UNIVERSITY UTRECHT / UMC UTRECHT

Patient-Reported Outcomes after Breast Cancer: Longitudinal Analysis of Real-World Data

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26-08-2022

Master's Thesis	Epidemiology
Research Project	65 EC
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Lekensamenvatting onderzoeksproject
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Aantal woorden (499/500)

Patiënt-gerapporteerde uitkomsten in de jaren na borstkanker

Achtergrond: Doordat er de afgelopen decennia veel verbeteringen hebben plaatsgevonden op het gebied van borstkanker screening en behandeling is de incidentie van borstkanker toegenomen en is de overleving verbeterd. Vrouwen die behandeld zijn voor borstkanker kunnen nog jaren na de behandeling nadelige effecten ervaren wat invloed heeft op de kwaliteit van leven. Daarom is onderzoek naar de lange termijn behandelingseffecten van borstkanker erg belangrijk. Dit onderzoek heeft gekeken naar patiënt-gerapporteerde uitkomsten van kwaliteit van leven in de eerste vijf jaar na borstkanker behandeling. Hierbij zijn ook uitkomsten van borstkanker patiënten vergeleken met uitkomsten van gezonde Nederlandse vrouwen en er zijn factoren geïdentificeerd die geassocieerd zijn met klinisch relevante verslechtering in kwaliteit van leven domeinen.

Methode: Borstkanker patiënten die behandeld worden in het UMC Utrecht, Alexander Monro Ziekenhuis, Antonius Ziekenhuis, Ziekenhuisgroep Twente en Alrijne zijn gevraagd om deel te nemen aan de UMBRELLA cohortstudie. Daarvan zijn vrouwen geselecteerd die ten minste één vragenlijst over vijf jaar tijd hebben ingevuld. Zowel tijdens als na de behandeling zijn verschillende kwaliteit van leven domeinen, depressie en angst gemeten aan de hand van vragenlijsten. Aan de hand van drempelwaardes is bepaald of er klinisch relevante verslechtering in een kwaliteit van leven domein is. Klinische gegevens van patiënten zijn verzameld via het Nederlandse Kankerregister en patiënt-gerapporteerde uitkomsten van gezonde Nederlandse vrouwen zijn verkregen via PROFIEL. Eerst zijn gemiddelde scores van borstkanker patiënten over vijf jaar tijd vergelijken met gezonde vrouwen. Daarna zijn de verhoudingen van vrouwen die klinisch relevante verslechteringen in kwaliteit van leven rapporteren met elkaar vergeleken. Logistische regressie analyse is uitgevoerd om te onderzoeken welke factoren geassocieerd zijn met klinisch relevante verslechteringen in kwaliteit van leven na vijf jaar tijd.

Resultaten: In totaal zaten er 3966 borstkankerpatiënten in het UMBRELLA cohort waarvan er 3197 vrouwen zijn geselecteerd. De meeste patiënten (86%) hebben aan het begin van de studie een chirurgische behandeling gehad, maar ze krijgen meestal nog radiotherapie. In de meeste kwaliteit van leven (zoals emotioneel of sociaal functioneren, vermoeidheid, of depressie) nam de kwaliteit van leven af in de eerste zes maanden na studie-inclusie. Daarna nam de kwaliteit van leven in de meeste domeinen ook weer toe en steeg het zelfs naar een vergelijkbaar niveau als voor gezonde vrouwen. Na vijf jaar rapporteerden meer borstkanker patiënten klinisch relevante verslechteringen in fysiek functioneren (29% vs. 23%), cognitief functioneren (30% vs. 13%), kortademigheid (28% vs. 19%) en angst (20% vs. 16) in vergelijking met gezonde vrouwen. Factoren die geassocieerd waren met klinisch relevante verslechteringen in deze vier kwaliteit van leven domeinen waren: laag opleidingsniveau, hoog BMI, slechte scores voor de vier domeinen bij studie-inclusie, uitgebreidere chirurgische behandeling, lokaal regionale radiotherapie, en chemotherapie.

Conclusie: Na vijf jaar heeft de meerderheid van de borstkanker patiënten vergelijkbare kwaliteit van leven als gezonde vrouwen. Borstkanker patiënten ervaren wel meer klinisch relevante problemen in fysiek en cognitief functioneren, kortademigheid en angst in vergelijking met gezonde vrouwen. Deze resultaten zijn belangrijk om vrouwen met borstkanker goed te kunnen informeren over de eventuele impact op de lange termijn kwaliteit van leven.

ABSTRACT

Purpose: To evaluate patient-reported outcomes (PROs) in an unselected, real-life population in the first five years after breast cancer treatment, to compare these outcomes with a normative Dutch female population, and to identify determinants associated with clinically important impairment in quality of life (QoL) domains.

Methods: Patients with breast cancer referred to the UMC Utrecht (department of Radiotherapy), Alexander Monro Hospital, Antonius Hospital, Ziekenhuisgroep Twente, and Alrijne were asked to participate in the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion cohort (UMBRELLA; 2013-2022). Female patients who returned at least one questionnaire at enrolment, at 3, 6 and then every 6 months were selected. QoL domains, depression and anxiety were assessed by EORTC QLQ-C30/-BR23 and HADS during and after treatment. Thresholds for clinical importance were used to identify patients with clinically relevant impairment in PROs. Clinical data and PRO data of the general population (Dutch women without cancer, comparable age-range, n=879) were provided by the Netherlands Cancer Registry and PROFILES, respectively. Mean scores and proportions of participants reporting clinically relevant impairment in QoL were examined over time and compared to the general population. Determinants associated with clinically relevant impairments in QoL domains at five years follow-up were identified with the use of age-adjusted logistic regression.

Results: Of the 3966 patients enrolled in UMBRELLA, 3197 were included. Most patients (86%) were enrolled after surgery and shortly before radiotherapy. A deterioration was observed for most QoL domains (e.g. emotional- and social functioning, fatigue, depression) within the first 6 months from enrolment, after which QoL in most domains increased to a comparable level as the general population. At five years, more patients reported clinically relevant and important problems or symptoms in physical functioning (PF)(29% vs. 23%, p=0.02), cognitive functioning (CF)(30% vs. 13%, p=0.00), dyspnea (DY)(28% vs. 19%, p=0.00), and anxiety (Anx)(20% vs. 16%, p=0.06) compared to the general population. Factors associated with long-term clinically relevant impairment in QoL were lower educational level (OR 0.58, 95% CI 0.38-0.87 for PF; OR 0.55, 95% CI 0.37-0.83 for DY), higher body mass index (OR 1.12, 95% CI 1.07-1.17 for PF; OR 1.06, 95% CI 1.02-1.11 for DY), poorer baseline scores for all four domains (OR 0.95, 95% CI 0.94-0.96 for PF; OR 0.97, 95% CI 0.96-0.98 for CF; OR 1.04, 95% CI 1.03-1.5 for DY; OR 4.59, 95% CI 2.82-7.48 for Anx), more extensive surgical treatment (mastectomy without direct reconstruction OR 2.03, 95% CI 1.0-3.74 for PF; extensive axillary surgery OR 2.67, 95% CI 1,50-4.73 for DY, and OR 2.33, 95% CI 1.28-4.24 for Anx), locoregional radiotherapy for physical functioning (OR 1.61, 95% 1.00-2.59), and chemotherapy for cognitive functioning (OR 1.72, 95% CI 1.14-2.61).

Conclusion: Five years after breast cancer treatment, the majority of women treated for breast cancer have similar quality of life and symptom scores as the general population. However, they experience more physical and cognitive problems, dyspnea and anxiety compared to the general population. These findings provide indications for further research to improve and predict long-term outcomes of women treated for breast cancer. With the aim of informing women with breast cancer.

INTRODUCTION

Breast cancer is the most prevalent cancer among women in the Netherlands (1). Through the improvements in screening methods and treatment options, the prognosis of breast cancer has improved over the last decades (2–5). As a consequence of the increasing breast cancer incidence and improved survival, there is an increasing number of women living with the consequences of breast cancer or its treatment (6–8). Women can still experience adverse treatment effects many years after completion of their therapy (9). The long-term and adverse effects following breast cancer diagnosis and treatment are characterized by physical, cognitive, psychosocial, emotional, and sexual problems, as well as pain, fatigue, insomnia, lymphedema, movement restrictions of the arm and shoulder, neuropathy, cardio toxic effects, vasomotor complaints, anxiety, depression, fear of recurrence, and impaired body image (7,8,10–15). The disease and treatment-related health symptoms can have an impact on all aspects of life and consequently lower the quality of life (QoL)(7,8,16,17). Therefore, research on the long-term treatment effects and QoL in breast cancer patients are becoming increasingly relevant.

Patient Reported Outcome Measures (PROMs) are effective in obtaining long-term outcome data and in identifying all potential short and long-term breast cancer treatment effects and their impact on health-related QoL (7,8,18,19). The European Organization for Research and Treatment of Cancer (EORTC) developed and validated quality of life questionnaires (QLQ-C30 and QLQ-BR23) to assess the short- and long-term treatment related health symptoms of breast cancer (20). Understanding of the long-term effects of breast cancer and its treatment can be used by clinicians and researchers to develop, adapt and compare interventions, with the aim to further improve QoL of women treated for breast cancer (21,22). As PROMs provide data about the impact of different therapies on QoL, it can also be used to inform patients about possible benefits and harms of treatment options. By enabling patients to make better informed decisions that are in line with their values and preferences, the use of PROMs in health care improves shared-decision making (23). Therefore, implementation of PROMs in clinical settings can be used to improve follow-up care and rehabilitation for enhancing long-term survivorship (7,8,19). PROMs are also useful to improve the knowledge about the late treatment effects and the long-term QoL of breast cancer since the effects on QoL up to one year after treatment are commonly known but more knowledge on the long-term QoL of breast cancer patients is needed (7,16,19,24). Most long-term research is performed on prevalent health symptoms as pain, fatigue, insomnia and depression (17,25).

Until now, studies that have been examining QoL among breast cancer patients were considerably problematic. First of all, QoL among breast cancer patients was often evaluated in cross-sectional studies (7,16,26–34). The use of cross-sectional designs limits the interpretation of the results because of the inability to make a causal inference. Secondly, heterogeneity in follow up time makes it difficult to state what exactly is being investigated (7,16,27–29,31,33–36). And also selection bias is an issue in previous QoL research among breast cancer patients. The results of the survey of B-force in 2017 on late treatment effects in breast cancer patients showed that nearly three-quarters (73%) of women treated for breast cancer experience late effects. Fatigue was the most common complaint in 77% of women treated for breast cancer (37). This research of B-force is an open survey in an existing panel instead of a random sample. Leading to results that are based on a highly selected group and not on a representative sample. Besides that, low response rates produce selection bias as a consequence of substantial differences between responders and non-responders (7,27). Additionally only a few studies followed breast cancer patients longitudinally after treatment (25,38–46) or beyond 5 years after diagnosis (36,39,47,48). The review of Wu et al. emphasized the importance of longitudinal studies that investigate symptom burden over time for both the patients as for the caregivers, along with the long-term and late symptom effects (17).

Previous longitudinal studies on QoL have shown that women treated for breast cancer have impairments in multiple QoL dimensions that persist or even increase in the years after diagnosis (39,49). Also in comparison to the general population, impairments in QoL domains as for physical-, social-, cognitive- and emotional functioning remain in women living after breast cancer. And women may still suffer from late adverse treatment effects as pain, fatigue and insomnia. Withal, most long-term effects improve after one year and global QoL of breast cancer patients even seemed comparable to QoL of the general population (39).

Nevertheless, more research on long-term QoL in breast cancer patients is needed because of the limited amount of longitudinal studies after treatment and due to inconclusive results of the available research. This present study longitudinally evaluate patient-reported outcomes (PROs) in an unselected, real-life breast cancer population (i.e. Real World Evidence), compares outcomes to normative values of a cancer-free female population, and examined clinically relevant and important problems or symptoms (50). The information that will be generated with the use of this study can be used in clinical practice to inform patients during shared decision making.

The longitudinal assessment of PROs of an unselected group breast cancer patients in relation to the healthy female population led to the following research question: *What is the evolution of QoL in the first five years after breast cancer treatment and which determinants are associated with clinically important impairments of QoL in women living after breast cancer?* To answer those questions, this study aims to evaluate long-term PROs of breast cancer patients, to compare outcomes with the normative Dutch female population, to evaluate the prevalence of clinically relevant and important impairments in QoL domains up to five years following breast

cancer treatment, and to identify determinants associated with clinically relevant impairment in QoL domains in women living after breast cancer.

METHODS

Study Design and Participants

This study was conducted within the prospective observational 'Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuaAtion' (UMBRELLA)(51). From 2013 on, the UMBRELLA cohort has been enrolling patients with histologically proven invasive breast cancer or ductal carcinoma in situ (DCIS). Since 2013, patients from hospitals in the Utrecht region referred for radiotherapy at the UMC Utrecht were systematically invited to the 'innovation clinic', where they were asked by a researcher or a research assistant to participate in the UMBRELLA study. Since 2017, four hospitals from other parts of the country (Alexander Monro Hospital, Antonius Hospital, Ziekenhuisgroep Twente, and Alrijne) accompanied UMBRELLA and systematically approached breast cancer patients for enrolment. Inclusion criteria were wide: patients above the age of 18 years and with the ability to understand the Dutch language (written and spoken). For this current study, we excluded males and participants who did not fill in any questionnaire. Patients were also excluded when their clinical data was not provided by IKNL (52).

For the UMBRELLA study, breast cancer patients were asked to provide informed consent for 1) use of routine (clinical) data in- and outside the hospital, 2) longitudinal collection of Patient-Reported Outcomes (PROs) through online or paper questionnaires at regular time intervals during and after treatment and 3) broad consent for (randomization into) future intervention studies (51). The UMBRELLA study was approved by the Medical Ethical Committee of the UMC Utrecht, the Netherlands (NL52651.041.15, Medical Ethics Committee 15-165) and is registered on Clinicaltrials.gov (NCT02839863). The study is in compliance with the Dutch law on Medical Research Involving Human Subjects (WMO) and the Declaration of Helsinki (version 2013).

Data Collection

Clinical data were provided by the Netherlands Cancer Registry (NCR) of the Netherlands Comprehensive Cancer Organization (IKNL)(52) and included age at breast cancer diagnosis, tumor characteristics, surgical treatment, most invasive axillary treatment, (neo)-adjuvant radiation therapy and systemic treatment. Body mass index (BMI, calculated with first measured height and weight), highest educational level (dichotomized into "no education, secondary or vocational education" and "higher professional education or university degree") were collected in the context of UMBRELLA. For women with synchronous bilateral breast cancer, the tumor and treatment characteristics of the most advanced tumor were used in the study.

Data on PROs were collected using the PROFILES platform (53) through self-reported questionnaires at baseline (after cohort enrolment, which is after diagnosis and mostly shortly before radiotherapy), at three months, six months and every six months thereafter. Baseline measurements are prior to radiotherapy but after surgery and/or neo-adjuvant treatment.

The European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) assesses the quality of life in cancer patients, incorporating five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health and quality-of-life scale, and six single-item symptom measures (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) (54). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module (EORTC QLQ-BR23) assesses the quality of life of breast cancer patients, and incorporates two functional scales (body image and sexuality), three symptom scales (arm, breast, and systemic side effects) and three single-item measures (sexual enjoyment, future perspective, and upset by hair loss) (55). For both EORTC questionnaires, each subscale consists of one to five items, all evaluated on a 4-point Likert scale. Only Global QoL is measured on a 7-point Likert scale (54). Quality of life data were linearly transformed according to the EORTC manual, into scores ranging from 0 to 100 and handled as continuous outcomes. A higher score represents a better outcome for functional scales (i.e. QoL, physical-, role-, cognitive-, social-, emotional- and sexual functioning, body image, future perspective, and sexual enjoyment), but a worse outcome for symptom scales (i.e. fatigue, pain, nausea and vomiting, upset by hair loss, arm, breast, and systemic side effects) (20).

Thresholds for clinical importance (TCIs) have been identified for the five functioning and nine symptom scales of the EORTC QLQ-C30 (50). Here, patients who score below the TCI for functioning scales, or above the TCI for symptom scales, experience clinically relevant and important problems or symptoms.

The 14-item HADS questionnaire was used to assess symptoms of anxiety and depression (56). The HADS comprises 7 items on depression and 7 items on anxiety. Each item has a 4-point Likert scale where an

item can be scored with 0 to 3 points. Patients with scores of 8 or higher have a probability of having anxiety and depressive disorders (57).

