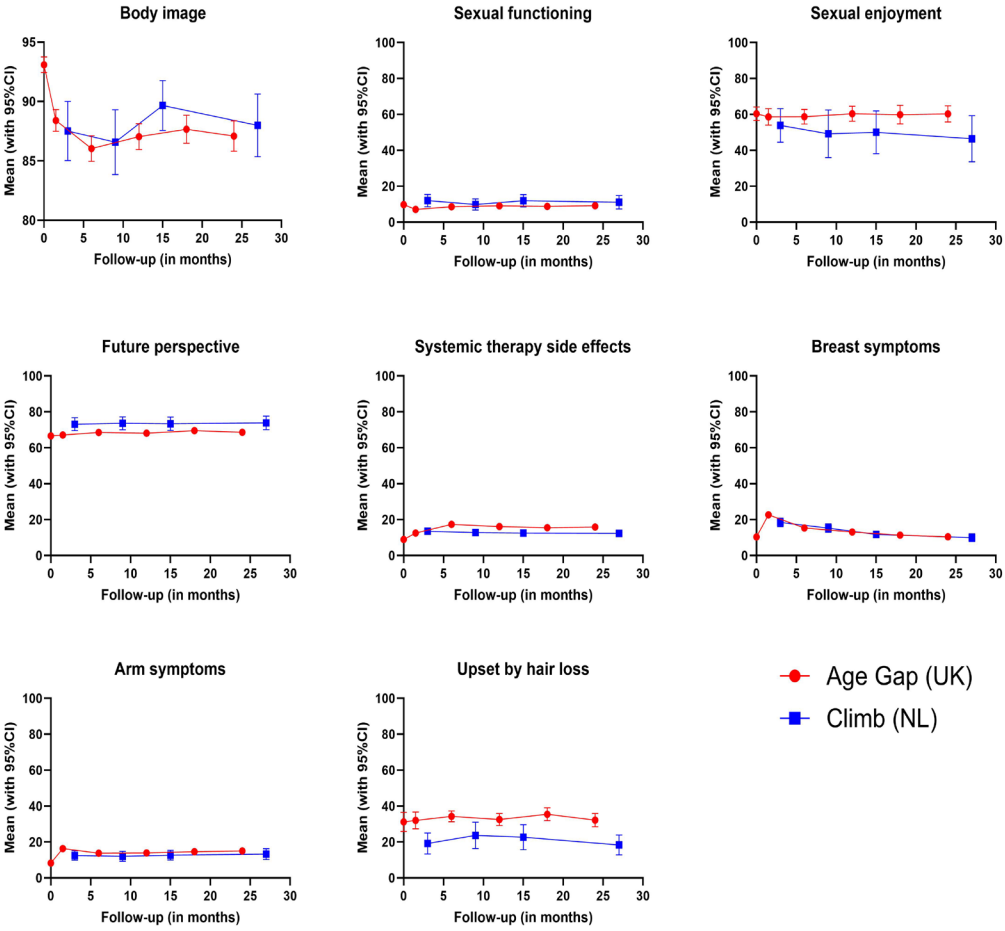
Supplementary data



Supplemental Fig. 1: Global health and functioning subscales of the EORTC QLQ-C30 questionnaire for Dutch women from the CLIMB study and British women from the Age Gap study in the first 27 months after diagnosis of early-stage breast cancer.
Higher scores on the functioning and global health status scale indicate better functioning.



Supplemental Fig. 2: Symptom subscales of the EORTC QLQ-C30 questionnaire for Dutch women from the CLIMB study and British women from the Age Gap study in the first 27 months after diagnosis of early-stage breast cancer.
Higher scores represent more severe symptoms.



Supplemental Fig. 3: Functioning and symptom subscales of the EORTC QLQ-BR23 questionnaire for Dutch women from the CLIMB study and British women from the Age Gap study in the first 27 months after diagnosis of early-stage breast cancer.
Higher scores on the functioning scales indicate better functioning and higher scores on the symptom scales represent more severe symptoms .

Supplemental Table 1: Differences in the use of adjuvant endocrine therapy between cohort studies

	Age Gap						CLIMB					
	Lymph node-negative			Lymph node-positive			Lymph node-negative			Lymph node-positive		
Receiving adjuvant ET	Yes *N=1561 (94%)*	No *N=109 (6%)*	p-value	Yes *N=686 (94%)*	No *N=43 (6%)*	p-value	Yes *N=154 (46%)*	No *N=178 (54%)*	p-value	Yes *N=91 (84%)*	No *N=18 (16%)*	p-value
Age												
70-74	716 (93.7)	48 (6.3)	0.690	236 (92.9)	18 (7.1)	0.612	81 (48.8)	85 (51.2)	0.075	47 (87.0)	7 (13.0)	0.704
75-79	468 (93.8)	31 (6.2)		250 (95.4)	12 (4.6)		39 (46.4)	45 (53.6)		15 (78.9)	4 (21.1)	
80-84	267 (93.4)	19 (6.6)		139 (93.3)	10 (6.7)		30 (49.2)	31 (50.8)		20 (83.3)	4 (16.7)	
≥ 85	110 (90.9)	11 (9.1)		61 (95.3)	3 (4.7)		4 (19.0)	17 (81.0)		9 (75.0)	3 (25.0)	
Grade												
I	301 (92.3)	25 (7.7)	<0.001	79 (92.9)	6 (7.1)	0.166	13 (12.3)	93 (87.7)	<0.001	18 (85.7)	3 (14.3)	0.821
II	1026 (94.6)	59 (5.4)		459 (95.4)	22 (4.6)		94 (59.9)	63 (40.1)		46 (82.1)	10 (17.9)	
III	232 (91.7)	21 (8.3)		147 (90.7)	15 (9.3)		43 (67.2)	21 (32.8)		25 (86.2)	4 (13.8)	
Unknown	2 (33.3)	4 (66.7)		1 (100.0)	0 (0.0)		4 (80.0)	1 (20.0)		2 (66.7)	1 (33.3)	
Histopathology												
Ductal	1073 (93.3)	77 (6.7)	0.424	492 (94.3)	30 (5.7)	0.828	107 (43.0)	142 (57.0)	0.022	66 (83.5)	13 (16.5)	0.606
Lobular	239 (95.6)	11 (4.4)		126 (94.7)	7 (5.3)		39 (63.9)	22 (36.1)		18 (78.3)	5 (21.7)	
Other	247 (92.2)	21 (7.8)		67 (91.8)	6 (8.2)		6 (35.3)	11 (64.7)		5 (100.0)	0 (0.0)	
Unknown	2 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)		2 (40.0)	3 (60.0)		2 (100.0)	0 (0.0)	
Tumour size												
0-2 cm	880 (92.5)	71 (7.5)	0.198	195 (96.1)	8 (3.9)	0.341	97 (38.2)	157 (61.8)	<0.001	35 (83.3)	7 (16.7)	0.961
2-5 cm	619 (94.6)	35 (5.4)		407 (93.1)	30 (6.9)		51 (72.9)	19 (27.1)		47 (83.9)	9 (16.1)	
>5 cm	62 (95.4)	3 (4.6)		84 (94.4)	5 (5.6)		6 (85.7)	1 (14.3)		8 (80.0)	2 (20.0)	
Unknown	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	1 (100.0)		1 (100.0)	0 (0.0)	
HER2-status												
Negative	1342 (94.1)	84 (5.9)	0.039	576 (94.3)	35 (5.7)	0.171	128 (47.4)	142 (52.6)	0.015	65 (81.3)	15 (18.8)	0.467
Positive	150 (89.8)	17 (10.2)		80 (90.9)	8 (9.1)		13 (68.4)	6 (31.6)		11 (84.6)	2 (15.4)	
Unknown	69 (89.6)	8 (10.4)		30 (100.0)	0 (0.0)		13 (30.2)	30 (69.8)		15 (93.8)	1 (6.3)	
Charlson Comorbidity Index (CCI)												
0	814 (93.7)	55 (6.3)	0.512	367 (94.3)	22 (5.7)	0.718	89 (46.6)	102 (53.4)	0.877	45 (78.9)	12 (21.1)	0.149
1	246 (91.4)	23 (8.6)		114 (91.9)	10 (8.1)		33 (49.3)	34 (50.7)		33 (94.3)	2 (5.7)	
2	329 (94.3)	20 (5.7)		133 (95.0)	7 (5.0)		16 (41.0)	23 (59.0)		11 (73.3)	4 (26.7)	
≥ 3	172 (94.0)	11 (6.0)		72 (94.7)	4 (5.3)		16 (45.7)	19 (54.3)		2 (100.0)	0 (0.0)	

Supplemental Table 1: Continued

	Age Gap						CLIMB					
	Lymph node-negative			Lymph node-positive			Lymph node-negative			Lymph node-positive		
Receiving adjuvant ET	Yes *N=1561 (94%)*	No *N=109 (6%)*	p-value	Yes *N=686 (94%)*	No *N=43 (6%)*	p-value	Yes *N=154 (46%)*	No *N=178 (54%)*	p-value	Yes *N=91 (84%)*	No *N=18 (16%)*	p-value
Polypharmacy												
No	926 (92.8)	72 (7.2)	0.166	374 (92.8)	29 (7.2)	0.098	90 (48.1)	97 (51.9)	0.453	55 (83.3)	11 (16.7)	0.884
Yes	635 (94.5)	37 (5.5)		312 (95.7)	14 (4.3)		57 (42.9)	76 (57.1)		33 (84.6)	6 (15.4)	
Unknown	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		7 (58.3)	5 (41.7)		3 (75.0)	1 (25.0)	
BMI												
<18.5	11 (84.6)	2 (15.4)	0.163	4 (66.7)	2 (33.3)	0.036	3 (100.0)	0 (0.0)	0.182	0 (0.0)	0 (0.0)	0.420
18.5-25	414 (91.8)	37 (8.2)		164 (92.1)	14 (7.9)		51 (44.3)	64 (55.7)		31 (79.5)	8 (20.5)	
25-30	513 (93.4)	36 (6.6)		215 (94.7)	12 (5.3)		60 (43.5)	78 (56.5)		31 (81.6)	7 (18.4)	
>30	387 (94.4)	23 (5.6)		193 (95.1)	10 (4.9)		39 (52.0)	36 (48.0)		29 (90.6)	3 (9.4)	
Unknown	230 (95.8)	10 (4.2)		107 (95.5)	5 (4.5)		1 (100.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mental status (MMSE)												
Normal (≥24)	1059 (93.1)	78 (6.9)	0.706	452 (93.0)	34 (7.0)	0.071	139 (45.7)	165 (54.3)	0.640	83 (84.7)	15 (15.3)	0.591
Impaired (<24)	38 (95.0)	2 (5.0)		15 (88.2)	2 (11.8)		6 (60.0)	4 (40.0)		3 (75.0)	1 (25.0)	
Unknown	464 (94.1)	29 (5.9)		219 (96.9)	7 (3.1)		9 (50.0)	9 (50.0)		2 (28.6)	2 (28.6)	
Functional status (Barthel)*												
Independent	1398 (93.0)	105 (7.0)	0.032	604 (93.9)	39 (6.1)	0.794	140 (46.2)	163 (53.8)	0.561	76 (82.6)	16 (17.4)	0.778
Partially or minimally dependent	26 (89.7)	3 (10.3)		13 (92.9)	1 (7.1)		7 (38.9)	11 (61.1)		10 (90.9)	1 (9.1)	
Very or fully dependent	1 (100.0)	0 (0.0)		0	0		3 (75.0)	1 (25.0)		2 (100.0)	0 (0.0)	
Unknown	136 (99.3)	1 (0.7)		69 (95.8)	3 (4.2)		4 (57.1)	3 (42.9)				
Most extensive breast surgery												
Breast conserving	1093 (94.0)	70 (6.0)	0.060	312 (96.3)	12 (3.7)	0.060	80 (38.3)	129 (61.7)	<0.001	37 (86.0)	6 (14.0)	0.561
Mastectomy	462 (92.6)	37 (7.4)		368 (92.5)	30 (7.5)		74 (60.2)	49 (39.8)		54 (81.8)	12 (18.2)	
Unknown	6 (75.0)	2 (25.0)		6 (85.7)	1 (14.3)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Supplemental Table 1: Continued

	Age Gap						CLIMB					
	Lymph node-negative			Lymph node-positive			Lymph node-negative			Lymph node-positive		
Receiving adjuvant ET	Yes *N=1561 (94%)*	No *N=109 (6%)*	p-value	Yes *N=686 (94%)*	No *N=43 (6%)*	p-value	Yes *N=154 (46%)*	No *N=178 (54%)*	p-value	Yes *N=91 (84%)*	No *N=18 (16%)*	p-value
Most extensive axillary surgery												
None	59 (92.2)	5 (7.8)	0.268	4 (100.0)	0 (0.0)	0.090	3 (27.3)	8 (72.7)	0.190	0 (0.0)	0 (0.0)	0.973
Sentinel lymph node procedure	1458 (93.6)	99 (6.4)		330 (96.2)	13 (3.8)		123 (45.1)	150 (54.9)		56 (83.6)	11 (16.4)	
Axillary lymph node dissection	37 (92.5)	4 (7.5)		347 (92.3)	29 (7.7)		25 (59.5)	17 (40.5)		35 (83.3)	7 (16.7)	
Unknown	7 (77.8)	2 (22.2)		5 (83.3)	1 (16.7)		3 (50.0)	3 (50.0)		0 (0.0)	0 (0.0)	
Neo-adjuvant systemic treatment												
None	1485 (93.8)	99 (6.3)	0.137	639 (94.8)	35 (5.2)	0.018	146 (45.5)	175 (54.5)	0.173	81 (85.3)	14 (14.7)	0.393
CT	18 (90.0)	2 (10.0)		18 (85.7)	3 (14.3)		1 (100.0)	0 (0.0)		4 (66.7)	2 (33.3)	
ET	58 (87.9)	8 (12.1)		29 (85.3)	5 (14.7)		7 (70.0)	3 (30.0)		6 (75.0)	2 (25.0)	
Adjuvant chemotherapy												
No	1464 (93.9)	95 (6.1)	0.007	557 (95.5)	26 (4.5)	<0.001	149 (45.6)	178 (54.4)	0.015	80 (82.5)	17 (17.5)	0.418
Yes	97 (87.4)	14 (12.6)		129 (88.4)	17 (11.6)		5 (100.0)	0 (0.0)		11 (91.7)	1 (8.3)	
Adjuvant radiotherapy												
No	582 (88.9)	73 (11.1)	<0.001	189 (87.5)	27 (12.5)	<0.001	79 (55.2)	64 (44.8)	0.005	36 (83.7)	7 (16.3)	0.958
Yes	979 (96.5)	36 (3.5)		497 (96.9)	16 (3.1)		75 (39.7)	114 (60.3)		55 (83.3)	11 (16.7)	

*Without the questions on bladder and bowel incontinence

Abbreviations: ER - oestrogen receptor; PR - progesterone receptor; HER2 - human epidermal growth factor receptor 2; CCI - Charlson Comorbidity Index; BMI - body mass index; MMSE - mini-mental state examination; CT - chemotherapy; ET - endocrine therapy

Supplemental Table 2: Adjuvant endocrine therapy received according to country-specific guidelines

	Age Gap			CLIMB			
	Yes *N=2247 (94%)*	No *N=152 (6%)*	p-value	Yes *N=350 (76%)*	No *N=91 (20%)*	Unknown *N=17 (4%)*	p-value
Age							
70-74	952 (42.4)	66 (43.4)	0.755	186 (53.1)	29 (31.9)	10 (58.8)	<0.001
75-79	718 (32.0)	43 (28.3)		82 (23.4)	21 (23.1)	2 (11.8)	
80-84	406 (18.1)	29 (19.1)		60 (17.1)	23 (25.3)	5 (29.4)	
≥ 85	171 (7.6)	14 (9.2)		22 (6.3)	18 (19.8)	0 (0.0)	
Grade							
I	380 (16.9)	31 (20.4)	<0.001	113 (32.3)	17 (18.7)	1 (5.9)	<0.001
II	1485 (66.1)	81 (53.3)		159 (45.4)	54 (59.3)	4 (23.5)	
III	379 (16.9)	36 (23.7)		78 (22.3)	20 (22.0)	3 (17.6)	
Unknown	3 (0.1)	4 (2.6)		0 (0.0)	0 (0.0)	9 (52.9)	
Histopathology							
Ductal	1565 (69.7)	107 (70.4)	0.337	262 (74.9)	66 (72.5)	10 (58.8)	0.252
Lobular	365 (16.2)	18 (11.8)		66 (18.9)	20 (22.0)	4 (23.5)	
Other	314 (14.0)	27 (17.8)		18 (5.1)	2 (2.2)	2 (11.8)	
Unknown	3 (0.1)	0 (0.0)		4 (1.1)	3 (3.3)	1 (5.9)	
Tumour size							
0-2 cm	1075 (47.8)	79 (52.0)	0.575	240 (68.6)	59 (64.8)	9 (52.9)	<0.001
2-5 cm	1026 (45.7)	65 (42.8)		95 (27.1)	29 (31.9)	3 (17.6)	
>5 cm	146 (6.5)	8 (5.2)		15 (4.3)	3 (3.3)	2 (11.8)	
Unknown	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	3 (17.6)	
Nodal status							
Node-negative	1561 (69.5)	109 (71.7)	0.561	255 (72.9)	67 (73.6)	10 (58.8)	0.006
Node-positive	686 (30.5)	43 (28.3)		88 (25.1)	16 (17.6)	5 (29.4)	
Unknown	0 (0.0)	0 (0.0)		7 (2.0)	8 (8.8)	2 (11.8)	
HER2-status							
Negative	1918 (85.4)	119 (78.3)	0.044	284 (81.1)	64 (70.3)	13 (76.4)	0.067
Positive	230 (10.2)	25 (16.4)		26 (7.4)	6 (6.6)	2 (11.8)	
Unknown	99 (4.4)	8 (5.3)		40 (11.4)	21 (23.1)	2 (11.8)	
Charlson Comorbidity Index (CCI)							
0	1181 (52.5)	77 (50.7)	0.310	196 (56.0)	51 (56.0)	11 (64.7)	0.427
1	360 (16.0)	33 (21.7)		86 (24.6)	16 (17.6)	5 (29.4)	
2	462 (20.6)	27 (17.8)		39 (11.1)	15 (16.5)	1 (5.9)	
≥ 3	244 (10.9)	15 (9.9)		29 (8.3)	9 (9.9)	0 (0.0)	
Polypharmacy							
No	1300 (57.9)	101 (66.4)	0.038	206 (58.9)	47 (51.6)	10 (58.8)	0.697
Yes	947 (42.1)	51 (33.6)		132 (37.7)	40 (44.0)	7 (41.2)	
Unknown	0 (0.0)	0 (0.0)		12 (3.4)	4 (4.4)	0 (0.0)	
BMI							
<18.5	15 (0.7)	4 (2.5)	0.008	3 (0.9)	0 (0.0)	1 (5.9)	0.171
18.5-25	578 (25.8)	51 (33.8)		118 (33.7)	34 (37.4)	8 (47.1)	
25-30	728 (32.5)	48 (31.8)		138 (39.4)	42 (46.2)	6 (35.3)	
>30	580 (25.9)	33 (21.9)		90 (25.7)	15 (16.5)	2 (11.8)	
Unknown	337 (15.1)	15 (10.0)		1 (0.3)	0 (0.0)	0 (0.0)	
Mental status (MMSE)							
Normal (≥24)	1511 (67.2)	112 (73.7)	0.217	321 (91.7)	81 (89.0)	15 (88.2)	0.668
Impaired (<24)	53 (2.4)	4 (2.6)		10 (2.9)	4 (4.4)	0 (0.0)	
Unknown	683 (30.4)	36 (23.7)		19 (5.4)	6 (6.6)	2 (11.8)	

Supplemental Table 2: Continued

	Age Gap			CLIMB			
	Yes *N=2247 (94%)*	No *N=152 (6%)*	p-value	Yes *N=350 (76%)*	No *N=91 (20%)*	Unknown *N=17 (4%)*	p-value
Functional status (Barthel)							
Independent	2002 (89.1)	144 (94.7)	0.044	319 (91.1)	74 (81.3)	16 (94.1)	0.037
Partially or minimally dependent	39 (1.7)	4 (2.6)		18 (5.1)	12 (13.2)	1 (5.9)	
Very or fully dependent	1 (0.0)	0 (0.0)		6 (1.7)	0 (0.0)	0 (0.0)	
Unknown	205 (9.1)	4 (2.6)		7 (2.0)	5 (5.5)	0 (0.0)	
Most extensive breast surgery							
Breast conserving	1405 (62.5)	82 (53.9)	0.015	209 (59.7)	45 (49.5)	6 (35.3)	0.040
Mastectomy	830 (36.9)	67 (44.1)		141 (40.3)	46 (50.5)	11 (64.7)	
Unknown	12 (0.6)	3 (2.0)					
Most extensive axillary surgery							
No axillary surgery	63 (2.8)	5 (3.3)	0.080	7 (2.0)	12 (13.2)	2 (11.8)	<0.001
Sentinel lymph node procedure	1788 (79.6)	112 (73.7)		268 (76.6)	68 (74.7)	10 (58.8)	
Axillary lymph node dissection	384 (17.1)	32 (21.0)		70 (20.0)	10 (11.0)	5 (29.4)	
Unknown	12 (0.5)	3 (2.0)		5 (1.4)	1 (1.1)	0 (0.0)	
Neo-adjuvant systemic treatment							
None	2124 (94.5)	134 (88.2)	0.005	334 (95.4)	84 (92.3)	12 (70.6)	<0.001
Chemotherapy (CT)	36 (1.6)	5 (3.3)		4 (1.1)	1 (1.1)	3 (17.6)	
Hormonal therapy (HT)	87 (3.9)	12 (8.5)		12 (3.4)	6 (6.6)	2 (11.8)	
Adjuvant chemotherapy							
No	2021 (89.9)	121 (79.6)	<0.001	335 (95.7)	89 (97.8)	16 (94.1)	0.603
Yes	226 (10.1)	31 (20.4)		15 (4.3)	2 (2.2)	1 (5.9)	
Adjuvant radiotherapy							
No	771 (34.3)	100 (65.8)	<0.001	139 (39.7)	49 (53.8)	9 (52.9)	0.037
Yes	1476 (65.7)	52 (34.2)		211 (60.3)	42 (46.2)	8 (47.1)	

Supplemental Table 3: Comparison between the Age Gap study and the Climb study per EORTC QLQ-C30 subscale, using linear mixed models

	Crude model			Adjusted model*		
	bèta	95% CI	p value	bèta	95% CI	p value
Global health status / QoL						
Global health						
Age Gap	Ref			Ref		
CLIMB	9.26	7.22-11.29	<0.001	9.96	7.94 - 11.98	<0.001
Functional scales						
Physical function						
Age Gap	Ref			Ref		
CLIMB	0.19	-2.26 - 2.64	0.879	1.74	-0.24 - 3.73	0.085
Role function						
Age Gap	Ref			Ref		
CLIMB	6.83	4.08 - 9.59	<0.001	8.76	6.15 - 11.37	<0.001
Emotional function						
Age Gap	Ref			Ref		
CLIMB	4.54	2.39 - 6.70	<0.001	5.30	3.02 - 7.59	<0.001
Cognitive function						
Age Gap	Ref			Ref		
CLIMB	3.53	1.58 - 5.47	<0.001	4.41	2.38 - 6.44	<0.001
Social function						
Age Gap	Ref			Ref		
CLIMB	3.80	1.57 - 6.03	<0.001	4.52	2.29 - 6.74	<0.001
Symptom scales / items						
Fatigue						
Age Gap	Ref			Ref		
CLIMB	-5.02	-7.46 - -2.58	<0.001	-6.07	-8.48 - -3.65	<0.001
Nausea and vomiting						
Age Gap	Ref			Ref		
CLIMB	-0.23	-1.17 - 0.71	0.632	0.11	-0.89 - 1.11	0.828
Pain						
Age Gap	Ref			Ref		
CLIMB	-6.86	-9.45 - -4.26	<0.001	-8.36	-10.88 - -5.83	<0.001
Dyspnoea						
Age Gap	Ref			Ref		
CLIMB	-2.33	-5.08 - 0.42	0.097	-1.71	-4.47 - 1.05	0.225
Insomnia						
Age Gap	Ref			Ref		
CLIMB	-7.09	-10.24 - -3.93	<0.001	-7.35	-10.73 - -3.96	<0.001
Appetite loss						
Age Gap	Ref			Ref		
CLIMB	-4.55	-6.69 - -2.41	<0.001	-4.27	-6.49 - -2.05	<0.001
Constipation						
Age Gap	Ref			Ref		
CLIMB	-2.65	-5.05 - -0.26	0.030	-3.30	-5.83 - -0.78	0.010
Diarrhoea						
Age Gap	Ref			Ref		
CLIMB	-0.87	-2.32 - 0.59	0.242	-1.27	-2.84 - 0.30	0.114
Financial difficulties						
Age Gap	Ref			Ref		
CLIMB	-0.03	-1.40 - 1.35	0.968	-0.42	-1.82 - 0.98	0.554

*Adjusted for age, tumour grade, tumour size, nodal status, Charlson Comorbidity Index, polypharmacy, Body Mass Index, Mini Mental State Examination, functional status (ADL), breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, and adjuvant radiotherapy

Supplemental Table 4: Comparison between the Age Gap study and the Climb study per EORTC QLQ-BR23 subscale, using linear mixed models

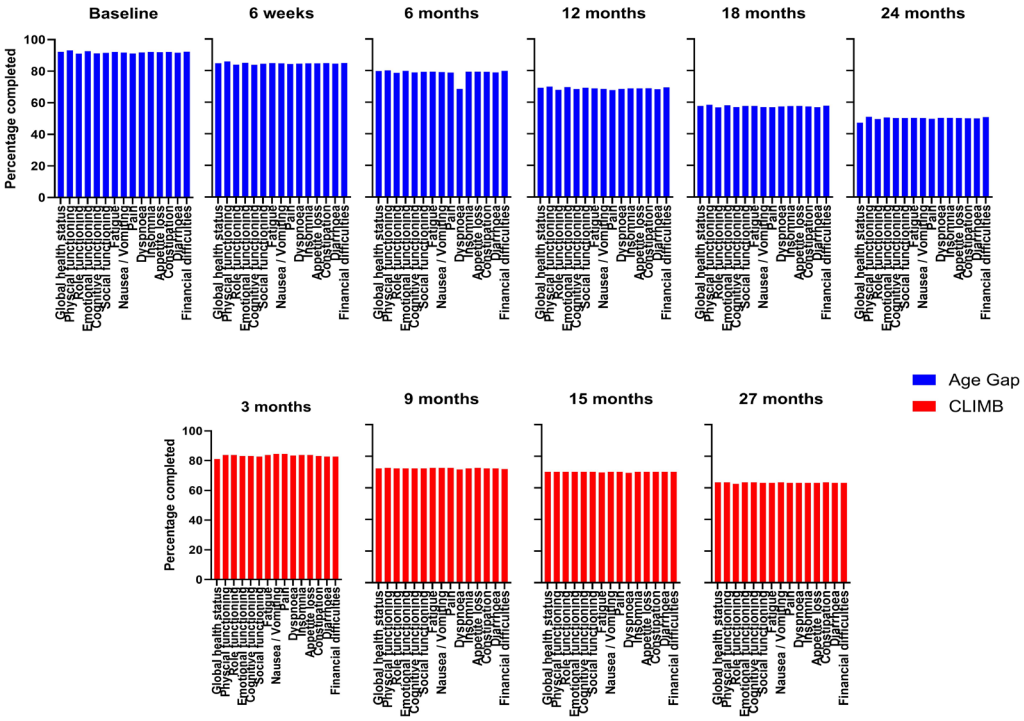
	Crude model			Adjusted model*		
	bèta	95% CI	p-value	bèta	95% CI	p-value
Functional scales						
Body Image						
Age Gap	Ref			Ref		
CLIMB	-0.02	-2.09 - 2.04	0.984	-0.03	-2.22 - 2.16	0.981
Sexual functioning						
Age Gap	Ref			Ref		
CLIMB	2.33	-0.11 - 4.78	0.061	1.46	-1.11 - 4.03	0.265
Sexual enjoyment						
Age Gap	Ref			Ref		
CLIMB	-11.41	-18.81 - -4.01	0.003	-11.52	-19.51 - -3.54	0.005
Future perspective						
Age Gap	Ref			Ref		
CLIMB	5.12	2.24 - 8.01	<0.001	4.53	1.44 - 7.62	0.004
Symptom scales / items						
Systemic therapy side effects						
Age Gap	Ref			Ref		
CLIMB	-1.91	-3.38 - -0.45	0.010	-1.94	-3.48 - -0.40	0.013
Breast symptoms						
Age Gap	Ref			Ref		
CLIMB	1.09	-0.46 - 2.64	0.169	1.08	-0.56 - 2.73	0.197
Arm symptoms						
Age Gap	Ref			Ref		
CLIMB	-1.14	-3.03 - 0.75	0.239	-1.58	-3.52 - 0.35	0.109
Upset by hair loss						
Age Gap	Ref			Ref		
CLIMB	-13.99	-18.98 - -9.00	<0.001	-12.70	-18.11 - -7.30	<0.001

*Adjusted for age, tumour grade, tumour size, nodal status, Charlson Comorbidity Index, polypharmacy, Body Mass Index, Mini Mental State Examination, functional status (ADL), breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, and adjuvant radiotherapy

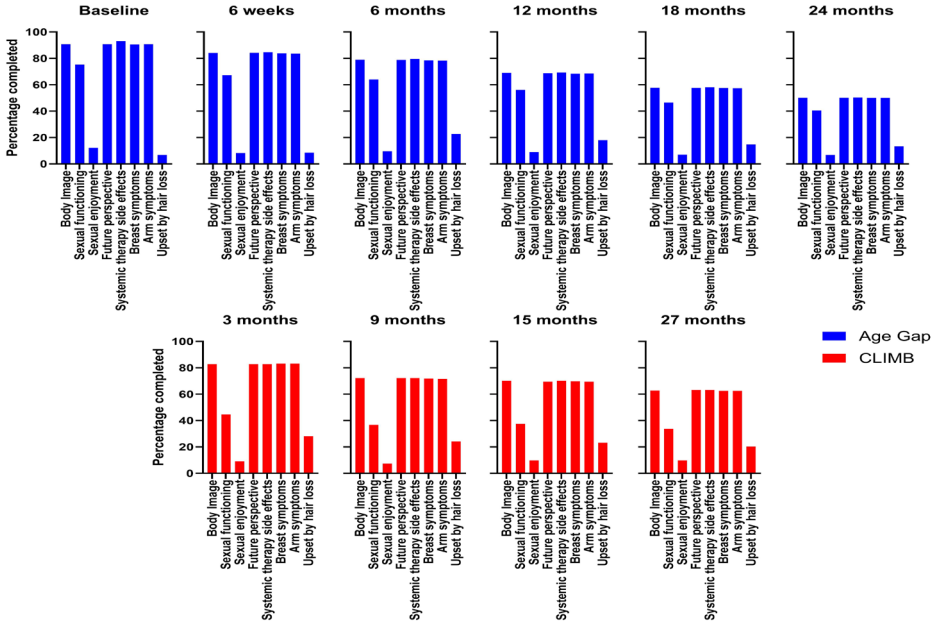
Analysis according to whether the curves of the different subscales from the two countries had different slopes over time, showed statistically significant differences for global health, physical function, role function, cognitive function, fatigue, pain, dyspnoea, insomnia, financial difficulties, body image, systemic therapy side effect, and breast symptoms subscales. Nevertheless, absolute changes were small and probably clinically irrelevant (Supplemental Fig. 1, Supplemental Fig. 2, Supplemental Fig. 3, Supplemental Table 4).

