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Original Research

Reference values for the EORTC QLQ-C30 in early and metastatic breast cancer

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Abstract ***Background:*** Considering the worldwide incidence of breast cancer (BC) and the importance of health-related quality of life (HRQoL) assessment, there is a growing need to have accurate and up-to-date reference values (RVs). RVs are useful for the design of randomised controlled trials (RCTs) and as benchmarks for comparison of cancer RCTs and health care interventions. This study aimed to provide RVs for the QLQ-C30 in early BC (EBC) and metastatic BC (MBC). General patterns of main results from the EORTC dataset (main dataset) were compared with the PDS dataset (comparison dataset) to see whether they would be consistent across pre-defined covariates.
Methods: European Organization for Research and Treatment of Cancer (EORTC) (main dataset) and Project Data Sphere (PDS) (comparison dataset) were searched to identify BC

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RCTs where baseline HRQoL (before treatment) was assessed with the QLQ-C30. RVs were calculated and stratified by disease stage, age, and when available, performance status (PS), comorbidity and region. RVs were reported using descriptive statistics.
Results: Data from three EORTC (n = 4115) and three PDS RCTs (n = 1406) were included in the analysis. While EBC patients presented better HRQoL with high baseline functioning scores and low prevalence of symptoms, MBC patients reported worse HRQoL with lower functioning scores and more prevalence of symptoms. In MBC, poor PS and presence of comorbidities reflected worse baseline HRQoL. No consistent differences were found for age and countries.
Conclusion: These up-to-date RVs for the EORTC QLQ-C30 in BC show differences in HRQoL scores between stages, PS, and comorbidities. These findings, supported by an independent dataset, will help the clinical interpretation of scores for BCpatients.

1. Background

Health-related quality of life (HRQoL) is increasingly recognised as an important outcome in cancer research [1] and care [2]. However, findings from HRQoL data are only relevant if they are interpreted in a clinically meaningful way [3]. Reference values (RVs) address this need by providing information about HRQoL scores for specific cancer populations. Their value is recognised for the design of randomised controlled trials (RCTs) and as a benchmark for comparison and interpretation of cancer RCTs and interventions [4].

HRQoL is often assessed in breast cancer (BC) RCTs [5]. In 2018, around two million new BC cases were diagnosed worldwide [6]. It is a complex and heterogeneous disease with over five biological subtypes [7]. It is mainly divided into early BC (EBC) and metastatic BC (MBC). EBC is characterised by a good prognosis, whereas MBC is considered as treatable but incurable with a median overall survival of three years [2]. As more BC patients are surviving, it is important to know how the disease and the treatment impact their HRQoL. Several HRQoL outcomes matter to BC patients including pain, fatigue, and general HRQoL to name a few [8]. Considering the evolving landscape in BC, there is a need to have up-to-date RVs to interpret HRQoL scores in different patients.

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 is a patient-reported outcome measure to assess HRQoL among cancer patients. The EORTC QLQ-C30 includes 30 items, which are transformed into 15 scales according to a standardised scoring procedure [9]. The QLQ-C30 includes five functional scales (physical, role, emotional, cognitive, and social functioning); eight symptom scales or single items (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea); an item to assess financial difficulties; and one global health status scale (GHQ) [9] (See Table A1).

This study aimed to update previously published RVs for HRQoL scores [4] in EBC and MBC patients using the EORTC QLQ-C30 and compare it with an independent external dataset. Moreover, potential differences in RVs based on pre-specified covariates were explored.

2. Materials and methods

2.1. RCTs selection

Closed (i.e. no longer recruiting) RCTs were identified from the EORTC (main dataset) [10] and Project Data Sphere (comparison dataset) [11] databases. PDS is an independent non-profit platform designed to provide patient-level data from RCTs [11]. Inclusion criteria were phase II/III RCTs, involving BC patients with baseline HRQoL assessment using the EORTC QLQ-C30 (version 3.0). Baseline HRQoL assessment was defined as an assessment occurring one week before or after randomization, before treatment starts (Figs. 1 and 2).