To be able to compare the breast cancer patients to the (healthy) general population for the EORTC QLQ-C30 and HADS questionnaires and the sexual functioning and sexual enjoyment scales of the EORTC QLQ-BR23 questionnaire, data on the general population were provided by PROFILES (53). For the normative population we selected Dutch women, without cancer, and with a comparable age-range- and distribution as the UMBRELLA study population (age categories from 30 till 90 years, with a mean age category of 50-55 years). Data was from 2011 and 2013 with respectively 811 and 888 healthy women selected for further analysis.

Statistical Analysis

Patient-, tumor-, and treatment characteristics (baseline) and PROs were described by using frequencies and percentages for categorical data, means and standard deviations for normally distributed continuous data, and otherwise medians with interquartile ranges were used.

The UMBRELLA study population was examined by comparing patient, treatment, and tumor characteristics of responders to at least one questionnaire with those who did not (i.e. non-responders). To investigate to what extent the UMBRELLA study population was representative for all breast cancer patients we compared the baseline characteristics of UMBRELLA participants to the characteristics of breast cancer patients in the Netherlands Cancer Registry (6,52).

Descriptive statistics were used to descriptively examine outcomes of the different QoL domains over time in breast cancer patients. Mean scores of the breast cancer population from baseline (cohort entry) up until 5-years thereafter were compared to a single mean score of the normative population.

Next, thresholds for clinical importance (TCIs)(50) were used to identify participants who reported clinically relevant and important problems or symptoms. We examined the proportion of participants reporting clinically relevant and important problems or symptoms over time, and compared them to the general population. In comparison to the general population, QoL domains with a minimal clinically important difference of 5% in proportions of clinically relevant impairments at five years were chosen for further analysis. Chi-squared test was used to compare the proportions of UMBRELLA patients reporting clinically relevant and important problems and symptoms at five years with the normative population. However, QoL domains with the most clinically relevant impairments in QoL at five years were rather chosen based on clinical relevance instead of statistical significance.

Univariable logistic regression analysis was performed to identify determinants associated with long-term (at five years) clinically relevant impairments in QoL, based on TCIs (50). This was done for each clinically relevant impaired QoL domain at five years in relation to the normative population, which were the domains physical functioning, cognitive functioning, dyspnea, and anxiety ($\geq 8/<8$). Potential determinants for clinically relevant impaired QoL were: age (continuous), educational level (low/high), BMI (continuous), smoking (non-smoker/previous smoker/ smoker), pathological T stadium (T0/in situ, T1, T2, T3/T4, Tx), pathological N stadium (N0/N+/Nx), type of surgery (lumpectomy/mastectomy with or without breast reconstruction), type of axillary surgery (axillary lymph node dissection/sentinel node procedure), type of radiation therapy (local/locoregional), radiotherapy boost (yes/no), chemotherapy (yes/no), hormonal therapy (yes/no), targeted therapy (yes/no) and patient-reported baseline scores for physical functioning, cognitive functioning, dyspnea and anxiety (≥ 8 / <8). Subgroups of independent variables were merged to have enough counts in each cell. After univariable analyses, we performed multivariable logistic regression by correcting for age.

Multivariate Imputation by Chained Equations (10 imputed datasets with 10 iterations per imputation) was used for the imputation of missing values of clinical data and baseline PROs. It was assumed that those missing values were missing at random (58). The variables used as predictor variables for the imputations were baseline patient, treatment, and tumor characteristics and longitudinal measurements of PROMs (i.e. scores from baseline up to 4,5 years follow up for the four QoL domains)(59). To investigate whether the number of iterations was enough, we checked the convergence of the imputed data with convergence plots (60). Both complete case analysis and imputed data analysis were performed. In addition, sensitivity analysis was performed to explore the impact of imputed data on the identification of factors associated with clinically relevant impairments of QoL domains in breast cancer patients. With the use of Rubin's Rules, we obtained pooled estimates of the coefficients (60). The results from logistic regression analyses were presented as Odds Ratios (OR) with 95% confidence intervals (CI). Statistical analyses were performed with the use of Statistical Package for Social Sciences software (IBM SPSS Statistics version 27) and R Studio open-source software (version 4.0.3).

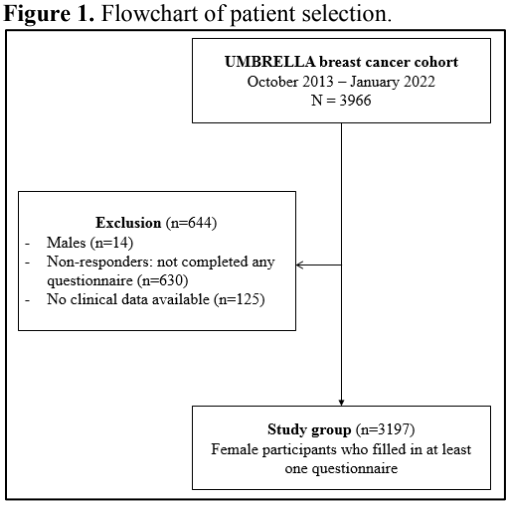
In order to get insight into reasons for non-response in the cohort, we performed a non-response analysis because there was a group of participants who repeatedly non-responded to the questionnaires. Around the period of November 2019, the non-response analysis was performed and participants were marked as 'non-responder' if three consecutive questionnaires were not completed. The non-responders were approached by mail (for participants of paper questionnaires (PAPI)) or by e-mail (for participants of online questionnaires (CAWI)) and they were asked to give a reason for their previous discontinuity of PROMs (Appendix 1). Reasons for non-

responding were categorized and a distinction was made between those who wanted to continue with the study and those who did not. Two researchers independently identified the reasons underlying non-responding and discussed those mutually until consensus was reached.

RESULTS

In total, 3966 patients were enrolled in the UMBRELLA cohort between October 2013 and January 2022 (Figure 1). We excluded all males, non-responders (i.e. not responding to any questionnaire), and participants from whom clinical data was not available. The 3197 female patients who filled in at least one questionnaire were selected for further analysis.

Figure 1. Flowchart of patient selection.



PROM response rates within the UMBRELLA cohort decreased from 79% at baseline to 53% after 5 years follow-up (Appendix 2, Table 1). This is an approximation for the overall expected response rates in the cohort study. The total number of patients is decreasing as follow-up increases because UMBRELLA is a dynamic cohort and participant enrollment is still ongoing.

Within the UMBRELLA study population, there were no substantial differences in most clinical characteristics between patients who responded to questionnaires and non-responders (Appendix 3, Table 1). Although, 77.0% of the responders (n = 2557) and 66.5% of the non-responders (n = 412) were treated with breast-conserving surgery. And more non-responders were not treated with radiotherapy (17.9%, n = 103; 6.3%, n = 200 for responders).

The UMBRELLA study population was representative of the population of Dutch breast cancer patients (Appendix 3, Table 1), with the exception of the UMBRELLA study population with radiotherapy in comparison to the Dutch breast cancer population (respectively 92% vs. 61% received radiotherapy).

In the study population (Table 1), the mean age at cohort enrolment was 58 years (range 24-94). The median body image index (BMI) was 26.5 kg/m^2 and more than half of the patients had a low educational level (52.3%, n=1672).

T-stages 1 and 2 were the most common pathological tumor stages (57.1%, n = 1825 for T1; 19.9%, n = 635 for T2). Most patients were treated with breast-conserving surgery (79.9%, n = 2556) and 82.4% of the patients (n = 2663) had a sentinel node procedure. More than half of the patients were not treated with chemotherapy (58.8%, n = 1880), nor with hormone therapy (52.2%, n = 1669), nor with targeted therapy (88.4%, n = 2826). Only 6% of the patients were not treated with radiation therapy (n = 200) and most women received local radiotherapy (38.3%, n = 1226 without boost; 27.3%, n = 874 with boost).

Table 1. Patient, tumor, and treatment characteristics of current study population (n=3197).

	***n* = 3197**
Age at inclusion in years [mean (range)]	58.1 (24-94)
Body mass index [a] in kg/m^2 [median (IQR)]	26.5 (5.3)
Unknown	210 (6.6)
Smoking status	
Smoker	201 (6.3)
Previous smoker	1458 (45.6)
Non-smoker	1320 (41.3)
Unknown	218 (6.8)
Educational level [b]	
Low	1672 (52.3)
High	1433 (44.8)
Unknown	92 (2.9)
Pathological T stadium	
T0/Tis [c]	530 (16.6)
T1	1825 (57.1)
T2	635 (19.9)
T3/T4	90 (2.8)
Tx[d]	74 (2.3)
Unknown	43 (1.3)
Pathological N stadium	
N0	2024 (63.3)
N+ (1-3)[e]	915 (28.6)
Nx [d]	215 (6.7)
Unknown	43 (1.3)
Type of breast surgery	
Breast-conserving surgery	2556 (79.9)
Mastectomy without direct reconstruction	339 (10.6)
Direct reconstruction	258 (8.1)
No breast surgery	29 (0.9)
Unknown	15 (0.5)
Axillary treatment	
Sentinel node procedure (SNP)	2633 (82.4)
Axillary lymph node dissection +/- SNP	238 (7.4)
No axillary treatment	326 (10.2)
Unknown	0
Chemotherapy	
Yes	1317 (41.2)
No	1880 (58.8)
Unknown	0
Hormone therapy	
Yes	1528 (47.8)
No	1669 (52.2)
Unknown	0
Targeted therapy	
Yes	371 (11.6)
No	2826 (88.4)
Unknown	0
Type of radiotherapy	
No radiation therapy	200 (6.3)
Local without boost	1226 (38.3)
Local with boost	874 (27.3)
Locoregional without boost [f]	476 (14.9)
Locoregional with boost [f]	291 (9.1)
Other type of radiotherapy [g]	111 (3.5)
Unknown	19 (0.6)

The study population are female participants, who filled in at least one questionnaire, and those with available clinical data.
The numbers are shown as *n (%)* unless it is stated otherwise. Continuous outcomes are shown as mean (SD) when normally distributed and otherwise as median (IQR).
n number of participants, *%* percentage of participants, *SD* standard deviation, *IQR* interquartile range.
[a] Calculated as weight divided by height^2. The first measured BMI is used. [b] Low when no schooling, secondary or vocational education is completed. High when completed college, graduate or professional degree. [c] *T0* means there is no evidence of the primary tumor. *Tis* means tumor is in situ. [d] The tumor or lymph nodes cannot be assessed. [e] >N0, so pathological N stages 1, 2 and 3. [f] Radiation therapy on periclavicular and / or axillary lymph nodes. [g] Partial breast and other types, e.g. radiation on the regional glands.

Longitudinal examination of PROMs are shown in Figure 2. Global QoL score of breast cancer patients reached the lowest at 3 months ($score_{baseline}$ = 73.3; $score_{3\ months}$ = 71.1). Thereafter, global QoL of breast cancer patients slightly increased and stabilized around 24 months (score = 78.9). At five years, global QoL of breast cancer patients is increased to a level comparable as the general population (scores 78.2 vs. 76.3).

For most QoL domains (e.g. emotional- and social functioning, fatigue, pain), QoL scores deteriorated within the first 6 months after inclusion, after which QoL in most domains increased to a comparable level as the general population. Emotional functioning scores improved from 77.0 at baseline to 83.9 at 60 months follow-up, with no deterioration during the first months. Social functioning decreased from 82.2 at baseline to 80.3 at 3 months. After 3 months, social functioning increased to 90.4 at five years follow-up in comparison with the social functioning score of 92.6 in the general population. As for fatigue, scores increased to 35.4 at 3 months ($score_{baseline}$ = 29.3) where after fatigue decreased again. At five years, the levels of fatigue of breast cancer patients were comparable to those of healthy women (22.3 vs. 20.8). Scores of pain were higher in relation to the normative population within the first six months after enrolment ($score_{baseline}$ = 21.1; $score_{6\ months}$ = 19.9 vs. $score_{normative\ population}$ = 18.3). After five years follow-up, pain of breast cancer patients decreased to a level lower than the normative population (16.4 vs. 18.3).

After five years follow-up, sum scores of sexual functioning are higher for breast cancer patients compared to healthy women (37.4 vs. 32.3). Sum scores for sexual enjoyment are lower for breast cancer patients in comparison to the healthy female population (60.1 vs. 72.0).

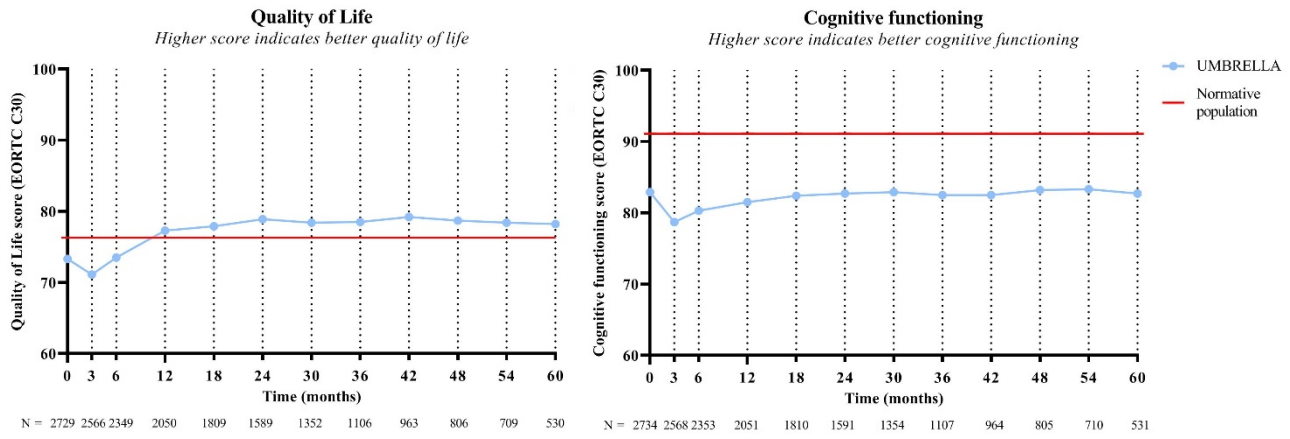
Over five years' time, scores for physical functioning, cognitive functioning, and dyspnea were always worse compared to the mean value of the general population ($score_{baseline}$ = 86.0 and $score_{60\ months}$ = 85.9 vs. $score_{normative\ population}$ = 88.9 for physical functioning; $score_{baseline}$ = 82.9 and $score_{60\ months}$ = 82.7 vs. $score_{normative\ population}$ = 91.1 for cognitive functioning; $score_{baseline}$ = 10.3 and $score_{60\ months}$ = 11.4 vs. $score_{normative\ population}$ = 7.5 for dyspnea), as a higher score indicated better outcomes for functioning scales (physical-, and cognitive functioning) and worse outcomes for symptom scales (i.e. dyspnea).

Besides the mean scores of the different QoL domains were also the proportions of women reporting clinically relevant and important problems or symptoms examined over time with the use of TCIs (50) (Appendix 4, Figure 1). In accordance with the longitudinal evaluation of the mean scores, for most domains (e.g. emotional functioning, fatigue, depression) higher proportions of clinically relevant impairments in QoL were observed within the first 6 months after treatment, after which the proportions of patients reporting clinically relevant impaired QoL decreased to comparable proportions as the general population. Proportions of women who reported clinically relevant and important problems or symptoms in emotional functioning, social functioning, fatigue and pain were quite similar for breast cancer patients as for healthy Dutch women at five years (23.5% vs. 19.0% for emotional functioning; 6.0% vs. 5.0% for social functioning; 18.9% vs. 16.5% for fatigue; and 28.1% vs. 30.8% for pain).

Up to five years follow-up, the minimal clinically important difference of 5% between proportions of women reporting clinically relevant impairments in QoL for breast cancer patients as for healthy Dutch women was observed for physical functioning (29% vs. 23%), cognitive functioning (30% vs. 13%), and dyspnea (28% vs. 19%) (Figure 3).

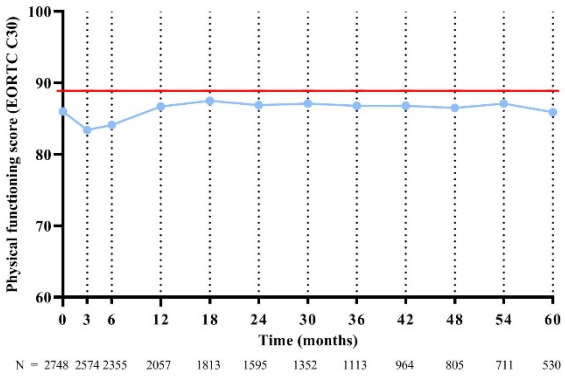
Anxiety and depression were assessed with the use of the HADS questionnaire (57). Longitudinal evaluation of the proportions of anxiety and depression showed that the proportion of anxiety is over five years' time always higher for breast cancer patients compared to healthy women ($proportion_{baseline}$ = 24.2%; $proportion_{60\ months}$ = 19.7% vs. $proportion_{normative\ population}$ = 15.7%) (Appendix 4, Figure 2). There appeared to be no difference in depression proportions for the two populations at five years (13.6% for UMBRELLA population vs. 13.2% for normative population).