Supplemental Table 5: Tests for interaction between time and study for all EORTC QLQ-C30 and QLQ-BR23 subscales

Subscale	p value
Global health	<0.001
Physical function	<0.001
Role function	0.002
Emotional function	0.215
Cognitive function	0.017
Social function	0.281
Fatigue	<0.001
Nausea and vomiting	0.217
Pain	<0.001
Dyspnoea	<0.001
Insomnia	0.045
Appetite loss	0.117
Constipation	0.101
Diarrhoea	0.598
Financial difficulties	0.025
Body Image	<0.001
Sexual functioning	0.263
Sexual enjoyment	0.765
Future perspective	0.252
Systemic therapy side effects	<0.001
Breast symptoms	0.005
Arm symptoms	0.099
Upset by hair loss	0.071



Supplemental Fig. 1: Completion of the EORTC QLQ-C30 questionnaire at each time point for women from the Age Gap study (blue) and CLIMB study (red)



Supplemental Fig. 2: Completion of the EORTC QLQ-BR23 questionnaire at each time point for women from the Age Gap study (blue) and CLIMB study (red)

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Chapter 5

A comparison of treatment allocation and survival between younger and older patients with HER2-overexpressing de novo metastatic breast cancer.

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Abstract

Introduction

There have been several developments in the treatment of HER2-overexpressing metastatic breast cancer. However, pivotal trials mainly included younger and healthier patients, resulting in a lack of information about the benefits and harms of treatment for most older patients. The aim of this study was to provide an overview of the differences in treatment allocation and survival outcomes over time between younger and older patients with HER2-overexpressing metastatic breast cancer.

Materials and Methods

All patients from the Netherlands Cancer Registry with de novo metastatic breast cancer between 2005 and 2021 were included. Patients were divided into three age groups: <65, 65-74, and ≥75 years. Changes in treatment allocation were graphically depicted over time. Cox proportional hazard models were used to calculate overall survival and Poisson models for relative survival.

Results

Overall, 2,722 patients were included. Between 2005 and 2021, the use of targeted therapy as first-line treatment increased for all age groups (<65 years from 33.8% to 90.6%, $p < 0.001$; 65-74 years from 29.2% to 86.5%, $p = 0.001$; ≥75 years from 4.3% to 55.8%, $p < 0.001$). Use of chemotherapy as first-line treatment also increased for all age groups (<65 years from 73.5% to 89.8%, $p < 0.001$; 65-74 years from 50.0% to 78.4%, $p = 0.01$; ≥75 years from 8.7% to 37.2%, $p = 0.04$). Although not statistically significant, the use of endocrine therapy, both as monotherapy and in combination with targeted therapy in the first line, decreased (<65 years 19.1% to 5.5 %, $p < 0.001$; 65-74 years 25.0% to 13.5%, $p = 0.03$; ≥75 years 65.2% to 37.2%, $p = 0.16$). Changes in relative and overall survival were similar and improved in all age groups, but most in the youngest age group (relative excess risk [RER] 0.93, 95% confidence interval [CI] 0.91–0.94 per year, $p < 0.001$), and least in patients ≥75 (RER 0.96, 95% CI 0.93–0.98 per year, $p = 0.001$).

Discussion

The use of first-line chemotherapy and targeted therapy increased in all age groups, while the use of endocrine therapy decreased over time. Nevertheless, the uptake of chemotherapy and targeted therapies was substantially slower in the oldest age group. Overall survival and relative survival improved for all age groups, but these improvements were smaller in the older age groups.

Introduction

Breast cancer is the most frequently diagnosed malignancy in women and is increasingly common in women over 65 years of age [1]. Among older patients, about 4-9% have metastases at the time of diagnosis [2]. Although older patients generally have more favourable biological tumour characteristics compared to younger patients, 10-15% of their tumours overexpress the human epidermal growth factor receptor 2 (HER2) protein [3]. The overexpression of HER2 is associated with a poor prognosis, because HER2 mediates cell growth, differentiation, and survival of cells [4]. However, since the registration of the anti-HER2 antibody trastuzumab two decades ago, and later other HER2-directed monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates, treatment of this aggressive subtype has improved considerably. The marketing authorisation of trastuzumab in Europe was issued in 2000 and included in Dutch guidelines from 2002 [5]. Unfortunately, the pivotal trials on this targeted therapy mainly included younger and healthier patients, which means that less is known about the benefits and harms of treatment for older patients [6-9]. This information is crucial, because this growing older population represents a heterogeneous group with large differences in fitness and frailty, potentially putting them at higher risk of side effects than younger patients [10]. As a result of this lack of evidence, older patients are often under- or overtreated but there are limited data on age-related differences in HER2-overexpressing metastatic breast cancer.

The aim of this study was therefore to provide an overview of the differences in treatment allocation and survival outcomes over time between younger and older patients with HER2-overexpressing de novo metastatic breast cancer.

Methods

All patients from the Netherlands Cancer Registry who were diagnosed with metastatic breast cancer between 2005 and 2021 were included [11]. For this registry, trained data managers collected data from medical records on patient, tumour, and treatment characteristics of all patients in the Netherlands with newly diagnosed breast cancer up to one year after diagnosis. Incident cases are identified through the national pathology archive and, since tumour data of patients are not updated, only information on patients with metastatic breast cancer at the time of diagnosis (i.e., de novo) is complete. Vital status and date of death are obtained by a yearly linkage of the Netherlands Cancer Registry to the municipal Personal Records Databases with the latest linkage on February 1, 2023.

If patients were diagnosed with bilateral breast cancer, the most aggressive tumour was used for the analyses. This was defined in the following order: tumour size, grade, or hormone receptor-negative disease.

The proportion of patients with undetermined or unknown HER2 status increased with age, ranging from 0% in patients aged 20-29 years up to 30.4% in patients aged 90-99 years (Supplemental Figures 1 and 2). For the current analyses, only patients with known HER2 status and HER2 overexpression were included. A score of 3+ determined by immunohistochemistry and/or HER2 gene amplification detected by in situ hybridization or PCR was considered HER2 overexpression.

Patients were divided into three age groups: <65 years, 65-74 years, ≥75 years. Tumour morphology was divided into four categories (i.e., lobular, ductal, a combination of both, or unknown). Tumours were classified as hormone receptor-positive if the estrogen receptor (ER) and/or progesterone receptor (PR) expression was more than 10%. The number of metastatic sites was categorized into three groups: 1, 2, or 3 or more. Since the Netherlands Cancer Registry collected data until one year after diagnosis, information on second- or third-line systemic treatment may not be complete for every patient. Therefore, only first-line systemic treatment was used for the analyses. This was defined as the first systemic treatment given or, if another therapy was already given within two months (cut-off: 65 days) after initiation, the second therapy. Targeted therapy mainly includes trastuzumab, followed by pertuzumab. Lapatinib, trastuzumab emtansine, and tucatinib were all rarely prescribed in this time period as first-line treatment.

Statistical Analysis

Differences in tumour characteristics and treatment allocation between the age groups were assessed with the chi-square test, stratified for the hormone receptor status, and illustrated in bar graphs. Second, the percentage of patients receiving first-line systemic treatment (i.e., chemotherapy, endocrine therapy, and/or targeted therapy) was graphically depicted over time as three-year moving means. Moreover, logistic regression models were used to assess changes in treatment patterns (chemotherapy, targeted therapy, and endocrine therapy) per year, stratified by age group. Next, median overall survival with interquartile ranges (IQR) and five-year overall survival rates by age group were estimated using the Kaplan-Meier method. Cox proportional hazard models were used to additionally adjust for (1) tumour characteristics (i.e., grade, morphology, hormone receptor status, number of metastatic sites) and (2) tumour characteristics and adjuvant systemic treatment (i.e., chemotherapy, endocrine therapy, and targeted therapy) to assess the additional effect of these variables on overall survival.

Sensitivity analyses were performed to assess overall survival over time for all age groups and for the hormone receptor status.

Lastly, as older patients with breast cancer often die from other causes than breast cancer, the relative survival over time was calculated using the Ederer II method [12]. Relative survival is the observed survival of patients divided by the expected survival of the general population, matched by age, sex, and year of diagnosis. This ratio provides an estimate of survival if breast cancer were the only possible cause of death and is thereby a proxy for breast cancer-specific survival. This analysis can be performed under the assumption that the background mortality (i.e., the risk of dying if a patient would not have had breast cancer) of patients with metastatic breast cancer is similar to that of the general population. As the prevalence of most comorbidities is comparable among patients with breast cancer and the general population, relative survival is frequently used in this tumour type and is considered a valid method [13]. Relative excess risks (RER) were calculated with Poisson models and were adjusted for tumour characteristics (i.e., grade, morphology, hormone receptor status, and number of metastatic sites) and systemic treatment (i.e., chemotherapy, endocrine therapy, and targeted therapy).

The statistical tests were performed in SPSS version 29.0 (IBM, Armonk, New York, USA) and STATA version 16.1 (StataCorp, College Station, Texas, USA). All analyses were two-sided and a p-value of <0.05 was considered statistically significant.

Results

Between 2005 and 2021, 13,347 patients were diagnosed with de novo metastatic breast cancer. Of them, 2,722 (20.4%) patients had HER2 overexpressing disease and were included in the current study (Table 1). Of patients <65 years, 26.3% of tumours had HER2 overexpression; of patients 65-74 years, 16.8%; and of patients ≥75 years, 12.3%.

1. Tumour Histology and Hormone Receptor Status

The tumour morphology differed between different age groups, with patients under 65 years of age having more ductal tumours than older patients, whereas older patients had relatively more lobular tumours (Table 1). Hormone receptor status did not significantly differ between age groups (<65 years: 56.6%, 65-74 years: 54.1%, ≥75 years: 60.2% of patients had ER and/or PR-positive breast cancer, p = 0.41). Irrespective of age, most tumours metastasized to bone, followed by the liver for the youngest and the middle age groups, and by the lung for those aged 75 years and older.

Table 1: Patient- and tumour characteristics

	<65 years	65-74 years	≥75 years	p-value*
Number of patients	1801	458	463	
Median age (range)	52 (22-64)	69 (65-74)	82 (75-102)	
Year of inclusion				0.446
2005-2008	322(17.9)	79 (17.2)	85 (18.4)	
2009-2012	388 (21.5)	78 (17.0)	98 (21.2)	
2013-2016	438 (24.3)	123 (26.9)	108 (23.3)	
2017-2021	653 (36.3)	178 (38.9)	172 (37.1)	
Morphology				<0.001
Lobular	73 (4.1)	34 (7.4)	37 (8.0)	
Ductal	1445 (80.2)	343 (74.9)	342 (73.9)	
Combination	29 (1.6)	7 (1.5)	2 (0.4)	
Other	254 (14.1)	74 (16.2)	82 (17.7)	
ER and/or PR-status				0.406
Negative	769 (42.7)	206 (45.0)	180 (38.9)	
Positive	1020 (56.6)	248 (54.1)	279 (60.2)	
Unknown	12 (0.7)	4 (0.9)	4 (0.9)	
Number of metastatic sites				<0.001
1	962 (53.4)	207 (45.2)	262 (56.6)	
2	472 (26.2)	119 (26.0)	114 (24.6)	
≥3	367 (20.4)	132 (28.8)	87 (18.8)	
Metastatic site**				
Bone	1070 (59.4)	280 (61.1)	261 (56.4)	0.320
Lung	388 (21.5)	149 (32.5)	153 (33.0)	<0.001
Liver	840 (46.6)	178 (38.9)	146 (31.5)	<0.001
Brain	60 (3.3)	14 (3.1)	16 (3.5)	0.939
Distant lymph nodes	463 (25.7)	165 (36.0)	126 (27.2)	<0.001
Other/unknown	191 (10.6)	52 (11.4)	42 (9.1)	0.501

* A p-value of 0.050 was considered statistically significant

** Higher total number as several patients had more than one metastatic site

2. First-Line Treatment

Between 2005-2021, the use of chemotherapy and targeted therapy as first-line treatment gradually increased for patients under the age of 65 (chemotherapy use from 73.5% of patients in 2005 to 89.8% in 2021, $p < 0.001$; targeted therapy from 33.8% in 2005 to 90.6% in 2021, $p < 0.001$), while the use of first-line endocrine therapy, both as monotherapy or in combination with targeted therapy, decreased (19.1% in 2005 to 5.5% in 2021, $p < 0.001$) (Fig. 1, Supplemental Table 1). For patients aged 65-74 years, the use of first-line chemotherapy increased from 50.0% of patients in 2005 to 78.4% in 2021 ($p = 0.01$), while the use of endocrine therapy decreased from 25.0% to 13.5% in that same period ($p = 0.03$) (Fig. 1). The prescription of targeted therapy increased from 29.2% of patients in 2005 to 86.5% in 2021 ($p < 0.001$). The use of chemotherapy and targeted therapy also increased for the oldest age group (from 8.7% of patients in 2005 to 37.2% of patients in 2021 ($p = 0.04$) and from 4.3% in 2005 to 55.8% of patients in 2021 ($p < 0.001$), respectively. Although not statistically significant, the use of endocrine therapy decreased from 65.2% in 2005 to 37.2% in 2021 ($p = 0.16$). In total, 69.8% of patients aged <65 years, 51.2% aged 65-74 years, and 24.1% aged ≥75 years received chemotherapy in combination with targeted therapy (Supplemental Fig. 2).

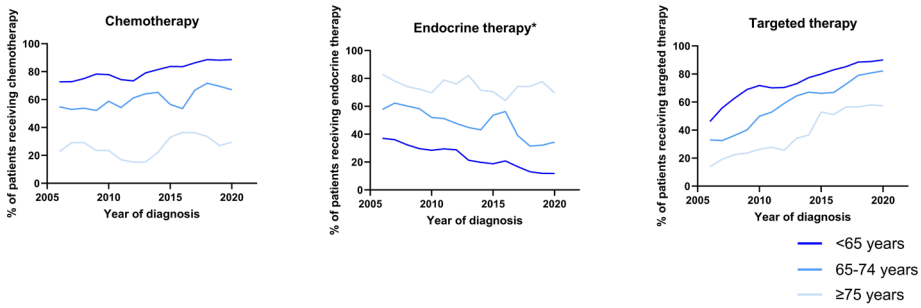


Fig. 1: First-line treatment allocation over time per age group
All figures are shown as three-year moving means. *Only hormone receptor-positive tumours included

2.1 Hormone Receptor-Negative Disease

For hormone receptor-negative disease, 13.1% of patients below 65 years of age received first-line chemotherapy as monotherapy and 78.2% of patients in combination with targeted therapy over the entire study period (Fig. 2A). The other patients either received no therapy (6.0%), targeted therapy only (2.1%), or endocrine therapy only (0.7%).

Of patients aged 65-74 years with hormone receptor-negative disease 79.1% were treated with first-line chemotherapy, 9.7% with monotherapy and 69.4% combined with targeted therapy (Fig. 2A). In the same age group, 16.0% of patients with hormone receptor-negative disease did not receive any first line systemic treatment. Very few patients received targeted therapy (2.4%) or endocrine therapy (1.9%) only.

Of patients aged 75 years and older with hormone receptor-negative disease, 42.2% of patients were treated with a first-line treatment combination of chemotherapy and targeted therapy (Fig. 2A). Also, 37.2% of patients did not receive any form of systemic therapy in the first line. Chemotherapy, endocrine therapy, and targeted therapy were given as monotherapy in 6.7%, 9.4%, and 4.4% of patients, respectively.

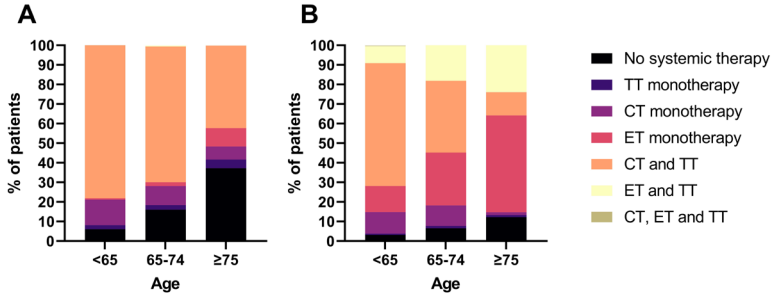


Fig. 2: First-line systemic treatment schedule per age group between 2005 and 2021 for patients with hormone receptor-negative (A) and hormone receptor-positive (B) disease
TT – Targeted Therapy; CT – Chemotherapy; ET – Endocrine Therapy

2.2 Hormone Receptor-Positive Disease

For those patients aged <65 years with hormone receptor-positive disease, 11.0% received first-line chemotherapy as monotherapy and 62.8% in combination with targeted therapy over the entire study period (Fig. 2B). Thirteen percent of this age group received endocrine therapy only, whereas 8.6% received endocrine therapy in combination with targeted therapy.

Of those patients aged 65-74 with hormone receptor-positive disease, 36.7% received a first-line treatment combination of chemotherapy and targeted therapy and 10.5% chemotherapy only (Fig. 2B). More than a quarter of patients (27.0%) received endocrine therapy only and 18.1% received endocrine therapy in combination with targeted therapy. No first-line systemic therapy was given to 6.5% of patients.

Nearly three-quarters of patients aged 75 years and older with hormone receptor-positive disease were treated with first-line endocrine therapy: 49.5% as monotherapy and 24.0% combined with targeted therapy (Fig. 2B). Chemotherapy in combination with targeted therapy was prescribed in 11.8% of patients, and 1.4% of patients received chemotherapy as monotherapy. Moreover, 12.2% of patients had no first-line systemic therapy.

3. Survival

3.1 Overall Survival

Median follow-up was 6.55 years (IQR 3.87 – 9.76). Median overall survival was 3.19 years (IQR 1.16 – 7.58) and was statistically significantly different per age group and after adjusting for tumour- and first-line systemic treatment characteristics (Table 2). Median overall survival was lowest for the oldest age group (1.30 [IQR 0.37 – 3.15] years), followed by patients between 65 and 74 years of age (2.04 [IQR 0.64 – 5.19] years) and was highest for the youngest age group (4.34 [IQR 1.83 – 10.23] years), $p < 0.001$. The overall survival of the whole cohort of patients improved statistically significantly over time (multivariable-adjusted hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.93 – 0.95 per year, $p < 0.001$) (Fig. 3).

Table 2: Comparison of unadjusted and adjusted overall mortality between the age groups

	Crude HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI)**
<65y	1 (reference)	1 (reference)	1 (reference)
65-74y	1.79 (1.58 - 2.03)	1.65 (1.46 - 1.87)	1.44 (1.27 - 1.63)
≥75y	2.70 (2.40 - 3.04)	2.74 (2.44 - 3.09)	1.75 (1.53 - 1.99)

*Adjusted for tumour characteristics: grade, morphology, hormone receptor-status, and number of metastatic sites

**Adjusted for tumour- and first-line systemic treatment characteristics (i.e., chemotherapy, endocrine therapy and targeted therapy)

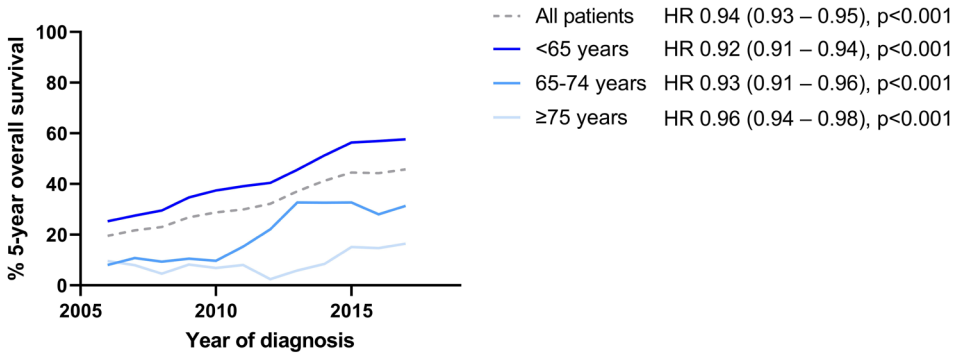


Fig. 3: 5-year overall survival over time per age group
Data is shown as three-year moving means. The hazard ratios (HR) and 95% confidence intervals are adjusted for age at diagnosis, grade, morphology, hormone receptor-status, and number of metastatic sites.
HR – Hazard Ratio

3.2 Relative Survival

The RER has improved over time for the entire cohort (multivariable-adjusted RER 0.93, 95% CI 0.92 – 0.94 per year, $p < 0.001$), indicating increased relative survival over the years of 7% (Fig. 4). The improvement was observed in all age groups, and was largest in the youngest age group (multivariable-adjusted RER 0.93, 95% CI 0.91 – 0.94 per year, $p < 0.001$) and patients aged 65-74 years of age (multivariable-adjusted RER 0.93, 95% CI 0.91 – 0.96 per year, $p < 0.001$), followed by patients over 75 (multivariable-adjusted RER 0.96, 95% CI 0.93 – 0.98 per year, $p = 0.001$).

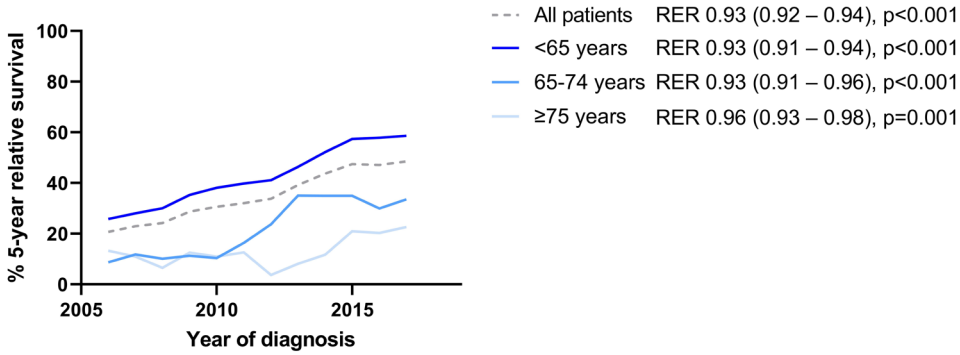


Fig. 4: 5-year relative survival over time per age group
Data is shown as three-year moving means. The relative excess risks (RER) and 95% confidence intervals are adjusted for age at diagnosis, grade, morphology, hormone receptor-status, and number of metastatic sites.
RER – Relative Excess Risk

Discussion

This population-based study showed that between 2005 and 2021, the use of first-line chemotherapy and targeted therapy for patients with HER2-overexpressing de novo metastatic breast cancer increased in all age groups, while the use of first-line endocrine therapy, both as monotherapy and in combination with targeted therapy, decreased. Over the same period, both overall survival and relative survival improved for every age group. Nevertheless, survival was still statistically significantly better for patients younger than 65 years of age than for those older than 65, and the greatest improvement over time was observed in the youngest age group.

Most guidelines recommend a combination of targeted therapy and chemotherapy as first-line treatment for patients with HER2-overexpressing metastatic breast cancer, except for those with congestive heart failure or a severely reduced left ventricular ejection fraction (LVEF), who should first undergo an individual risk evaluation [14-16]. Therefore, it seems plausible that older patients are less likely to receive targeted therapy because of an increased occurrence of congestive heart failure, a higher risk of reduced LVEF, and an increased risk of cardiac adverse events from targeted therapy with increasing age [6, 17]. The lack of specific guidance for older patients due to the fact that most guidelines have been based on trials conducted in fit younger patients may further lead to treatment variation in the older population [18]. It is therefore not surprising that the overall percentage of patients receiving the preferred first-line treatment decreased with advancing age (<65 years: 69.4%, 65-74 years: 51.3%, ≥75 years: 23.5% of patients received a combination of targeted therapy and chemotherapy). Yet, the lower use of the preferential treatment in the middle and oldest age groups cannot be entirely attributed to heart failure or frailty, as the number of patients not treated with this therapy is higher than the prevalence of these conditions in the general older population [19, 20]. Unfortunately, this late introduction of new therapies is often at the expense of potential survival gains for older patients. Moreover, some patients can continue targeted therapy despite a reduced LVEF [21-23].

Differences in treatment allocation in older versus younger patients with HER2-overexpressing breast cancer have also been investigated in other countries. In a recent French study by Annonay and colleagues, 89.1% of patients younger than 70 years compared to 65.0% of patients aged 70 years and older received targeted therapy in combination with chemotherapy [24]. These are much higher percentages than found in our study (<65 years: 69.4%, 65-74 years: 51.3%, ≥75 years: 23.5%). A combination of endocrine therapy and targeted therapy was rarely given in France: 1.5% of patients aged <70 and 7.7% of patients aged ≥70, while 63.0% versus 68.8% of patients had hormone receptor-positive tumours, respectively.

The studies are, however, not completely comparable for several reasons: the French study only selected patients from 18 comprehensive cancer centers if patients had not received first-line treatment elsewhere, they used a different age cut-off, their time window was shorter (2008-2016), no distinction between hormone receptor-status was made, and they also included patients whose breast cancer had recurred after initial diagnosis and treatment. Another, observational study (registHER) from the United States that included patients with recurrent metastatic HER2-overexpressing breast cancer or de novo metastatic breast cancer diagnosed between 2003 and 2006 found that 57.2% of patients aged <65 years, 56.9% of patients aged 65-74, and 46.2% of patients aged ≥75 years received a combination of chemotherapy and targeted therapy [25]. These percentages are high for that period, but it may have to do with the fact that relatively healthy patients are included in these studies. Numbers were also very small, whereas our study addressed an unselected nationwide cohort of patients with only de novo metastatic breast cancer. However, it may be possible that Dutch clinicians are more reluctant to administer these types of therapy, for instance for fear of side effects.

Although no distinction in hormone receptor status was made in the aforementioned studies from France and the United States, endocrine therapy can be considered as a substitution of chemotherapy in patients with hormone receptor-positive disease, especially if patients have contraindications for chemotherapy or if the tumour is not rapidly progressive and without multiorgan metastases [18, 26]. HER2-overexpressing tumours have previously been shown to be associated with a negative hormone receptor status [27]. Yet 57% of all patients included in the current study had hormone receptor-positive disease. Older patients are usually more likely to have hormone receptor-positive disease than younger patients, but, remarkably, the number of patients with a positive hormone receptor status did not differ between the age groups in the current study [28, 29]. Nevertheless, endocrine therapy was prescribed more frequently in the older population. Moreover, patients with hormone receptor-negative disease, which is generally considered a more aggressive form of breast cancer, were more often denied any type of first-line systemic therapy than patients with hormone receptor-positive disease.

In early-stage breast cancer, we have previously demonstrated that survival gains in older patients lag behind those of younger patients [30]. Also, in the entire Dutch cohort of older women with de novo metastatic disease, hardly any survival gain was achieved in older patients (with all types of breast cancer) between 1990 and 2012 [31]. In sharp contrast, we demonstrated an increase in survival for all age groups in patients with HER2-overexpressing breast cancer, even after adjusting for tumour and treatment characteristics. Most likely, this was a result of the increased availability of active agents and use of targeted therapy.