2.2. Statistical analyses

RVs were presented overall and by disease stage (EBC and MBC), age (<40, 40–65, and >65) and, when available, World Health Organisation (WHO) performance status (PS) (0–2; scale ranges from 0 to 5) [12], comorbidities (not present or present), and region (Southern Europe, Anglo-Saxon countries, Northern Europe, Eastern Europe, and Rest of the World) [13]. Comorbidity was derived from the Common Terminology Criteria for Adverse Events (CTCAE) assessment at baseline (not present or present). The presence of the comorbidity was considered wherever a patient reported one or more adverse events at baseline. The absence of the comorbidity was considered when no adverse event has been reported at baseline. Cut-offs for age and comorbidities were chosen following discussions with clinicians. Findings were reported using descriptive statistics: mean, median, and standard deviations [14]. As for the overall RVs, proportion of patients with floor and ceiling effects was also reported. A threshold of 15%, derived from existing recommendations, was used to signify a potential effect [15].

To interpret differences in scores based on pre-defined covariates, the interpretation of clinically

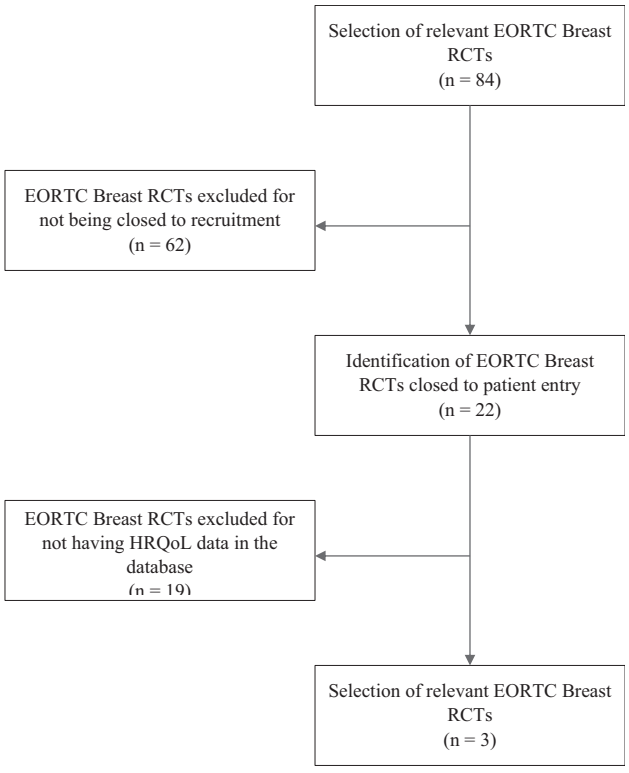

Fig. 1. Flowchart of RCTs identified in EORTC database.

meaningful important differences (MIDs) between scores was evaluated following Cocks *et al.*'s guidelines (small, medium, and large), where MIDs differed depending on the QLQ-C30 subscales (see Table 4 of Cocks *et al.*'s manuscript for the full range of scores for small, medium, and large differences) [16]. These guidelines were derived by combining results from high quality HRQoL studies, expert opinions, and meta-analysis techniques.

All EORTC QLQ-C30 scale scores range from 0 to 100. A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology [9]. Missing data were handled according to the EORTC scoring manual [17].

Data preparation and statistical analyses were performed with SAS (version 9.4, SAS Institute Inc, Cary, NC) [18].

3. Results

3.1. Datasets

A search through databases found three eligible EORTC [19–21] and three PDS RCTs [22–24] (Table 1).

3.2. Sample

Out of 4806 EBC and 127 MBC patients from EORTC trials, 4021 (83.7%) EBC and 94 (74%) MBC patients had valid baseline HRQoL assessment. Less than 2% of missing values were found for all items in EBC whereas in MBC, more than 2% were found in some scales (Q8, Q18, Q19, Q21, and Q25).