Figure 2. Longitudinal examination of the mean scores of different QoL domains for the UMBRELLA population (n=3197) compared to the general population (n=879).



Physical functioning

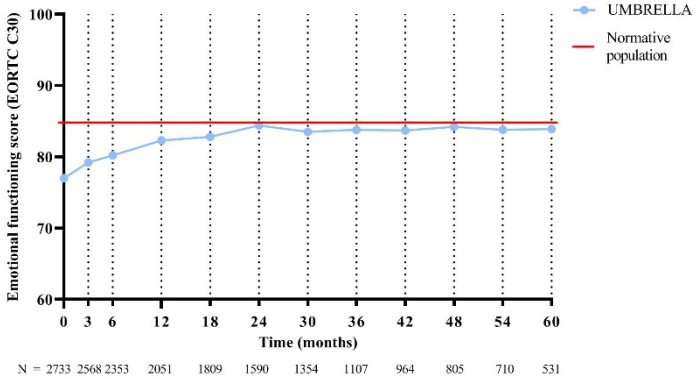
Higher score indicates better physical functioning



N = 2748 2574 2355 2057 1813 1595 1352 1113 964 805 711 530

Emotional functioning

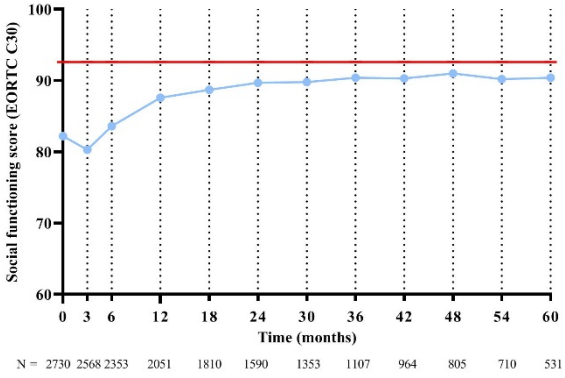
Higher score indicates better emotional functioning



N = 2733 2568 2353 2051 1809 1590 1354 1107 964 805 710 531

Social functioning

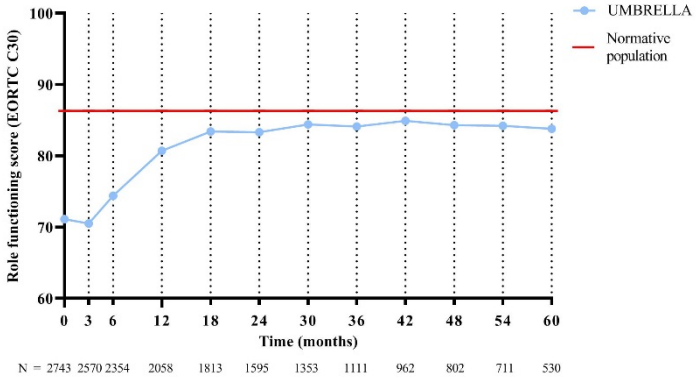
Higher score indicates better social functioning



N = 2730 2568 2353 2051 1810 1590 1353 1107 964 805 710 531

Role functioning

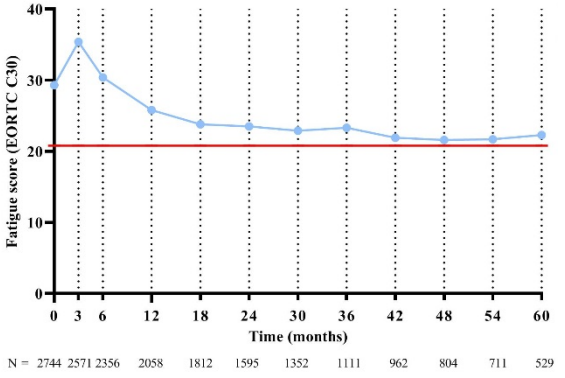
Higher score indicates better role functioning



N = 2743 2570 2354 2058 1813 1595 1353 1111 962 802 711 530

Fatigue

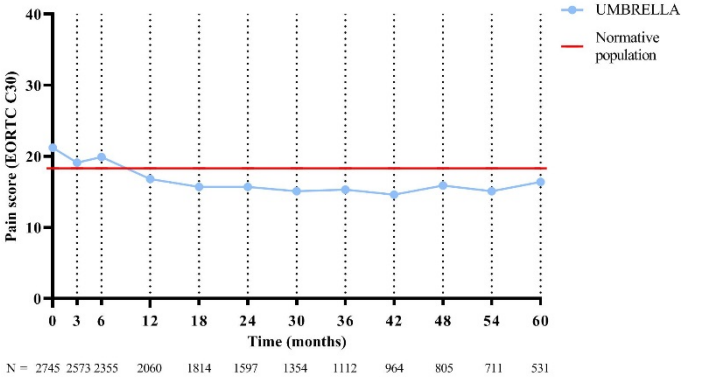
Higher score indicates more symptoms of fatigue



N = 2744 2571 2356 2058 1812 1595 1352 1111 962 804 711 529

Pain

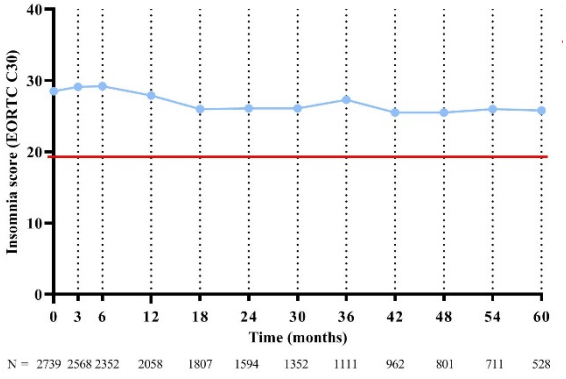
Higher score indicates more symptoms of pain



N = 2745 2573 2355 2060 1814 1597 1354 1112 964 805 711 531

Insomnia

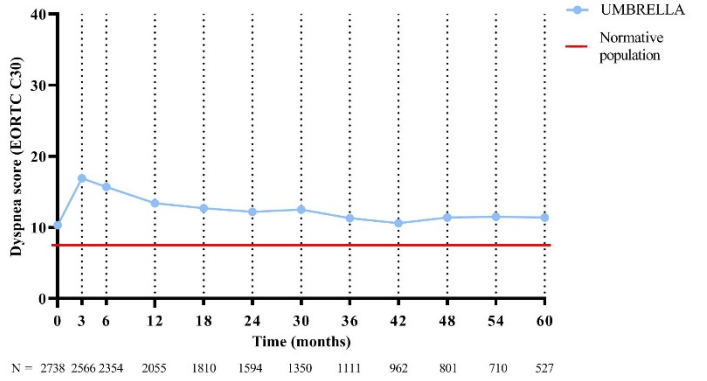
Higher score indicates more symptoms of insomnia



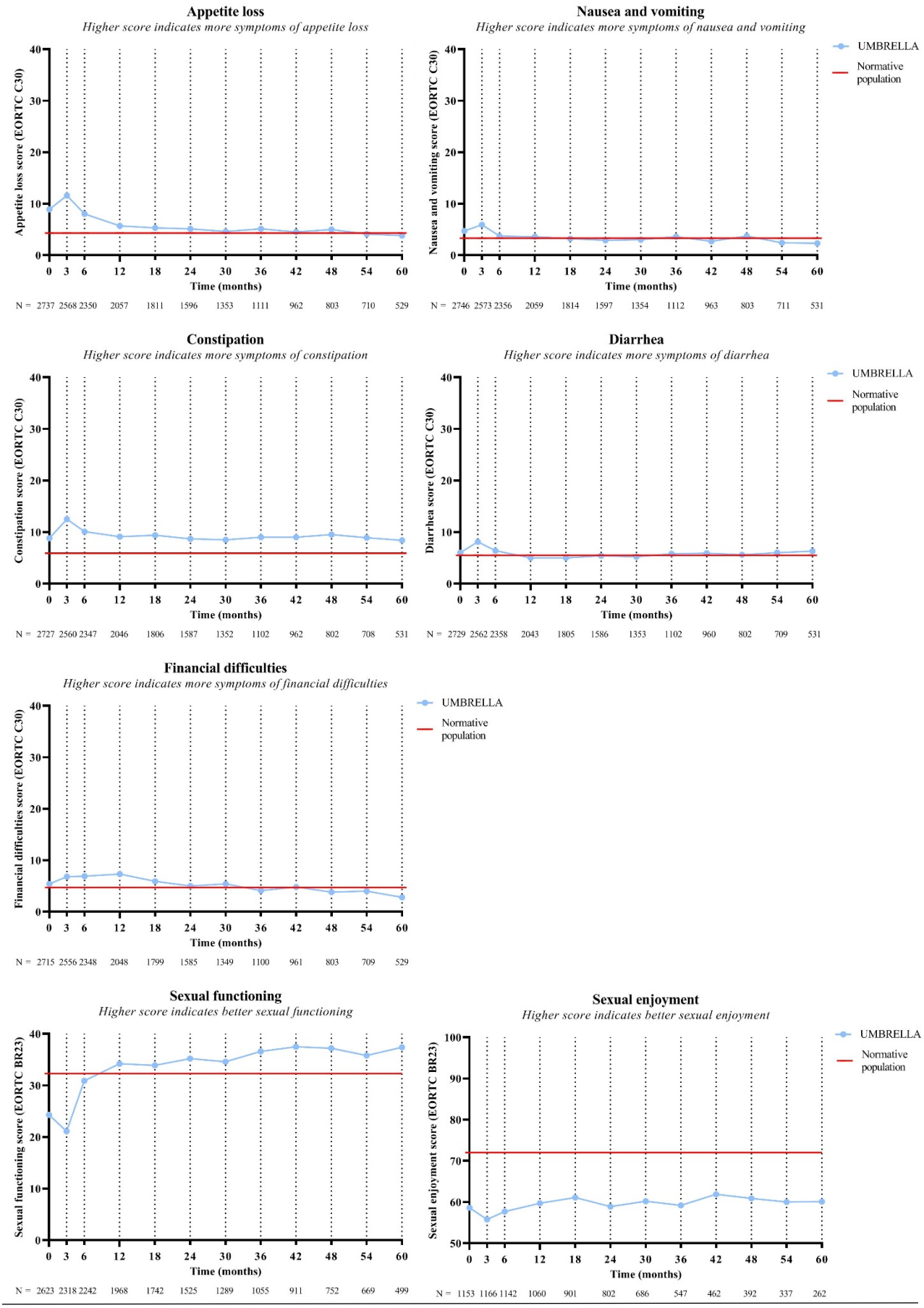
N = 2739 2568 2352 2058 1807 1594 1352 1111 962 801 711 528

Dyspnea

Higher score indicates more symptoms of dyspnea

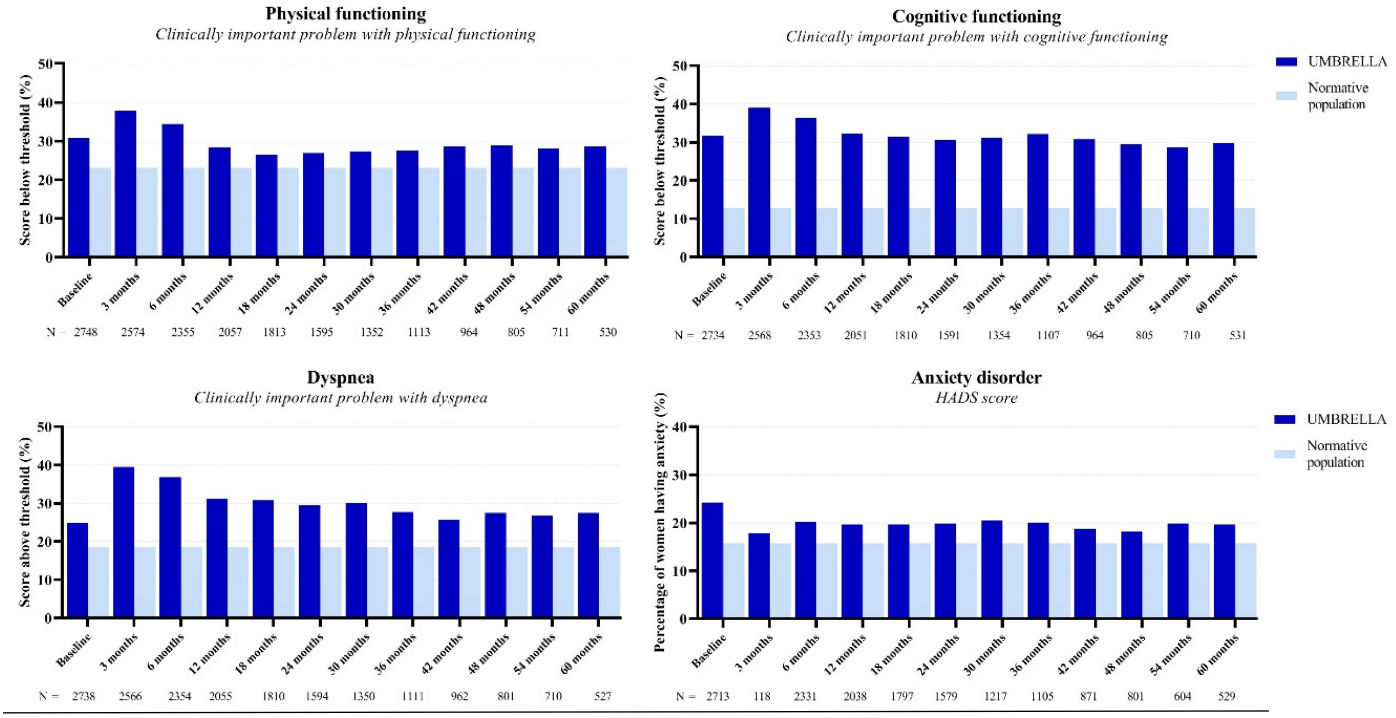


N = 2738 2566 2354 2055 1810 1594 1350 1111 962 801 710 527



QoL was assessed by means of the EORTC QLQ-C30 and -BR23 (i.e. sexual functioning and -enjoyment) questionnaires. A higher score represents a better outcome for functional scales (i.e. physical- and emotional functioning) and a worse outcome for symptom scales (i.e. pain).

Figure 3. The four most clinically relevant impaired QoL domains after five years follow-up in relation to the general population, which were physical functioning (29% vs. 23%), cognitive functioning (30 vs. 13%), dyspnea (28% vs. 19%) and anxiety (20% vs. 16%).



Thresholds for clinical importance were used to identify patient with clinically important PROs for the EORTC C30 questionnaire. Women who score below the TCI for functioning scales, or above the TCI for symptom scales, experience clinically relevant and important problems or symptoms.
Physical functioning, cognitive functioning and dyspnea were assessed by means of the EORTC C30 questionnaire. A higher score represents a better outcome for functional scales (i.e. physical- and cognitive functioning) and a worse outcome for symptom scales (i.e. dyspnea). Anxiety and depression were assessed by means of the HADS questionnaire. Scores of 8 or higher indicate an increased risk of having anxiety and depressive disorders.
Proportions of clinically relevant impairments in QoL of the UMBRELLA population and the general population were compared for most QoL domains. The UMBRELLA population were all female patients who filled in at least one questionnaire (n=3197) The normative population were Dutch cancer-free women with a comparable age-range and age-distribution as the UMBRELLA population (n=879). Clinically relevant impaired QoL after five years follow-up was observed in the domains: physical functioning, cognitive functioning, dyspnea and anxiety. Additionally, univariable logistic regression analysis was performed to identify determinants associated with clinically relevant impairments in those four domains.
n number of participants, *%* percentage of participants.

Chi-squared test was performed to compare the proportions of breast cancer patients reporting clinically relevant and important problems or symptoms at five years with the normative population (Appendix 5). Results of the chi-squared test largely corresponded to the results based on eye-balling, which was ultimately decisive for the choices of the most clinically relevant impaired QoL domains. Anxiety did not met the criterion of a minimal clinically difference of 5% (19.7% for UMBRELLA population; 15.7% for normative population. Since the proportion of anxiety is over five years' time always higher for breast cancer patients compared to healthy women, anxiety was selected as a clinically relevant impaired QoL domain.