The relatively lower survival gain for the older population may again be attributable to a delay in the introduction of the next line of anti-HER2 therapies, such as pertuzumab, trastuzumab-emtansine (TDM1), and tucatinib, especially because the survival in patients with metastatic breast cancer is likely to be dominated by breast cancer rather than competing risks [32]. Moreover, the median overall survival in the current study was worse than in the French study: 3.2 years compared to 4.1 years, respectively (<70: 4.5 years, ≥70: 2.9 years in French patients, compared to <65: 4.3 years, 65-74: 2.0 years, ≥75: 1.3 years in our study). Unfortunately, the breast cancer-specific survival was not analysed in that study. Again, the study design makes it difficult to draw firm conclusions about the differences between the two studies, but the increased use of targeted therapy in the French study could imply that the Netherlands may achieve further survival gain by prescribing "standard" therapy. However, this also largely depends on patient characteristics, such as comorbidity and treatment preferences. To better individualise treatment, further research should focus on the effect of treatment in patients from specific subgroups (e.g., patients with comorbidity or frailty) and the impact of therapy on quality of life and independence [33, 34]. Moreover, therapy is led by diagnostics and the available data revealed an increasing proportion of patients with undetermined or unknown HER2-status with advancing age (ranging from 0% in patients aged 20-29 years up to 30.4% in patients aged 90-99 years). Of note, in the early years of trastuzumab use, the side effect heart failure received a considerable amount of attention. Furthermore, HER2 diagnostics were still considered cumbersome and expensive and were therefore typically omitted in patients known to have heart failure, which is more common in older patients. This omission deserves attention, as it may only be justified in patients who are unsuitable for therapy or have other preferences, but it already seems to be improving as targeted therapy use continues.

The main strength of this study is the inclusion of all patients with HER2-overexpressing de novo metastatic breast cancer diagnosed in the Netherlands, resulting in many patients with detailed information on tumour and treatment characteristics over a long period of time collected by the quality-assured Netherlands Cancer Registry. The study also has its limitations. No detailed information was available on factors that particularly affect treatment decisions and outcomes in the older population, such as patient characteristics (e.g., comorbidity, polypharmacy, geriatric characteristics), patient preferences, or toxicity. Therefore, it was not possible to discuss whether patients should have been treated according to the guidelines. As the Netherlands Cancer Registry collected data until one year after diagnosis, we only included de novo metastatic breast cancer and the first-line treatment allocation. Inclusion of second-line therapies and patients whose breast cancer had recurred after initial diagnosis and treatment might have resulted in different treatment and survival rates compared to patients with recurrent metastatic disease [35, 36].

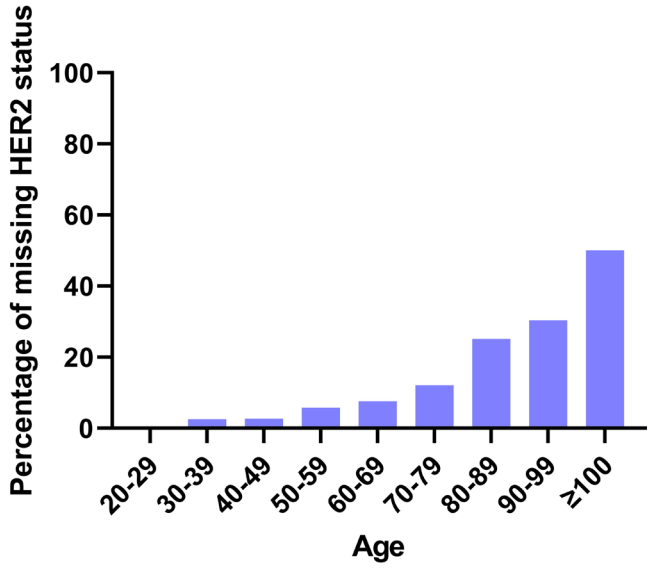
Finally, we were unable to assess long-term progression-free survival and breast cancer-specific survival, because this information was not available and the cause of death was not recorded. However, we do believe that relative survival is a valid proxy for breast cancer-specific survival, especially for the older population in whom autopsies are often omitted [37, 38].

In conclusion, the use of first-line chemotherapy and targeted therapy has increased in all age groups, while the use of endocrine therapy has decreased over time. The uptake of chemotherapy and targeted therapies, however, has been substantially slower in the oldest age groups, which may not be fully attributable to the prevalence of heart failure or frailty in these age groups. This study also showed that both overall survival and relative survival improved for every age group in patients with HER2-overexpressing metastatic breast cancer, albeit with the smallest improvements in the oldest age group.

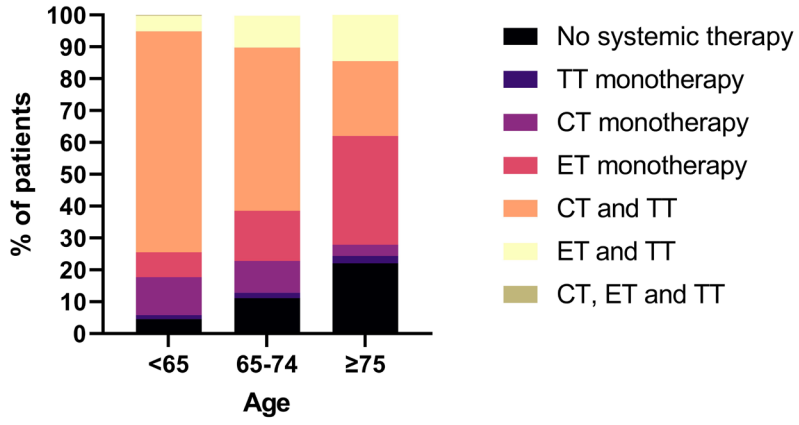
Supplementary data

Supplemental Table 1: Type of first-line targeted therapy per age group

	<65y	65-74y	≥75y
Trastuzumab and Pertuzumab	762 (55.9)	141 (48.8)	51 (27.3)
Trastuzumab	577 (42.3)	142 (49.1)	133 (71.1)
Other	25 (1.8)	6 (2.1)	3 (1.6)



Supplemental Fig. 1: Missing HER2 status per age group



Supplemental Fig. 2: First-line systemic treatment schedule per age group between 2005-2021

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PART II:
PATIENT REPORTED OUTCOME MEASURES IN OLDER WOMEN

Chapter 6

Physical Function and Physical Activity in Older Breast Cancer Survivors: 5-Year Follow-Up from the Climb Every Mountain Study.

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The Oncologist

Abstract

Background

A decline in physical activity and the ability to perform activities of daily living (ADL) and instrumental activities of daily living (IADL) could interfere with independent living and quality of life in older patients, but may be prevented with tailored interventions. The aim of the current study was to assess changes in physical activity and ADL/IADL in the first 5 years after breast cancer diagnosis in a real-world cohort of older patients and to identify factors associated with physical decline.

Methods

Patients aged ≥70 years with in situ or stages I-III breast cancer were included in the prospective Climb Every Mountain cohort study. Linear mixed models were used to assess physical activity (according to Metabolic Equivalent of Task (MET) hours per week) and ADL/ IADL (according to the Groningen Activity Restriction Scale (GARS)) over time. Secondly, the association with geriatric characteristics, treatment, quality of life, depression, apathy, and loneliness was analyzed.

Results

A total of 239 patients were included. Physical activity and ADL/IADL changed in the first 5 years after diagnosis (mean change from baseline −11.6 and +4.2, respectively). Geriatric characteristics at baseline were strongly associated with longitudinal change in physical activity and ADL/IADL, whereas breast cancer treatment was not. A better quality of life was associated with better physical activity and preservation of ADL/IADL, while depression and loneliness were negatively associated with these outcomes.

Discussion

Geriatric characteristics, loneliness, and depressive symptoms were associated with physical decline in older patients with breast cancer, while breast cancer treatment was not.

Introduction

Breast cancer is the most commonly diagnosed malignancy among women, with more than 30% of patients being over 70 years of age at the time of diagnosis [1]. This proportion is expected to increase due to the rapidly aging population. The older population is a heterogeneous group, with large differences in fitness, comorbidities, and socioeconomic status. Consequently, older patients may experience very different levels of decline in physical, cognitive, and psychological functioning after breast cancer diagnosis and its related treatment [2, 3].

Previous research has shown the potential of physical activity to improve psychological outcomes, body composition, and quality of life [4]. Furthermore, physical activity plays an important role in the prevention of other health problems in older patients, such as cardiovascular diseases, hypertension, obesity, and osteoporosis. These conditions may ultimately contribute to decreased levels of physical activity and an increased need for assistance with activities of daily living (ADL) and instrumental activities of daily living (IADL). Therefore, it is important to maintain physical activity levels and ADL/IADL independency after breast cancer diagnosis and treatment.

The aim of the current study was to assess changes in physical activity and ADL/IADL dependency in the first 5 years after breast cancer diagnosis in a real-world cohort of older women with in situ or stages I-III breast cancer and to investigate whether geriatric characteristics, breast cancer treatment, quality of life, depression, apathy, and loneliness were associated with these changes.

Materials and Methods

Study Design and Participants

This study used data from the prospective, multicenter observational Climb Every Mountain study, which has been previously described in detail [5, 6] In short, patients aged 70 years and older who underwent surgery for primary, in situ or stages I-III breast cancer were recruited from 9 Dutch hospitals between 2013 and 2018. At baseline, patients underwent a geriatric assessment as part of standard care and they were followed up at 3, 9, 15, 27, and 60 months after surgery. Participants were included in this paper if questionnaires on both physical activity and ADL/IADL were available at baseline and at least at one other time point during follow-up. Written informed consent was obtained from all participants and the study was approved by the medical ethics committee of the Leiden University Medical Center.

Data Collection

The baseline geriatric assessment included comorbidities prior to breast cancer diagnosis (Charlson Comorbidity Index (CCI)) [7], medication use, cognition (Mini Mental State Examination (MMSE)), ADL/IADL (Groningen Activity Restriction Scale (GARS)) [8], and the Timed Up and Go test [9]. The CCI is a method of categorizing comorbidities of patients to predict 10-year survival rates (range 0-33). A higher CCI reflects more comorbidities. The MMSE ranges from 0 to 30, with higher scores indicating better cognitive functioning. ADL/IADL were assessed with the GARS questionnaire. The GARS contains 18 questions, of which 11 items are about ADL and 7 about IADL. The total score ranges from 18 to 72. The GARS was categorized into 4 groups (<19: no dependency, 19-28: some dependency, ≥29: disabled, and unknown) [10]. If less than 10% of the answers were missing per individual (i.e., only one question), the average of the other answers was taken and recorded. If more than 10% of all answers in an independent questionnaire were missing, the whole questionnaire was classified as unknown. The TUG test measures the time that patients need to get up from a chair, walk a distance of 3 meters, turn around, and sit down again. This was done 3 times and the average score was used for the analyses. The cutoff point for normal mobility is ≤12 seconds [11].

Trained personnel collected clinical data including patient-, tumor-, and treatment characteristics from medical records. Follow-up consisted of multiple assessments and questionnaires, including quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23) [12, 13] the Cantril Ladder (range 0-10) for overall patient satisfaction [14], depression (15-item Geriatric Depression Scale) [15], loneliness (De Jong Gierveld Loneliness Scale) [16], apathy (Starkstein Apathy Scale) [17], ADL/IADL (GARS) and physical activity. For the EORTC QLQ-BR23 questionnaire, the optional questions about sexual function, sexual enjoyment, and upset by hair loss were excluded from the total score, because these questions were answered by a limited number of patients. The 15-item Geriatric Depression Scale is a shortened questionnaire to assess depression in older adults. The total score ranges from 0 to 15 and higher scores indicate more depressive symptoms. Loneliness scores add up to a score between 0 and 11 with higher scores reflecting more severe loneliness. The Starkstein Apathy Scale consists of 14 questions with a score ranging from 0 to 42 with higher scores indicating greater apathy.

ADL/IADL were assessed with the GARS questionnaire at baseline, 3, 9, 15, 27, and 60 months after diagnosis. Physical activity was assessed according to the Nurses' Health Study II Activity and Inactivity Questionnaire for Metabolic Equivalent of Task (MET) Hours at 15, 27, and 60 months after diagnosis [18]. At 3 months after diagnosis, patients were asked to record prediagnostic physical activity. In this questionnaire, patients indicate the average frequency of varying activities in that year, ranging from household activities to vigorous sports. MET-hours per week were calculated by multiplying the average hours per week spent at each activity with its specific intensity score based on

the updated Physical Activity Compendium [19]. Total physical activity per person was calculated by summing up all MET-hours per activity in each individual.

Statistical Analyses

Baseline characteristics of patients with missing scores on the GARS or physical activity questionnaires at follow-up (15, 27, and 60 months) were compared with patients without missing data using the chi-square test. Changes in ADL/IADL and physical activity from baseline were evaluated for minimal clinically important differences. Based on previously reported cutoffs, a mean change of 3 MET-hours per week was considered as clinically relevant.20 No clinically significant cutoff has been determined for the GARS questionnaire [21]. Linear mixed models were estimated to assess the longitudinal behavior of physical activity and ADL/IADL. Baseline characteristics of age, tumor stage, most extensive breast surgery, adjuvant systemic therapy, CCI, and BMI were incorporated into the models. To study whether longitudinal changes differed for both outcome variables (ADL/IADL and physical activity) per age group or GARS at baseline, interaction terms between time and age or GARS at baseline were included in the model. Linear mixed models were also used to analyze associations between variables assessed at 3 months post-diagnosis (Timed Up and Go test, quality of life, depression, apathy, and loneliness) and changes in ADL/IADL or physical activity between 15 and 60 months after diagnosis. The significance threshold for all analyses was set to an alpha of 0.05, and analyses were performed in IBM SPSS Statistics version 25.

Results

A total of 239 patients were included (Table 1). The median age was 74 years (interquartile range (IQR) 72-78 years). Of all patients, 93 (39%) had a CCI of one or more and 117 (49%) patients were not fully independent in their ADL and IADL. Most patients were diagnosed with stage I or II breast cancer. Ninety-eight (41%) patients were treated with a mastectomy and 141 (59%) patients with breast conserving surgery. A total of 154 (65%) patients received postoperative radiotherapy. Around half of all patients received adjuvant systemic treatment, of which 109 (46%) patients endocrine therapy, 8 (3%) chemotherapy, and 8 (3%) a combination of both.

The response rates to the questionnaires were 93%, 96%, and 88% at 15, 27, and 60 months after diagnosis, respectively (Supplemental Fig. 1). At 60 months of follow-up, patients with missing data were statistically significantly older than patients without missing questionnaires. CCI, polypharmacy, GARS at baseline, tumor stage, and adjuvant systemic treatment were similar for these 2 groups at 15, 27, and 60 months follow-up.

Table 1: Patient-, tumour- and treatment characteristics at baseline

	N	%
Age		
70-74	132	55.2
75-79	54	22.6
≥ 80	53	22.2
Charlson Comorbidity Index (CCI)		
0	146	61.1
1	52	21.8
≥ 2	41	17.1
Polypharmacy		
No	147	61.5
Yes	80	33.5
Unknown	12	5.0
BMI		
20-24.9	78	32.6
< 20	11	4.6
≥ 25	150	62.8
Functional status (GARS) [a]		
< 19: no dependency	122	51.0
19 – 28: some dependency	105	44.0
≥29: disabled	12	5.0
MET-hours/week [b]		
Continuous (median (IQR))	23 (8-55)	
Stage		
0	10	4.2
I	122	51.0
II	78	32.6
III	14	5.9
Unknown	15	6.3
Grade		
I	55	23.0
II	105	44.0
III	72	30.1
Unknown	7	2.9
Most extensive surgery		
Breast conserving	141	59.0
Mastectomy	98	41.0
Most extensive axillary surgery		
No axillary surgery	13	5.4
Sentinel lymph node dissection	182	76.2
Axillary lymph node dissection	44	18.4
Adjuvant systemic treatment		
No systemic adjuvant treatment	114	47.7
Endocrine therapy (ET)	109	45.7
Chemotherapy (CT)	8	3.3
Combination of ET and CT	8	3.3
Adjuvant radiotherapy		
No	85	35.6
Yes	154	64.4

[a] Higher scores on the GARS questionnaire indicate a worse functional status, range 18-72
[b] Higher numbers of MET-hours per week indicate more physical activity, range 0-∞
CCI – Charlson Comorbidity Index; BMI – Body Mass Index; GARS – Groningen Activity Restriction Scale; MET – Metabolic Equivalent of Task; IQR – Interquartile Range; ET – Endocrine Therapy; CT – Chemotherapy

Mean values for physical activity measured in MET-hours per week at baseline, 15, 27, and 60 months after diagnosis are shown in Fig. 1A. In the first 5 years after diagnosis, physical activity decreased in all age groups, and was lowest for patients aged 80 years and older in a multivariate model (Table 2). Mean changes over 5-year follow-up were clinically relevant for all age groups (age 70-74: −13.4; 75-79: −10.6; ≥80: −10.2). Patients with dependencies in ADL/IADL at baseline remained less active over the first 5 years after breast cancer diagnosis (GARS ≥19: β = −9.68, 95% CI, −15.61 to −3.76, P = .001, compared to GARS <19), but the longitudinal change was not statistically significantly different from patients who were independent in their ADL/IADL at baseline. Moreover, patients with a CCI of 1 and more had lower levels of physical activity over time. Type of surgery and adjuvant systemic therapy were not associated with physical activity.

Table 2: Changes in physical activity (MET-hours/week) and ADL/IADL (GARS) during 5 year follow-up, multivariate linear mixed model

	MET-hours/week[a]			GARS[b]		
	ß	95% CI	p-value	ß	95% CI	p-value
Age						
70-74	Ref.			Ref.		
75-79	-8.44	-15.11 - -1.76	0.013	-0.61	-1.46 - 0.25	0.166
≥ 80	-20.37	-28.22 - -12.52	<0.001	1.91	0.89 - 2.92	<0.001
Stage						
0-I	Ref.			Ref.		
II	-2.14	-9.29 - 5.01	0.556	0.29	-0.62 - 1.19	0.534
III	-12.35	-24.83 - 0.14	0.053	0.62	-0.95 - 2.20	0.437
Unknown	15.00	3.40 - 26.61	0.011	-1.80	-3.26 - -0.34	0.016
Most extensive breast surgery						
Breast conserving	Ref.			Ref.		
Mastectomy	4.17	-1.81 - 10.16	0.171	0.09	-0.67 - 0.85	0.823
Adjuvant systemic therapy						
No	Ref.			Ref.		
Yes	-1.03	-7.14 - 5.09	0.742	-0.51	-1.28 - 0.26	0.195
Charlson Comorbidity Index (CCI)						
0	Ref.			Ref.		
1	-15.12	-22.09 - -8.14	<0.001	2.22	1.33 - 3.10	<0.001
≥ 2	-11.50	-19.14 - -3.87	0.003	3.02	2.05 - 3.99	<0.001
BMI						
20-24.9	Ref.			Ref.		
< 20	-13.72	-27.25 - -0.20	0.047	0.40	-1.33 - 2.13	0.651
≥ 25	-8.78	-14.80 - -2.77	0.004	1.06	0.28 - 1.83	0.008
GARS at baseline						
<19	Ref.			Ref.		
≥ 19	-9.68	-15.61 - -3.76	0.001	3.51	2.76 - 4.26	<0.001
MET-hours/week at baseline						
Continuous	N/A	N/A	N/A	-0.02	-0.03 - -0.01	<0.001

[a] Higher numbers of MET-hours per week indicate more physical activity, range 0-∞

[b] Higher scores on the GARS questionnaire indicate a worse functional status, range 18-72

Abbreviations: ADL – Activities of daily living; IADL – Instrumental activities of daily living; CCI – Charlson Comorbidity Index; BMI – Body Mass Index; GARS – Groningen Activity Restriction Scale; MET – Metabolic Equivalent of Task

The GARS gradually increased over time with a relatively stronger increase for patients aged 80 years and older (Fig. 1B). Patients with dependencies in ADL/IADL at baseline experienced further decline over time in a multivariate model (Table 2), but with a similar longitudinal change to those who were fully independent in their ADL/IADL at baseline. A higher level of physical activity in MET-hours per week at baseline was associated with a small, but statistically significant better GARS during follow-up (β = −0.02, 95% CI, −0.03 to −0.01, P < 0.001). Patients with a CCI of ≥2 developed more deficiencies in ADL/IADL over time (β = 3.02, 95% CI, 2.05-3.99, P < 0.001) when compared to patients without comorbidities according to the CCI. Type of surgery and adjuvant systemic therapy were not associated with changes in ADL/IADL.

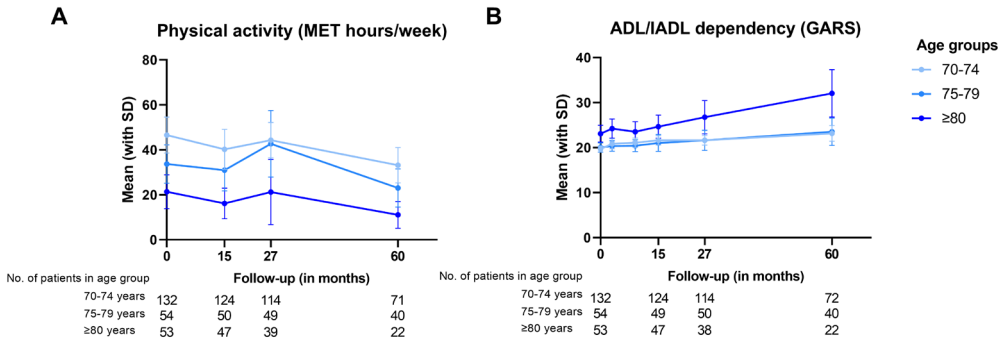


Fig. 1: Physical activity (A) and ADL/IADL dependency (B) during 5-year follow-up.

Linear mixed models were estimated to investigate whether the Timed Up and Go test, quality of life, depression, apathy, and loneliness at 3 months after diagnosis were associated with changes in physical activity and ADL/IADL between 15 and 60 months after diagnosis (Table 3). Quality of life was associated with physical activity after adjustment for confounders: every point increase on the generic or breast cancer-specific quality of life questionnaires was associated with a longitudinal increase of 0.8 and 0.5 MET-hour per week, respectively (P < 0.001). A higher life satisfaction, as assessed by the Cantril Ladder, was associated with greater physical activity levels (β = 6.91, 95% CI, 4.02-9.79, P < 0.001). Patients with increasing depression or loneliness symptoms at 3 months follow-up were less physically active over time.

Similar results were seen for changes in ADL/IADL between 15 and 60 months follow-up (Table 3), in which a better quality of life was associated with better preservation of ADL/IADL (EORTC QLQ-C30: β = −0.25, 95% CI, −0.31 to −0.20, P < 0.001; EORTC QLQ-BR23: β = −0.19, 95% CI, −0.24 to −0.15, P < 0.001; Cantril Ladder: β = −1.51, 95% CI, −2.04 to −0.99, P < 0.001). Depression and loneliness scores after 3 months post-diagnosis were associated with an increase in dependency during follow-up.

Table 3: Association between assessments/questionnaires assessed at 3 months follow-up and physical activity (MET-hours/week) and ADL/IADL (GARS) between 15 and 60 months follow-up, univariate linear mixed model[a]

	MET-hours/week[b]			GARS[c]		
	ß	95% CI	p-value	ß	95% CI	p-value
Timed Up and Go test						
<12 sec	Reference			Reference		
>12 sec	0.50	-10.61 - 11.61	0.930	5.36	3.34 - 7.39	<0.001
Generic quality of life (EORTC QLQ-C30)[d]						
Continuous	0.80	0.47 - 1.12	<0.001	-0.25	-0.31 - -0.20	<0.001
Breast cancer-specific quality of life (EORTC QLQ-BR23)[d]						
Continuous	0.52	0.25 - 0.79	<0.001	-0.19	-0.24 - -0.15	<0.001
Life satisfaction (Cantril Ladder)[d]						
Continuous	6.91	4.02 - 9.79	<0.001	-1.51	-2.04 - -0.99	<0.001
Geriatric Depression Scale[e]						
Continuous	-3.59	-5.18 - -2.01	<0.001	1.10	0.82 - 1.38	<0.001
Starkstein Apathy Scale[e]						
Continuous	-0.43	-1.14 - 0.28	0.236	0.12	-0.01 - 0.24	0.077
De Jong Gierveld Loneliness Scale[e]						
Continuous	-1.59	-3.01 - -0.17	0.028	0.36	0.10 - 0.62	0.007

[a] All variables are adjusted for age, tumour stage, most extensive breast surgery, adjuvant systemic therapy, Charlson Comorbidity Index, and BMI. Unknown values are not included in this table.
[b] Higher numbers of MET-hours per week indicate more physical activity, range 0-∞
[c] Higher scores on the GARS questionnaire indicate a worse functional status, range 18-72
[d] Higher scores indicate a better quality of life/life satisfaction
[e] Higher scores indicate greater symptoms
Abbreviations: MET – Metabolic Equivalent of Task; ADL – Activities of daily living; IADL – Instrumental activities of daily living; GARS – Groningen Activity Restriction Scale

Discussion

This real-world cohort study of patients aged 70 years and older with breast cancer showed a small decline in physical activity and a small increase in dependency in the first 5 years after diagnosis. Physical activity in each age group at the end of follow-up was similar to baseline levels of the older age groups, which implies a natural course of aging. Geriatric characteristics at baseline (i.e., age, comorbidities, BMI, and GARS) were strongly associated with longitudinal change in ADL/IADL dependency and physical activity, whereas breast cancer characteristics and treatment were not. Moreover, after completion of locoregional treatment, quality of life, depression, and loneliness were associated with changes in physical activity and ADL/IADL dependency during 5-year follow-up.

Although changes in ADL/IADL and physical activity were small, it is important to assess these parameters in the older population as they could interfere with independent living. Older patients may value quality of life and functional independence over other treatment outcomes, such as recurrence and survival [22]. The deterioration of ADL/IADL and physical activity is mainly age-related.

Nevertheless, our results show a significant association between depressive symptoms and loneliness with both ADL/IADL dependency and physical activity. Depressive symptoms have previously been linked with impaired ADL/IADL in patients with breast cancer, but the studies had a short follow-up period and did not specifically focus on older patients [23, 24]. Since association is different from causation, it is unclear whether reduced physical activity and dependency are a consequence of depressive symptoms or rather a cause. Nevertheless, our results in an older population with a relatively long follow-up support the need for early detection of psychological disorders and incorporation of not only exercise interventions but also psychological interventions into breast cancer care for older patients. Previous meta-analyses investigated the effectiveness of specific psychological interventions in women with breast cancer and showed that individually delivered cognitive behavioural therapy effectively reduces depressive symptoms [25, 26]. However, the meta-analyses included studies with several limitations and none to very few older patients. The same applies to studies on specific intervention programs for loneliness [27-29]. Further research is required to identify effective intervention strategies for older patients with breast cancer.

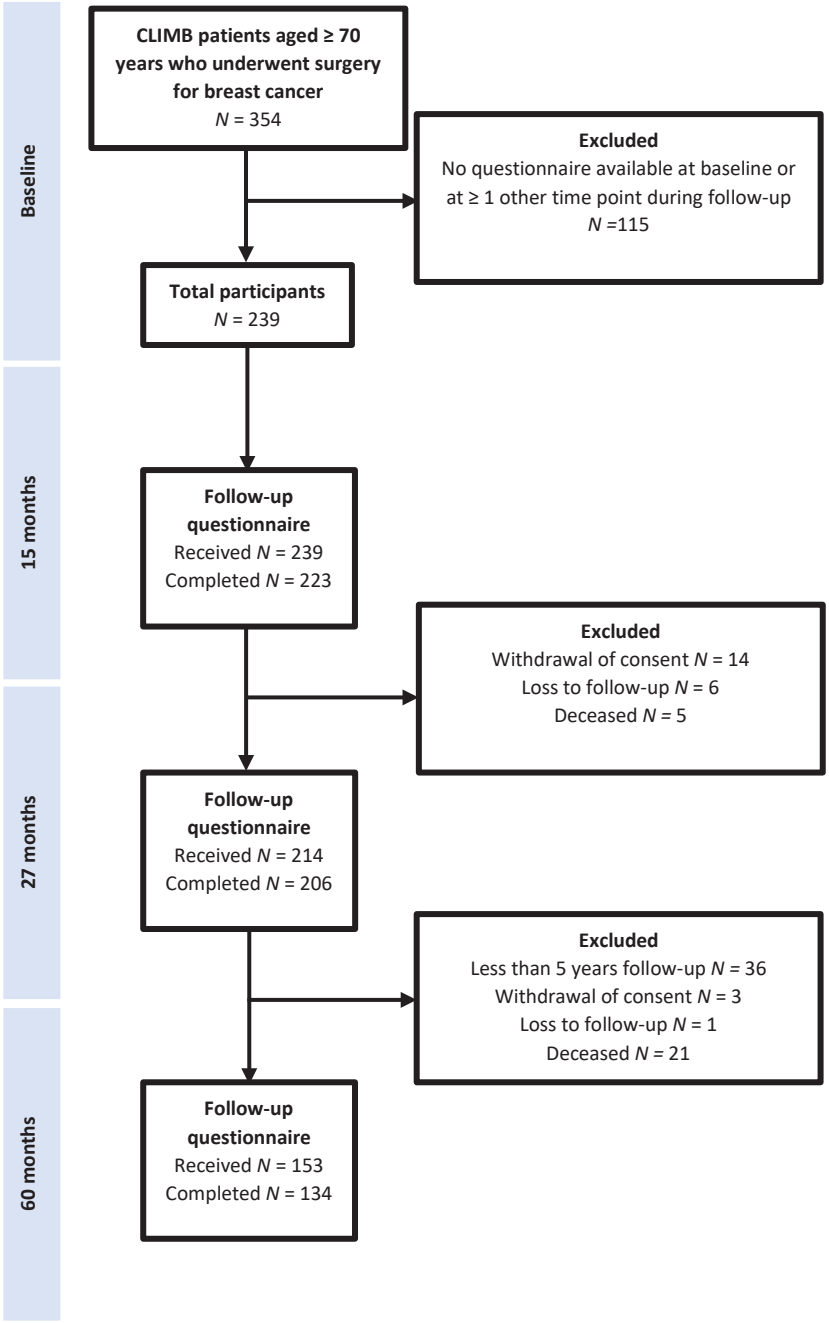
The association between geriatric characteristics, rather than the association between cancer-specific variables and changes in ADL/IADL is in line with previous studies. A study including nearly 6000 nursing-home residents from the US, found a higher ADL score (signifying greater dependency) in more than half of all patients one year after breast cancer surgery.30 In contrast, in 2 studies with younger and fitter women, a fifth of patients had a functional decline at one-year follow-up [31, 32]. Another study focusing specifically on relatively fit older patients treated with chemotherapy demonstrated that 30% had a functional decline 1 year after chemotherapy initiation.33 However, all 4 studies assessed functional decline during a short time-window. The Age Gap observational cohort study into 3300 women aged 70 years and older with breast cancer assessed ADL in the first 24 months after diagnosis [34]. They found that patients who received surgery had an early decrease in functional status between baseline and 6 weeks which failed to recover to baseline levels at 24 months follow-up, while patients treated with primary endocrine therapy had a more gradual decline. In this study, functional status was assessed with one question while our study used a complete questionnaire. Nevertheless, our study shows a similar pattern in physical function in the first 27 months of follow-up but additionally shows that the decline in physical function continues over the subsequent 36 months, especially in the oldest age group. The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial investigated functional decline and physical activity in both younger and older patients and the authors found that patients of all age groups who were treated with surgery and adjuvant endocrine therapy became less physically active in the first 2 years after diagnosis [2]. Older patients did not fully recover to their pre-diagnostic independency levels in the first 2

years, while younger patients did. This study only included relatively fit older patients with an Eastern Cooperative Oncology Group performance status of zero or one and the questionnaire on a physical dependency was limited. Finally, a cohort study by Huy et al assessed physical activity one year after breast cancer surgery by including both young (aged < 65 years) and old patients [35]. The authors showed a median decrease of 4 MET-hours per week one year after surgery in older patients, while younger patients showed a median increase of 2.2 MET-hours per week.

The most important strength of this study is the longitudinal design with detailed information on older patients with a long follow-up period and a high response rate (88%-96%). There are also limitations to this research. Although the aim of the study was to present a real-time cohort, it only included patients whose questionnaires on both physical activity and ADL/IADL were available at baseline and at least at one other time point during follow-up, resulting in a relatively healthy older population. Another limitation is that recall bias might exist in measuring baseline physical activity as this was assessed 3 months after diagnosis. Nevertheless, all other questionnaires were examined prospectively. In addition, physical activity was not objectively assessed via accelerometers. However, a previous study showed that patient-reported physical activity is concordant with more objective accelerometers [36]. Finally, this study did not include a control group to compare the observed physical decline with patients without breast cancer. However, our research group is currently comparing the GARS questionnaire of older patients diagnosed with breast cancer with a similar cohort of older adults without breast cancer. Preliminary results confirm our findings and show no longitudinal differences in ADL/IADL between these cohorts.

In conclusion, patients aged 70 years and older with breast cancer showed a small decline in physical activity and a small increase in ADL/ IADL dependency in the first 5 years after diagnosis. However, these changes did not seem to be related to breast cancer or its treatment, but rather to pre-existent geriatric characteristics, loneliness, and depressive symptoms. These findings may help to provide patients and their caregivers with additional information to reassure them that in older patients with breast cancer, the long-term effects of breast cancer and its treatment on physical activity and ADL/IADL dependency are likely to be minimal.

Supplementary data



Supplemental Fig. 1: Flowchart

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Chapter 7

Mental health outcomes in older breast cancer survivors: Five-year follow-up from the CLIMB study.

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European Journal of Cancer

Abstract

Background

There is a lack of information on mental health outcomes for the increasing older population. Therefore, the aim of the current study is to assess depressive symptoms, loneliness, and apathy in older patients with breast cancer within the first 5 years after diagnosis.

Methods

Women aged ≥70 years with early-stage breast cancer were included. Multivariate linear mixed models were used to assess longitudinal changes in symptoms of depression (according to the 15-item Geriatric Depression Scale), loneliness (according to the De Jong Gierveld Loneliness Scale) and apathy (according to the Starkstein Apathy Scale) over time at 3, 9, 15, 27 and 60 months follow-up.

Results

In total, 299 patients were included (mean [standard deviation (SD)] age: 75.8 [5.2] years). At 3 months follow-up, shortly after the acute treatment, 10% of patients had significant depressive symptoms, while loneliness and apathy were present in 31% and 41% of all patients, respectively. Depression, loneliness and apathy scores showed no clinically relevant changes over time in the whole cohort. Patients who received adjuvant systemic therapies (i.e. endocrine therapy and/or chemotherapy and/or targeted therapy (trastuzumab)) had similar mental health outcomes as those who did not. However, frail patients had more symptoms ($p < 0.001$) and were more prone to develop depressive symptoms over time than non-frail patients ($p = 0.002$).

Discussion

Depression, loneliness and apathy were frequently observed in older women with breast cancer and did not change over time. Patients who received adjuvant systemic therapies had similar mental health outcomes as those who did not. However, frail patients were at higher risk to experience these symptoms.

Introduction

Breast cancer is the most frequently diagnosed malignancy in women, and more than 30% of patients are over the age of 70 years at the time of diagnosis [1]. Older patients form a heterogeneous group with disparities in fitness and frailty. Frailty is a condition in which a person's physiological reserve has deteriorated due to the accumulation of ageing processes in multiple organ systems, making them more susceptible to side effects and complications of treatment [2]. Consequently, older patients are often excluded from participating in large randomised controlled trials, making it challenging to guide individualised, evidence-based treatment for older patients. As the proportion of older patients with breast cancer is expected to increase due to ageing populations, more research in this group is needed.

Although prolongation of life has always been the key aim of cancer treatment, a more comprehensive approach is often required, especially in the older population. An important, perhaps sometimes underestimated, aspect of breast cancer care is the impact of breast cancer diagnosis and treatment on mental health and social functioning [3–8]. Mental health is associated with quality of life and may even have implications for treatment adherence and survival [9,10].

Several studies have investigated mental health outcomes in patients with breast cancer [11–14]. However, few studies have focused on older patients and most studies have a short follow-up, while for the majority of patients the processing and acceptance of their diagnosis and disease begins once the acute symptoms of the disease and its treatment have resolved. Therefore, the aim of the current study was to assess depressive symptoms, loneliness and apathy in older women with early-stage breast cancer in the first 5 years after diagnosis.

Methods

The Climb Every Mountain study prospectively included women aged 70 years and older with primary, in situ or stage I-III breast cancer from nine Dutch hospitals between 2013 and 2018. Patients were excluded if they had a previous breast cancer history, stage IV disease, were unable to read Dutch, or had advanced dementia. For the current analysis, only patients who completed at least two questionnaires for either depression, loneliness or apathy were included. All patients gave written informed consent, and the study was approved by the medical ethics committee of Leiden University Medical Centre.

Data collection

Details of this longitudinal cohort study have been extensively described in previous publications [15,16]. In short, a geriatric assessment was performed at baseline, using validated questionnaires on nutritional status (using the Malnutrition Universal Screening Tool (MUST)) [17], cognition (using the Mini-Mental State Examination (MMSE)) [18], functional status (using the Groningen Activity Restriction Scale (GARS)) [19], and mobility (using the Timed Up and Go test (TUG)) [20]. Age, comorbidities (using the Charlson Comorbidity Index, without adjustment for age and breast cancer diagnosis) [21], medication use (categorised as less than five or five or more types of medication), and tumour- and treatment characteristics were also collected at baseline.

Patients were followed up at 3, 9, 15, 27 and 60 months after surgery (Supplemental Fig. 1). Follow- up consisted of multiple assessments and questionnaires, including depression, loneliness and apathy questionnaires. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS) [22,23]. The 15-item GDS is a shortened screening questionnaire to assess depressive symptoms in older adults. The total score ranges from 0 to 15 and a score of 5 or higher indicates clinically relevant depressive symptoms [23]. De Jong Gierveld Loneliness Scale was used to assess loneliness [24,25]. The 11 items add up to a score between 0 and 11 with a cut-off of 3 for moderate loneliness and a cut-off of 9 for severe loneliness [26]. Apathy was evaluated with the Starkstein Apathy Scale [27]. This questionnaire consists of 14 questions with a maximum score of 42. A score of at least 14 is considered indicative for the presence of clinically relevant apathy [28]. If 10% was missing in any of these three questionnaires, the average of the other questions was taken. If more than 10% of a single questionnaire was missing, that questionnaire was scored as 'unknown'. Recurrences were assessed until 27 months after treatment initiation.

Frailty was defined as impairments in two or more domains: cognitive (MMSE < 24), physical (timed up and go > 12 s), somatic (Charlson Comorbidity Index ≥ 2 or polypharmacy) or nutrition (high risk on the Malnutrition Universal Screening Tool). Patients with a GARS score of ≥29 were also considered frail [29].

Statistical analysis

The chi-square test was used to assess differences between patients who had completed questionnaires on at least two time points and those who had not. Least square means were estimated to evaluate average longitudinal trajectories in depressive symptoms, loneliness and apathy during the first 5 years after diagnosis, using linear mixed models. All three outcome measures were separately analysed as dependent variable, with a random intercept and time as a fixed parameter. To adjust for predefined confounders, baseline characteristics age, tumour stage, Charlson Comorbidity Index, type of surgery,

and adjuvant systemic therapy were added as fixed parameters to the models [30,31]. Longitudinal trajectories were evaluated for minimal clinically important changes. According to previous studies, any change of two points on the 15-item GDS questionnaire represents a clinically relevant change [32]. As no thresholds exist for the loneliness and apathy questionnaires, clinical relevance was assessed according to Norman's rule-of-thumb [33]. Norman and his colleagues determined that changes of at least half the standard deviation of the baseline mean are considered clinically relevant.

Second, additional analyses were conducted to assess whether the use of adjuvant systemic therapy (yes or no endocrine therapy and/or chemotherapy and/or targeted therapy (trastuzumab)) affected the longitudinal behaviour of depressive symptoms, loneliness and apathy using linear mixed models. An interaction term between time and adjuvant systemic therapy was added to the model to analyse whether longitudinal changes in depressive symptoms, loneliness and apathy differed between patients who were treated with adjuvant systemic therapy and those who were not. This model was repeated with adjustment for age, tumour stage, Charlson Comorbidity Index, and type of surgery. Of note, the median time between start of endocrine therapy and return of the first questionnaire was 2.5 months (interquartile range (IQR): 1–3 months).

Third, differences in outcomes between frail and non- frail patients were studied using linear mixed models. Interaction terms between time and frailty were used to estimate the difference in longitudinal change between frail and non-frail patients. This model was additionally adjusted for age, tumour stage, Charlson Comorbidity Index, type of surgery, and adjuvant systemic therapy.

Fourth, previous studies showed that patients with vascular diseases are at higher risk of developing apathy [34,35]. Therefore, a sensitivity analysis was performed to assess whether the presence of vascular diseases (i.e. myocardial infarction, angina pectoris, myocardial ischaemia, intermittent claudication, arterial surgery, or stroke) was associated with a higher risk of apathy, using linear mixed models.

The results of all linear mixed models were presented as beta coefficients (ß), 95% confidence intervals (CI) and p-values. The threshold for a two-sided, statistically significant p-value was 0.050. All analyses were performed in SPSS® version 25.0 (IBM, Armonk, New York, USA).

Results

A total of 299 patients completed questionnaires on at least two different time points and were included in the current analysis (Supplemental Fig. 1). Compared to patients who were excluded, included patients were younger, had less comorbidities and polypharmacy, were less dependent, had more breast (conserving) surgery, and received more radiotherapy (Supplemental Table 1). In the current analysis, half of all patients were 75 years and older and 123 patients (41.1%) had a Charlson Comorbidity Index of 1 or more (Table 1). Very few patients (2.0%) had cognitive deficits (i.e. MMSE < 24) at baseline. Hundred fifty-eight patients (52.9%) were not completely independent in their activities of daily living and instrumental activities of daily living (i.e. GARS ≥ 19). Approximately half of all patients (50.8%) had stage I breast cancer and 246 (82.3%) had oestrogen receptor (ER)-positive tumours. Almost all patients underwent breast surgery (96.3%), of whom 170 patients (56.8%) had breast-conserving surgery and 118 patients (39.5%) a mastectomy. The majority underwent a sentinel lymph node procedure (74.6%). Over half of all patients (51.2%) were not treated with any form of adjuvant systemic treatment, whereas 127 patients (42.5%) received endocrine therapy, 10 patients (3.3%) chemotherapy and 9 patients (3.0%) both. Of note, 10 out of 299 (3.3%) patients had a recurrence within 27 months after treatment initiation. Six of them continued to complete questionnaires afterwards, three died soon after and one was lost to follow-up.

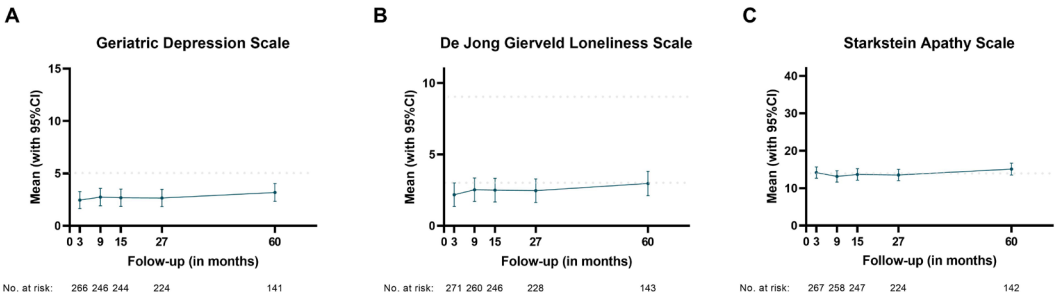


Fig. 1: Depressive symptoms (A), loneliness (B) and apathy (C) over a five-year follow-up period.
All graphs are adjusted for age, tumour stage, Charlson Comorbidiy Index, type of breast surgery, and adjuvant systemic therapy. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

Table 1: Patients-, tumour-, and treatment characteristics at baseline

Age	
70-74	154 (51.5)
75-79	67 (22.4)
80-84	54 (18.1)
≥ 85	24 (8.0)
TNM stage	
0	11 (3.7)
I	152 (50.8)
II	100 (33.5)
III	18 (6.0)
Unknown	18 (6.0)
Grade	
I	70 (23.4)
II	122 (40.8)
III	91 (30.4)
Unknown	16 (5.4)
ER-status	
Negative	33 (11.0)
Positive	246 (82.3)
Unknown	20 (6.7)
PR-status	
Negative	86 (28.8)
Positive	191 (63.9)
Unknown	22 (7.3)
HER2-status	
Negative	217 (72.6)
Positive	27 (9.0)
Unknown	55 (18.4)
Charlson Comorbidity Index (CCI)	
0	176 (58.9)
1	67 (22.4)
≥ 2	56 (18.7)
Polypharmacy	
No	177 (59.2)
Yes	108 (36.1)
Unknown	14 (4.7)
BMI	
<20	12 (4.0)
20-25	102 (34.2)
25-30	116 (38.8)
>30	68 (22.7)
Unknown	1 (0.3)
Mental status (MMSE)	
Normal (≥24)	276 (92.3)
Impaired (<24)	6 (2.0)
Unknown	17 (5.7)
Functional status (GARS)	
No dependency (<19)	138 (46.2)
Some dependency (19-28)	133 (44.5)
Disabled (≥ 29)	25 (8.4)
Unknown	3 (0.9)

Table 1: Continued

Highest education level	
Low	185 (61.9)
Middle	39 (13.0)
High	52 (17.4)
Unknown	23 (7.7)
Employment status during working life	
Full time	70 (23.4)
Part time	84 (28.1)
Housewife	104 (34.8)
Other/Unknown	41 (13.7)
Marital status	
Married/living with partner	143 (47.8)
Divorced/widowed	113 (37.8)
Never married	13 (4.3)
Unknown	30 (10.0)
Living situation	
Independent	293 (98.0)
Assisted living	5 (1.7)
Unknown	1 (0.3)
Neo-adjuvant systemic treatment	
None	257 (85.9)
Chemotherapy (CT)	5 (1.7)
Endocrine therapy (ET)	19 (6.4)
Unknown	18 (6.0)
Most extensive breast surgery	
No surgery	11 (3.7)
Breast conserving	170 (56.8)
Mastectomy	118 (39.5)
Most extensive axillary surgery	
No axillary surgery	21 (7.0)
Sentinel lymph node procedure	223 (74.6)
Axillary lymph node dissection	52 (17.4)
Unknown	3 (1.0)
Adjuvant systemic treatment	
None	153 (51.2)
Chemotherapy (CT)	10 (3.3)
Endocrine therapy (ET)	127 (42.5)
Combination of ET and CT	9 (3.0)
Adjuvant radiotherapy	
No	116 (38.8)
Yes	183 (61.2)
Adjuvant Herceptin (trastuzumab)	
No	288 (96.3)
Yes	11 (3.7)

Abbreviations: ER – oestrogen receptor; PR – progesterone receptor; HER2 – human epidermal growth factor receptor 2; CCI – charlson comorbidity index; BMI – body mass index; MMSE – mini mental state examination; GARS – groningen activity restriction scale; CT – chemotherapy; ET – endocrine therapy

Depression

Thirty-one patients (10.4%) had depressive symptoms three months after diagnosis. After adjustment for predefined confounders, depressive scores barely increased over time (ß = 0.01; 95% CI = 0.01–0.02; p < 0.001) (Fig. 1). Patients who received adjuvant systemic therapies had similar rates of depression as those who did not (ß = −0.02; 95% CI = −0.61 to 0.57; p = 0.95) and the longitudinal trajectories of depressive symptoms were also equal for both groups (p = 0.73) (Fig. 2). Patients who were classified as frail at baseline experienced more depressive symptoms over the entire study period than non-frail patients (ß = 2.13; 95% CI = 1.25–3.01; p < 0.001) (Fig. 3). Moreover, according to the statistically significant interaction term between frailty and time (p = 0.002), frail patients developed (clinically significantly) more depressive symptoms during follow-up than non-frail patients.

Loneliness

Ninety-two patients (30.8%) experienced loneliness at three months follow-up, of whom 83 (27.8%) had moderate and 9 (3.0%) severe loneliness. Linear mixed models showed a very small increase in symptoms over time (ß = 0.01; 95% CI = 0.01–0.02; p < 0.001) (Fig. 1). Patients treated with adjuvant systemic therapy were not lonelier than patients not treated with adjuvant systemic therapy (ß = −0.07; 95% CI = −0.67 to 0.53; p = 0.83) and their longitudinal trajectories were similar (p = 0.05) (Fig. 2). Patients who were classified as frail at baseline were lonelier than non-frail patients (ß = 1.67; 95% CI = 0.76–2.57; p < 0.001). Moreover, frail patients had mean scores above the clinically relevant threshold for moderate loneliness over the entire study period, while non-frail patients did not (Fig. 3). The longitudinal changes were the same for frail and non- frail patients (p = 0.52).

Apathy

Apathy was prevalent in 121 patients (40.5%) at 3 months after diagnosis and the average apathy score grew marginally each month (ß = 0.02; 95% CI = 0.01–0.04; p = 0.002) (Fig. 1). Patients who were treated with adjuvant systemic therapy had similar apathy scores (ß = 0.50; 95% CI = −0.60 to 1.60; p = 0.38) and similar longitudinal trajectories over time (p = 0.31) than patients without adjuvant systemic therapy (Fig. 2). Frail patients scored worse on the apathy questionnaire than non-frail patients during follow-up (ß = 3.21; 95% CI = 1.57–4.86; p < 0.001), exceeding the threshold for clinically relevant apathy (Fig. 3). Moreover, frail patients developed more apathy during follow-up than non-frail patients (p = 0.03). Vascular diseases at baseline were not associated with a higher occurrence of apathy over the entire study period (ß = 0.26; 95% CI = −1.44 to 1.95; p = 0.77) and were not associated with an increased risk of developing apathy over time (p = 0.69).

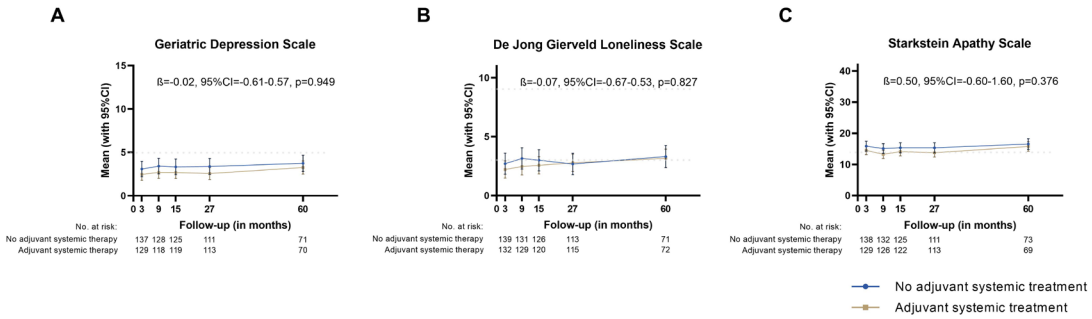


Fig. 2: Depressive symptoms (A), loneliness (B) and apathy (C) stratified for adjuvant systemic therapy over a five-year follow-up period.
All graphs are adjusted for age, tumour stage, Charlson Comorbidiy Index, and type of breast surgery. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

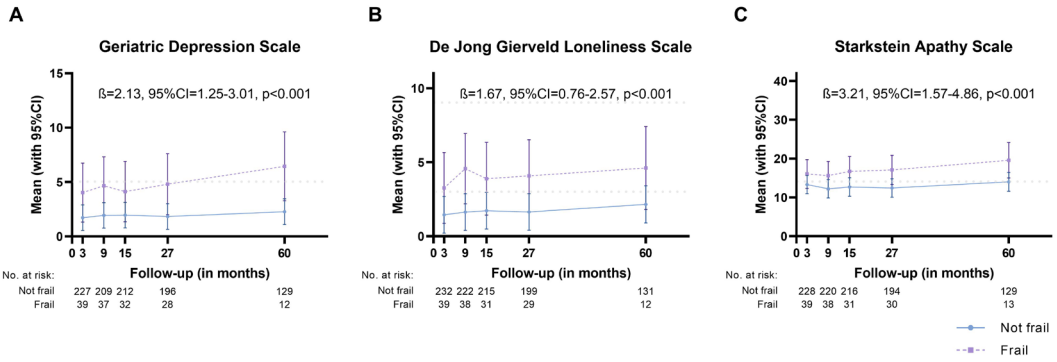


Fig. 3: Depressive symptoms (A), loneliness (B) and apathy (C) stratified for frailty over a five-year follow-up period.
All graphs are adjusted for age, tumour stage, Charlson Comorbidiy Index, type of breast surgery, and adjuvant systemic therapy. The horizontal dashed lines indicate cut-off values. The number of completed questionnaires are described below the graphs.

Discussion

This real-world multicentre cohort study of older women with early-stage breast cancer showed that shortly after surgery, 10%, 31% and 41% of patients had depressive symptoms, loneliness and apathy, respectively. Longitudinal trajectories of these outcomes did not change clinically significantly in the first 5 years of follow-up for the whole group. Importantly, patients who received adjuvant systemic therapies had similar mental health outcomes as those who did not. Frail patients had more symptoms after surgery and were more prone to developing clinically relevant depression over time.

A recent systematic review showed that single (divorced or widowed) women who have a low income, an advanced diagnosis, functional limitations, comorbidities, and low social support are at higher risk of emotional distress, which are all factors inherent in many older patients with breast cancer [30]. Our study showed that around a third of older patients experienced loneliness after the acute phase of treatment and that frail patients were more likely to be lonely than non-frail patients. The prevalence of loneliness is consistent with previous reports. Deckx and colleagues found that 22% of around one hundred older patients with early-stage breast or colorectal cancer were lonely at the time of diagnosis and 35% at 1-year follow-up [6]. De Boer et al. demonstrated that one-third of older patients with metastasised breast cancer (N = 80) experienced loneliness at baseline and throughout a 6-month follow-up period [36]. To put the high prevalence of loneliness among breast cancer survivors into perspective, a previous study found that 39% of older adults from the general population without cancer experienced loneliness [6]. Nevertheless, extensive research has shown that loneliness is a major health concern as it is associated with unhealthy behaviours, impaired physical functioning, worse quality of life, and increased morbidity and mortality [37,38]. Therefore, this high prevalence still requires further attention. Effective loneliness interventions already exist, but sample sizes are small and no studies have specifically focused on older patients with breast cancer [39–42].

Depression is generally quite common in breast cancer survivors, with a prevalence ranging from 8% to 66% [12,13,43,44]. The occurrence of clinically relevant depression in the current study is similar to what has been previously reported in the general older population (5–15%) and much lower than has been found in the advanced setting (46%) [36,43,45]. This relatively low percentage of depressive symptoms in older breast cancer survivors may reflect different treatment allocation and an increased psychological resilience in this age group due to their life stage, while the latter is probably less in frail older patients. Moreover, the majority of patients in the current analysis had hormone receptor- positive disease in which recurrences rarely occur within the first 5 years. According to a study at longer follow- up (cross sectional at 5–16 years post-diagnosis), older breast cancer survivors without recurrences had similar depression rates as controls with no history of breast cancer [46]. However, patients aged 80 years and younger with a recurrence had considerably higher rates of depression than their controls, but not when they were 80–89 years old.

A less frequently reported mental health outcome in patients with breast cancer is apathy [47]. Apathy is characterised by diminished goal-directed behaviour, cognition and emotion, leading to reduced daily functioning [48]. Apathy can be present as a symptom of depression, but can also occur on its own [49].

A previous study of over 1100 Dutch community-dwelling older adults aged 75 years and older found that 11% of them experienced apathy [28]. This percentage is much lower than was found in our study of older patients with breast cancer and than what has been previously reported in the advanced setting [36]. Apathy is often overlooked by physicians as it is usually not perceived as a nuisance by patients themselves. Moreover, patients with apathy typically have low degrees of suffering and tend to be indifferent, which can result in neglect and caregiver distress [50]. As apathy also interferes with poor treatment adherence and outcome, it requires further attention [51]. There are currently no specific interventions available for this population.

Although it is difficult to identify an aetiological association between systemic therapy and mental health outcomes, endocrine therapy and chemotherapy are believed to exacerbate it, especially depressive symptoms. Fear of these side effects may be a reason for withholding therapy. Nevertheless, the current study showed no difference in apathy, loneliness and depression in patients treated with adjuvant systemic therapy and those not. The results suggest that adjuvant systemic therapy in older patients should not be withheld in fear of worse mental health outcomes, although it must be noted that in this observational cohort, patients with pre-existing mental health problems may have been more reluctant to start adjuvant treatment.

Previous research has shown that patients are reluctant to ask for psychological help [52]. Also, healthcare professionals are not always familiar with all psychological care facilities, do not know how to discuss these topics or simply lack time to do so [52]. Nevertheless, it is important for patients, caregivers and physicians to be aware of the potential impact of cancer and its treatment on mental health outcomes, as well as the possibility of psychosocial support. Psychological care should therefore be given more prominence in breast cancer care to ensure timely detection of patients with a wish for referral to psychological care. Training in communication skills for physicians proved useful in integrating the discussion on mental health outcomes into daily clinical practice [53].

The most important strength of this study is its longitudinal design with extensive information on older women with breast cancer. The study also has limitations. Although the intention was to include all women aged 70 years and older with breast cancer into our study, a relatively fit older population was included. Since frailty exacerbates depressive symptoms, loneliness and apathy, the current study may underestimate the prevalence of these outcomes. Nevertheless, the current study revealed that depressive symptoms, loneliness and apathy are common and frailty probably warrants more attention by physicians.

Another limitation of the study is that patients that experienced disease recurrence were not excluded from follow-up, which may have impacted the outcome. However, the number of recurrences was very small, so the impact of this factor is likely to be limited. Furthermore, the first questionnaires on depression, loneliness and apathy were completed at a median time of three months after surgery (IQR: 3–4 months). It is therefore difficult to draw conclusions about the direct effect of surgery on these mental health outcomes. However, baseline questionnaires on mental health outcomes may be burdensome for patients at the time of diagnosis (as the questionnaires are quite time-consuming) and the results at that time may also be biased because of the large mental stress the cancer diagnosis already brings.

In conclusion, depression, loneliness and apathy are common in older women with breast cancer, especially in frail patients. Although depressive symptoms and loneliness do not appear to be more prevalent than in the general older population, apathy is. Importantly, adjuvant systemic therapy does not seem to exacerbate these symptoms. As mental health outcomes may interfere with adherence to therapy, survival and quality of life, it is important to address the potential impact of cancer on mental health outcomes and to inform patients about the possibility of psychosocial support.