At five years after cohort entry, clinically relevant and important problems with physical functioning were observed in 152 of 530 patients (29%). Univariable analyses showed that clinically relevant and important problems in physical functioning were associated with age, educational level, body mass index, pathological T-stadia 3 and 4, and baseline physical functioning. After correcting for age, also mastectomy without breast reconstruction, N-stadium + (i.e. N1, N2, or N3), and locoregional radiotherapy became significant. Low educational level (OR 0.58, 95% for high education compared to low education), higher body mass index (OR 1.12, 95% CI 1.07-1.17), T-stages 3 and 4 (OR 5.74, 95% CI 1.74-18.90), N+ (OR 1.55, 95% CI 1.02-2.40), mastectomy without direct breast reconstruction (OR 2.03, 95%CI 1.10-3.74), locoregional radiotherapy (OR 1.61, 95% CI 1.00-2.59), and lower baseline physical functioning (OR 0.95, 95% CI 0.94-0.96 for higher scores) were significantly associated with clinically relevant and important problems in physical functioning (Table 2A).

Table 2A. Results of age-adjusted logistic regression analysis after multiple imputation assessing baseline determinants associated with clinically relevant and important problems in physical functioning (n=152/530) after five years of enrolment.

	Physical functioning OR (95% CI)	OR (95% CI) corrected for age
Age, per year	1.05 (1.03-1.07)*	
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	1.18 (0.80-1.74)	1.10 (0.74-1.63)
Smoker	0.97 (0.33-2.81)	0.82 (0.28-2.41)
Education		
Low	Ref.	Ref.
High	0.47 (0.32-0.70)*	0.58 (0.38-0.87)*
Body mass index	1.13 (1.08-1.18)*	1.12 (1.07-1.17)*
T-stadium		
T0/Tis	Ref.	Ref.
T1	1.17 (0.66-2.07)	1.15 (0.64-2.06)
T2	1.56 (0.79-3.06)	1.63 (0.82-3.25)
T3/T4	4.68 (1.47-14.90)*	5.74 (1.74-18.90)*
Tx	1.70 (0.55-5.23)	1.72 (0.55-5.40)
N-stadium		
N0	Ref.	Ref.
N+	1.40 (0.93-2.10)	1.55 (1.02-2.40)*
Nx	1.19 (0.50-2.82)	1.13 (0.47-2.75)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Ablation without breast reconstruction	1.71 (0.95-3.10)	2.03 (1.10-3.74)*
Breast reconstruction	0.52 (0.21-1.29)	0.80 (0.31-2.03)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	1.13 (0.63-2.02)	1.40 (0.77-2.58)
No axillary surgery	0.47 (0.18-1.25)	0.42 (0.16-1.14)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.51 (0.95-2.39)	1.61 (1.00-2.59)*
No radiation therapy received	2.31 (0.84-6.30)	2.35 (0.83-6.35)
Radiotherapy boost		
No	Ref.	Ref.
Yes	0.80 (0.54-1.18)	0.96 (0.64-1.44)
No radiation therapy received	1.92 (0.70-5.32)	2.08 (0.73-5.90)
Chemotherapy		
No	Ref.	Ref.
Yes	0.92 (0.63-1.35)	1.42 (0.92-2.18)
Hormonal therapy		
No	Ref.	Ref.
Yes	1.14 (0.78-1.66)	1.29 (0.87-1.90)
Targeted therapy		
No	Ref.	Ref.
Yes	0.72 (0.37-1.42)	0.94 (0.47-1.88)
Baseline physical functioning, score 0-100 [b]	0.95 (0.93 – 0.96)*	0.95 (0.94-0.96)*

Univariable logistic regression analyses were conducted to identify variables associated with clinically relevant impairments in QoL in five years after breast cancer treatment.
All variables in the table were used for multiple imputation of missing variables, as well as the longitudinal scores of physical functioning (0 months till 54 months, so none scores at 5 years).
*Significant odds ratios. *N.A.* not applicable, category is too small for calculation.
Abbreviations: OR = odds ratio; CI = confidence interval; Ref. = reference category.
[a] Including patients treated with partial breast irradiation. [b] By means of the EORTC QLQ-C30 questionnaire. A higher score represents a better outcome for functional scales.

Clinically relevant and important problems with cognitive functioning were observed in 150 of 531 patients (30%) at five years after breast cancer treatment. After univariable logistic regression analyses, only pathological N+, chemotherapy, and baseline cognitive functioning score were significantly associated with clinically relevant and important problems in cognitive functioning (Table 2B). These determinants remained significant after adjustment for age. After five years follow-up, N+ (OR 1.51, 95% CI 1.00-2.25), chemotherapy (OR 1.72, 95% CI 1.14-2.61)

and lower baseline cognitive functioning (OR 0.97, 95% CI 0.96-0.98 for higher scores) were significantly associated with clinically relevant and important problems in cognitive functioning.

Table 2B. Results of age-adjusted logistic regression analysis after multiple imputation assessing baseline determinants associated with clinically relevant and important problems in cognitive functioning (n=150/531) after five years of enrolment.

	Cognitive functioning OR (95% CI)	OR (95% CI) corrected for age
Age, per year	0.98 (0.96-1.00)	
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	0.97 (0.66-1.42)	1.00 (0.69-1.48)
Smoker	0.82 (0.29-2.38)	0.89 (0.31-2.59)
Education		
Low	Ref.	Ref.
High	1.26 (0.87 – 1.83)	1.15 (0.78-1.70)
Body mass index	0.99 (0.95-1.04)	1.00 (0.96-1.04)
T-stadium		
T0/Tis	Ref.	Ref.
T1	1.33 (0.76-2.33)	1.33 (0.76-2.33)
T2	1.43 (0.73-2.80)	1.41 (0.72-2.76)
T3/T4	0.74 (0.19-2.88)	0.70 (0.18-2.74)
Tx	0.84 (0.25-2.84)	0.85 (0.25-2.89)
N-stadium		
N0	Ref.	Ref.
N+	1.56 (1.04-2.23)*	1.51 (1.00-2.25)*
Nx	0.96 (0.39-2.36)	0.98 (0.40-2.40)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Ablation without breast reconstruction	1.08 (0.58-2.02)	1.01 (0.54-1.91)
Breast reconstruction	0.94 (0.44-2.02)	0.78 (0.36-1.73)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	1.08 (0.60-1.94)	1.00 (0.55-1.80)
No axillary surgery	0.68 (0.29-1.62)	0.70 (0.29-1.67)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.35 (0.86-2.12)	1.32 (0.84-2.08)
No radiation therapy received	1.12 (0.38-3.29)	1.12 (0.38-3.32)
Radiotherapy boost		
No	Ref.	Ref.
Yes	1.33 (0.91-1.95)	1.25 (0.85-1.84)
No radiation therapy received	1.28 (0.43-3.82)	1.25 (0.42-3.77)
Chemotherapy		
No	Ref.	Ref.
Yes	1.82 (1.25-2.65)*	1.72 (1.14-2.61)*
Hormonal therapy		
No	Ref.	Ref.
Yes	1.29 (0.89-1.88)	1.24 (0.85-1.81)
Targeted therapy		
No	Ref.	Ref.
Yes	1.28 (0.70-2.35)	1.16 (0.62-2.15)
Baseline cognitive functioning, score 0-100 [b]	0.97 (0.96-0.98)*	0.97 (0.96-0.98)*

Univariable logistic regression analyses were conducted to identify variables associated with clinically relevant impairments in QoL in five years after breast cancer treatment.
All variables in the table were used for multiple imputation of missing variables, as well as the longitudinal scores of cognitive functioning (0 months till 54 months, so none scores at 5 years).
*Significant odds ratios. *N.A.* not applicable, category is too small for calculation.
Abbreviations: OR = odds ratio; CI = confidence interval; Ref. = reference category.
[a] Including patients treated with partial breast irradiation. [b] By means of the EORTC QLQ-C30 questionnaire. A higher score represents a better outcome for functional scales.

Five years after inclusion, 145 of 527 patients (28%) reported clinically relevant and important symptoms of dyspnea. Univariable analyses showed that age, educational level, body mass index, extensive axillary surgery,

chemotherapy and poor baseline dyspnea were significantly associated with clinically relevant and important symptoms of dyspnea. After age-correction, also chemotherapy became statistically significant. Lower educational level (OR 0.55, 95% CI 0.37-0.83 for high education compared to low education), higher body mass index (OR 1.06, 95% CI 1.02-1.11), axillary lymph node dissection +/- sentinel node procedure (OR 2.67, 95% CI 1.50-4.73), chemotherapy (OR 1.77, 95% CI 1.15-2.74) and poor baseline dyspnea score (OR 1.04, 95% 1.03-1.05) were significantly associated with clinically relevant impaired dyspnea (Table 4C).

Table 2C. Results of age-adjusted logistic regression analysis after multiple imputation assessing baseline determinants associated with clinically relevant and important symptom of dyspnea (n=147/527) after five years of enrolment.

	Dyspnea OR (95% CI)	OR (95% CI) corrected for age
Age, per year	1.03 (1.01-1.05)*	
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	1.09 (0.74-1.61)	1.05 (0.71-1.55)
Smoker	0.73 (0.23-2.29)	0.66 (0.21-2.08)
Education		
Low	Ref.	Ref.
High	0.50 (0.34-0.75)*	0.55 (0.37-0.83)*
Body mass index	1.07 (1.03-1.11)*	1.06 (1.02-1.11)*
T-stadium		
T0/Tis	Ref.	Ref.
T1	0.83 (0.48-1.43)	0.82 (0.47-1.42)
T2	1.20 (0.62-2.31)	1.22 (0.63-2.37)
T3/T4	0.97 (0.28-3.42)	1.07 (0.30-3.80)
Tx	1.31 (0.43-3.98)	1.31 (0.43-4.00)
N-stadium		
N0	Ref.	Ref.
N+	1.37 (0.90-2.07)	1.45 (0.95-2.21)
Nx	2.12 (0.94-4.77)	2.08 (0.92-4.72)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Mastectomy without breast reconstruction	1.14 (0.60-2.17)	1.25 (0.65-2.39)
Breast reconstruction	0.92 (0.42-2.03)	1.18 (0.52-2.67)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	2.29 (1.32-4.00)*	2.67 (1.50-4.73)*
No axillary surgery	1.43 (0.65-3.13)	1.37 (0.62-3.02)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.15 (0.72-1.85)	1.19 (0.74-1.92)
No radiation therapy received	1.23 (0.42-3.62)	1.22 (0.41-3.63)
Radiotherapy boost		
No	Ref.	Ref.
Yes	0.97 (0.66-1.44)	1.08 (0.72-1.62)
No radiation therapy received	1.26 (0.42-3.75)	1.30 (0.43-3.88)
Chemotherapy		
No	Ref.	Ref.
Yes	1.29 (0.88-1.90)	1.77 (1.15-2.74)*
Hormonal therapy		
No	Ref.	Ref.
Yes	0.86 (0.59-1.26)	0.91 (0.62-1.35)
Targeted therapy		
No	Ref.	Ref.
Yes	1.45 (0.79-2.66)	1.72 (0.92-3.23)
Baseline dyspnea, score 0-100 [b]	1.04 (1.03-1.05)*	1.04 (1.03-1.05)*

Univariable logistic regression analyses were conducted to identify variables associated with clinically relevant impairments in QoL in five years after breast cancer treatment.
All variables in the table were used for multiple imputation of missing variables, as well as the longitudinal scores of dyspnea (0 months till 54 months, so none scores at 5 years).
*Significant odds ratios. *N.A.* not applicable, numbers were too low.
Abbreviations: OR = odds ratio; CI = confidence interval; Ref. = reference category.
[a] Including patients treated with partial breast irradiation. [b] By means of the EORTC QLQ-C30 questionnaire. A higher score represents a worse outcome for symptom scales.

At five years after inclusion, 104 of 529 patients (20%) had clinically relevant anxiety disorder. After univariable analyses, N-stadium +, axillary lymph node dissection +/- SNP, and baseline anxiety score were significantly associated with clinically relevant anxiety at five years. Adjustment for age resulted in the same significant determinants. After five years follow-up, N+ (OR 1.71, 95% CI 1.09-2.70), extensive axillary surgery (OR 2.33,

95% CI 1.28-4.24), and presence of anxiety at baseline (OR 4.59, 95% CI 2.82-7.48) were significantly associated with clinically relevant anxiety (Table 4D).

Table 2D. Results of age-adjusted logistic regression analysis after multiple imputation assessing baseline determinants associated with clinically relevant anxiety disorder (n=104/529) after five years of enrolment.

	Anxiety OR (95% CI)	OR (95% CI) corrected for age
Age, per year	0.99 (0.97-1.02)	
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	1.05 (0.67-1.62)	1.06 (0.68-1.65)
Smoker	1.12 (0.35-3.55)	1.15 (0.36-3.66)
Education		
Low	Ref.	Ref.
High	1.02 (0.66-1.57)	0.99 (0.63-1.55)
Body mass index	1.00 (0.95-1.04)	1.00 (0.95-1.05)
T-stadium		
T0/Tis	Ref.	Ref.
T1	0.93 (0.49-1.75)	0.93 (0.49-1.75)
T2	1.55 (0.75-3.23)	1.55 (0.74-3.23)
T3/T4	0.98 (0.25-3.90)	0.97 (0.24-3.86)
Tx	1.21 (0.35-4.21)	1.21 (0.35-4.23)
N-stadium		
N0	Ref.	Ref.
N+	1.72 (1.10-2.71)*	1.71 (1.09-2.70)*
Nx	0.86 (0.28-2.58)	0.86 (0.29-2.59)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Mastectomy without breast reconstruction	1.66 (0.86-3.22)	1.66 (0.86-3.22)
Breast reconstruction	1.88 (0.86-4.09)	1.87 (0.83-4.20)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	2.34 (1.30-4.24)*	2.33 (1.28-4.24)*
No axillary surgery	1.37 (0.57-3.30)	1.37 (0.57-3.30)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.33 (0.79-2.27)	1.32 (0.78-2.25)
No radiation therapy received	1.73 (0.53-5.66)	1.73 (0.53-5.68)
Radiotherapy boost		
No	Ref.	Ref.
Yes	0.93 (0.60-1.45)	0.90 (0.57-1.42)
No radiation therapy received	1.54 (0.47-5.04)	1.53 (0.46-5.02)
Chemotherapy		
No	Ref.	Ref.
Yes	1.42 (0.92-2.18)	1.43 (0.89-2.30)
Hormonal therapy		
No	Ref.	Ref.
Yes	1.50 (0.96-2.33)	1.48 (0.95-2.31)
Targeted therapy		
No	Ref.	Ref.
Yes	1.41 (0.72-2.76)	1.39 (0.70-2.73)
Baseline anxiety [b]		
< 8, no anxiety	Ref.	Ref.
≥ 8 anxiety disorder	4.60 (2.83-7.45)*	4.59 (2.82-7.48)*

Univariable logistic regression analyses were conducted to identify variables associated with clinically relevant impairments in QoL in five years after breast cancer treatment.
All variables in the table were used for multiple imputation of missing variables, as well as the longitudinal scores of dyspnea (0 months till 54 months, so none scores at 5 years).
*Significant odds ratios.
Abbreviations: OR = odds ratio; CI = confidence interval; Ref. = reference category.
[a] Including patients treated with partial breast irradiation. [b] By means of the HADS questionnaire. A score of ≥ 8 indicates an increased risk of anxiety disorders.

Clinical data and baseline PROs of the crude dataset and the imputed datasets were similar (Appendix 6, Table 1). Also sensitivity analysis investigating the univariable analyses in crude data and in the imputed data showed similar results (Appendix 6, Table 2A/B/C/D). All variables that were statistically significant in the analysis with imputed data were also statistically significant in the complete case analysis.

There were differences in patient, tumor, and treatment characteristics of responding and non-responding participants up to five years (Appendix 7). Non-responders smoked more (8.2% vs. 3.9%), had a lower educational level (60.1% vs. 51.9%), received less breast-conserving surgery (78.4% vs. 84.0%), received more extensive axillary surgery (15.6% vs. 10.1%), received more locoregional radiotherapy (25.8% vs. 19.9%), and had more clinically relevant and important problems or symptoms at baseline (36.2% vs. 29.0% for physical functioning; 32.0% vs. 30.4% for cognitive functioning; 30.3% vs. 21.0% for dyspnea; 28.5% vs. 23.5% for anxiety) than responders.