Supplementary data

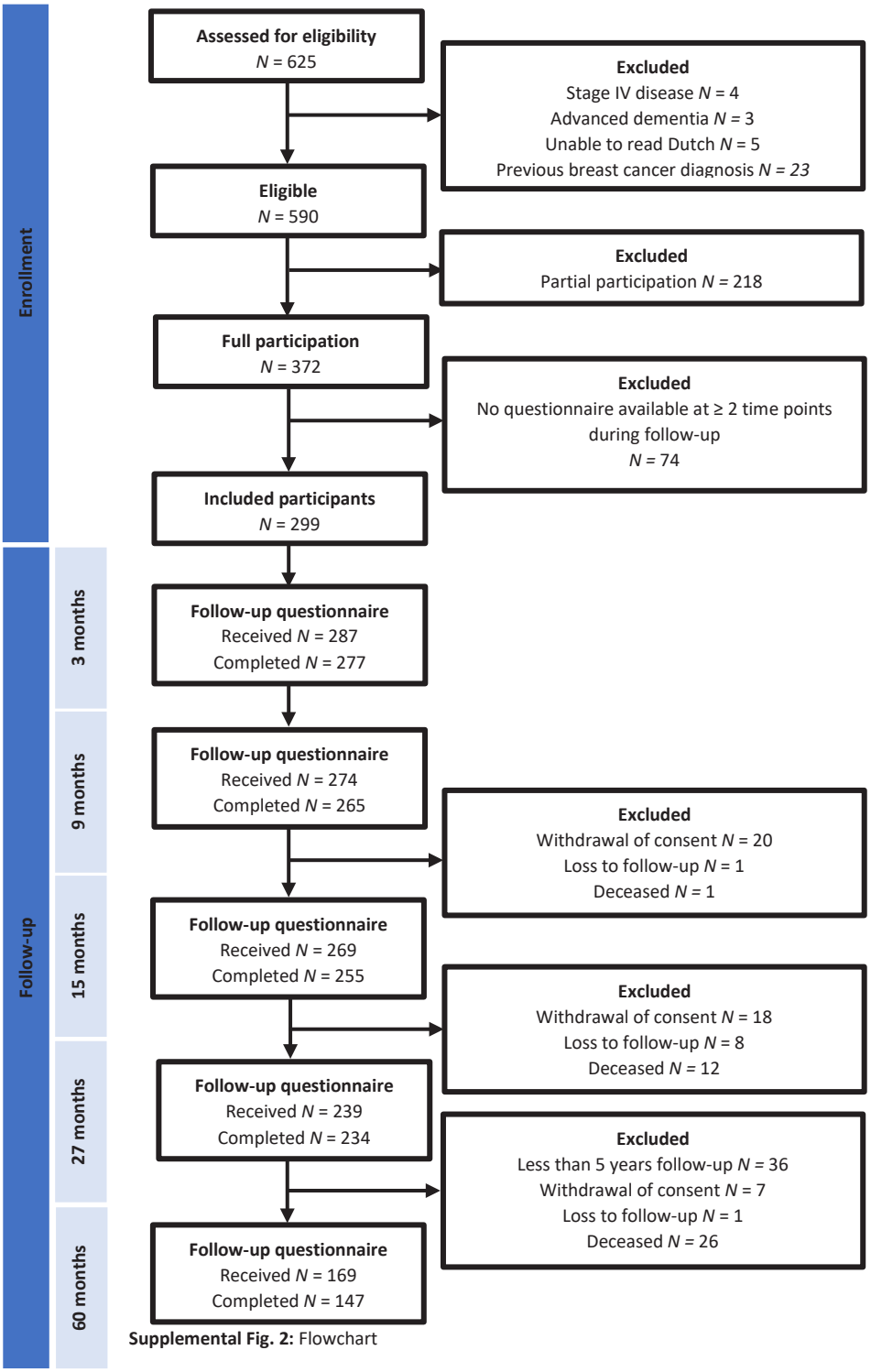
Supplemental Table 1: Patients-, tumour-, and treatment characteristics at baseline of patients who were either included or excluded in the current analysis

	Included in current analysis n(%)	Excluded in current analysis n(%)	p-value
Age			
70-74	154 (51.5)	114 (39.2)	0.001
75-79	67 (22.4)	59 (20.3)	
80-84	54 (18.1)	61 (20.9)	
≥ 85	24 (8.0)	57 (19.6)	
TNM stage			
0	11 (3.7)	10 (3.4)	0.073
I	152 (50.8)	127 (43.6)	
II	100 (33.5)	94 (32.4)	
III	18 (6.0)	33 (11.3)	
Unknown	18 (6.0)	27 (9.3)	
Grade			
I	70 (23.4)	54 (18.6)	0.017
II	122 (40.8)	119 (40.9)	
III	91 (30.4)	82 (28.2)	
Unknown	16 (5.4)	36 (12.3)	
ER-status			
Negative	33 (11.0)	48 (16.5)	0.140
Positive	246 (82.3)	222 (76.3)	
Unknown	20 (6.7)	21 (7.2)	
PR-status			
Negative	86 (28.8)	104 (35.8)	0.142
Positive	191 (63.9)	163 (56.0)	
Unknown	22 (7.3)	24 (8.2)	
HER2-status			
Negative	217 (72.6)	192 (66.0)	0.078
Positive	27 (9.0)	23 (7.9)	
Unknown	55 (18.4)	76 (26.1)	
Charlson Comorbidity Index (CCI)			
0	176 (58.9)	131 (45.0)	0.002
1	67 (22.4)	78 (26.8)	
≥ 2	56 (18.7)	82 (28.2)	
Polypharmacy			
No	177 (59.2)	143 (49.1)	0.026
Yes	108 (36.1)	137 (47.1)	
Unknown	14 (4.7)	11 (3.8)	
BMI			
<20	12 (4.0)	11 (3.8)	0.730
20-25	102 (34.2)	85 (29.2)	
25-30	116 (38.8)	122 (41.9)	
>30	68 (22.7)	71 (24.4)	
Unknown	1 (0.3)	2 (0.7)	
Mental status (MMSE)			
Normal (≥24)	276 (92.3)	258 (88.7)	0.149
Impaired (<24)	6 (2.0)	14 (4.8)	
Unknown	17 (5.7)	19 (6.5)	
Functional status (GARS)			
No dependency (<19)	138 (46.2)	94 (32.3)	<0.001
Some dependency (19-28)	133 (44.5)	107 (36.8)	
Disabled (≥ 29)	25 (8.4)	81 (27.8)	
Unknown	3 (0.9)	9 (3.1)	

Supplemental Table 1: Continued

	Included in current analysis n(%)	Excluded in current analysis n(%)	p-value
Neo-adjuvant systemic treatment			
None	257 (85.9)	255 (87.6)	0.819
Chemotherapy (CT)	5 (1.7)	4 (1.4)	
Endocrine therapy (ET)	19 (6.4)	16 (5.5)	
Combination of ET and CT	0 (0.0)	1 (0.3)	
Unknown	18 (6.0)	15 (5.2)	
Most extensive breast surgery			
No surgery	11 (3.7)	33 (11.3)	0.001
Breast conserving	170 (56.8)	136 (46.8)	
Mastectomy	118 (39.5)	122 (41.9)	
Most extensive axillary surgery			
No axillary surgery	21 (7.0)	51 (17.5)	<0.001
Sentinel lymph node procedure	223 (74.6)	177 (60.8)	
Axillary lymph node dissection	52 (17.4)	53 (18.2)	
Unknown	3 (1.0)	10 (3.3)	
Adjuvant systemic treatment			
None	153 (51.2)	181 (62.2)	0.047
Chemotherapy (CT)	10 (3.3)	5 (1.7)	
Endocrine therapy (ET)	127 (42.5)	99 (34.0)	
Combination of ET and CT	9 (3.0)	6 (2.1)	
Adjuvant radiotherapy			
No	116 (38.8)	152 (52.2)	0.001
Yes	183 (61.2)	139 (47.8)	

Abbreviations: ER – oestrogen receptor; PR – progesterone receptor; HER2 – human epidermal growth factor receptor 2; CCI – charlson comorbidity index; BMI – body mass index; MMSE – mini mental state examination; GARS – groningen activity restriction scale; CT – chemotherapy; ET – endocrine therapy



Supplemental Fig. 2: Flowchart

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Chapter 8

Differences in quality of life of older patients with early-stage breast cancer between the United Kingdom and the Netherlands: two-year follow-up from two national prospective longitudinal multi-centre cohort studies.

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Submitted

Abstract

Background

Whilst numerous studies have compared the effect of different treatment strategies on survival rates between different countries, very few have focused on quality of life comparisons. Therefore, the aim of this study was to compare medium term (two year) quality of life outcomes in older patients with early-stage breast cancer between the United Kingdom (UK) and the Netherlands.

Methods

Women aged ≥70 years with early-stage breast cancer in two large prospectively collected datasets: the UK Age Gap dataset and the Dutch CLIMB dataset were studied. Quality of life was evaluated during follow-up using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (generic) and QLQ-BR23 (breast cancer-specific) questionnaires. Linear mixed models were used to assess longitudinal differences in quality of life between the UK and the Netherlands.

Results

A total of 2798 older patients were included, of whom 2430 were from the UK, and 368 from the Netherlands. While patients from both countries had comparable tumours, those in the UK were slightly older, less fit and received more systemic therapy (chemo and endocrine therapy). British patients reported worse quality of life scores over time when compared to Dutch patients, which was most apparent on the global health (comparative change $\beta = 9.55$; 95% CI = 7.61 – 11.48; $p < 0.001$) and role functioning subscales ($\beta = 8.84$; 95% CI = 6.32 – 11.35; $p < 0.001$).

Conclusions

Quality of life outcomes are slightly better in older Dutch women with breast cancer than women in the UK. This may reflect slightly more aggressive treatment schedules, older age or worse health status in the UK. Some of the differences may be due to known baseline variance in quality of life between nations.

Introduction

Breast cancer is the most commonly diagnosed malignancy in women, with approximately 30% of patients being over 70 years of age at the time of diagnosis [1]. Older adults comprise a heterogeneous group with large differences in fitness and frailty, which means that the effectiveness of treatment and the risk of side effects and complications may vary widely. The older population is vastly underrepresented in clinical trials and, therefore, treatment options for older patients are often based on clinical trials in younger and generally healthy patients [2]. As a result, physicians are more likely to deviate from current guidelines in older patients, or those with pre-existing comorbidities and frailty [3, 4]. Interestingly, treatment strategies for older patients differ greatly between European countries and may contribute to different survival rates [5].

However, survival outcomes are not the only important aspect of cancer treatment, especially in older adults. A more holistic approach to breast cancer care has been advocated recently, recognising the importance of quality of life [6]. Quality of life is a multidimensional and dynamic concept of an individual's perception of their position in life and is especially important to the older population as they may value quality of life over longevity [7, 8]. Nevertheless, numerous studies have compared the effect of different treatment strategies on survival rates between different countries, while only very few have focused on quality of life comparisons [5, 9-12]. A previous study found important differences between treatment allocation in older patients with breast cancer between the UK and the Netherlands, in particular higher rates of use of endocrine therapy and chemotherapy in UK patients, and conversely higher rates of surgery in Dutch patients, but these did not affect overall survival [9]. These differences may reflect the fact that National Guidelines differ slightly between the two countries, in particular relating to use of endocrine therapy. Therefore, the aim of this study was to compare medium term (two year) quality of life outcomes in older patients with early-stage breast cancer between the United Kingdom (UK) and the Netherlands.

Methods

Patients aged 70 years and older who were diagnosed with early-stage breast cancer (TNM stages: T1-3, N0-2, M0) were recruited into two different cohort studies: the British Bridging the Age Gap in Breast Cancer study (Age Gap) and the Dutch Climb Every Mountain study (CLIMB). The Age Gap study received ethics and research governance approval (IRAS: 115550). Approval for the CLIMB study was obtained from the medical ethics committee of the Leiden University Medical Centre (CCMO: NL43463.058.13). All patients gave written informed consent. Both cohort studies have been extensively described in previous papers [9, 13].

Design and study population

The Age Gap study included women aged 70 years and older who were diagnosed with early-stage breast cancer from 56 sites across England and Wales between 2013 and 2018. Participants could participate at three levels: full (including quality of life questionnaires), partial (no quality of life questionnaires), or by proxy (no quality of life questionnaires and only data collection by third parties). Only patients who fully participated received questionnaires on quality of life during follow-up and were therefore included in the current analyses.

The CLIMB study included women aged 70 years and older who were diagnosed with early-stage breast cancer from 9 sites across the western part of the Netherlands between 2013 and 2018. Participants could participate at two levels: full or partial (no quality of life questionnaires). Only patients who fully participated received questionnaires on quality of life during follow-up and were therefore included in the current analyses.

Data collection

At baseline, both studies collected the following patient characteristics: age, comorbidity according to the Charlson Comorbidity Index (CCI, without age adjustment and breast cancer diagnosis), medication use, Body Mass Index (BMI), activities of daily living (ADL), and cognition, using the Mini Mental State Examination (MMSE) [14, 15]. Polypharmacy was defined as five or more daily medications at the time of diagnosis. Both studies used different questionnaires to assess activities of daily living (ADL); the Age Gap study used the Barthel (ADL) questionnaire and the Lawton and Brody Instrumental ADL (IADL) score, while the CLIMB study used the Groningen Activity Restriction Scale (GARS), which consists of eleven items on ADL and seven items on Instrumental Activities of Daily Living (IADL) [16, 17]. To compare baseline levels of ADL between the two cohorts, the GARS questionnaire was converted into a modified Barthel score which excluded items not collected in the CLIMB study (bladder and bowel incontinence). The same cut-off values were used for analysis of the Barthel (i.e., 0-31 points: very/fully dependent, 32-63 points: partially/minimally dependent, 64-80 points: independent, or unknown if data was missing) [9]. If one or more answers to questions within a questionnaire were missing, the total Barthel score was categorised as unknown. For the MMSE questionnaire to assess cognition, the maximum score was given to a single item if less than 10% of the total questionnaire was missing. If more than 10% of the items were missing, the total MMSE score was categorised as unknown. Tumour characteristics were also collected at baseline and included: tumour grade, tumour size, laterality, uni- or multi-focality, lymph node status, oestrogen receptor status, progesterone receptor status, and HER2 receptor status. Data about treatment was also recorded including surgery, antioestrogen use, HER2 targeting therapy, chemotherapy and radiotherapy.

The most extensive type of breast surgery and axillary surgery was recorded. Primary endocrine therapy was defined as patients who received endocrine therapy and did not undergo surgery within the first year after diagnosis. Neoadjuvant systemic therapy (either chemotherapy or endocrine therapy) was defined as patients who started on systemic therapy and who did not receive surgery within the first six weeks after initiation, but no later than the first year.

Outcome measures

Quality of life was the primary outcome, which was assessed similarly in both studies by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (generic cancer) and its breast cancer-specific module (QLQ-BR23) [18, 19]. The EORTC QLQ-C30 questionnaire consists of 30 health-related questions, which are aggregated into different scales (functioning, symptom and global health status scales). The EORTC QLQ-BR23 comprises 23 questions related to breast cancer-specific quality of life and consists of functioning and symptom scales. Both questionnaires have been validated in Dutch and English [18, 19]. Scores are linearly transformed from 0 to 100 with higher scores on the functioning and global health status scale indicating better functioning and higher scores on the symptom scales representing more severe symptoms. Missing data were handled according to the EORTC QLQ-C30 Scoring Manual [20]. Both cohort studies assessed quality of life at different time-points. Patients in the Age Gap study received questionnaires at baseline (i.e., shortly after breast cancer diagnosis, before commencement of treatment), 6 weeks, and 6, 12, 18 and 24 months after diagnosis, while patients in the CLIMB study had to complete these questionnaires at 3, 9, 15 and 27 months after diagnosis. Clinically relevant differences in quality of life between both studies were assessed according to the findings of Cocks and colleagues [21]. For the quality of life subscales that were not evaluated by Cocks et al., a difference of 10 points or more was considered clinically relevant [22].

Statistical analysis

Differences in baseline characteristics between patients who participated in the Age Gap and CLIMB studies were compared with Pearson's chi-square test and Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. Linear mixed models were estimated to assess longitudinal differences in quality of life subdomains between the two cohorts and to assess whether the slopes changed over time. All subscales were separately analysed as dependent variable, with a random intercept and time as a fixed parameter. An interaction term between time and study (i.e., Age Gap or CLIMB) was added to assess differences in longitudinal trajectories between both countries. Linear mixed models were adjusted for the following potential confounders measured at baseline: age, tumour grade, tumour size, nodal status, CCI, polypharmacy, BMI, MMSE, functional status (ADL), and breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, adjuvant radiotherapy, and primary endocrine therapy.

For sensitivity analysis, the quality of life subscales were compared when excluding patients receiving chemotherapy, primary endocrine therapy or who were treated with major surgery (i.e. mastectomy and/or axillary lymph node dissection), respectively to determine whether these factors are a major cause of any differences in outcomes. Results of the linear mixed models are presented as the beta coefficient (β), a degree of change in the outcome variable over the entire follow-up period (i.e. 2 years), with 95% confidence intervals and p-values. All analyses were performed in SPSS version 25.0 (IBM, Armonk, New York, USA). For all analyses, the threshold for a two-sided, statistically significant p-value was 0.05.

Results

Patient characteristics and demographic comparison between datasets

A total of 2798 older patients with early-stage breast cancer were included, of whom 2430 patients were from the British Age Gap study and 368 patients from the Dutch CLIMB study. In both cohorts, patients who participated fully (completing QoL questionnaires) were generally younger and fitter than those not included (i.e., more comorbidities/polypharmacy, and a worse mental status and/or functional status; Supplemental Table 1). In the current analyses, patients from the Age Gap study were slightly older than patients from the CLIMB study with a median age of 76.0 (IQR: 72-81) and 75.0 (IQR: 72-80), respectively (Table 1). The CLIMB study included more patients with grade III tumours than the Age Gap study (29.6% versus 20.6%, respectively). Nodal status was similar for both studies (72.0% in Age Gap versus 70.9% in CLIMB had lymph node-negative disease). The Age Gap study included more patients with ER-positive tumours (87.4% in Age Gap versus 81.8% in CLIMB) and with relatively larger tumour sizes (53.8% in Age Gap versus 34.0% in CLIMB had tumours of >2cm). The proportion of patients with a Charlson Comorbidity Index of two or more was higher in the Age Gap study (33.4% in the Age Gap study and 21.7% in the CLIMB study), whilst the percentage of patients receiving 5 drugs or more was comparable (41.3% in Age Gap versus 39.7% in CLIMB). Patients in the Age Gap study received more primary endocrine therapy (12.8% versus 4.9%, $p<0.001$), adjuvant endocrine therapy (81.2% versus 46.9%, $p<0.001$), adjuvant chemotherapy (14.9% versus 6.3%, $p<0.001$), and trastuzumab (5.8% versus 3.3%, $p = 0.046$) when compared to patients in the CLIMB study.

Table 1: Patient-, tumour-, and treatment characteristics

	CLIMB **N=368 (60%)**	Age Gap **N=2430 (74%)**	p-value
Age			
Median (IQR)	75.0 (72-80)	76.0 (72-81)	0.006
70-74	180 (48.8)	975 (40.1)	0.010
75-79	86 (23.4)	729 (30.0)	
80-84	65 (17.7)	462 (19.0)	
≥ 85	37 (10.1)	264 (10.9)	
Grade			
I	82 (22.3)	392 (16.1)	<0.001
II	151 (41.0)	1517 (62.4)	
III	109 (29.6)	499 (20.6)	
Unknown	26 (7.1)	22 (0.9)	
Tumour size*			
0-2 cm	239 (64.9)	1111 (45.8)	<0.001
2-5 cm	112 (30.4)	1148 (47.2)	
>5 cm	13 (3.6)	161 (6.6)	
Unknown	4 (1.1)	10 (0.4)	
Nodal status*			
Node-negative	261 (70.9)	1751 (72.0)	<0.001
Node-positive	90 (24.5)	675 (27.8)	
Unknown	17 (4.6)	4 (0.2)	
ER-status			
Negative	43 (11.7)	293 (12.1)	<0.001
Positive	301 (81.8)	2125 (87.4)	
Unknown	24 (6.5)	12 (0.5)	
PR-status			
Negative	110 (29.9)	383 (15.8)	<0.001
Positive	231 (62.8)	874 (36.0)	
Unknown	27 (7.3)	1173 (48.2)	
HER2-status			
Negative	264 (71.7)	1943 (80.0)	<0.001
Positive	34 (9.3)	278 (11.4)	
Unknown	70 (19.0)	209 (8.6)	
Charlson Comorbidity Index (CCI)			
0	202 (54.9)	1226 (50.4)	<0.001
1	86 (23.4)	393 (16.2)	
2	49 (13.3)	535 (22.0)	
≥ 3	31 (8.4)	276 (11.4)	
Polypharmacy**			
No	206 (56.0)	1427 (58.7)	<0.001
Yes	146 (39.7)	1003 (41.3)	
Unknown	16 (4.3)	0 (0.0)	
BMI			
<18.5	3 (0.8)	24 (1.0)	<0.001
18.5-25	132 (35.8)	703 (28.9)	
25-30	146 (39.7)	777 (32.0)	
>30	86 (23.4)	612 (25.2)	
Unknown	1 (0.3)	314 (12.9)	
Mental status (MMSE)			
Normal (≥24)	333 (90.5)	1807 (74.4)	<0.001
Impaired (<24)	10 (2.7)	71 (2.9)	
Unknown	25 (6.8)	552 (22.7)	

Table 1: Continued

	CLIMB N=368 (60%)	Age Gap N=2430 (74%)	p-value
Functional status (Barthel)* **			
Independent	335 (91.0)	2222 (91.5)	<0.001
Partially or minimally dependent	23 (6.3)	73 (3.0)	
Very or fully dependent	2 (0.5)	5 (0.2)	
Unknown	8 (2.2)	130 (5.3)	
Most extensive breast surgery (excl PET)			
No surgery	0 (0.0)	34 (1.6)	0.022
Breast conserving	203 (58.0)	1267 (59.8)	
Mastectomy	147 (42.0)	802 (37.9)	
Unknown	0 (0.0)	15 (0.7)	
Most extensive axillary surgery (excl PET)			
No axillary surgery	18 (5.1)	87 (4.1)	0.187
Sentinel lymph node procedure	267 (76.3)	1645 (77.7)	
Axillary lymph node dissection	65 (18.6)	364 (17.2)	
Unknown	0 (0.0)	22 (1.0)	
Primary Endocrine Therapy (PET)			
No	350 (95.1)	2118 (87.2)	<0.001
Yes	18 (4.9)	312 (12.8)	
Neo-adjuvant systemic treatment (excl PET)			
None	330 (94.3)	1986 (93.8)	0.255
Chemotherapy (CT)	5 (1.4)	59 (2.8)	
Hormonal therapy (HT)	15 (4.3)	73 (3.4)	
Combination of HT and CT	0 (0.0)	0 (0.0)	
Adjuvant systemic treatment (excl PET)			
None	176 (50.3)	269 (12.7)	<0.001
Chemotherapy (CT)	10 (2.9)	130 (6.1)	
Hormonal therapy (HT)	152 (43.4)	1533 (72.4)	
Combination of HT and CT	12 (3.4)	186 (8.8)	
Adjuvant radiotherapy (excl PET)			
No	137 (39.1)	795 (37.5)	0.566
Yes	213 (60.9)	1323 (62.5)	
Herceptin (trastuzumab)			
No	356 (96.7)	2289 (94.2)	0.046
Yes	12 (3.3)	141 (5.8)	

*Pathological tumour size or nodal status, if unavailable, clinical tumour size or nodal status was used
**Polypharmacy was defined as five or more daily medications at the time of diagnosis.
***Without the questions on bladder and bowel incontinence
Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CCI, Charlson Comorbidity Index; BMI, body mass index; MMSE, mini-mental state examination; PET, primary endocrine therapy; CT, chemotherapy; ET, endocrine therapy

Generic quality of life outcomes (EORTC QLQ-C30)

The completion of quality of life questionnaires decreased over time in both studies (Supplemental Fig. 1). Patients in the CLIMB study had better scores on several subscales. The greatest clinically significant difference over the entire two-year follow-up period between the two countries was found on the global health status subdomain, consisting of the following two Likert scale questions: 'how would you rate your overall health during the past week?' and 'how would you rate your overall quality of life during the past week?' (difference for the global health status subdomain: $\beta = 9.99$; 95% CI = 8.11 – 11.88; $p < 0.001$) (Fig. 1, Table 2, Supplemental Table 3a).

After adjustment for pre-defined confounders at baseline (i.e., tumour characteristics, patient characteristics and treatment allocation), this difference remained almost unchanged (β = 9.55; 95% CI = 7.61 – 11.48; p < 0.001) (Table 2). Considering the difference in treatment strategies between both study cohorts, additional analyses were performed to assess whether exclusion of patients treated with chemotherapy or primary endocrine therapy or who had undergone major surgery (i.e. mastectomy, ALND) affected the results. However, no apparent differences were found (Supplemental Table 2a).

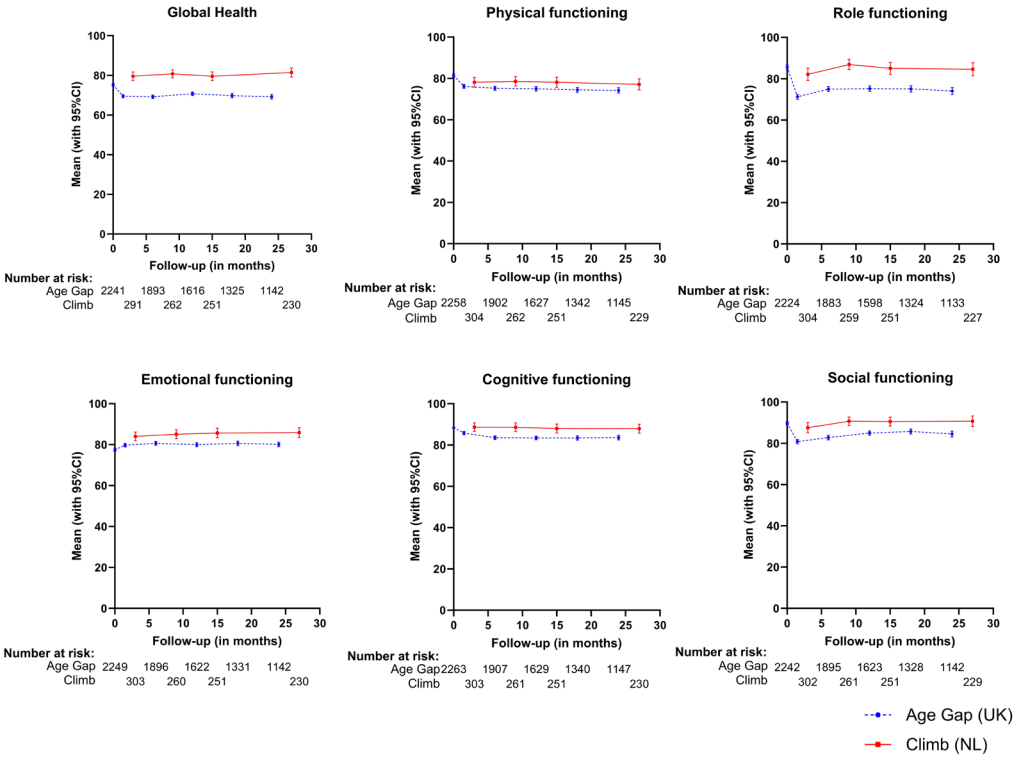


Fig. 1: Functioning and global health status subscales of the EORTC QLQ-C30 questionnaire for Dutch patients from the CLIMB study (red line) and British patients from the Age Gap study (dashed blue line) in the first 27 months after diagnosis of early-stage breast cancer
Higher scores on the functioning and global health status scale indicate better functioning and higher scores on the symptom scales represent more severe symptoms

Table 2: Comparison between the Age Gap study and the CLIMB study of each EORTC QLQ-C30 subscale, using linear mixed models

	Crude model			Adjusted model*		
	bèta	95% CI	p value	bèta	95% CI	p value
Global health status / QoL						
Global health						
Age Gap	Ref			Ref		
CLIMB	9.99	8.11 - 11.88	<0.001	9.55	7.61 - 11.48	<0.001
Functional scales						
Physical function						
Age Gap	Ref			Ref		
CLIMB	1.93	-0.44 - 4.30	0.110	1.78	-0.15 - 3.68	0.070
Role function						
Age Gap	Ref			Ref		
CLIMB	8.61	5.98 - 11.25	<0.001	8.84	6.32 - 11.35	<0.001
Emotional function						
Age Gap	Ref			Ref		
CLIMB	4.91	2.96 - 6.87	<0.001	5.27	3.10 - 7.45	<0.001
Cognitive function						
Age Gap	Ref			Ref		
CLIMB	4.01	2.20 - 5.82	<0.001	3.39	1.40 - 5.39	0.001
Social function						
Age Gap	Ref			Ref		
CLIMB	4.75	2.65 - 6.85	<0.001	5.26	3.11 - 7.40	<0.001
Symptom scales / items						
Fatigue						
Age Gap	Ref			Ref		
CLIMB	-4.98	-7.22 - -2.74	<0.001	-4.25	-6.56 - -1.93	<0.001
Nausea and vomiting						
Age Gap	Ref			Ref		
CLIMB	-0.59	-1.48 - 0.29	0.188	0.02	-0.95 - 0.98	0.974
Pain						
Age Gap	Ref			Ref		
CLIMB	-7.19	-9.57 - -4.81	<0.001	-7.43	-9.87 - -4.99	<0.001
Dyspnoea						
Age Gap	Ref			Ref		
CLIMB	-3.36	-5.96 - -0.76	0.011	-1.28	-3.99 - 1.44	0.357
Insomnia						
Age Gap	Ref			Ref		
CLIMB	-7.34	-10.17 - -4.52	<0.001	-6.52	-9.72 - -3.32	<0.001
Appetite loss						
Age Gap	Ref			Ref		
CLIMB	-4.61	-6.64 - -2.59	<0.001	-3.29	-5.48 - -1.09	0.003
Constipation						
Age Gap	Ref			Ref		
CLIMB	-3.42	-5.55 - -1.29	0.002	-2.67	-5.05 - -0.29	0.028
Diarrhoea						
Age Gap	Ref			Ref		
CLIMB	-1.17	-2.52 - 0.17	0.087	-0.81	-2.32 - 0.69	0.290
Financial difficulties						
Age Gap	Ref			Ref		
CLIMB	-0.45	-1.74 - 0.83	0.491	-0.18	-1.58 - 1.22	0.799

*Adjusted for age, tumour grade, tumour size, nodal status, Charlson Comorbidity Index, polypharmacy, Body Mass Index, Mini Mental State Examination, functional status (ADL), breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, adjuvant radiotherapy, and primary endocrine therapy

Older British patients with breast cancer also seemed to be clinically significantly more restricted in pursuing their hobbies, work, or other daily activities throughout the study period than patients in the CLIMB study, as indicated by the role functioning subscale (difference after adjustment for confounders between both countries: β = 8.84; 95% CI = 6.32 – 11.35; p < 0.001) (Fig. 1, Table 2). While role functioning in the CLIMB study was not assessed until three months after diagnosis, patients from the Age Gap study had a steep drop in mean scores between baseline and six weeks, which decreased from a mean score of 85.6 to 76.1 (Fig. 1, Supplemental Table 3a) (surgery takes place usually between baseline and the 6 week time point). After the initial drop in the Age Gap study, both studies showed an increase in role functioning in the first year of follow-up, followed by stabilisation (Fig. 1). The effects of chemotherapy, primary endocrine therapy and major surgery on the difference in role functioning between the two countries were minimal (after adjustment for confounders: β = 8.38; 95% CI = 5.73 – 11.04; p < 0.001 and β = 8.64; 95% CI = 6.12 – 11.16; p < 0.001 and β = 8.59; 95% CI = 5.01 – 12.16; p < 0.001, respectively) (Supplemental Table 2a).

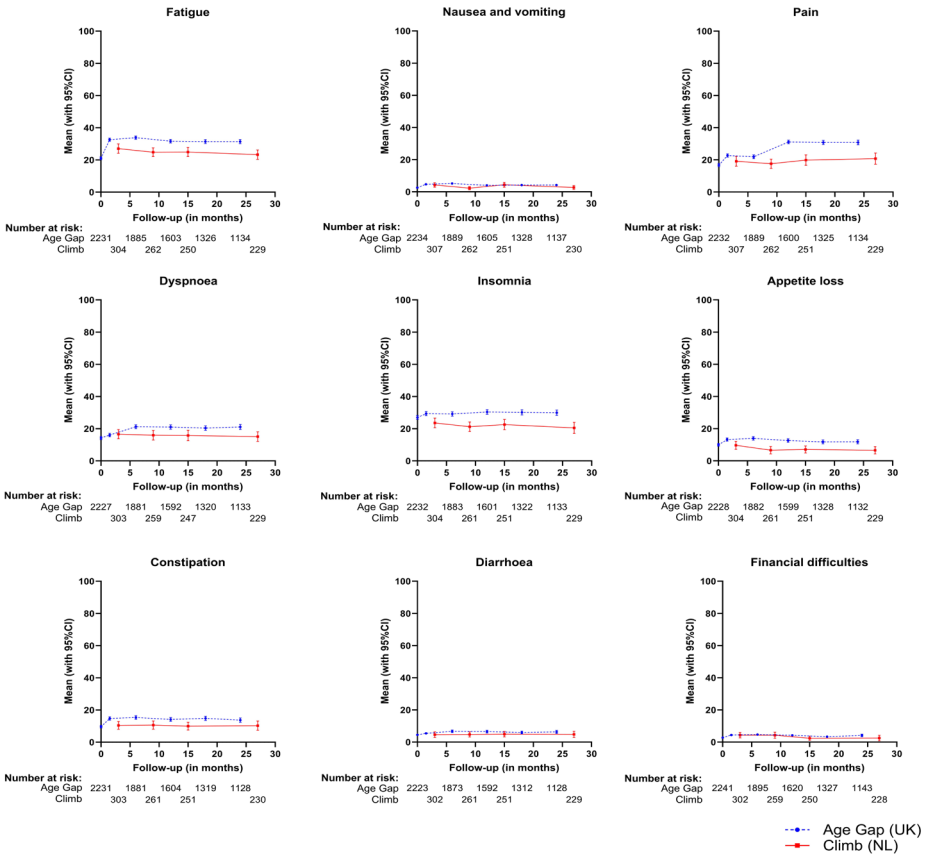


Fig. 2: Symptom subscales of the EORTC QLQ-C30 questionnaire for Dutch patients from the CLIMB study (red line) and British patients from the Age Gap study (dashed blue line) in the first 27 months after diagnosis of early-stage breast cancer. Higher scores represent more severe symptoms.

Small but clinically relevant differences between the two cohort studies were found for emotional functioning (β = 5.27; 95% CI = 3.10 – 7.45; p < 0.001), cognitive functioning (β = 3.39; 95% CI = 1.40 – 5.39; p = 0.001), and social functioning (β = 5.26; 95% CI = 3.11 – 7.40; p < 0.001), all in favour of patients from the CLIMB study (Table 2).

Fatigue and insomnia were less apparent in the CLIMB study than in the Age Gap study (after adjustment for confounders (i.e., tumour characteristics, patient characteristics and treatment allocation): β = -4.25; 95% CI = -6.56 – -1.93; p < 0.001 and β = -6.52; 95% CI = -9.72 – -3.32; p < 0.001, respectively) (Table 2). However, the mean difference for fatigue was not clinically meaningful. Fatigue decreased over time in both cohorts (after an initial steep increase between baseline and 6 weeks in the Age Gap study), whilst the curves for insomnia diverged (p = 0.027) (Fig. 2, Supplemental table 3a and 4). Patients in the Age Gap study experienced more pain over time than patients in the CLIMB study (after adjustment for confounders: β = -7.43; 95% CI = -9.87 – -4.99; p < 0.001) (Table 2).

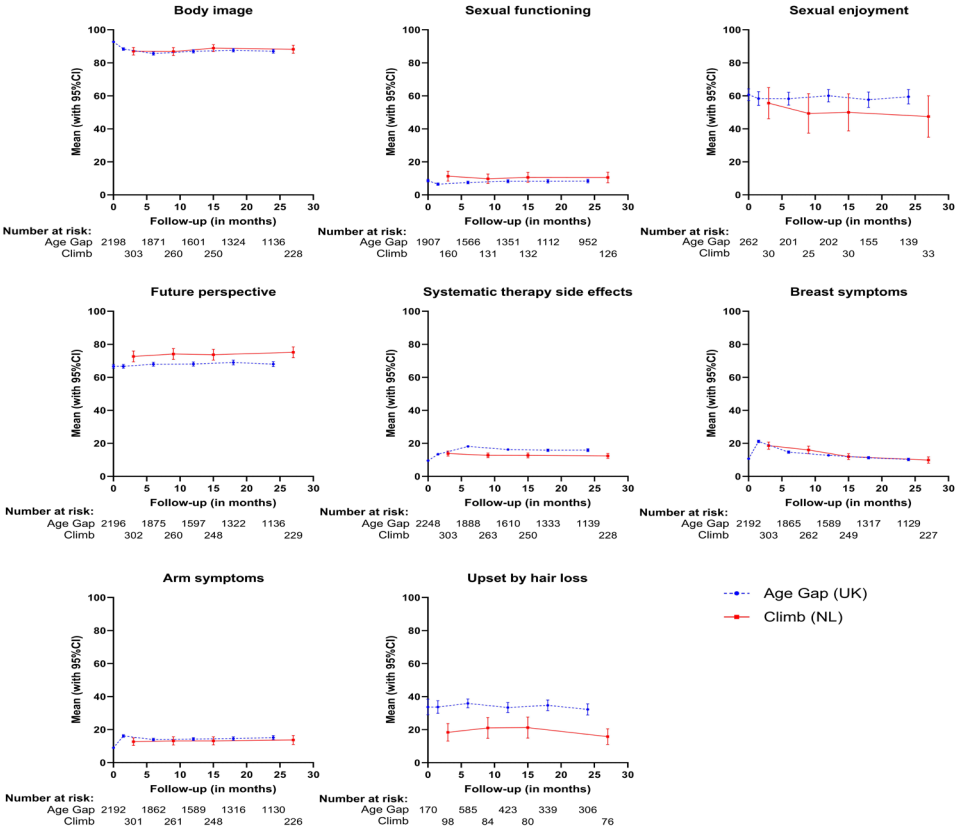


Fig. 3: Functioning and symptom subscales of the EORTC QLQ-BR23 questionnaire for Dutch patients from the CLIMB study (red line) and British patients from the Age Gap study (dashed blue line) in the first 27 months after diagnosis of early-stage breast cancer

Higher scores on the functioning scales indicate better functioning and higher scores on the symptom scales represent more severe symptom

Analysis according to whether the two curves had different slopes over time, showed a statistically significant difference between the two studies (p<0.001), indicating that pain scores in the CLIMB study remained stable over time, whereas pain scores increased in the Age Gap study (Fig. 2, Supplemental Table 4). The effect of exclusion of patients treated with chemotherapy, primary endocrine therapy or major surgery compared with minor, was small and broadly similar for all three subscales (Supplemental Table 2a).

Breast cancer-specific quality of life outcomes (EORTC QLQ-BR23)

Differences in breast cancer-specific quality of life were less apparent and no clinically meaningful differences were found between the two countries (Fig. 3, Table 3, Supplemental Table 3b). The sexual enjoyment and upset by hair loss comparison is not reliable, as these question were optional and were only completed by a limited number of patients in both studies (Fig. 3, Supplemental Table 3b, Supplemental Fig. 2).

Table 3: Comparison between the Age Gap study and the CLIMB study of each EORTC QLQ-BR23 subscale, using linear mixed models

	Crude model			Adjusted model*		
	bèta	95% CI	p value	bèta	95% CI	p value
Functional scales						
Body Image						
Age Gap	Ref			Ref		
CLIMB	-0.12	-1.99 - 1.75	0.898	-0.14	-2.19 - 1.90	0.890
Sexual functioning						
Age Gap	Ref			Ref		
CLIMB	2.93	0.87 - 4.98	0.005	1.80	-0.45 - 4.06	0.117
Sexual enjoyment						
Age Gap	Ref			Ref		
CLIMB	-9.57	-16.52 - -2.62	0.007	-9.55	-18.06 - -1.05	0.028
Future perspective						
Age Gap	Ref			Ref		
CLIMB	5.79	3.21 - 8.37	<0.001	5.13	2.22 - 8.03	0.001
Symptom scales / items						
Systemic therapy side effects						
Age Gap	Ref			Ref		
CLIMB	-2.12	-3.45 - -0.79	0.002	-0.58	-2.03 - 0.87	0.435
Breast symptoms						
Age Gap	Ref			Ref		
CLIMB	1.81	0.41 - 3.20	0.011	1.63	0.09 - 3.17	0.039
Arm symptoms						
Age Gap	Ref			Ref		
CLIMB	-0.94	-2.67 - 0.80	0.290	-0.96	-2.82 - 0.90	0.313
Upset by hair loss						
Age Gap	Ref			Ref		
CLIMB	-16.27	-20.76 - -11.78	<0.001	-13.28	-18.43 - -8.12	<0.001

*Adjusted for age, tumour grade, tumour size, nodal status, Charlson Comorbidity Index, polypharmacy, Body Mass Index, Mini Mental State Examination, functional status (ADL), breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, adjuvant radiotherapy, and primary endocrine therapy

Discussion

There was a significant difference in quality of life between older patients who were diagnosed with and treated for early-stage breast cancer between the Netherlands and the UK. Although the study population (older and less fit in the UK) and treatment strategies (more chemotherapy and endocrine therapy in the UK) of the two countries differed significantly, quality of life differences seemed to be only minimally affected by tumour differences, health and fitness characteristics and treatment allocation.

The reason for the differences in quality of life between both countries is likely to be multifactorial. One of the explanations may be found in the recently published World Happiness Report (23). This report showed that in general British people score seven per cent lower on average life evaluation than the Dutch population (6.9 versus 7.4 on a scale of 0 to 10, respectively). The same report points out that this difference in happiness can be partly explained by better scores in the Netherlands in six key domains that can play a role in an individual's quality of life, including Gross Domestic Product (GDP) per capita, social support, healthy life expectancy, freedom, generosity, and corruption. Another important aspect of an individual's quality of life is deprivation. Deprivation is a multidimensional concept that encompasses a general lack of resources and opportunities needed to participate in the society to which a person belongs (24). The European Union has created a 13-item indicator of material and social deprivation, which showed that deprivation levels are generally worse in the UK than in the Netherlands (25). Moreover, in the current analysis, the regions under study in the Netherlands were generally relatively affluent whereas many of the recruiting sites in the UK were of below average affluence, with a preponderance of recruiting sites in the Northern half of the UK, where deprivation rates are generally higher. Therefore, rates of deprivation on average are likely to be higher in the Age Gap population.

Physical activity is another key component that has been positively associated with quality of life in numerous studies (26). Although not specifically focused on the older population, Institut Public de Sondage d'Opinion Secteur (Ipsos) found that citizens from the Netherlands are the most physically active out of 29 countries worldwide and spend on average 12.8 hours per week on physical exercise, whereas British citizens spend 6.3 hours per week on physical exercise (27). Four per cent of the Dutch population does no exercise at all during a normal week, whilst 11% in the UK are not engaged in physical exercise. The British Heart Foundation found even higher percentages and showed that the proportion of adults who do not exercise or play sport is 35% in the UK and 29% in the Netherlands (28). They also found that British people are more inactive than the Dutch in activities other than sport (23% versus 6%, respectively). Moreover, cancer survivors are even less likely to engage in physical activity than those with no history of cancer (29). Physical activity is also associated with fatigue and depression, which may explain the differences in other subscales (26).

Nolte and colleagues investigated normative data for the EORTC QLQ-C30 questionnaire in around 1000 people per country from the general population across 13 European countries, Canada and the United States (30). The authors showed that the mean global health status score was highest in the Netherlands with an average score of 77.4 and the third lowest was in the UK with an average score of 62.3. Interestingly, both scores are much lower than the global health scores that we have found in the current study, especially for the Age Gap study. This may reflect variation in sampling, sex differences or the impact of age. Additionally, the difference in role functioning scores between the two countries is in line with the country-specific general population data with average scores of 89.1 in the Netherlands versus 80.2 in the UK, which is, for both countries, approximately 5 points higher than found in the current study (30). The limitation in hobby, work or leisure time activities participation is consistent with previous studies showing that patients with cancer are more likely to refrain from doing so (29, 31).

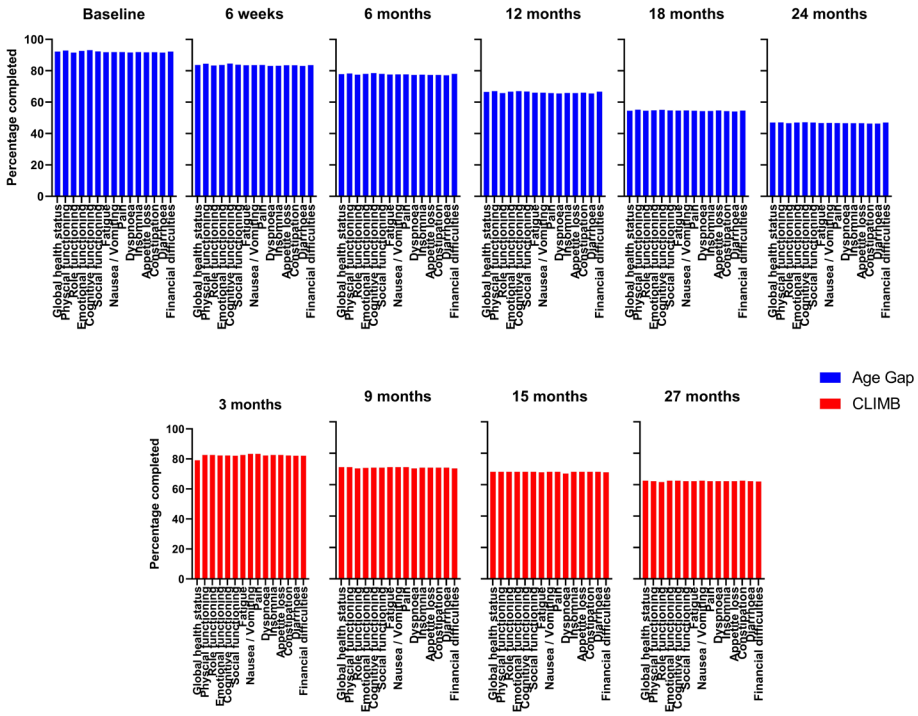
Although the cross-sectional differences in quality of life between the two countries remained more or less constant during follow-up, it is still possible that treatment and health related differences significantly contributed to quality of life differences. Especially since previous analyses showed different, albeit mostly temporary, effects of surgery, radiotherapy and chemotherapy on quality of life (32-35). Moreover, older patients in the Netherlands receive less (primary) endocrine therapy and chemotherapy and the lack of differential impact on quality of life in our study is remarkable and requires further exploration (5, 9). In addition to the observed differences in quality of life between the UK and the Netherlands in the current study, the EURECCA Breast Cancer Group showed substantial differences in treatment allocation and a worse survival of older women with breast cancer in the UK (5). However, survival outcomes have been previously reported for the CLIMB and Age Gap studies and no significant difference was noted, despite differences in treatment strategies and patient characteristics (9). It is possible that outcomes may diverge with longer follow-up (presently at 52 months for both studies), especially considering that the majority of cancers in this age group are ER-positive, where longer follow-up is usually necessary to identify survival differences.

The main strength of this study is that we have combined the two largest longitudinal cohort studies that provide comprehensive information on patient-reported outcome measures of the frequently underrepresented group of older patients with breast cancer. Both cohorts included large numbers of older patients with detailed information on patient characteristics, treatment allocation and quality of life during follow-up. This study has some limitations. First, patients included in both cohort studies were generally fitter and younger than the age matched population in the host country due to slightly skewed recruitment (36). The results may therefore not fully reflect those of the general older population.

In addition, there may have been further bias towards younger and fitter women over age 70 due to the optional nature of quality of life form completion for both studies. This will further limit the generalisability of the results. Moreover, patients from the CLIMB study did not receive questionnaires on quality of life at baseline, which makes it difficult to compare the direct effect of treatment on quality of life as most treatment was given in the first three months after diagnosis. However, longer-term follow-up information on quality of life is also very important and some clinically significant differences between British and Dutch patients were observed during this period. Furthermore, patients in both cohorts received different translations of the same questionnaire which may have led to different interpretations. However, all questionnaires have been validated independently in each country and are therefore expected to give relatively similar results for any given level of quality of life (18, 19).

In conclusion, this study demonstrated significant differences in quality of life during a two-year follow-up period in older women with early-stage breast cancer between two European countries. This study probably reflects largely social and cultural differences rather than the effect of different treatment allocations based on our sensitivity analyses, although some effects from this are likely. Treatment decisions should ideally factor in the individual impact of treatments on quality of life and integration of quality of life outcomes into decision support tools would be a valuable way to support this.

Supplementary data



Supplemental Fig. 1: Completion of the EORTC QLQ-C30 questionnaire at each time point for patients from the Age Gap study (blue) and CLIMB study (red)

Supplemental Table 1: Comparison of patient-, tumour-, and treatment characteristics at baseline of patients who fully participated versus partially participated in the CLIMB study and the Age Gap study

	CLIMB			Age Gap		
	Full participation n(%) **N=368 (60%)**	Partial participation n(%) **N=250 (40%)**	p-value	Full participation n(%) **N=2430 (74%)**	Partial participation n(%) **N=832 (26%)**	p-value
Age						
70-74	180 (48.8)	108 (43.2)	0.040	975 (40.1)	253 (30.4)	<0.001
75-79	86 (23.4)	49 (19.6)		729 (30.0)	238 (28.6)	
80-84	65 (17.7)	50 (20.0)		462 (19.0)	170 (20.4)	
≥ 85	37 (10.1)	43 (17.2)		264 (10.9)	171 (20.6)	
Grade						
I	82 (22.3)	52 (20.8)	0.692	392 (16.1)	123 (14.8)	0.217
II	151 (41.0)	96 (38.4)		1517 (62.4)	502 (60.3)	
III	109 (29.6)	79 (31.6)		499 (20.6)	198 (23.8)	
Unknown	26 (7.1)	23 (9.2)		22 (0.9)	9 (1.1)	
Tumour size*						
0-2 cm	239 (64.9)	152 (60.8)	0.386	1111 (45.8)	387 (46.5)	0.428
2-5 cm	112 (30.4)	79 (31.6)		1148 (47.2)	400 (48.1)	
>5 cm	13 (3.6)	13 (5.2)		161 (6.6)	43 (5.2)	
Unknown	4 (1.1)	6 (2.4)		10 (0.4)	2 (0.2)	
Nodal status*						
Node-negative	261 (70.9)	178 (71.2)	0.041	1751 (72.0)	566 (68.0)	0.083
Node-positive	90 (24.5)	49 (19.6)		675 (27.8)	264 (31.8)	
Unknown	17 (4.6)	23 (9.2)		4 (0.2)	2 (0.2)	
Oestrogen Receptor-status						
Negative	43 (11.7)	40 (16.0)	0.268	293 (12.1)	95 (11.4)	0.110
Positive	301 (81.8)	192 (76.8)		2125 (87.4)	737 (88.6)	
Unknown	24 (6.5)	18 (7.2)		12 (0.5)	0 (0.0)	
Progesterone Receptor-status						
Negative	110 (29.9)	89 (35.6)	0.273	383 (15.8)	108 (13.0)	0.129
Positive	231 (62.8)	141 (56.4)		874 (36.0)	300 (36.0)	
Unknown	27 (7.3)	20 (8.0)		1173 (48.2)	424 (51.0)	

Supplemental Table 1: Continued

	CLIMB			Age Gap		
	Full participation n(%) **N=368 (60%)**	Partial participation n(%) **N=250 (40%)**	p-value	Full participation n(%) **N=2430 (74%)**	Partial participation n(%) **N=832 (26%)**	p-value
HER2-status						
Negative	264 (71.7)	170 (68.0)	0.186	1943 (80.0)	665 (79.9)	0.937
Positive	34 (9.3)	18 (7.2)		278 (11.4)	98 (11.8)	
Unknown	70 (19.0)	62 (24.8)		209 (8.6)	69 (8.3)	
Charlson Comorbidity Index (CCI)						
0	202 (54.9)	115 (46.0)	0.192	1226 (50.4)	379 (45.6)	<0.001
1	86 (23.4)	69 (27.6)		393 (16.2)	146 (17.5)	
2	49 (13.3)	41 (16.4)		535 (22.0)	152 (18.3)	
≥ 3	31 (8.4)	25 (10.0)		276 (11.4)	155 (18.6)	
Polypharmacy**						
No	206 (56.0)	124 (49.6)	0.164	1427 (58.7)	404 (48.6)	<0.001
Yes	146 (39.7)	118 (47.2)		1003 (41.3)	428 (51.4)	
Unknown	16 (4.3)	8 (3.2)		0 (0.0)	0 (0.0)	
BMI (kg/m2)						
<18.5	3 (0.8)	1 (0.4)	0.661	24 (1.0)	15 (1.8)	<0.001
18.5-25	132 (35.8)	89 (35.6)		703 (28.9)	161 (19.4)	
25-30	146 (39.7)	100 (40.0)		777 (32.0)	223 (26.8)	
>30	86 (23.4)	57 (22.8)		612 (25.2)	160 (19.2)	
Unknown	1 (0.3)	3 (1.2)		314 (12.9)	273 (32.8)	
Mental status (MMSE)						
Normal (≥24)	333 (90.5)	226 (90.4)	0.140	1807 (74.4)	330 (39.7)	<0.001
Impaired (<24)	10 (2.7)	13 (5.2)		71 (2.9)	37 (4.4)	
Unknown	25 (6.8)	11 (4.4)		552 (22.7)	465 (55.9)	
Functional status (Barthel)***						
Independent	335 (91.0)	202 (80.8)	0.001	2222 (91.5)	593 (71.3)	<0.001
Partially or minimally dependent	23 (6.3)	33 (13.2)		73 (3.0)	40 (4.8)	
Very or fully dependent	2 (0.5)	8 (3.2)		5 (0.2)	9 (1.1)	
Unknown	8 (2.2)	7 (2.8)		130 (5.3)	190 (22.8)	

Supplemental Table 1: Continued

	CLIMB			Age Gap		
	Full participation n(%) **N=368 (60%)**	Partial participation n(%) **N=250 (40%)**	p-value	Full participation n(%) **N=2430 (74%)**	Partial participation n(%) **N=832 (26%)**	p-value
Most extensive breast surgery (excl PET)						
No surgery	0 (0.0)	2 (0.9)	0.044	34 (1.6)	9 (1.3)	0.479
Breast conserving	203 (58.0)	114 (50.0)		1267 (59.8)	380 (56.9)	
Mastectomy	147 (42.0)	112 (49.1)		802 (37.9)	275 (41.2)	
Unknown	0 (0.0)	0 (0.0)		15 (0.7)	4 (0.6)	
Most extensive axillary surgery (excl PET)						
No axillary surgery	18 (5.1)	23 (10.1)	0.002	87 (4.1)	30 (4.5)	0.053
Sentinel lymph node procedure	267 (76.3)	158 (69.3)		1645 (77.7)	485 (72.6)	
Axillary lymph node dissection	65 (18.6)	41 (18.0)		364 (17.2)	145 (21.7)	
Unknown	0 (0.0)	6 (2.6)		22 (1.0)	8 (1.2)	
Primary Endocrine Therapy (PET)						
No	350 (95.1)	228 (91.2)	0.053	2118 (87.2)	668 (80.3)	<0.001
Yes	18 (4.9)	22 (8.8)		312 (12.8)	164 (19.7)	
Neo-adjuvant systemic treatment (excl PET)						
None	330 (94.3)	216 (94.8)	0.351	1986 (93.8)	626 (93.7)	0.427
Chemotherapy (CT)	5 (1.4)	6 (2.6)		59 (2.8)	14 (2.1)	
Endocrine therapy (ET)	15 (4.3)	6 (2.6)		73 (3.4)	28 (4.2)	
Combination of ET and CT	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Adjuvant systemic treatment (excl PET)						
None	176 (50.3)	132 (57.9)	0.319	269 (12.7)	93 (13.9)	0.057
Chemotherapy (CT)	10 (2.9)	6 (2.6)		130 (6.1)	28 (4.2)	
Endocrine therapy (ET)	152 (43.4)	85 (37.3)		1533 (72.4)	503 (75.3)	
Combination of ET and CT	12 (3.4)	5 (2.2)		186 (8.8)	44 (6.6)	
Adjuvant radiotherapy (excl PET)						
No	137 (39.1)	113 (49.6)	0.013	795 (37.5)	250 (37.4)	0.959
Yes	213 (60.9)	115 (50.4)		1323 (62.5)	418 (62.6)	
Herceptin (trastuzumab)						
No	356 (96.7)	249 (99.6)	0.019	2289 (94.2)	792 (95.2)	0.279
Yes	12 (3.3)	1 (0.4)		141 (5.8)	40 (4.8)	

*Pathological tumour size or nodal status, if unavailable, clinical tumour size or nodal status was used. **Polypharmacy was defined as five or more daily medications at the time of diagnosis. ***Without the questions on bladder and bowel incontinence. PET, primary endocrine therapy; CT, chemotherapy; ET, endocrine therapy

Supplemental Table 2a: Difference between the Age Gap study and the CLIMB study of EORTC QLQ-C30 subscales when excluding patients receiving chemotherapy, PET or those who were treated with major surgery (i.e. mastectomy and/or axillary lymph node dissection), respectively*

	Without patients receiving chemotherapy			Without patients receiving PET			Without patients receiving major surgery		
	bèta	95% CI	p value	bèta	95% CI	p value	bèta	95% CI	p value
Global health status / QoL									
Global health									
Age Gap	Ref			Ref			Ref		
CLIMB	9.33	7.29 – 11.38	<0.001	10.05	8.09 – 12.01	<0.001	9.69	6.91 – 12.46	<0.001
Functional scales									
Physical function									
Age Gap	Ref			Ref			Ref		
CLIMB	1.40	-0.64 – 3.44	0.177	1.67	-0.25 – 3.59	0.088	1.67	-1.09 – 4. 24	0.236
Role function									
Age Gap	Ref			Ref			Ref		
CLIMB	8.38	5.73 – 11.04	<0.001	8.64	6.12 – 11.16	<0.001	8.59	5.01 – 12.16	<0.001
Emotional function									
Age Gap	Ref			Ref			Ref		
CLIMB	5.04	2.74 – 7.34	<0.001	5.66	3.47 – 7.85	<0.001	7.87	4.71 – 11.03	<0.001
Cognitive function									
Age Gap	Ref			Ref			Ref		
CLIMB	3.22	1.12 – 5.32	0.003	3.92	1.92 – 5.92	<0.001	4.39	1.60 – 7.18	0.002
Social function									
Age Gap	Ref			Ref			Ref		
CLIMB	4.42	2.19 – 6.66	<0.001	5.34	3.18 – 7.52	<0.001	5.90	2.88 – 8.92	<0.001
Symptom scales / items									
Fatigue									
Age Gap	Ref			Ref			Ref		
CLIMB	-4.55	-6.99 – -2.10	<0.001	-5.07	-7.41 – -2.74	<0.001	-5.48	-8.79 – -2.16	0.001
Nausea and vomiting									
Age Gap	Ref			Ref			Ref		
CLIMB	0.01	-1.00 – 1.01	0.991	0.10	-0.86 – 1.06	0.844	-0.27	-1.67 – 1.13	0.704
Pain									
Age Gap	Ref			Ref			Ref		
CLIMB	-6.91	-9.53 – -4.29	<0.001	-8.01	-10.45 – -5.57	<0.001	-8.04	-11.57 – -4.50	<0.001