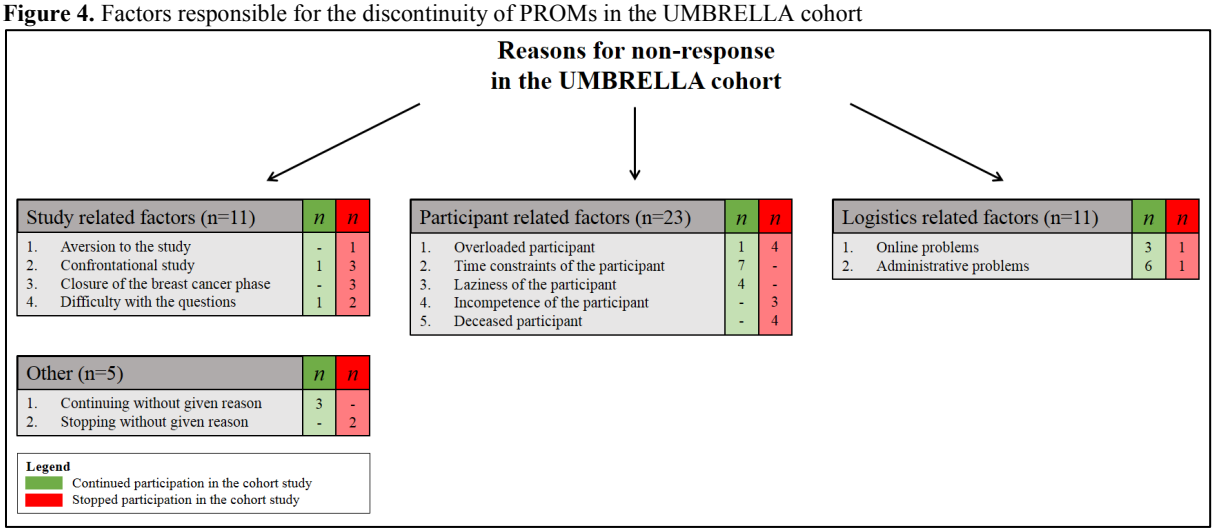
Non-response analysis resulted in 628 non-responding participants (i.e. not filled in three consecutive questionnaires; 21%) of the 2993 UMBRELLA cohort participants, from which 50 participants (n=8%) clarified their reason for discontinuing of PROMs (Appendix 8, Figure 1). Reasons for not responding to questionnaires included: study related factors, participant related factors, and logistics related factors (Figure 4). Five non-responders did not gave a reason for their discontinuity of the questionnaires.

Study related factors (n=11) included aversion to the study, study participation being too confrontational, wanting closure of the breast cancer period, and difficulty answering questions (Appendix 8, Table 1). Most study related factors were given by patients who eventually stopped participating in the cohort study. Predominant reasons for non-response were the confrontational character of the study and that participants did not wanted to be reminded of the disease period after finishing treatment.

Participant related factors (n=23) included feeling overloaded, time constraints of the participant, self-reported laziness of the participant, incompetence of the participant (e.g. visual impairment or dementia), and when the participant was deceased (informed by the family as response on the non-response analysis) (Appendix 8, Table 2). A reason for non-response, which eventually made participants to stop with the study, was that patients were overloaded due to personal circumstances.

Logistic related factors (n=11) included both online (i.e. difficulty with completing the online questionnaire via computer or telephone) and administrative problems (i.e. wrong (email) address in the administration system).

Figure 4. Factors responsible for the discontinuity of PROMs in the UMBRELLA cohort



n number of participants.

DISCUSSION

Main findings

This study evaluated PROMs of QoL during and in the years after breast cancer treatment and identified factors associated with clinically relevant impairments in QoL. Longitudinal analysis of PROs in an unselected group breast cancer patients showed that QoL in most domains (e.g. emotional- and role functioning, pain, nausea, depression) declined within the first 6 months after cohort inclusion. Thereafter, QoL in most domains increased to a comparable level as the general population. Up to five years after enrolment, women reported more clinically relevant physical and cognitive problems, dyspnea and anxiety compared to the general population. Women with more invasive breast cancer treatment, lower educational level, higher body mass index, and poorer baseline scores for the four QoL domains (i.e. physical- and cognitive functioning, dyspnea, and anxiety) were more likely to report clinically relevant impairments for physical- and cognitive functioning, dyspnea, and anxiety at the long-term.

Comparison with existing studies

This study is in accordance with the growing literature suggesting that in the long run, breast cancer patients reach comparable levels in different QoL domains as the general population (25,36,46,48). However, as also found in this study, previous research among breast cancer patients also reported some long-term impairments in QoL (27,39,40).

With regard to the evolution of QoL, global QoL of breast cancer patients increased to a level higher than at the beginning of patient's trajectory and even stabilized at a level higher than the general population. This increase in QoL may be explained by the phenomenon called response shift. Response shift is the change in patient's internal standards and values and the change in conceptualization of QoL, which is all triggered by a change in health status (61). The perceived QoL of breast cancer patients can be higher after treatment completion as a result of the re-evaluation of breast cancer patient's general heath perception (62). However, global QoL is not a very discriminating measurement domain compared to other domains (62). On the other hand, the increase in QoL can also be explained by the increasing age of patients. Previous research showed that different age groups of breast cancer patients have different risks for experiencing poor HRQoL at long-term follow-up (63–65). Younger age is significantly associated with poorer HRQoL as the psychosocial impact of breast cancer is greater for younger patients than for older patients (31,66,67). Furthermore with regard to the evolution of QoL, this present study showed for most QoL domains a decrease in QoL within the first six months after enrolment. Thereafter QoL increased again. The decrease in QoL in the first six months is in accordance with previous research. Most patients have completed radiotherapy or chemotherapy in the six months after surgery. And therefore an increase in QoL after six months was expected because patients were probably recovered from their surgery, hospitalization and maybe even from their initial emotional reaction (68).

Previous longitudinal research of Schmidt et al. support our findings on the evaluation of QoL domains over time (25). As in our study, QoL is assessed by means of EORTC QLQ-C30 and -BR23 and outcomes were compared to values of the general population. However, measurements in the study of Schmidt et al. occurred only five times in the first year after therapy and once at five years follow-up. Evaluation by Schmidt et al. of breast cancer patients up to five years post-diagnosis has shown that QoL-related functions and symptoms were worse during treatment and improved over time, even reaching comparable scores as the general healthy population. Differences between the study of Schmidt et al. and this present study were found for the long-term effects that remained significantly worse. In contrast to our results, sleep problems (39%) were significantly worse after 5-years follow-up. Other prevalent long-term problems were sexual issues (45%), pain (43%), and fatigue (24%). As in our study, cognitive functioning remained significantly worse in breast cancer patients compared to cancer-free women. The study of Schmidt et al. included breast cancer patients from two exercise intervention studies, for which patients were excluded when having contraindications for resistance training (e.g. severe cardiac disease, severe respiratory insufficiency, acute infectious disease) or other concomitant malignant diseases. Participants in the study of Schmidt et al. may be more healthy than the average breast cancer patients, what makes the sample in the study of Schmidt et al. less representative.

The findings on cognitive impairment on the long-term were also in line with previous research of Hsu et al. (46). Here is shown that while global QoL and other QoL domains were comparable to the general population, cognitive functioning remained significantly impaired. However, this study is performed in only 166 patients compared to the 530 patients in our study. Cognitive impairment was also observed in two other longitudinal studies that compared breast cancer patients with the general population (39,49). However in the latter two studies, impairments are also found in more QoL domains than only in cognitive functioning. Koch et al. also showed clinically relevant differences in fatigue, social-, and role functioning up to 10-years post-diagnosis in comparison with the general population. This difference between studies might be due to the inclusion of cancer recurrence, which not has been done in the study of Hsu et al. or in this present study. In addition, the cohort of Hsu et al. is not very representative as its includes younger patients, with fewer comorbid conditions, and less aggressive local and systematic treatments as tumor stage 3 is underrepresented.

Nevertheless, there are results from several previous studies that are not in accordance with the results of this study. As some of the well-known adverse effects, such as fatigue, insomnia, pain, and depression (16,17,25,69) did not appear in our analyses as prominently as we had expected. Fatigue is a prevalent complaint in most patients treated for breast cancer with a huge impact on functioning and HRQoL (7,15–17,25,26,37,40,69). Literature review of Pinto et al. stated that fatigue is a very persistent problem in women treated for breast cancer, namely for 30% up to 10 years post-diagnosis (69). In contrast to our study, previous research predominately investigated fatigue with the use of SaP questionnaire, in a cross-sectional study, and with none comparison with the general population. Fatigue that is experienced in women living after breast cancer may be the cause of natural aging (46). Furthermore, other studies have not shown prevalent impairments of anxiety at the long-term. This is because anxiety among breast cancer patients is mostly not examined on the long-term, but there are studies available indicating increased anxiety levels over a longer period of time (70,71).

Based on the available literature on long-term QoL among breast cancer patients it was not expected for dyspnea to be a clinically relevant impaired QoL domain. Although, research of Doege et al. showed more dyspnea in breast cancer patients compared to healthy controls (27). However, the differences in symptom burden due to dyspnea were of small clinical relevance. So this does not explain the results of this present study yet and therefore more research on dyspnea among breast cancer patients is still needed. The UMBRELLA population has an overrepresentation of irradiated patients. Research has shown that chest irradiation as part of breast cancer treatment is associated with an increased risk for acute radiation pneumonitis and late lung fibrosis (72). In the future, the underlying biological pathways involved in radiation toxicity should be further investigated for dyspnea in breast cancer patients. Since fatigue was not significant in this study but dyspnea was, there is a possibility that participants confused physical fatigue with dyspnea. This is supported by the percentage of agreement between clinically relevant and important symptom of fatigue and clinically relevant and important symptom of dyspnea at five years, which was 76.6% (Appendix 9, Table 1).

In this current study, a contradictory result among breast cancer patients was found for two scales of EORTC QLQ-BR23 (i.e. sexual functioning and sexual enjoyment)(55) when comparing the outcomes to normative values. At five years follow-up, breast cancer patients reported better sexual functioning but worse sexual enjoyment than healthy women (scores 37.4 vs. 32.3 for sexual functioning; scores 60.1 vs. 72.0 for sexual enjoyment). Sexual functioning is based on two items: 1) To what extent were you interested in sex?, and 2) To what extent were you sexually active? Both items are scored on a 4-point Likert-scale (i.e. not at all, a little, quite a bit, very much). The single item on sexual enjoyment (i.e. To what extent was sex enjoyable for you?) may only be answered if the person has been sexually active. Therefore, the response for this item was much less compared to all other scales. On average, breast cancer patients are more sexually active than healthy women, but they do find sex less enjoyable. This might be a consequence of breast cancer treatment because of premature menopause including hot flashes and vaginal dryness (12).

Our study aims to identify factors at baseline that are associated with clinically relevant impaired QoL after five years. The determinants at baseline are a reflection of clinical practice in which the doctor sees the patient and treatment decisions have to be made. BMI is calculated by means of length and height. As those measures are largely missing in the cohort study, the first measured length and height is used for the calculation of BMI. By using the first measured BMI and imputing the missing values, an attempt was made to get as close as possible to the baseline measurement in the clinic.

Multivariable logistic regression made it possible to control for age. The choice has not been made to stratify for age because that probably would resulted in logistic regression analyzes with not enough power as the number of participants at five years follow-up is decreased. In our analyses, baseline functioning for the four QoL domains (i.e. physical- and cognitive functioning, dyspnea, and anxiety) was associated with clinically relevant impairments in those same QoL domains on the long-term. In this study, baseline is prior to radiotherapy, but mostly after surgery and other adjuvant treatment (e.g. chemotherapy). Therefore, we did not correct for baseline functioning as it would remove part of the treatment effect.

Some variables are categorized to have adequate observations per category resulting in logistic regression analyzes with enough power. Educational level is dichotomized into low/high, tumor stages T0 with in situ and T3 and T4 are grouped together, and N-stages 1 till 3 are categorized into N+. These combined categories are clinically equivalent to each other and therefore categorizing will not affect the outcome.

The results from the univariable analyzes from this study support previous research in the identifications of factors responsible for impaired QoL in women after breast cancer treatment. Research of Tian et al. found significant associations between poorer functioning and axillary surgery or adjuvant radiotherapy (31). This is in accordance with the finding of clinically relevant impairments in QoL and extensive axillary surgery or locoregional radiotherapy. Previous study of Janz et al. showed that mastectomy did not significantly decreased QoL compared to breast-conserving surgery, although it did have a negative influence on body image (67). This may explain why the association of clinically relevant and important problems in physical functioning with mastectomy without direct reconstruction is statistically significant and the association of breast reconstruction is not, since the female body image is then preserved. Research of Ganz et al. showed that decreased physical functioning was mostly reported by patients who received mastectomy or chemotherapy (73). This is in contrast to our findings for chemotherapy as chemotherapy was associated with clinically relevant impairments in cognitive functioning and dyspnea. It is commonly known from previous research that chemotherapy has a negative influence on cognitive functioning in breast cancer patients (74,75). Univariable analyzes showed that tumor size and lymph nodes metastases were determinants for clinically relevant QoL impairments as tumor size and lymph nodes metastases influences the choice for surgical and adjuvant treatments (68). Like in our study, previous studies found inverse associations between BMI and QoL in breast cancer patients (76,77). In view of developing interventions, the result on educational level is less positive as this factor is unmodifiable. However, the result of univariable analysis is still useful for informing women.

From the non-response analysis it can be concluded that discontinuity of PROMs in the UMBRELLA study cannot be devoted to one factor but to several factors related to the study, participant and/or logistics. Main

reasons for non-response were the confrontational character of the study, the need for closure after finishing treatment, lack of time, and feeling overloaded or incompetent. Reasons for non-participation were consistent with previous research (78), specifically that the study was perceived as too confronting or too burdensome, and that participants lacked of time or were being too ill.

Strengths and limitations

This present study has several strengths. This is one of the few longitudinal studies that examined PROMs of QoL systematically at different time intervals in the years after treatment. The study is also performed in an unselected, real-life breast cancer population. Using real world data (i.e. data collection during every day practice) produces minimal selection bias (79). All this resulted in robust and scientifically proven results on patient-, tumor- and treatment characteristics and clinically relevant and important problems or symptoms at the long-term.

This study provides prospectively collected data from a large group of breast cancer patients. As a consequence of the large population size, abnormalities on individual level have a minimal influence on the outcomes of the study (i.e. robust results). To date more than 4500 patients have been included in the UMBRELLA cohort. Nonetheless, there is a strong decrease in study participants over the years. Selection bias through selective drop-out would have happened if particularly patients with worse long-term QoL outcomes or if patients with particular factors (e.g. treatment modality, educational level, age) were lost to follow-up. Characteristics of participants and drop-outs were not compared. Meanwhile within the UMBRELLA study population, characteristics of patients who responded to questionnaires were compared to characteristics of non-responders. This showed no substantial differences and even if there were differences between responders and non-responders, we cannot evaluate the potential effect of this difference on the outcomes.

Bias may occur when selective study termination or selective non-response are associated with the outcome (80,81). Selective non-response can result in under- or overestimated odds ratios. And so non-response may not be a problem when it is random. PROM response rates within the UMBRELLA cohort decreased from 79% at baseline to 53% at 60 months. In order to investigate if non-responding had an effect on the outcomes at five years, baseline characteristics of the responders and non-responders up to five years were compared. Differences between responders and non-responders were present as non-responders had more clinically relevant and important problems or symptoms at baseline, smoked more, had a lower educational level, received less breast-conserving surgery, but received more extensive axillary surgery or locoregional radiotherapy than responders. These differences were all associated with clinically relevant impairments in QoL at five years, except for smoking. Non-response may have led to underestimated odds ratios in the identification for factors associated clinically relevant impairments in QoL. And also the prevalence of clinically relevant and important problems or symptoms on the long-term would be underestimated when patients with worse functioning stopped returning questionnaires. Although measured characteristics are compared between responders and non-responders, there may also be other unknown or unmeasured factors relating to QoL. Nevertheless, a response rate of 53% after five years follow-up is considered high. Similar decreasing response rates within different studies are observed in a systematic review by van Egdom et al. (82).

Another strength of this study is the comparison of outcomes to normative values of a cancer-free female population. The comparison with age-comparable healthy women is of importance because mature women without breast cancer can also have complaints in the same QoL domain(s). By making the comparison, it can be investigated which part is due to breast cancer and its treatment. Normative data on the HADS questionnaire and two scales of the EORTC BR23 questionnaire (i.e. sexual functioning and sexual enjoyment) were available from 2011 and normative data on the EORTC C30 questionnaire was from 2013. Since women of 10 years ago probably not perform different on several QoL domains as physical functioning or cognitive functioning, it is not expected that the use of normative data from 2013 would have had an influence on the outcomes of the comparisons. In addition, there is unfortunately no longitudinal data on the general population. If longitudinal normative data would be made available in the future, breast cancer patients and cancer-free women could be equated for both age and time.

This study used PROMs on QoL what gives the opportunity to explore how breast cancer patients experience their QoL. This is not only useful for research but also for monitoring patients (82). The generated information of this study on the long-term effects of treatment modality and other patient characteristics can be used to inform patients and facilitates shared-decision making. The EORTC QLQ–C30, EORTC QLQ–BR23, and HADS were used as valid, reliable, and useful clinical measures (20,55,56,78,83). Recall bias may occur when patients underreported their symptoms because they were not able to recall all symptoms they encountered. However, recall bias is almost impossible as the recall period of those questionnaires were mostly the prior week.