Supplemental Table 2a: Continued

	Without patients receiving chemotherapy			Without patients receiving PET			Without patients receiving major surgery		
	bèta	95% CI	p value	bèta	95% CI	p value	bèta	95% CI	p value
Dyspnoea									
Age Gap	Ref			Ref			Ref		
CLIMB	-1.05	-3.98 – 1.87	0.478	-1.54	-4.19 – 1.11	0.255	-1.08	-5.01 – 2.86	0.591
Insomnia									
Age Gap	Ref			Ref			Ref		
CLIMB	-5.74	-9.13 – -2.35	0.001	-7.23	-10.48 – -3.98	<0.001	-8.65	-13.22 – -4.07	<0.001
Appetite loss									
Age Gap	Ref			Ref			Ref		
CLIMB	-3.32	-5.62 - -1.02	0.005	-4.07	-6.25 – -1.90	<0.001	-3.86	-6.95 – -0.78	0.014
Constipation									
Age Gap	Ref			Ref			Ref		
CLIMB	-2.55	-5.05 – -0.05	0.046	-2.96	-5.39 – -0.54	0.017	-4.21	-7.55 – -0.86	0.014
Diarrhoea									
Age Gap	Ref			Ref			Ref		
CLIMB	-0.78	-2.35 – 0.79	0.329	-0.87	-2.38 – 0.65	0.260	-0.48	-2.72 – 1.76	0.672
Financial difficulties									
Age Gap	Ref			Ref			Ref		
CLIMB	-0.48	-1.88 – 0.92	0.501	-0.32	-1.71 – 1.08	0.656	0.79	-1.22 – -2.79	0.441

*Linear mixed models are adjusted for age, tumour grade, tumour size, nodal status, CCI, polypharmacy, BMI, MMSE, functional status (ADL), breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, adjuvant radiotherapy, and PET

Supplemental Table 2b: Difference between the Age Gap study and the CLIMB study of EORTC QLQ-BR23 subscales when excluding patients receiving chemotherapy, PET or those who were treated with major surgery (i.e. mastectomy and/or axillary lymph node dissection), respectively*

	Without patients receiving chemotherapy			Without patients receiving PET			Without patients receiving major surgery		
	bèta	95% CI	p value	bèta	95% CI	p value	bèta	95% CI	p value
Functional scales									
Body Image									
Age Gap	Ref			Ref			Ref		
CLIMB	-0.08	-2.18 – 2.02	0.939	0.00	-2.08 – 2.09	0.999	1.85	-0.65 – 4.34	0.147
Sexual functioning									
Age Gap	Ref			Ref			Ref		
CLIMB	1.51	-0.85 – 3.86	0.209	1.79	-0.60 – 4.18	0.142	1.50	-1.79 – 4.79	0.372
Sexual enjoyment									
Age Gap	Ref			Ref			Ref		
CLIMB	-13.67	-22.47 – -4.87	0.002	-9.79	-18.38 – -1.21	0.025	-7.45	-18.60 – 3.69	0.189
Future perspective									
Age Gap	Ref			Ref			Ref		
CLIMB	4.04	0.99 – 7.09	0.009	5.40	2.43 – 8.36	<0.001	5.17	1.11 – 9.22	0.013
Symptom scales / items									
Systemic therapy side effects									
Age Gap	Ref			Ref			Ref		
CLIMB	-0.77	-2.27 – 0.74	0.319	-1.16	-2.62 – 0.31	0.122	-0.76	-2.81 – 1.30	0.471
Breast symptoms									
Age Gap	Ref			Ref			Ref		
CLIMB	1.01	-0.60 – 2.62	0.218	1.55	-0.04 – 3.14	0.057	2.31	0.16 – 4.45	0.035
Arm symptoms									
Age Gap	Ref			Ref			Ref		
CLIMB	-1.25	-3.19 – 0.70	0.208	-1.63	-3.51 – 0.26	0.091	-1.18	-3.69 – 1.33	0. 357
Upset by hair loss									
Age Gap	Ref			Ref			Ref		
CLIMB	-11.87	-17.21 – -6.54	<0.001	-13.06	-18.36 – -7.75	<0.001	-11.09	-18.41 – -3.78	0.003

*Linear mixed models are adjusted for age, tumour grade, tumour size, nodal status, CCI, polypharmacy, BMI, MMSE, functional status (ADL), breast surgery, axillary surgery, neoadjuvant therapies, adjuvant systemic therapy, adjuvant radiotherapy, and PET

Supplemental Table 3a: EORTC QLQ-C30 mean scores at each time point for patients from the Age Gap study (UK) and CLIMB study (the Netherlands)

Subscale	Time point		Age Gap*	CLIMB**
Global health status / QoL	0	n	2241	
		Mean (SD)	75.2 (19.0)	
	1	n	2034	291
		Mean (SD)	69.5 (19.2)	79.6 (18.2)
	2	n	1893	262
		Mean (SD)	69.2 (19.9)	80.8 (16.6)
	3	n	1616	251
		Mean (SD)	70.7 (18.8)	79.6 (17.9)
	4	n	1325	
		Mean (SD)	69.8 (20.0)	
	5	n	1142	230
		Mean (SD)	69.2 (19.8)	81.4 (17.6)
Physical functioning	0	n	2258	
		Mean (SD)	81.4 (21.2)	
	1	n	2054	304
		Mean (SD)	76.1 (21.1)	78.1 (21.0)
	2	n	1902	262
		Mean (SD)	75.3 (21.5)	78.5 (19.3)
	3	n	1627	251
		Mean (SD)	75.0 (21.9)	78.1 (20.1)
	4	n	1342	
		Mean (SD)	74.4 (22.2)	
	5	n	1145	229
		Mean (SD)	74.2 (21.9)	77.1 (20.7)
Role functioning	0	n	2224	
		Mean (SD)	85.6 (24.7)	
	1	n	2027	304
		Mean (SD)	71.3 (27.6)	82.1 (26.8)
	2	n	1883	259
		Mean (SD)	74.9 (27.6)	86.8 (20.2)
	3	n	1598	251
		Mean (SD)	75.2 (27.3)	85.0 (23.6)
	4	n	1324	
		Mean (SD)	75.1 (28.4)	
	5	n	1133	227
		Mean (SD)	74.1 (28.4)	84.6 (24.1)
Emotional functioning	0	n	2249	
		Mean (SD)	77.5 (19.9)	
	1	n	2035	303
		Mean (SD)	79.7 (19.6)	84.0 (18.8)
	2	n	1896	260
		Mean (SD)	80.6 (19.7)	85.1 (17.8)
	3	n	1622	251
		Mean (SD)	80.0 (19.9)	85.7 (18.6)
	4	n	1331	
		Mean (SD)	80.6 (19.9)	
	5	n	1142	230
		Mean (SD)	80.1 (19.0)	85.9 (18.5)
Cognitive functioning	0	n	2263	
		Mean (SD)	88.4 (16.5)	
	1	n	2056	303
		Mean (SD)	85.9 (18.4)	88.6 (18.3)

Supplemental Table 3a: Continued

Subscale	Time point		Age Gap*	CLIMB**
Cognitive functioning	2	n	1907	261
		Mean (SD)	83.6 (19.0)	88.6 (17.5)
	3	n	1629	251
		Mean (SD)	83.4 (18.4)	88.0 (17.3)
	4	n	1340	
		Mean (SD)	83.4 (19.8)	
	5	n	1147	230
		Mean (SD)	83.6 (19.0)	87.9 (16.9)
Social functioning	0	n	2242	
		Mean (SD)	89.7 (19.9)	
	1	n	2038	302
		Mean (SD)	80.8 (23.9)	87.6 (21.7)
	2	n	1895	261
		Mean (SD)	82.8 (24.6)	90.7 (17.0)
	3	n	1623	251
		Mean (SD)	85.0 (22.3)	90.5 (17.6)
	4	n	1328	
		Mean (SD)	85.8 (23.0)	
	5	n	1142	229
		Mean (SD)	84.5 (23.7)	90.7 (19.5)
Fatigue	0	n	2231	
		Mean (SD)	21.0 (20.9)	
	1	n	2028	304
		Mean (SD)	32.5 (22.1)	27.0 (25.8)
	2	n	1885	262
		Mean (SD)	33.8 (23.7)	24.8 (22.2)
	3	n	1603	250
		Mean (SD)	31.6 (22.0)	24.9 (22.5)
	4	n	1326	
		Mean (SD)	31.4 (22.7)	
	5	n	1134	229
		Mean (SD)	31.4 (22.2)	23.3 (22.3)
Nausea and vomiting	0	n	2234	
		Mean (SD)	2.6 (8.0)	
	1	n	2032	307
		Mean (SD)	4.7 (11.3)	4.3 (12.6)
	2	n	1889	262
		Mean (SD)	5.2 (12.3)	2.3 (8.1)
	3	n	1605	251
		Mean (SD)	4.0 (10.2)	4.4 (12.3)
	4	n	1328	
		Mean (SD)	4.2 (11.3)	
	5	n	1137	230
		Mean (SD)	4.2 (10.7)	2.7 (9.3)
Pain	0	n	2232	
		Mean (SD)	16.7 (23.6)	
	1	n	2034	307
		Mean (SD)	22.7 (23.7)	19.1 (26.8)
	2	n	1889	262
		Mean (SD)	21.9 (25.2)	17.6 (23.5)
	3	n	1600	251
		Mean (SD)	31.1 (23.2)	19.9 (26.1)
	4	n	1325	
		Mean (SD)	30.8 (24.5)	

Supplemental Table 3a: Continued

Subscale	Time point		Age Gap*	CLIMB**
	5	n	1134	229
		Mean (SD)	30.8 (24.2)	20.7 (26.7)
Dyspnoea	0	n	2227	
		Mean (SD)	14.2 (23.5)	
	1	n	2019	303
		Mean (SD)	16.1 (24.4)	16.6 (25.4)
	2	n	1881	259
		Mean (SD)	21.2 (26.6)	16.0 (24.4)
	3	n	1592	247
		Mean (SD)	21.0 (27.0)	15.8 (25.5)
	4	n	1320	
		Mean (SD)	20.4 (26.8)	
	5	n	1133	229
		Mean (SD)	21.1 (26.5)	15.1 (22.8)
Insomnia	0	n	2232	
		Mean (SD)	27.0 (28.8)	
	1	n	2021	304
		Mean (SD)	29.4 (29.5)	23.6 (27.0)
	2	n	1883	261
		Mean (SD)	29.2 (30.0)	21.2 (24.7)
	3	n	1601	251
		Mean (SD)	30.4 (29.3)	22.6 (26.1)
	4	n	1322	
		Mean (SD)	30.2 (30.0)	
	5	n	1133	229
		Mean (SD)	30.0 (28.9)	20.5 (26.5)
Appetite loss	0	n	2228	
		Mean (SD)	10.0 (20.0)	
	1	n	2028	304
		Mean (SD)	13.2 (21.9)	9.6 (22.4)
	2	n	1882	261
		Mean (SD)	14.0 (24.3)	6.6 (18.9)
	3	n	1599	251
		Mean (SD)	12.6 (22.5)	7.0 (17.9)
	4	n	1328	
		Mean (SD)	11.8 (22.5)	
	5	n	1132	229
		Mean (SD)	11.8 (21.7)	6.6 (17.4)
Constipation	0	n	2231	
		Mean (SD)	9.7 (19.7)	
	1	n	2029	303
		Mean (SD)	14.8 (23.7)	10.5 (21.5)
	2	n	1881	261
		Mean (SD)	15.4 (24.7)	10.6 (21.3)
	3	n	1604	251
		Mean (SD)	14.1 (23.4)	10.0 (19.6)
	4	n	1319	
		Mean (SD)	14.8 (24.5)	
	5	n	1128	230
		Mean (SD)	13.7 (23.1)	10.3 (21.9)
Diarrhoea	0	n	2223	
		Mean (SD)	4.5 (13.6)	
	1	n	2020	302
		Mean (SD)	5.4 (15.3)	4.6 (15.4)

Supplemental Table 3a: Continued

Subscale	Time point		Age Gap*	CLIMB**
Diarrhoea	2	n	1873	261
		Mean (SD)	6.7 (17.2)	4.7 (13.4)
	3	n	1592	251
		Mean (SD)	6.5 (16.9)	4.9 (13.9)
	4	n	1312	
		Mean (SD)	5.9 (15.8)	
	5	n	1128	229
		Mean (SD)	6.4 (17.0)	4.8 (15.0)
Financial difficulties	0	n	2241	
		Mean (SD)	2.8 (10.9)	
	1	n	2031	302
		Mean (SD)	4.4 (14.0)	4.3 (15.1)
	2	n	1895	259
		Mean (SD)	4.7 (14.8)	4.2 (15.4)
	3	n	1620	250
		Mean (SD)	4.2 (13.8)	2.4 (10.9)
	4	n	1327	
		Mean (SD)	3.4 (12.9)	
	5	n	1143	228
		Mean (SD)	4.2 (13.6)	2.5 (13.2)

* Patients in the Age Gap study received quality of life questionnaires at baseline, 6 weeks, and 6, 12, 18 and 24 months after diagnosis (time points 0-5)

** Patients in the CLIMB study received quality of life questionnaires at 3, 9, 15 and 27 months after diagnosis (time points 1, 2, 3, and 5)

Supplemental Table 3b: EORTC QLQ-BR23 mean scores at each time point for patients from the Age Gap study (UK) and CLIMB study (the Netherlands)

Subscale	Time point		Age Gap*	CLIMB**
Body Image	0	n	2198	
		Mean (SD)	92.7 (14.4)	
	1	n	2008	303
		Mean (SD)	88.3 (18.6)	87.0 (20.2)
	2	n	1871	260
		Mean (SD)	85.6 (21.6)	86.8 (20.0)
	3	n	1601	250
		Mean (SD)	87.0 (19.8)	88.9 (17.0)
	4	n	1324	
		Mean (SD)	87.6 (19.8)	
	5	n	1136	228
		Mean (SD)	87.0 (20.0)	88.2 (18.6)
Sexual functioning	0	n	1907	
		Mean (SD)	8.6 (18.2)	
	1	n	1697	160
		Mean (SD)	6.5 (15.3)	11.4 (18.9)
	2	n	1566	131
		Mean (SD)	7.5 (16.5)	9.8 (16.4)
	3	n	1351	132
		Mean (SD)	8.3 (17.1)	10.6 (17.5)
	4	n	1112	
		Mean (SD)	8.3 (17.6)	
	5	n	952	126
		Mean (SD)	8.4 (17.1)	10.6 (18.3)
Sexual enjoyment	0	n	262	
		Mean (SD)	60.7 (29.2)	
	1	n	181	30
		Mean (SD)	58.4 (28.7)	55.6 (25.3)
	2	n	201	25
		Mean (SD)	58.2 (27.9)	49.3 (29.1)
	3	n	202	30
		Mean (SD)	60.1 (27.2)	50.0 (30.0)
	4	n	155	
		Mean (SD)	57.6 (29.3)	
	5	n	139	33
		Mean (SD)	59.5 (26.2)	47.5 (35.4)
Future perspective	0	n	2196	
		Mean (SD)	66.7 (27.2)	
	1	n	2014	302
		Mean (SD)	66.6 (26.9)	72.6 (28.9)
	2	n	1875	260
		Mean (SD)	67.9 (27.0)	74.1 (26.8)
	3	n	1597	248
		Mean (SD)	68.1 (26.5)	73.7 (26.4)
	4	n	1322	
		Mean (SD)	69.0 (27.2)	
	5	n	1136	229
		Mean (SD)	68.0 (26.7)	75.1 (25.3)
Systemic therapy side effects	0	n	2248	
		Mean (SD)	9.5 (10.7)	
	1	n	2024	303
		Mean (SD)	13.4 (13.3)	13.9 (13.7)
	2	n	1888	263
		Mean (SD)	18.2 (15.4)	12.8 (11.7)

Supplemental Table 3b: Continued

Subscale	Time point		Age Gap*	CLIMB**
Systemic therapy side effects	3	n	1610	250
		Mean (SD)	16.2 (13.9)	12.7 (11.9)
	4	n	1333	
		Mean (SD)	15.8 (14.1)	
	5	n	1139	228
		Mean (SD)	15.9 (14.3)	12.4 (11.0)
Breast symptoms	0	n	2192	
		Mean (SD)	10.7 (13.3)	
	1	n	2014	303
		Mean (SD)	21.2 (18.6)	18.6 (19.3)
	2	n	1865	262
		Mean (SD)	14.7 (15.5)	16.0 (18.7)
	3	n	1589	249
		Mean (SD)	12.8 (14.2)	11.9 (14.4)
	4	n	1317	
		Mean (SD)	11.3 (14.0)	
	5	n	1129	227
		Mean (SD)	10.3 (13.2)	9.9 (14.3)
Arm symptoms	0	n	2192	
		Mean (SD)	9.0 (14.9)	
	1	n	2004	301
		Mean (SD)	16.1 (18.4)	12.7 (20.1)
	2	n	1862	261
		Mean (SD)	13.9 (17.7)	13.2 (20.3)
	3	n	1589	248
		Mean (SD)	14.3 (18.2)	13.1 (19.4)
	4	n	1316	
		Mean (SD)	14.6 (19.1)	
	5	n	1130	226
		Mean (SD)	15.2 (20.5)	13.7 (20.9)
Upset by hair loss	0	n	170	
		Mean (SD)	33.7 (31.2)	
	1	n	249	98
		Mean (SD)	33.7 (30.7)	18.4 (26.3)
	2	n	585	84
		Mean (SD)	35.9 (32.8)	21.0 (29.2)
	3	n	423	80
		Mean (SD)	33.4 (31.1)	21.3 (28.7)
	4	n	339	
		Mean (SD)	34.7 (30.1)	
	5	n	306	76
		Mean (SD)	32.2 (30.0)	15.8 (20.7)

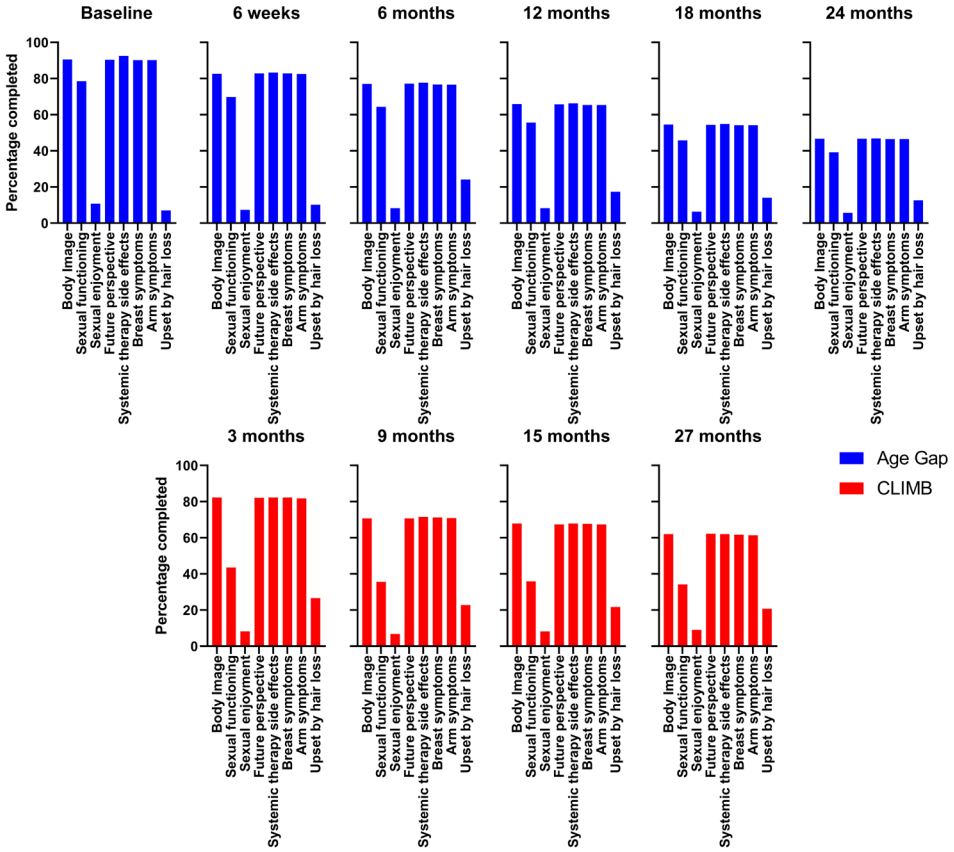
* Patients in the Age Gap study received quality of life questionnaires at baseline, 6 weeks, and 6, 12, 18 and 24 months after diagnosis (time points 0-5)

** Patients in the CLIMB study received quality of life questionnaires at 3, 9, 15 and 27 months after diagnosis (time points 1, 2, 3, and 5)

Supplemental Table 4: Tests for interaction between time and study for all EORTC QLQ-C30 and QLQ-BR23 subscales

Subscale	p value
Global health	<0.001
Physical function	<0.001
Role function	<0.001
Emotional function	0.405
Cognitive function	0.003
Social function	0.027
Fatigue	<0.001
Nausea and vomiting	0.050
Pain	<0.001
Dyspnoea	<0.001
Insomnia	0.027
Appetite loss	0.057
Constipation	0.057
Diarrhoea	0.366
Financial difficulties	0.005
Body Image	<0.001
Sexual functioning	0.336
Sexual enjoyment	0.826
Future perspective	0.856
Systemic therapy side effects	<0.001
Breast symptoms	<0.001
Arm symptoms	0.078
Upset by hair loss	0.148

The interaction terms indicate whether the longitudinal trajectories of all quality of life subscales differed between patient from the Netherlands and the United Kingdom



Supplemental Fig. 2: Completion of the EORTC QLQ-BR23 questionnaire at each time point for patients from the Age Gap study (blue) and CLIMB study (red)

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PART III:
SUMMARY AND APPENDICES

Chapter 9

Summary, General discussion

SUMMARY

PART I: EVALUATION OF BREAST CANCER TREATMENT OUTCOMES IN OLDER WOMEN

Treatment strategies vary over time, both due to new insights and the development of new therapies. For example, in patients aged 75 years and older with stage I-II breast cancer, surgery was increasingly replaced by primary endocrine therapy between 2000 and 2017 [1, 2]. The percentage of patients undergoing surgery also declined in patients with stage III disease, but the prescription of endocrine therapy remained more or less the same. These changes may be caused by fear of complications or the perceived impact of surgery on quality of life.

In **Chapter 2**, we identified factors associated with postoperative complications and assessed whether complications affected an individual's quality of life and independence. We included 547 Dutch patients aged 70 years and older from the Climb Every Mountain cohort study, who underwent surgery for early-stage breast cancer. Forty-one per cent of patients had a complication within 30 days after surgery, of which seroma, wound infection and haematoma were the most commonly reported complications. Severe adverse events were very rare. Moreover, a combination of age, type of breast surgery, type of axillary surgery, BMI, and polypharmacy provided a good risk estimate of postoperative complications in both internal and external validation. We also showed that quality of life and an individual's ability to perform (instrumental) activities of daily living was not affected by surgery or the occurrence of postoperative complications. These findings can be used to assist clinicians in preoperative counselling of older patients with breast cancer about what to expect postoperatively, and mainly imply that withholding surgery based on complication risk may not be justified.

In **Chapter 3**, we showed that 75% of older patients participating in the Climb Every Mountain study and on adjuvant endocrine therapy had at least one side effect and 36% discontinued therapy within two years after initiation, largely due to toxicity. One of the objectives of this chapter was to develop a tool to predict endocrine therapy-related side effects. We were unable to identify specific geriatric predictive factors for early discontinuation. Interestingly, we found that early discontinuation was inversely associated with tumour stage: patients with more favourable tumour characteristics were more likely to quit therapy.

It was hypothesised, and corroborated by previous literature, that motivation and recommendations from the oncologist play an important role in treatment continuation. The results showed that patients who discontinued therapy had worse scores in two quality of life domains: future perspective and fatigue. These domains did not improve after discontinuation.

This suggests that these lower scores were probably not linked to side effects of endocrine therapy, but rather reflected pre-existing quality of life. The questionnaires on activities of daily living showed no differences between patients who discontinued and those who continued therapy. Thus, although side effects and discontinuation rates were high, it did not seem to affect quality of life and independence.

Chapter 4 addresses the differences in the use of, and outcomes from, adjuvant endocrine therapy between the UK and the Netherlands using data from the Age Gap study and Climb Every Mountain study. Interestingly, of all patients aged 70 years and older who had been diagnosed with hormone receptor-positive, early-stage (TNM stages: T1-3, N0-2, M0) breast cancer, 94% of British patients compared to 56% of Dutch patients received adjuvant endocrine therapy. Moreover, side effects from adjuvant endocrine therapy were common in both studies, but the proportion of patients who discontinued therapy early was larger in the Netherlands. Although absolute differences were small, a survival benefit was found in favour of the British patients, especially in women with medium- and high-risk breast cancer. These findings may imply potential survival gains in the Netherlands from increased use of endocrine therapy. However, longer follow-up is needed.

Chapter 5 showed that between 2005 and 2021 patients from all age groups with HER2-positive metastatic breast cancer were increasingly treated with first-line chemotherapy and targeted therapy, while the use of first-line endocrine therapy decreased over time. With these changes in treatment allocation, the survival improved in all age groups. Nevertheless, the improvement in relative survival and overall survival was lowest in the oldest age groups. As survival in patients with metastatic breast cancer is likely to be dominated by breast cancer rather than competing risks, this lagging survival gain may reflect the lower use of chemotherapy and targeted therapies in the oldest age groups. However, the increased risk of cardiac failure complicating trastuzumab therapy in patients with pre-existing cardiac disease, explains why older patients are less likely to receive targeted therapy. Yet, the lower use of targeted therapies cannot be entirely attributed to pre-existing cardiac disease or frailty, as the number of patients not treated with this therapy is higher than the prevalence of these conditions in the general older population. Moreover, the proportion of patients with undetermined or unknown HER2-status increased with advancing age. Refraining from HER2 expression determination seems only justified if patients are unfit for anti-HER2 therapy or have other preferences. Further research is needed to evaluate the effect of HER2-directed treatment in patients from specific subgroup, such as patients without specific contraindications but with comorbidity or frailty, and the impact of therapy on quality of life.

PART II: PATIENT REPORTED OUTCOME MEASURES IN OLDER PATIENTS

Patient reported outcome measures are paramount in assessing the effect of breast cancer care on health and well-being, especially in the older population. In **Chapter 6**, we assessed changes in physical activity and the ability to carry out (instrumental) activities of daily living in the first five years after diagnosis and associated breast cancer and patient characteristics. Over a five-year follow-up period, levels of physical activity and physical functioning deteriorated only slightly. None of these changes were associated with breast cancer or its treatment, but rather with age, comorbidities, BMI, degree of dependence at baseline, and psychological status. The information that decreased physical activity and physical functioning were primarily observed in women with frailty characteristics at baseline make an important contribution to the decision-making process, especially since many older patients value quality of life more than longevity, and physical functioning and physical health are seen as key components of it [3, 4].

Mental health is another important factor determining an individual's quality of life [3]. The need for enhanced psychological awareness in breast cancer care is highlighted in **Chapter 7**, which showed that feelings of depression, loneliness and apathy were common shortly after surgery, especially in frail older patients. Although these rates were high, only apathy was observed more frequently among older patients with breast cancer than in the general older population. A concerning aspect of apathy is that it is often missed by clinicians because patients themselves usually do not perceive it as a problem. This can lead to poor treatment adherence, neglect and caregiver distress and therefore requires further attention. Another finding of this chapter was that patients who received adjuvant systemic therapy (i.e., endocrine therapy and/or chemotherapy) had similar mental health outcomes as those who did not.

In **Chapter 8**, we compared the quality of life of older patients with early-stage breast cancer between two cohort studies, one from the Netherlands and the other from the United Kingdom (UK). In our analyses, patients in the UK appeared slightly older, less fit and they generally received more chemotherapy and endocrine therapy than patients in the Netherlands. Interestingly, patients in the Netherlands had significantly better quality of life outcomes than patients in the UK. Even though the UK previously found, mostly temporary, effects of surgery, radiotherapy and chemotherapy on quality of life in their cohort, the currently observed differences between both countries probably reflect social and cultural differences rather than the effect of different treatment allocation.

As older patients are a heterogeneous group and may consider other outcomes more important than survival, the key message of this thesis is to strive to attain individualized care for every older patient with breast cancer. Individualized care requires careful evaluation of a patient's specific needs and preferences when developing a treatment plan, as opposed to routine care that is applied to all patients with the same disease. Especially in the heterogeneous older population, scientific evidence is often lacking and treatment decisions must be accomplished with shared decision-making, where clinicians and patients discuss all options and select the most optimal treatment pathway for the individual [5].

The studies described in this thesis contribute to filling the knowledge gap and help improve preoperative counselling and shared decision-making for older women with breast cancer. Although individualized care is considered very important, incorporating it into today's health care system can be difficult, especially because of the challenges health care systems already face today.

Clinical implications and its challenges for today's health care system

Health care costs

Health care systems in most Western countries are facing challenges due to ever-increasing health care costs [6-8]. These rising costs are mainly driven by rapidly advancing technologies and economic growth, but a third also by demographic changes with ageing of populations [9]. By 2040, people over 65 years of age will account for 59% of all health care spendings, while this was 44% in 2015 [9]. Moreover, the costs of treating cancer are anticipated to grow faster than for any other disease with a larger amount spent on health care for women than for men [9]. This means that difficult choices must be made for this large and growing population.

Shortage in time and personnel

A second challenge to implement individualized care into practice may come from the shortage in personnel with the prospect that by 2040, 1 in 4 employees in the Netherlands must work in health care, just to cover the current health care system [10]. Clinicians are already under great time pressure to run clinical visits efficiently, with often no more than 15-25 minutes per patient to initiate therapy in addition to numerous other patient-related duties, making their time precious and scarce [11]. Clinicians may therefore refrain from shared decision-making due to prevailing concerns of increased time consumption [12, 13].

Doubts about the value and practicality of shared decision-making and the concern that the most optimal treatment may not be chosen may also be a reason for this [12, 13]. Several studies have shown that shared decision-making is indeed likely to increase the duration of the consultation by several minutes, but may be improved with experience [14].

However, Chapter 3 of this thesis highlighted the impact of motivation and oncologist's recommendations on treatment adherence. So, investing time to allocate treatment with the right balance of risks and benefits will result in better treatment adherence, less overtreatment and therefore avoid unnecessary side effects, maintain quality of life and spare consultation and treatment time in the long run [15]. This ultimately results in more time and lower costs. Restructuring visits is therefore essential and can be a solution to save time and lower the administrative burden can be achieved through digital applications, such as decision aids that give patients reliable information on treatment options or the option for a patient to do some homework and fill in useful information on their overall health status [16-18]. Prediction models can also assist in clinical decision-making, but before these are developed on a large scale, clinical needs should be investigated as the current adoption of newly designed prediction tools is limited [19].

Deviation from guidelines

Another question that needs to be answered is if we dare to tailor treatment and thereby deviate from existing guidelines. In principle, guidelines are tools intended to guide evidence-based medicine and reduce variation between practices. The disadvantage of clinical guidelines is, however, that they usually make treatment recommendations based on single conditions, with limited guidance for specific subgroups with multimorbidity and/or functional impairments. It is therefore often suboptimal to fully adhere to these guidelines in the older population, resulting in the omission of recommended therapy in many older patients. On the other hand, clinicians are under pressure to follow guideline recommendations, because adherence to guidelines is often a key indicator in performance measurements. Diagnosis Treatment Combinations (in Dutch: Diagnose Behandel Combinaties (DBC)) that reimburse one price for the entire care pathway are also based on these recommendations.

Guidelines are also sometimes misused to hold clinicians accountable for deviant actions. In fact, a study conducted in the Netherlands in 2016 showed that 70% of clinicians sometimes act differently, generally more diagnostics and treatments, than they consider necessary, because of pressure from patients, family and 'third parties' or fear of claims [20]. This defensive medicine is a very costly and time-consuming problem [21].

Shockingly, a study conducted in the US found that clinicians with low average health care spending were more likely to have malpractice claims than those with high average expenditures [22]. Here shared decision-making offers a solution as well because choices made during shared decision-making have the consent of patients and are therefore likely to result in fewer claims. Moreover, a great initiative comes from the Choosing Wisely campaign in the United States that encourages conversations between clinicians and patients about avoiding unnecessary medical tests, treatments and procedures [23]. With ageing of populations, such initiatives for older patients are urgently needed, but may be constrained by the available evidence for this age group.

The position of PROMs in daily clinical practice

As seen in Chapter 2 and 3, quality of life was not affected by postoperative complications or side effects from adjuvant endocrine therapy. Similarly, the decline in physical activity and the ability to perform activities of daily living in the first 5 years after breast cancer diagnosis as shown in Chapter 6 was probably not more than expected compared to patients without breast cancer. Chapter 8 even showed that quality of life outcomes from Dutch older women significantly differed from British older women, even after adjustments for treatment strategies and tumour characteristics. These results imply that British older patients do not suffer more from their disease than Dutch patients, but rather that quality of life is largely affected by factors other than breast cancer and its treatment, such as cultural aspects or personality traits [24]. The results of this thesis can therefore be used to counsel patients that quality of life, activities of daily living, physical activity, or mental health outcomes, are, in general, not affected by the type of therapy that is given. However, since quality of life is determined by multiple factors, it remains difficult to extrapolate the experiences of others to accurately predict a person's quality of life before the start of therapy.

In the future, it is important to consider the purpose of PROMs before collecting them. Where such information can be useful for de-escalation research, the initiation of new therapies and providing general information to patients in shared decision-making, they may be too impractical, and even useless, to collect during or before every hospital visit for every individual. Moreover, not all questionnaires are perceived as equally relevant to an individual either [25]. An alternative for PROMs in the outpatient clinic should therefore be to simply ask how happy someone is and why. This gives an overall evaluation, and distinction, of all aspects of health (i.e., physical, emotional, social, spiritual, and intellectual) and possible opportunities for improvement [26]. Perhaps this provides information that cannot always be treated, but at least serves as a conversation starter. This is important especially since previous research has shown that the health state preferences of patients and clinicians are not always aligned [27].

Identification of frailty

While most chapters in this thesis showed little to no impact of breast cancer and its treatment on quality of life outcomes or levels of independence in older patients with breast cancer, this was not true for frail patients in Chapter 2, 6 and 7. Chapter 2 showed a higher occurrence of postoperative complications with increasing age and polypharmacy. Chapter 6 showed that deterioration of physical activity and independence was associated with geriatric characteristics, loneliness and depressive symptoms rather than with breast cancer treatment. Chapter 7 showed higher levels of depression, loneliness and apathy in frail patients and a higher chance to develop depression and apathy in these patients during the first 5 years after diagnosis.

Frailty is often defined as a state of decreased physiologic reserve caused by the accumulation of ageing processes across multiple organ systems, which affects the patient's resistance to stressors such as cancer or cancer therapy [28]. As this definition may be difficult to use in daily clinical practice, frailty is often defined as a deficit in two or more of the following domains: physical function, somatic function (i.e., comorbidity and/or polypharmacy), emotional function, nutrition, mobility, cognition, and social support [29]. A recent systematic review, including multiple definitions of frailty, showed that 45% of patients aged 70 years and older with breast cancer were classified as frail [30]. However, this prevalence may be biased as it varied greatly between different studies and it is known that older patients included in studies are not representative of the general breast cancer population [31]. Nevertheless, as frailty is associated with an increased risk of side effects and reduced benefit from treatment, and clinicians seem to misjudge and overestimate the health status of patients, detection of frailty is essential before the start of therapy [32-36]. Ideally, the identification of frail patients is done through a comprehensive geriatric assessment, which is a multidisciplinary evaluation that provides information on the domains mentioned above. With ageing of populations, limited financial resources and insufficient numbers of clinicians, it is not feasible and unnecessary to perform a comprehensive geriatric assessment in every older patient presenting with breast cancer. Therefore, SIOG and EUSOMA recommend using a geriatric screening tool, such as the G8, for all patients aged 70 years and older to distinguish fit from potentially frail patients [37, 38]. If the score is below the threshold, a comprehensive geriatric assessment can further determine whether a person needs special care. The need for special care is emphasised in the GAP70+ and GAIN trials, which showed that interventions specifically aimed at improving domains of the geriatric assessment resulted in fewer serious side effects in older patients with all types of cancer [39, 40]. Frailty is likely to increase in the coming decades with ageing of populations and to improve their care in the future, the barely time-consuming geriatric screening tools should be used in clinical practice.

Adjuvant systemic treatment

Even after careful geriatric evaluation, there is often no one-way approach to tailor breast cancer treatment for the older population. A discussion of the possible treatment burden (side effects, hospital visits) and the benefits of therapy is crucial prior to the use of adjuvant therapy.

Endocrine therapy

Endocrine therapy is mainly prescribed to reduce tumour progression and distant recurrences in patients with hormone receptor-positive disease. Therefore, most guidelines advocate adjuvant endocrine therapy for at least five years in all patients with hormone receptor-positive breast cancer [41]. However, the risk of recurrences is not the same for every patient and the benefit of endocrine therapy therefore differs strongly between patients. This has mainly to do with the "other-cause mortality" or "competing risk mortality", which indicates the risk of dying of other diseases than breast cancer. This other-cause mortality generally increases with age [42]. So where starting a statin for an old person with a life expectancy of less than 5 years is increasingly considered ineffective, so should the intended benefit of breast cancer therapy be evaluated before prescribing it for many years. Especially since we showed in the current thesis that more than a third of patients discontinued endocrine therapy within 2 years after initiation due to toxicity.

Thus, both de-escalation for patients with a combination of low-risk breast cancer and a high risk of other-cause mortality and escalation for patients with high-risk disease and a low risk of other-cause mortality is needed. Although obvious in theory, this selection may be difficult in practice: for example, Chapter 4 showed that withholding adjuvant endocrine therapy in almost three quarters of patients with a low risk of recurrences and in a quarter of patients with a medium or high risk of recurrences resulted in worse survival rates compared to the UK where almost all women were treated with adjuvant endocrine therapy.

Decision support tools can assist in these decisions, such as the Predict-Breast or PORTRET tool (Prediction of Outcome, Risk of Toxicity and quality of life in older patients TREaTed for breast cancer tool). The PORTRET tool is a prediction tool for adjuvant systemic therapy decision-making in patients aged 70 years and older with stage I-III breast cancer that, in addition to tumour-specific variables of the Predict-breast tool, incorporates patient-specific variables, such as comorbidity, polypharmacy, walking difficulties, and cognitive- and sensory impairments. The PORTRET tool therefore can make a more accurate prediction of breast cancer-specific mortality and other-cause mortality than the currently widely used Predict-breast tool.

Besides clinical risk, response to therapy is also important to consider: if a patient has high-risk disease but is resistant to therapy, treatment will likely fail. Gene expression profiles are promoted to predict the chance of response to therapy. Unfortunately, gene expression signatures have currently not been validated in the older population [43]. Also, if patients have high responsive tumours, but low-risk tumours, less therapy may be considered. This is what is currently being investigated in the LESS study in France [44]. Unfortunately, only very healthy patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 are included in this study. Further research into biomarkers and resistance in a representative group of older patients is needed.

Chemotherapy and targeted therapy

In Chapter 5, we investigated a specific subtype of metastatic breast cancer, namely those with HER2 overexpression. We found that clinicians were also cautious with administering chemotherapy and targeted therapy to older patients in the metastatic setting, which probably resulted in the lagging survival gain compared to younger patients. Strikingly, 12.2% and 37.2% of patients aged 75 years and older with hormone receptor-positive and hormone receptor-negative disease, respectively, did not receive any form of first-line systemic treatment and very few patients received targeted therapy as monotherapy. A promising RCT conducted in patients with HER2-positive metastatic breast cancer at several sites in France, Switzerland and the Netherlands found a similar overall survival at 2 years follow-up in patients with and without additional chemotherapy to a combination of pertuzumab and trastuzumab and therefore provides a solution for those who are unfit for chemotherapy [45].

With ageing of the population and to avoid that their treatment decisions are based on results in young or fit older patients, it is important to include a more representative group of older patients in the pivotal trials. Trial designs should therefore be modified to better align with the needs and interests of the older population [46]. For example, trials with broader eligibility criteria, more relevant endpoints, and with prior evaluation and elimination of local barriers to their inclusion [47]. On the other hand, as treatment of metastatic breast cancer is currently only given in the palliative setting to extend an individual's life, we must remain critical of the use of very expensive, high-toxicity therapy to extend life by no more than a few months in a poor condition. Especially with the knowledge that only a third of newly approved cancer drugs by the European Medicines Agency (EMA) had evidence of significant prolongation of survival at the time of approval, which remained uncertain for half of the indications during a median follow-up of 5.4 years [48]. Moreover, only 10% of these drugs improved quality of life at the time they came on the market. Initiatives such as the committee BOM (Commissie ter Beoordeling van Oncologische Middelen), which evaluate the effectiveness of drugs ten years after they have come on the market, are crucial.

Conclusion

This thesis showed that for non-frail older patients, little impact on quality of life, physical activity, mental health and independence can be expected from breast cancer and its treatment. Extensive evaluation of quality of life with questionnaires such as the EORTC QLQ-C30 and QLQ-BR23 can therefore be omitted in older patients with breast cancer. However, for frail older patients, regular care is often insufficient and close collaborations with other disciplines is needed to provide them with appropriate care. A reasonable way to start this would be the use of a geriatric screening tool, such as the G8, for all patients aged 70 years and older.

Future studies should focus on improved selection by tailoring treatment to the patient to de-escalate therapy where possible and escalate if necessary. Importantly, strong evidence is needed before de-implementation actually takes place, as it was also shown in this thesis that de-escalation may come at the expense of potential survival gains [23]. Once again, inclusion and subanalyses for older patients are therefore urgently needed. Yet it remains an arduous task to receive funding for de-escalation studies, possibly because major grant providers such as pharmaceutical companies do not benefit from these studies [49]. However, it is not always necessary to perform a trial, as much reliable information can be derived from alternative study designs, such as observational cohort studies and national registries, such as the CLIMB study and national cancer registries.

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Chapter 10

Dutch summary

NEDERLANDSE SAMENVATTING

Iedere vrouw heeft een kans van 1 op 7 om gedurende haar leven borstkanker te ontwikkelen, waarmee borstkanker de meest voorkomende vorm van kanker is onder vrouwen. De kans op het krijgen van borstkanker neemt toe met de leeftijd, waarbij ongeveer 30% van de vrouwen met borstkanker 70 jaar of ouder is op het moment dat de diagnose wordt gesteld. Door de vergrijzing wordt verwacht dat dit percentage van ouderen met borstkanker nog verder zal toenemen in de komende decennia.

Het is voor artsen niet gemakkelijk om de behandeling van borstkanker goed af te stemmen op de oudere patiënt, omdat er tussen oudere patiënten onderling grote gezondheidsverschillen bestaan, zoals verschillen in bijkomende ziekten en fitheid. De aanwezigheid van andere ziekten of beperkingen maakt namelijk dat het risico om te overlijden aan oorzaken anders dan borstkanker toeneemt. Zo blijkt uit een eerdere studie dat 50% van de vrouwen ouder dan 75 jaar met borstkanker overlijdt aan andere oorzaken dan borstkanker zelf, waardoor de meest agressieve borstkankerbehandeling voor hen vaak niet zinvol is. Bovendien hebben oudere patiënten een verhoogd risico op ernstige bijwerkingen door de behandeling en mogelijk achteruitgang in lichamelijk functioneren en kwaliteit van leven. Daarnaast hebben ouderen soms ook andere prioriteiten dan jongere patiënten, zoals behoud van onafhankelijkheid en kwaliteit van leven in plaats van levensverlenging tegen elke prijs. Helaas is er nog weinig onderzoek gedaan naar dergelijke uitkomsten bij oudere vrouwen met borstkanker.

Het hoofddoel van dit proefschrift is daarom om meer inzicht te krijgen in relevante uitkomsten van de behandeling van borstkanker bij oudere patiënten. De specifieke doelen van dit proefschrift zijn drieledig. Allereerst zal worden bestudeerd welke patiëntkarakteristieken geassocieerd zijn met het krijgen van postoperatieve complicaties en bijwerkingen van therapie. Ten tweede zullen langetermijneffecten van borstkankerbehandelingen op de kwaliteit van leven en lichamelijk en psychologisch functioneren in kaart worden gebracht. Tot slot zullen, op basis van een landelijke dataset van vrouwen met uitgezaaide HER2-positieve borstkanker, behandelpatronen en overleving in de loop van de tijd worden onderzocht onder verschillende leeftijdsgroepen.

DEEL I: EVALUATIE VAN DE UITKOMSTEN VAN DE BEHANDELING VAN BORSTKANKER BIJ OUDERE VROUWEN

Behandelstrategieën variëren in de loop van de tijd, zowel door nieuwe inzichten als door de ontwikkeling van nieuwe therapieën. Uit eerder onderzoek bleek dat het aantal patiënten van 75 jaar en ouder met vroeg-stadium (I-II) borstkanker dat een operatie onderging daalde in de afgelopen twee decennia, terwijl het aantal patiënten dat primair werd behandeld met hormoontherapie steeg. In vrouwen met stadium III borstkanker daalde ook het aantal operaties, terwijl de behandeling met hormoontherapie gelijk bleef. Waarom er minder geopereerd wordt is onduidelijk, maar zou kunnen komen door angst voor complicaties of de vernomen impact ervan op de kwaliteit van leven.

In **hoofdstuk 2** is een risicoprofiel opgesteld van factoren die geassocieerd zijn met postoperatieve complicaties. De combinatie van leeftijd, het type borstkanker operatie, de BMI en het gebruik van meer of minder dan 5 medicijnen voorafgaand aan de borstkankerbehandeling geeft een goede schatting van het risico op het ontwikkelen van een postoperatieve complicatie. Bovendien lieten de resultaten zien dat de kwaliteit van leven en de zelfredzaamheid niet werden beïnvloed door het ondergaan van een operatie of het optreden van postoperatieve complicaties. Deze bevindingen kunnen worden gebruikt om clinici te helpen bij de counseling van oudere patiënten met borstkanker over wat zij postoperatief kunnen verwachten. Daarnaast impliceren de resultaten dat het afzien van een operatie op basis van complicatierisico's waarschijnlijk niet gerechtvaardigd is in een groot deel van de patiënten.

Hoofdstuk 3 toont dat 75% van de oudere vrouwen behandeld met adjuvante hormoontherapie ten minste één bijwerking ervaarde en dat 36% van de vrouwen de therapie binnen twee jaar staakte, grotendeels vanwege toxiciteit. Helaas bleek het niet mogelijk om te voorspellen welke patiënten vroegtijdig de behandeling stoppen. Opvallend was wel dat het vroegtijdig staken van de behandeling omgekeerd geassocieerd was met het tumorstadium: vrouwen met een laag stadium waren eerder geneigd om de behandeling te staken dan vrouwen met een hoog stadium. De hypothese was, ondersteund door de huidige literatuur, dat motivatie en aanbevelingen van de oncoloog een belangrijke rol spelen bij het voortzetten van de behandeling. De resultaten toonden ook dat patiënten die vroegtijdig de behandeling stopten slechter scoorden op twee domeinen van de kwaliteit van leven vragenlijst: toekomstperspectief en vermoeidheid. Deze domeinen verbeterden echter niet na het staken van de behandeling, wat suggereert dat deze lagere scores waarschijnlijk geen verband hielden met bijwerkingen van hormoontherapie, maar eerder pre-existente kwaliteit van leven weerspiegelt.

Hoofdstuk 4 behandelt de verschillen in het gebruik en uitkomsten van adjuvante hormoontherapie tussen oudere vrouwen met borstkanker in het Verenigd Koninkrijk (VK) en Nederland. In het VK wordt van alle vrouwen met hormoongevoelige vroeg-stadium borstkanker (T1-3, N0-2, M0) 96% behandeld met adjuvante hormoontherapie in vergelijking met 56% in Nederland. In beide landen werden veel bijwerkingen gerapporteerd, waarbij in Nederland de therapie vaker vroegtijdig werd gestaakt. Hoewel de absolute verschillen klein waren, hadden Britse vrouwen met borstkanker een betere overleving dan in Nederland. Er is eerst langere follow-up van de data nodig voordat kan worden geconcludeerd dat er in Nederland meer hormoontherapie moet worden gebruikt in de behandeling van borstkanker bij oudere vrouwen.

Een van de meest invloedrijke ontwikkelingen in overlevingswinst bij vrouwen met borstkanker in de afgelopen decennia betreft de introductie van doelgerichte therapieën voor onder andere HER2-positieve tumoren. **Hoofdstuk 5** toont aan dat tussen 2005 en 2021 patiënten met HER2-positieve uitgezaaide borstkanker uit alle leeftijdsgroepen steeds vaker worden behandeld met eerstelijns chemotherapie en doelgerichte therapie, terwijl het gebruik van eerstelijns hormoontherapie in de loop van de tijd afnam. Ondanks dat de stijging in relatieve overleving in de oudste leeftijdsgroep (75+) het minst verbeterde, nam de overleving in alle leeftijdsgroepen toe. Deze achterblijvende overlevingswinst in de oudste leeftijdsgroep zou een weerspiegeling kunnen zijn van het relatief lagere gebruik van chemotherapie en doelgerichte therapieën in deze groep.

DEEL II: INGEVULDE VRAGENLIJSTEN DOOR OUDERE VROUWEN MET BORSTKANKER

Door patiënten gerapporteerde uitkomstmaten zijn uiterst belangrijk bij de evaluatie van het effect van borstkankerzorg op de gezondheid en het welzijn, vooral bij ouderen.

In **hoofdstuk 6** worden veranderingen in lichamelijke activiteit en de zelfredzaamheid in het dagelijks leven vijf jaar na de borstkankerdiagnose geëvalueerd, waaruit blijkt dat beide licht dalen over de tijd. Geen van deze veranderingen werd in verband gebracht met borstkanker of de behandeling ervan, maar eerder met leeftijd, bijkomende aandoeningen, BMI, mate van zelfredzaamheid ten tijde van de diagnose en psychologische status.

De behoefte aan psychologisch bewustzijn in de borstkankerzorg wordt behandeld in **hoofdstuk 7**, waaruit blijkt dat gevoelens van depressie, eenzaamheid en apathie veel voorkomen kort na de operatie, vooral bij kwetsbare oudere patiënten. Hoewel deze percentages hoog waren, werd alleen apathie vaker waargenomen bij oudere patiënten met borstkanker dan bij de algemene oudere bevolking.

Een andere bevinding was dat patiënten die adjuvante systemische therapie ondergingen (d.w.z. hormoontherapie en/of chemotherapie) vergelijkbare uitkomsten hadden in de psychische uitkomstmaten als patiënten die deze behandeling niet ondergingen.

In **hoofdstuk 8** werd de kwaliteit van leven van oudere patiënten met vroeg-stadium borstkanker vergeleken tussen het VK en Nederland. Uit de analyses bleek dat patiënten in het VK ouder en minder fit zijn en over het algemeen meer chemo- en hormoontherapie ondergingen dan in Nederland. Opvallend genoeg hadden patiënten in Nederland een significant betere kwaliteit van leven dan patiënten in het VK. Ondanks enkele behandelverschillen tussen beide landen, wordt gedacht dat de verschillen niet zozeer de borstkankerzorg in beide landen weerspiegelt, maar eerder sociale en culturele verschillen.

Concluderend toonde dit proefschrift aan dat voor fitte ouderen weinig invloed op kwaliteit van leven, fysieke activiteit, mentale gezondheid en zelfredzaamheid kan worden verwacht van borstkanker en de behandeling ervan. Uitgebreide vragenlijsten naar bovenstaande aspecten kunnen zodoende in de dagelijkse praktijk achterwege worden gelaten. Kwetsbare ouderen ervaren wel vaak negatieve impact op dergelijke uitkomstmaten, waardoor voor deze groep extra aandacht en een nauwe samenwerking met meerdere disciplines noodzakelijk is.

Toekomstige studies zullen zich moeten richten op het nog beter afstemmen van de behandeling op de patiënt om de behandeling waar mogelijk te de-escaleren en indien nodig te escaleren. Voordat de-implementatie van diagnostiek en behandelingen daadwerkelijk plaatsvindt is het belangrijk om dit goed te onderbouwen met bewijs, omdat ook in dit proefschrift werd aangetoond dat de-escalatie ten koste kan gaan van potentiële overlevingswinst. Helaas is het nog steeds moeilijk om financiering voor dergelijke gerandomiseerde studies te verkrijgen, waarbij men in de toekomst zal moeten zoeken naar alternatieve onderzoeksmethoden om alsnog betrouwbare informatie te kunnen verwerven. Hierbij is het van uiterst belang dat ouderen worden geïncludeerd in deze studies.

Appendices

List of publications

Curriculum vitae

Acknowledgement

LIST OF PUBLICATIONS

Lemij AA, de Glas NA, Bradburn M, Derks MGM, van den Bos F, Martin C, Kroep JR, Reed MWR, Liefers GJ, Morgan JL, Portielje JEA, Wyld L. Adjuvant endocrine therapy in older women with breast cancer: a comparison of practice and outcomes between the United Kingdom and the Netherlands. Submitted

Lemij AA, Morgan JL, de Glas NA, Derks MGM, van den Bos F, Martin C, Bradburn M, Reed MWR, Liefers GJ, Portielje JEA, Wyld L. Differences in quality of life of older patients with early-stage breast cancer between the United Kingdom and the Netherlands: two-year follow-up from two national prospective longitudinal multi-centre cohort studies. Submitted

Lemij AA, de Glas NA, Kroep JR, Siesling S, van den Bos F, Bastiaannet L, Liefers GJ, Portielje JEA. A comparison of treatment allocation and survival between younger and older patients with HER2-overexpressing de novo metastatic breast cancer. Journal of Geriatric Oncology 2024

Waaijer MEC, **Lemij AA**, de Boer AZ, Bastiaannet E, van den Bos F, Derks MGM, Kroep JR, Liefers GJ, Portielje JEA, de Glas NA. The impact of geriatric characteristics and comorbidities on distant metastases and other cause mortality in older women with non-metastatic breast cancer treated with primary endocrine therapy. Breast Cancer Research and Treatment 2023

Baltussen JC, Derks MGM, **Lemij AA**, de Glas NA, Fiocco M, Linthorst-Niers EMH, Vulink AJE, van Gerven L, Guicherit OR, van Dalen T, Merkus JWS, Lans TE, van der Pol CC, Mooijaart SP, Portielje JEA, Liefers GJ. Association between endocrine therapy and cognitive decline in older women with early breast cancer: Findings from the prospective CLIMB study. European Journal of Cancer 2023

Lemij AA, de Glas NA, Derks MGM, Linthorst-Niers EMH, Guicherit OR, van der Pol CC, Lans TE, van Dalen T, Vulink AJE, Merkus JWS, van Gerven L, van den Bos F, Rius Ottenheim N, Liefers GJ, Portielje JEA. Mental health in older breast cancer survivors: five-year follow-up from the CLIMB study. European Journal of Cancer 2022

Lemij AA, Liefers GJ, Derks MGM, Bastiaannet E, Fiocco M, Lans TE, van der Pol CC, Vulink AJE, van Gerven L, Guicherit OR, Linthorst-Niers EMH, Merkus JWS, van Dalen T, Portielje JEA, de Glas NA. Physical function and physical activity in older breast cancer survivors: five-year follow-up from the Climb Every Mountain study. The Oncologist 2022

Lemij AA, Baltussen JC, de Glas NA, Kroep JR, Derks MGM, Liefers GJ, Portielje JEA. Gene expression signatures in older patients with breast cancer: A systematic review. Critical Reviews in Oncology/Hematology 2022

Lemij AA, de Glas NA, Derks MGM, Bastiaannet E, Merkus JWS, Lans TE, van der Pol CC, van Dalen T, Vulink AJE, van Gerven L, Guicherit OR, Linthorst-Niers EMH, van den Bos F, Kroep JR, Liefers GJ, Portielje JEA. Discontinuation of adjuvant endocrine therapy and impact on quality of life and functional status in older patients with breast cancer. Breast Cancer Research and Treatment 2022

Lemij AA, van der Plas-Krijgsman WG, Bastiaannet E, Merkus JWS, van Dalen T, Vulink AJE, van Gerven L, Guicherit OR, Linthorst-Niers EMH, Lans TE, van der Pol CC, Wyld L, Morgan JL, Portielje JEA, de Glas NA, Liefers GJ. Predicting postoperative complications and their impact on quality of life and functional status in older patients with breast cancer. British Journal of Surgery 2022

Lemij AA, Bastiaannet E, de Glas NA, van den Bos F, Portielje JEA, Liefers GJ, Derks MGM. Breast cancer in the older population: a global challenge – an epidemiological perspective. Annals of Breast Surgery 2021

Lemij AA, van Veen LN, de Groot H. Voor de dagelijkse praktijk van de kinderarts – zijn huidtesten nog nodig bij een verdenking “penicillineallergie”? Nederlands Tijdschrift voor Allergie, Astma en Klinische Immunologie 2018

CURRICULUM VITAE

Annelieke Lemij was born on 4 April 1994 in Rotterdam. After graduating from secondary school (Rotterdams Montessori Lyceum), she went to study Medicine at Leiden University Medical Centre (LUMC). After obtaining her bachelor's degree, she went to Cambridge to improve her English and did a minor in Biomedical Engineering at the University of Delft. From 2016-2019, she did her rotations, doing one of her last internships in surgery at Groene Hart Hospital and a shorter internship anesthesiology in Houston in the United States. In 2020, she worked for almost a year as resident not in training at Groene Hart Hospital, before returning to LUMC as a PhD candidate in January 2021. In 2022, Annelieke went to the United Kingdom to do part of her research at the University of Sheffield under supervision of prof. dr. Wyld and dr. Morgan. During her PhD, she was a board member of the LUMC Association for PhD candidates (chair and promotion). After finishing her PhD, Annelieke continued her career as resident not in training at LUMC.

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