Moreover, this study compared clinically relevant and important problems or symptoms (50), which is not often done because previous studies mostly investigated QoL domains as continuous outcomes

(7,16,25,39,46). In the majority of studies, clinically significant differences in QoL were defined as a x number of point difference between groups (16,46,67).

This study suffers from several limitations. First, baseline measurement is after surgery. Therefore, we do not have pre-treatment information from the patients and thus lacked baseline QoL prior to breast cancer diagnosis and/or treatment. Although, in practice is this almost impossible to accomplish (40). Another limitation of this study is that patients were primarily enrolled in the UMBRELLA cohort when they were referred to the UMC Utrecht for radiotherapy. Resulting in an overrepresentation of irritated patients in the UMBRELLA study population compared to the breast cancer population (respectively 8% vs. 39% did not receive radiation therapy). However, as the UMBRELLA study population and all Dutch breast cancer patients were comparable on all other characterises, we can conclude that the UMBRELLA population is a representative sample and that this outweighs the overrepresentation of irradiated patients.

A limitation of this study could be that there was missing data and therefore multiple imputation has been performed. However, the outcomes of the sensitivity analysis showed similar results for the logistic regression analyzes using crude or imputed data. This implies that the imputed data will not have a major impact on the identification of factors associated with clinically relevant impairments in QoL in breast cancer patients. However, this study lacks the ability to make a causal inference between factors and clinically relevant and important problems or symptoms at the long-term. But finding causality was not the aim of this study. This study aimed to identify factors to explore a patient profile for clinically relevant impairments in QoL.

Additionally, the UMBRELLA cohort study is quite comprehensive but it is not comprehensive enough as information on the recurrence status was not available. Although it is known from previous research that recurrence, metastasis or secondary malignancy is associated with poorer HRQoL (48,84). Also ethnicity was not included in this current analysis. Ethnicity (i.e. race) is a factor that identifies women at risk for experiencing poor HRQoL (65,85). Therefore, correcting for ethnicity could prevent bias.

The use of the EORTC questionnaires is both a strength as well as a limitation. The EORTC QLQ-C30 and the BR23 are more useful in assessing acute and treatment-related symptoms rather than assessing long-term symptoms. And problems as physical and psychosocial may not be addressed properly for cancer survivors (e.g. fear of recurrence, return to work) (24).

And lastly, clinically important QoL is determined five years after study enrolment to have a large enough study population. However, there is need for longitudinal studies that follow breast cancer patients beyond five years after diagnosis (39).

Conclusion and suggestions for further research

Main priority for future research is the detection and management of long-term and adverse effects of breast cancer and its treatment (7,19). It is important to understand the prevalence and factors of clinically relevant impairments in QoL domains because this information can be used in clinical practice and should be discussed with patients during shared decision making. Besides guiding clinical decision making and informing patients about the impact on QoL, the generated information indicates also which problems and symptoms need better screening, counselling and tailored interventions.

For further research, it is interesting to analyze changes in QoL-domains over time with the use of linear mixed model for repeated measures, which takes into account the correlation between the measurements within subjects. Also, including recurrence as factor in the analyzes could improve the prediction of long-term QoL. Additionally more longitudinal studies need to be set up which follow breast cancer patients from initial diagnosis through the whole treatment trajectory, and even years thereafter, to give the most accurate information. And future studies need to investigate the underlying mechanisms, diagnostic evaluations, and short- and long-term effects of dyspnea in breast cancer patients as these are largely unclear. To conclude, this study is the first step towards improving supportive care and interventions for women living after breast cancer.

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APPENDICES

Appendix 1. The message sent to the non-responding participants of the UMBRELLA study

Geachte,

U doet al een langere tijd mee met de UMBRELLA studie. Dit is een studie vanuit het UMC Utrecht, waarbij we kijken naar de gevolgen van borstkanker op lange termijn. Hiervoor heeft u van ons meerdere vragenlijsten gekregen.

Van u hebben we al langere tijd geen ingevulde vragenlijsten meer ontvangen. Graag horen we van u of u nog met de UMBRELLA studie wil meedoen. Uw ervaringen zijn belangrijk voor ons, ook als het goed met u gaat, of als u klachten heeft die niet door de borstkanker of borstkankerbehandeling zijn veroorzaakt. U kunt aangeven dat u nog mee wil doen door een e-mail te sturen naar umbrella_study@umcutrecht.nl of te bellen naar 088-7567828.

Als u niet meer wil meedoen, hoeft u niks te doen. We zullen u automatisch over 4 weken uitschrijven. Wel zijn we benieuwd wat de rede is dat u niet meer mee wil doen. Zou u dat met ons willen delen door een e-mail te sturen of door ons te bellen?

Veel dank voor uw deelname aan UMBRELLA, uw bijdrage is zeer waardevol voor ons.

Vriendelijke groeten,

Het UMBRELLA team
E-mail: umbrella_study@umcutrecht.nl
Telefoonnummer: 088-75 678 28

Appendix 2. Response rates of Patient-Reported Outcome Measures from the UMBRELLA cohort

Table 1. Questionnaire response rates within the UMBRELLA breast cancer cohort.

Time intervals in months	Responders in % [a]
Baseline [b]	79% (n=3097/3904)
3 months	76% (n=2826/3705)
6 months	73% (n=2547/3512)
12 months	68% (n=2255/3325)
18 months	63% (n=1926/3071)
24 months	60% (n=1721/2881)
30 months	57% (n=1470/2576)
36 months	55% (n=1209/2215)
42 months	55% (n=1050/1899)
48 months	54% (n=880/1622)
54 months	56% (n=769/1380)
60 months	53% (n=588/1115)

% percentage of participants eligible for returning questionnaires.
[a] PROM response rates were calculated within the UMBRELLA cohort in April 2022.
[b] Cohort entry.

Appendix 3. Baseline characteristics of UMBRELLA participants: responders versus non-responders and UMBRELLA cohort versus all Dutch breast cancer patients

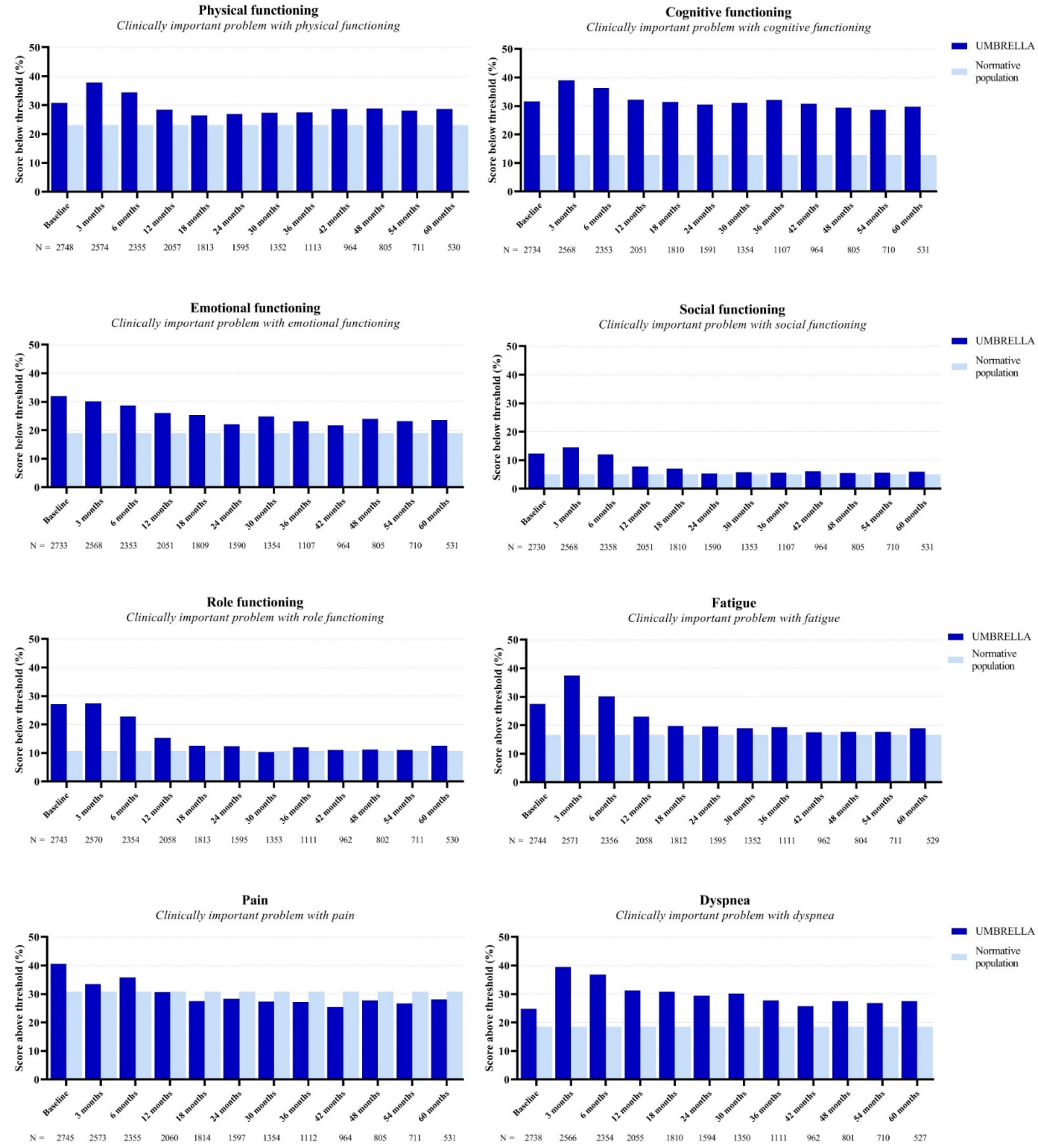
Table 1. Patient, tumor, and treatment characteristics of UMBRELLA participants (n=3966) who responded to the questionnaires (n=3334) versus non-responders (n=632); and of breast cancer patients from the UMBRELLA cohort (n=3966) versus all breast cancer patients in the Netherlands (n=162774), incidence years 2013-2021.

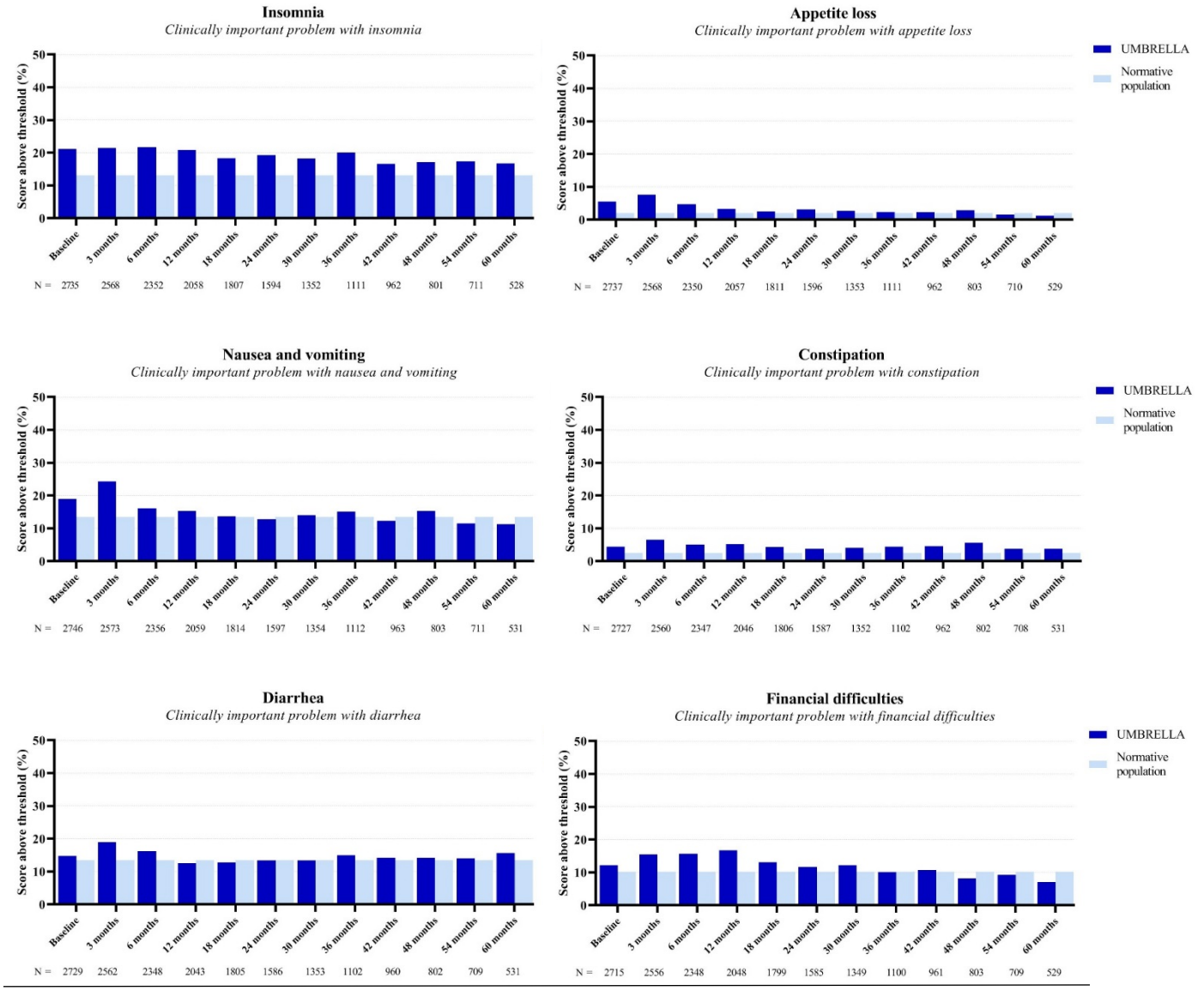
	Responders [a] *n* = 3334	Non-responders *n* = 632	UMBRELLA cohort *n* = 3966	Breast cancer patients [b] *n* =162774
Age at incidence in years [mean (SD)]	58.1 (11.0)	59.0 (12.5)	58 (11)	62 (13)
Body mass index [c] in kg/m^2 [median (IQR)]	25.4 (5.9)	26.0 (6.7)	26 (5)	N.A.
Sex [*n* (%)]				
Female	3322 (99.6)	630 (99.7)	3952 (100)	161678 (99)
Male	12 (0.4)	2 (0.3)	14 (<0.01)	1096 (1)
Smoking status [*n* (%)]				
Smoker	209 (6.7)	N.A.	212 (5)	N.A.
Previous smoker	1524 (48.9)		1533 (39)	
Non-smoker	1383 (44.4)		1392 (35)	
Unknown	218		829 (21)	
Highest educational level [*n* (%)]				
No education or primary school	125 (3.9)	N.A.	127 (3)	N.A.
Secondary education (VMBO/HAVO/VWO)	821 (25.3)		826 (21)	
Secondary vocational education (MBO)	783 (24.2)		791 (20)	
Higher professional education (HBO)	992 (30.6)		998 (25)	
University degree (WO)	521 (16.1)		525 (13)	
Unknown	92		699 (18)	
Pathological T stadium [*n* (%)]				
0	205 (6.5)	47 (8.5)	252 (6)	7262 (4)
In situ	325 (10.3)	50 (9.0)	375 (10)	19329 (12)
1	1832 (57.9)	295 (53.1)	2127 (54)	79269 (49)
2	640 (20.2)	125 (22.5)	765 (19)	30270 (19)
3	83 (2.6)	18 (3.2)	101 (3)	4164 (3)
4	7 (0.2)	4 (0.7)	11 (0)	967 (1)
X, not evaluated	74 (2.3)	17 (3.1)	91 (2)	19160 (12)
Unknown	168	76	244 (6)	2353 (1)
Pathological N stadium [*n* (%)]				
0	2024 (63.9)	337 (60.6)	2361 (60)	98477 (60)
1	810 (25.6)	145 (26.1)	955 (24)	29093 (18)
2	82 (2.5)	21 (3.8)	103 (3)	3960 (2)
3	35 (1.1)	12 (2.2)	47 (1)	2192 (1)
X, not evaluated	215 (6.8)	41 (7.4)	256 (7)	19155 (12)
Unknown	168	76	244 (6)	9897 (6)
Estrogen receptor status [*n* (%)]				
Positive [d]	2389 (84.0)	408 (77.9)	2797 (71)	118028 (73)
Negative	455 (16.0)	116 (22.1)	571 (14)	21021 (13)
Unknown	490	108	598 (15)	23725 (15)
HER2 receptor status [*n* (%)]				
Positive	405 (14.3)	87 (16.6)	492 (12)	17252 (11)
Negative	2418 (85.7)	436 (83.4)	2854 (72)	117555 (72)
Unknown	511	109	620 (16)	27967 (17)
Type of breast surgery [*n* (%)]				
Breast-conserving surgery	2557 (77.0)	412 (66.5)	2969 (75)	90958 (56)
Mastectomy without direct reconstruction	350 (10.5)	85 (13.7)	435 (11)	37634 (23)
Mastectomy with direct reconstruction	258 (7.8)	58 (9.4)	316 (8)	14660 (9)
No breast surgery	154 (4.6)	65 (10.5)	219 (6)	19225 (12)
Unknown [e]	15	12	27 (1)	297 (0)
Axillary treatment [*n* (%)]				
Sentinel node procedure	2642 (82.3)	446 (77.3)	3088 (78)	112321 (69)
Axillary lymph node dissection +/- SNP	240 (7.2)	51 (8.8)	291 (7)	15798 (10)
Not performed	327 (10.2)	80 (13.9)	407 (10)	34655 (21)
Unknown	125	55	180 (5)	-
Chemotherapy [*n* (%)]				
Yes	1323 (41.2)	269 (46.5)	1592 (40)	48982 (30)
No	1886 (58.8)	310 (53.5)	2196 (55)	113792 (70)
Unknown	125	53	178 (5)	-
Hormone therapy [f] [*n* (%)]				
Yes	1537 (47.9)	258 (44.6)	1795 (45)	79925 (49)
No	1672 (52.1)	321 (55.4)	1993 (50)	82849 (51)
Unknown	125	53	178 (5)	-
Targeted therapy [*n* (%)]				
Yes	371 (11.6)	79 (13.6)	450 (11)	14550 (9)
No	2838 (88.4)	500 (86.4)	3338 (84)	148224 (91)
Unknown	125	53	178 (5)	-
Type of radiotherapy [g] [*n* (%)]				
No radiation therapy	200 (6.3)	103 (17.9)	303 (8)	62687 (39)
Local with boost	874 (27.4)	110 (19.2)	984 (26)	25442 (16)
Local without boost	1127 (38.5)	171 (29.8)	1398 (35)	41370 (25)
Locoregional with boost	292 (9.2)	53 (9.2)	345 (9)	8575 (5)
Locoregional without boost	484 (15.2)	101 (17.6)	585 (15)	17435 (11)
Other type of radiotherapy [h]	113 (3.5)	36 (6.3)	149 (4)	5063 (3)
Unknown	144	58	202 (5)	2202 (1)

Categories may not sum to total N or 100% because of missing values or rounding. For the comparison of responders versus non-responders, percentages are calculated for the valid numbers. For the comparison of the UMBRELLA cohort versus all breast cancer patients, percentages are calculated for all numbers and are rounded to whole numbers.
Unknown is (mostly) when clinical data is not available by the Netherlands Cancer Registry.
Continuous outcomes are shown as mean (SD) when normally distributed and median (IQR) when not normally distributed.
N.A. not applicable, as measures are based on questionnaires and thus cannot be calculated. *HER2* human epidermal growth factor receptor 2.
[a] Responders are included in the study. Categorized to responders when at least one questionnaire is filled in.
[b] Breast cancer consists of invasive mamma carcinoma, ductal carcinoma in situ and lobular carcinoma in situ. Breast cancer patients are both males and females of 18 years and older. Incidence years 2013-2021, of which 2020 and 2021 are not fully registered yet.
[c] Calculated as weight divided by height^2. The first measured BMI is used.
[d] Estrogen receptor positive >10%.
[e] Surgery type unknown or when clinical data was not available for UMBRELLA participants.
[f] Aromatase inhibitor and/or tamoxifen.
[g] Radiotherapy on the breast or chest wall with or without boost on the tumor bed.
[h] Partial breast and other types, e.g. when radiotherapy is only given on the regional glands.

Appendix 4. Longitudinal examination of clinically relevant impairments in Quality of Life

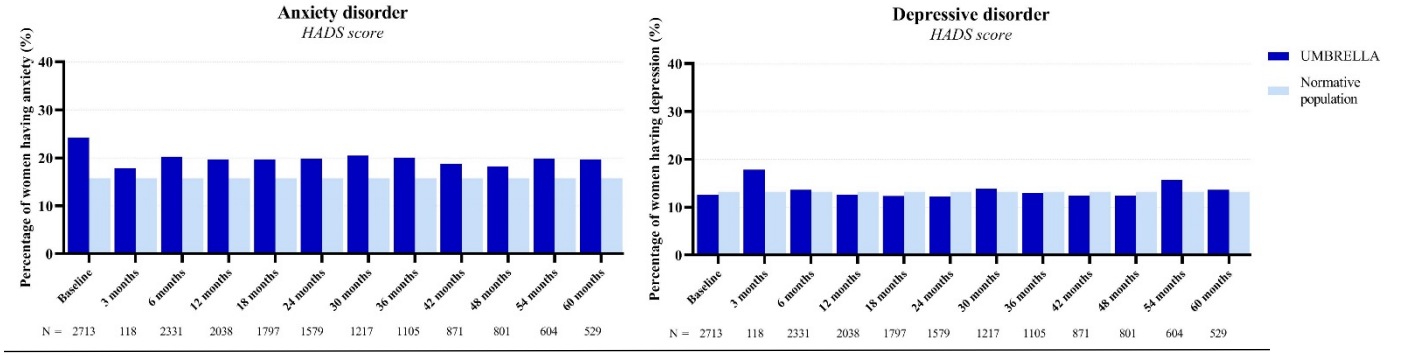
Figure 1. Examination over time of the proportions of clinically relevant and important QoL for the UMBRELLA population (n=3197) compared to the general population (n=879).





Thresholds for clinical importance were used to identify patient with clinically important PROs for the EORTC C30 questionnaire. Women who score below the TCI for functioning scales, or above the TCI for symptom scales, experience clinically relevant and important problems or symptoms.
n number of participants, *%* proportion of women.

Figure 2. Examination over time of the proportions of anxiety and depressive disorders for the UMBRELLA population (n=3197) compared to the general population (n=879).



Anxiety and depression were assessed by means of the HADS questionnaire. A score of ≥ 8 indicates an increased risk of anxiety or depressive disorders.
n number of participants, *%* proportion of women.

Appendix 5. Chi-squared test at five years follow-up

Table 1. Comparison of the proportions of clinically relevant and important problems of the QoL domains for the UMBRELLA population (n=531) versus the normative population (n=879) at five years using a chi-squared test.

Scale	P value	UMBRELLA population N (%)	Normative population N (%)
Physical functioning	**0.019**		
Problem		152 (28.7)	203 (23.1)
Good		378 (71.3)	676 (76.9)
Role functioning	0.313		
Problem		66 (12.5)	94 (10.7)
Good		464 (87.5)	785 (89.3)
Emotional functioning	**0.041**		
Problem		125 (23.5)	167 (19.0)
Good		406 (76.5)	712 (81.0)
Cognitive functioning	**0.000**		
Problem		158 (29.8)	112 (12.7)
Good		373 (70.2)	767 (87.3)
Social functioning	0.411		
Problem		32 (6.0)	44 (5.0)
Good		499 (94.0)	835 (95.0)
Fatigue	0.248		
Problem		100 (18.9)	145 (16.5)
Good		429(81.1)	734 (83.5)
Nausea and vomiting	0.221		
Problem		60 (11.3)	119 (13.5)
Good		471 (88.7)	760 (86.5)
Pain	0.270		
Problem		149 (28.1)	271 (30.8)
Good		382 (71.9)	608 (69.2)
Dyspnea	**0.000**		
Problem		145 (27.5)	163 (18.5)
Good		382 (72.5)	716 (81.5)
Insomnia	0.055		
Problem		88 (16.7)	114 (13.0)
Good		440 (83.3)	765 (87.0)
Appetite loss	0.319		
Problem		7 (1.3)	18 (2.0)
Good		522 (98.7)	861 (98.0)
Constipation	0.176		
Problem		20 (3.8)	22 (2.5)
Good		511 (96.2)	857 (97.5)
Diarrhea	0.277		
Problem		83 (15.6)	119 (13.5)
Good		448 (84.4)	760 (86.5)
Financial difficulties	**0.040**		
Problem		37 (7.0)	90 (10.2)
Good		492 (93.0)	789 (89.8)
Anxiety			
Anxiety disorder	0.061	104 (19.7)	126 (15.7)
No anxiety		425 (80.3)	677 (84.3)
Depression	0.830		
Depression disorder		72 (13.6)	106 (13.2%)
No depression		457 (86.4)	697 (86.8%)

The chi-squared test is used to examine the differences in proportions of clinically relevant problems at five years between the UMBRELLA and the general female population for the different QoL domains.
% is calculated for each scale within each population group.
P values are two-sided. P values that are statistically significant ($p<0.05$) are highlighted in bold.
Categories may not sum to total N because of missing values.

Appendix 6. Complete case analysis versus analysis of imputed data

Table 1. Patient-, tumor-, and treatment characteristics of crude data versus imputed data.

	Crude dataset *n* = 3197	**Imputed dataset** *n* = 3197
Age at inclusion in years [mean (SD)]	58 (11)	58 (11)
Body mass index [a] in kg/m² [median (IQR)]	26.5 (5.3)	25.5 (5.9)
Unknown	210 (7)	
Highest educational level		
Low	1672 (52)	1732 (54)
High	1433 (45)	1465 (46)
Unknown	92 (3)	
Pathological T stadium		
0 / In Situ	530 (17)	555 (17)
1	1825 (57)	1826 (57)
2	635 (20)	648 (20)
3/4	90 (3)	93 (3)
Cannot be evaluated	74 (2)	75 (2)
Unknown	43 (1)	
Pathological N stadium		
0	2024 (63)	2047 (64)
1,2,3	915 (29)	918 (29)
Cannot be evaluated	215 (7)	232 (7)
Unknown	43 (1)	
Type of breast surgery		
Breast-conserving surgery	2556 (80)	2560 (80)
Mastectomy without direct reconstruction	339 (11)	343 (11)
Direct reconstruction	258 (8)	261 (8)
No breast surgery	29 (1)	33 (1)
Unknown	15 (0.5)	
Axillary treatment		
Sentinel node procedure (SNP)	2633 (82)	2633 (82)
Axillary lymph node dissection +/- SNP	238 (7)	238 (7)
No axillary treatment	326 (10)	326 (10)
Type of radiotherapy		
Local	2142 (67)	2178 (68)
Locoregional	767 (24)	807 (25)
No radiation therapy	200 (6)	212 (7)
Unknown	88 (3)	
Radiotherapy boost		
RT without boost	1813 (57)	1817 (57)
RT with boost	1165 (36)	1173 (37)
No radiation therapy	200 (6)	207 (6.5)
Unknown	19 (1)	
Chemotherapy		
Yes	1317 (41)	1317 (41)
No	1880 (59)	1880 (59)
Hormone therapy		
Yes	1528 (48)	1528 (48)
No	1669 (52)	1669 (52)
Targeted therapy		
Yes	371 (12)	371 (12)
No	2826 (88)	2826 (88)
Baseline physical functioning (mean(SD))	86 (16)	86 (16)
Unknown	449 (14)	
Baseline cognitive functioning (mean(SD))	83 (20)	83 (20)
Unknown	463 (14)	
Baseline dyspnea (mean(SD))	10 (20)	10 (20)
Unknown	459 (14)	
Baseline anxiety		
Anxiety disorder	656 (21)	779 (24)
No anxiety disorder	2057 (64)	2418 (76)
Unknown	484 (15)	

Total percentage of categories may be other than 100% because of rounding The numbers are shown as *n (%)* unless it is stated otherwise.
Continuous outcomes are shown as mean (SD) when normally distributed and otherwise as median (IQR).
n number of participants, *%* percentage of participants, *SD* standard deviation, *IQR* interquartile range.
[a] Calculated as weight divided by height^2. The first measured BMI is used.

Table 2A. Sensitivity analysis for physical functioning (PF): complete cases univariable analysis versus analysis with imputed data.

	PF – crude dataset OR (95% CI)	**PF – imputed dataset** OR (95% CI)
Age, per year	1.05 (1.03-1.07)*	1.05 (1.03-1.07)*
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	1.18 (0.80-1.74)	1.18 (0.80-1.74)
Smoker	0.97 (0.34-2.80)	0.97 (0.33-2.81)
Education		
Low	Ref.	Ref.
High	0.47 (0.32-0.70)	0.47 (0.32-0.70)*
Body mass index	1.13 (1.08-1.18)	1.13 (1.08-1.18)*
T-stadium		
T0/Tis	Ref.	Ref.
T1	1.16 (0.66-2.06)	1.17 (0.66-2.07)
T2	1.55 (0.79-3.05)	1.56 (0.79-3.06)
T3/T4	4.74 (1.49-15.03)*	4.68 (1.47-14.90)*
Tx	1.72 (0.56-5.28)	1.70 (0.55-5.23)
N-stadium		
N0	Ref.	Ref.
N+	1.39 (0.93-2.09)	1.40 (0.93-2.10)
Nx	1.24 (0.52-2.95)	1.19 (0.50-2.82)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Mastectomy without breast reconstruction	1.71 (0.95-3.10)	1.71 (0.95-3.10)
Breast reconstruction	0.52 (0.21-1.29)	0.52 (0.21-1.29)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	1.13 (0.63-2.01)	1.13 (0.63-2.02)
No axillary surgery	0.47 (0.18-1.24)	0.47 (0.18-1.25)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.43 (0.90-2.29)	1.51 (0.95-2.39)
No radiation received	2.19 (0.80-6.04)	2.31 (0.84-6.30)
Radiotherapy boost		
No	Ref.	Ref.
Yes	0.80 (0.54-1.19)	0.80 (0.54-1.18)
No radiation received	1.82 (0.66-5.06)	1.92 (0.70-5.32)
Chemotherapy		
No	Ref.	Ref.
Yes	0.92 (0.63-1.35)	0.92 (0.63-1.35)
Hormonal therapy		
No	Ref.	Ref.
Yes	1.14 (0.78-1.66)	1.14 (0.78-1.66)
Targeted therapy		
No	Ref.	Ref.
Yes	0.72 (0.37-1.42)	0.72 (0.37-1.42)
Baseline physical functioning, score 0-100 [b]	0.95 (0.93-0.96)	0.95 (0.93 – 0.96)*

Table 2B. Sensitivity analysis for cognitive functioning (CF): complete cases univariable analysis versus analysis with imputed data.

	CF – crude dataset OR (95% CI)	**CF – imputed dataset** OR (95% CI)
Age, per year	0.98 (0.96-1.00)	0.98 (0.96-1.00)
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	0.97 (0.67-1.42)	0.97 (0.66-1.42)
Smoker	0.83 (0.29-2.38)	0.82 (0.29-2.38)
Education		
Low	Ref.	Ref.
High	1.26 (0.87 – 1.83)	1.26 (0.87 – 1.83)
Body mass index	0.99 (0.96-1.04)	0.99 (0.95-1.04)
T-stadium		
T0/Tis	Ref.	Ref.
T1	1.32 (0.76-2.32)	1.33 (0.76-2.33)
T2	1.43 (0.73-2.79)	1.43 (0.73-2.80)
T3/T4	0.74 (0.19-2.88)	0.74 (0.19-2.88)
Tx	0.84 (0.25-2.86)	0.84 (0.25-2.84)

N-stadium		
N0	Ref.	Ref.
N+	1.56 (1.04-2.32)*	1.56 (1.04-2.23)*
Nx	1.00 (0.41-2.46)	0.96 (0.39-2.36)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Mastectomy without breast reconstruction	1.08 (0.58-2.01)	1.08 (0.58-2.02)
Breast reconstruction	0.94 (0.44-2.02)	0.94 (0.44-2.02)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	1.08 (0.61-1.93)	1.08 (0.60-1.94)
No axillary surgery	0.68 (0.29-1.62)	0.68 (0.29-1.62)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.42 (0.89-2.25)	1.35 (0.86-2.12)
No radiation received	1.16 (0.40-3.42)	1.12 (0.38-3.29)
Radiotherapy boost		
No	Ref.	Ref.
Yes	1.33 (0.91-1.94)	1.33 (0.91-1.95)
No radiation received	1.23 (0.42-3.66)	1.28 (0.43-3.82)
Chemotherapy		
No	Ref.	Ref.
Yes	1.82 (1.25-2.65)*	1.82 (1.25-2.65)*
Hormonal therapy		
No	Ref.	Ref.
Yes	1.29 (0.89-1.88)	1.29 (0.89-1.88)
Targeted therapy		
No	Ref.	Ref.
Yes	1.28 (0.70-2.35)	1.28 (0.70-2.35)
Baseline cognitive functioning, score 0-100 [b]	0.97 (0.96-0.98)*	0.97 (0.96-0.98)*

Table 2C. Sensitivity analysis for dyspnea: complete cases univariable analysis versus analysis with imputed data.

	Dyspnea – crude dataset OR (95% CI)	**Dyspnea – imputed dataset** OR (95% CI)
Age, per year	1.03 (1.01-1.05)*	1.03 (1.01-1.05)*
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	1.09 (0.74-1.61)	1.09 (0.74-1.61)
Smoker	0.73 (0.23-2.28)	0.73 (0.23-2.29)
Education		
Low	Ref.	Ref.
High	0.50 (0.34-0.75)*	0.50 (0.34-0.75)*
Body mass index	1.07 (1.03-1.11)*	1.07 (1.03-1.11)*
T-stadium		
T0/Tis	Ref.	Ref.
T1	0.82 (0.48-1.42)	0.83 (0.48-1.43)
T2	1.20 (0.62-2.31)	1.20 (0.62-2.31)
T3/T4	0.97 (0.28-3.42)	0.97 (0.28-3.42)
Tx	1.33 (0.44-4.02)	1.31 (0.43-3.98)
N-stadium		
N0	Ref.	Ref.
N+	1.37 (0.90-2.07)	1.37 (0.90-2.07)
Nx	2.23 (0.98-5.04)	2.12 (0.94-4.77)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Mastectomy without breast reconstruction	1.14 (0.60-2.17)	1.14 (0.60-2.17)
Breast reconstruction	0.92 (0.42-2.03)	0.92 (0.42-2.03)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	2.29 (1.32-4.00)*	2.29 (1.32-4.00)*
No axillary surgery	1.43 (0.65-3.13)	1.43 (0.65-3.13)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.17 (0.72-1.89)	1.15 (0.72-1.85)
No radiation received	1.23 (0.42-3.62)	1.23 (0.42-3.62)
Radiotherapy boost		
No	Ref.	Ref.
Yes	0.97 (0.66-1.44)	0.97 (0.66-1.44)
No radiation received	1.20 (0.40-3.56)	1.26 (0.42-3.75)

Chemotherapy		
No	Ref.	Ref.
Yes	1.29 (0.88-1.90)	1.29 (0.88-1.90)
Hormonal therapy		
No	Ref.	Ref.
Yes	0.86 (0.59-1.26)	0.86 (0.59-1.26)
Targeted therapy		
No	Ref.	Ref.
Yes	1.45 (0.79-2.66)	1.45 (0.79-2.66)
Baseline dyspnea, score 0-100 [b]	1.04 (1.03-1.05)*	1.04 (1.03-1.05)*

Table 2D. Sensitivity analysis for anxiety: complete cases univariable analysis versus analysis with imputed data.

	Anxiety - crude dataset OR (95% CI)	**Anxiety - imputed dataset** OR (95% CI)
Age, per year	0.99 (0.97-1.02)	0.99 (0.97-1.02)
Smoking		
Non-smoker	Ref.	Ref.
Previous smoker	1.05 (0.67-1.62)	1.05 (0.67-1.62)
Smoker	1.12 (0.36-3.54)	1.12 (0.35-3.55)
Education		
Low	Ref.	Ref.
High	1.02 (0.67-1.57)	1.02 (0.66-1.57)
Body mass index	1.00 (0.95-1.04)	1.00 (0.95-1.04)
T-stadium		
T0/Tis	Ref.	Ref.
T1	0.93 (0.49-1.74)	0.93 (0.49-1.75)
T2	1.55 (0.75-3.22)	1.55 (0.75-3.23)
T3/T4	0.99 (0.25-3.90)	0.98 (0.25-3.90)
Tx	1.21 (0.35-4.24)	1.21 (0.35-4.21)
N-stadium		
N0	Ref.	Ref.
N+	1.72 (1.10-2.70)*	1.72 (1.10-2.71)*
Nx	0.89 (0.30-2.67)	0.86 (0.28-2.58)
Type of surgery		
Breast conserving surgery	Ref.	Ref.
Mastectomy without breast reconstruction	1.66 (0.86-3.21)	1.66 (0.86-3.22)
Breast reconstruction	1.88 (0.87-4.09)	1.88 (0.86-4.09)
No breast surgery	N.A.	N.A.
Type of axillary surgery		
Sentinel node procedure (SNP)	Ref.	Ref.
Axillary lymph node dissection +/- SNP	2.34 (1.30-4.23)*	2.34 (1.30-4.24)*
No axillary surgery	1.37 (0.57-3.29)	1.37 (0.57-3.30)
Type of radiotherapy		
Local radiotherapy [a]	Ref.	Ref.
Locoregional radiotherapy	1.27 (0.74-2.18)	1.33 (0.79-2.27)
No radiation received	1.66 (0.51-5.37)	1.73 (0.53-5.66)
Radiotherapy boost		
No	Ref.	Ref.
Yes	0.93 (0.60-1.44)	0.93 (0.60-1.45)
No radiation received	1.47 (0.45-4.78)	1.54 (0.47-5.04)
Chemotherapy		
No	Ref.	Ref.
Yes	1.42 (0.92-2.18)	1.42 (0.92-2.18)
Hormonal therapy		
No	Ref.	Ref.
Yes	1.50 (0.96-2.32)	1.50 (0.96-2.33)
Targeted therapy		
No	Ref.	Ref.
Yes	1.41 (0.73-2.76)	1.41 (0.72-2.76)
Baseline anxiety [b]		
< 8, no anxiety	Ref.	Ref.
≥ 8 anxiety disorder	5.03 (3.07-8.24)*	4.60 (2.83-7.45)*

Appendix 7. Baseline characteristics of responders and non-responders at five years follow-up

Table 1. Patient, tumor, and treatment characteristics of UMBRELLA participants (n=1115) who responded to the questionnaires (n=588, 53%) versus non-responders (n=527, 47%) at five years follow-up.

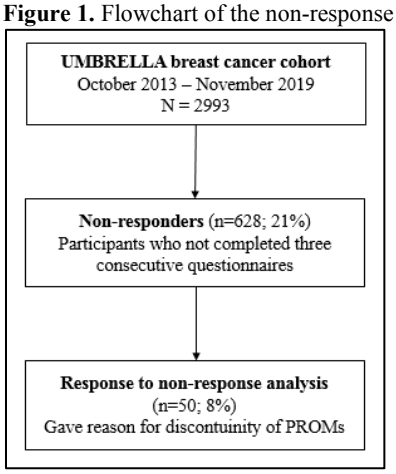
	Responders N = 588	**Non-responders** N = 527
Age at incidence in years [mean (SD)]	58.7 (9.8)	57.1 (11.5)
Body mass index in kg/m2 [median (IQR)] [a]	25.6 (5.6)	25.9 (6.6)
Smoking status [n (%)]		
Smoker	23 (3.9)	34 (8.2)
Previous smoker	293 (50.0)	184 (44.4)
Non-smoker	270 (46.1)	196 (47.3)
Unknown	2	113
Educational level [b]		
Low	304 (51.9)	274 (60.1)
High	282 (48.1)	182 (39.9)
Unknown	2	71
T-stadium [n (%)] [c]		
T0/Tis	87 (14.9)	69 (14.3)
T1	36 (61.5)	275 (57.2)
T2	105 (17.9)	110 (22.9)
T3/T4	15 (2.6)	18 (3.7)
Tx [d]	18 (3.1)	9 (1.9)
Unknown	3	46
N-stadium [n (%)]		
N0	378 (64.6)	302 (62.8)
N+ [e]	175 (29.9)	161 (33.5)
Nx [d]	32 (5.5)	18 (3.7)
Unknown	3	46
Type of surgery [n (%)]		
Breast conserving surgery	492 (84.0)	380 (78.4)
Mastectomy without breast reconstruction	53 (9.0)	68 (14.0)
Breast reconstruction	39 (6.7)	32 (6.6)
No breast surgery	2 (0.3)	5 (1.0)
Unknown	2	42
Type of axillary surgery [n (%)]		
Sentinel node procedure (SNP)	489 (83.4)	378 (77.8)
Axillary lymph node dissection +/- SNP	59 (10.1)	76 (15.6)
No axillary surgery	38 (6.5)	32 (6.6)
Unknown	2	41
Type of radiotherapy [n (%)] [f]		
Local radiotherapy [g]	441 (77.0)	331 (70.0)
Locoregional radiotherapy	114 (19.9)	122 (25.8)
No radiation received	18 (3.1)	20 (4.2)
Unknown	15	54
Radiotherapy boost [n (%)]		
Yes	259 (44.3)	209 (43.1)
No	307 (52.6)	256 (52.8)
No radiation received	18 (3.1)	20 (4.1)
Unknown	4	42
Chemotherapy [n (%)]		
Yes	244 (41.6)	221 (45.5)
No	342 (58.4)	265 (54.5)
Unknown	2	41
Hormonal therapy [n (%)]		
Yes	312 (53.2)	248 (51.0)
No	274 (46.8)	238 (49.0)
Unknown	2	41
Targeted therapy [n (%)]		
Yes	54 (9.2)	60 (12.3)
No	532 (90.8)	426 (87.7)
Unknown	2	41
Baseline physical functioning [n (%)]		
Clinically relevant and important problem	154 (29.0)	146 (36.2)
Good functioning	377 (71.0)	257 (63.8)
Unknown	57	124
Baseline cognitive functioning [n (%)]		
Clinically relevant and important problem	161 (30.4)	131 (32.9)
Good functioning	368 (69.6)	267 (67.1)
Unknown	59	129
Baseline dyspnea [n (%)]		
Clinically relevant and important problem	111 (21.0)	122 (30.3)
Good functioning	418 (79.0)	280 (69.7)
Unknown	59	402

Baseline anxiety [n (%)]		
Anxiety disorder	124 (23.5)	114 (28.5)
No anxiety disorder	404 (76.5)	286 (71.5)
Unknown	60	127

Responders filled in the questionnaire at 60 months. Non-responders did not completed the questionnaire at 60 months, dropped-out the study, or died during the five years follow-up.
Continuous outcomes are shown as mean (SD) when normally distributed and otherwise as median (IQR).
n number of participants, *%* percentage of participants, *SD* standard deviation, *IQR* interquartile range.
[a] Calculated as weight divided by height^2. The first measured BMI is used. [b] Low when no schooling, secondary or vocational education is completed. High when completed college, graduate or professional degree. [c] *T0* means there is no evidence of the primary tumor. *Tis* means tumor is in situ. [d] The tumor or lymph nodes cannot be assessed. [e] >N0, so pathological N stages 1, 2 and 3. [f] Radiation therapy on periclavicular and / or axillary lymph nodes. [g] Partial breast and other types, e.g. radiation on the regional glands.

Appendix 8. Non-response analysis

Figure 1. Flowchart of the non-response analysis within the UMBRELLA cohort.



n number of participants, *%* percentage of participants

Table 1. Quotes of breast cancer patients regarding study-related factors for non-responding

Quote number	Participation after analysis	Underlying reason	Quote
Quote 1	Stopped	Aversion to the study	"Het kostte mij erg veel moeite om er de motivatie voor op te brengen. Dat werd eigenlijk steeds erger naarmate ik merkte dat mij de zin van jullie onderzoek behoorlijk ontgaat. Als cijfer-gevoelig mens bestudeerde ik jullie grafieken en dacht: so what? Wie gaat hier wat dan ook mee doen?"
Quote 2	Stopped	Confrontational study	"Hierbij meld ik me af. Ik heb herhaaldelijk de vragenlijsten ingevuld. De gevolgen van borstkanker zijn voor mij zeer ingrijpend geweest. De vragenlijst en vind ik daarom te confronterend. Ik probeer, en dat kost heel veel moeite en energie, positief naar de toekomst te kijken."
Quote 3	Continued	Confrontational study	"Het spijt me dat u een aantal lijsten van mij niet heeft ontvangen. Eerlijk gezegd hikte ik steeds meer tegen de vragenlijst aan. Ondanks dat het best goed met mij gaat en ik weinig reden tot klagen heb, merkte ik met het invullen van de vragenlijsten dat het hele traject toch meer impact heeft dan ik zou willen. Op sommige punten vond ik dit confronterend."
Quote 4	Stopped	Closure of breast cancer phase	"Het periode dat ik bezig was met behandeling was heel zwaar voor me, en nu dat het goed met me gaat wil ik niet meer herinnerd worden is nog steeds pijnlijk voor me."
Quote 5	Stopped	Difficulty with the questions	"Mijn insteek was om zeker met jullie onderzoeken mee te doen, ik snap namelijk dat het belangrijk is. Maar het kostte mij te veel.. vond de vragenlijst lang en keuzes maken bij het invullen, is niet mijn sterke punt, ik twijfel nogal. En bracht het me onnodig meer 'stress' voor mij op."
Quote 6	Continued	Difficulty with questions	"Omdat het mogelijk van belang zou kunnen zijn, heb ik toch zojuist de laatste vragenlijst ingevuld. Ik zie er wel tegenop, omdat er veel vragen bij zijn, die ik lastig te bepalen vind wat ik daar moet invullen. Het kost ook meer energie dan voorheen om dingen op te pakken."

Table 2. Quotes of breast cancer patients regarding participant-related factors for non-responding

Quote number	Participation after analysis	Underlying reason	Quote
Quote 1	Stopped	Overloaded participant	"De reden waarom ik mij laat uitschrijven is simpelweg dat het mij momenteel niet lukt en het even niet past in mijn overvolle hoofd en leven. "
Quote 2	Continued	Overloaded participant	"Had eerder niet ingevuld vanwege allerlei omstandigheden. Wil wel blijven meedoen."
Quote 3	Continued	Time constraints of participant	"Ik wil mee blijven doen met het onderzoek. Door drukte de afgelopen tijd niet aan toe gekomen."
Quote 4	Continued	Laziness of the participant	"Ik wil zeker mee blijven doen, maar ik merk in de praktijk dat ik het invullen van het onderzoek vergeet. Een mail wordt gemakkelijker vergeten dan een brief. Ik heb het druk en stel het beantwoorden uit merk ik en na een tijdje is het zo lang geleden dat ik het vergeet. Wellicht helpt het om de vragenlijst op papier te ontvangen. "

Quote 5	Stopped	Incompetence of participant	“Wil stoppen, vindt zichzelf te oud om mee te doen. “
Quote 6	Stopped	Deceased participant	“Op 2 oktober jl. is mijn moeder overleden. Dit als gevolg van hartproblemen (dus niet a.g.v. borstkanker). “

Table 3. Quotes of breast cancer patients regarding logistics-related factors for non-responding

Quote number	Participation after analysis	Underlying reason	Quote
Quote 1	Stopped	Online problems	“Ik doe niet meer mee omdat het bijna niet te doen is de lijst op een telefoon in te vullen.“
Quote 2	Continued	Online problems	“De rede dat ik niet heb meegedaan met het onderzoek is voornamelijk dat ik het op de computer niet voor elkaar kreeg. Ben er niet handig mee, vond het te ingewikkeld.”
Quote 3	Continued	Online problems	“Ik heb diverse keren geprobeerd de ingevulde vragenlijsten per mail te retourneren wat steeds niet ging.”
Quote 4	Stopped	Administrative problems	“Mw. woont in Zwitserland.“
Quote 5	Continued	Administrative problems	“Reden dat u geen ingevulde vragenlijsten van mij meer heeft ontvangen, is dat u een oud adres heeft. Als u de wijziging aan past, dan kan ik in het vervolg de vragenlijsten op het juiste adres ontvangen.“
Quote 6	Continued	Administrative problems	“Ik heb al heel lang vragenlijsten meer ontvangen!!! Wel zie ik het nut ervan in om goed onderzoek te doen naar aanleiding van borstkanker en de behandelingen die plaats vinden en of daar eventueel lachten zijn door ontstaan. Misschien iets mis gegaan met het juiste email adres???? Mijn mailadres is overigens niet gewijzigd en zal het nogmaals opnieuw vermelden.“

Appendix 9. Agreement between fatigue and dyspnea at five years follow-up

Table 1. The level of agreement between clinically relevant fatigue and clinically relevant dyspnea at five years.

	Clinically important problem with dyspnea	No problem with dyspnea	Total [*n(%)*]
Clinically important problem with fatigue	60	38	98 (18.6)
% within dyspnea	41.4%	10.0%	
% of total	11.4%	7.2%	
No problem with fatigue	85	343	428 (81.4)
% within dyspnea	58.6%	90.0%	
% of total	16.2%	65.2%	
Total [*n(%)*]	145 (27.6)	381 (72.4)	526 (100)

Agreement = (60 + 343) / 526 = 76.6%