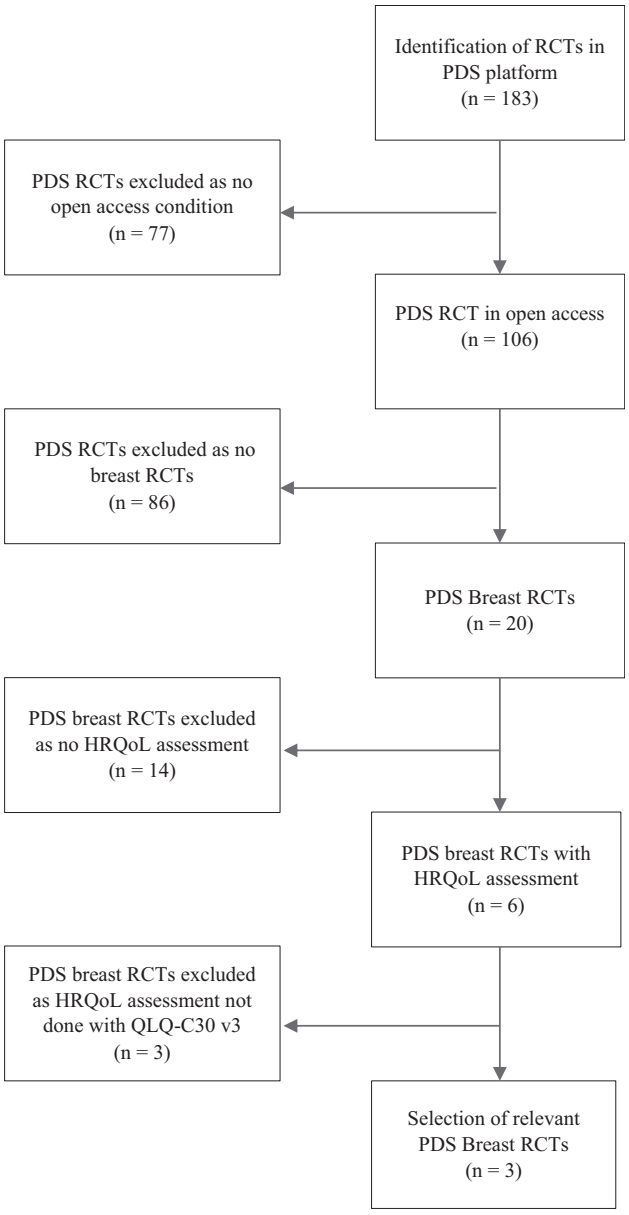

Fig. 2. Flowchart of RCTs identified in the PDS platform.

Out of 1651 EBC and 444 MBC patients from the PDS platform, 1065 EBC (64.5%) and 341 (76.8%) MBC patients were included in the analysis. Less than 2% of missing values were found for most items, with the exception of Q18 and Q27 in EBC and Q8, Q20, Q24, Q26, Q29, and Q30 in MBC.

3.3. Patient characteristics

Baseline demographic and clinical characteristics of patients are shown in Table 2. Most EBC patients were

Table 1
Description of trials included.

Trials	Database	Patient population	Number of patients available in the trial database/Number of patients included in the current study	Primary end-point	QoL end-point	Prior treatment	Line of therapy
10981-22023 NCT00014612	EORTC	Newly diagnosed EBC	4806/4021	Axillary recurrence rate	Secondary	No prior treatment	Axillary lymph node dissection versus axillary radiotherapy
10001 NCT00049660	EORTC	Pre-treated MBC	47/38	Response rate	Secondary	Prior taxane and anthracyclines therapy	Comparison of two single agent therapies (Vinorelbine versus Capecitabine)
75111 NCT01597414	EORTC	HER2-positive older and frail MBC	80/56	Progression free survival rate	Secondary	No chemotherapy for MBC	Pertuzumab with trastuzumab versus Pertuzumab with trastuzumab and metronomic chemotherapy
BCIRG-005 NCT00312208	PDS	EBC	1651/1065	Disease-free survival	Secondary	No prior systemic therapy	Doxorubicin in combination with cyclophosphamide followed by docetaxel versus docetaxel in combination with doxorubicin and cyclophosphamide
EFC6089 NCT00081796	PDS	MBC	227/170	Time to progression	Secondary	Prior anthracycline and taxane	Larotaxel versus Capecitabine
CA012-0 NCT00046527	PDS	MBC	217/171	Overall response rate	Secondary	No taxanes in MBC	ABI-007 (albumin-bound paclitaxel) versus Taxol

All information have been found in protocols.

40–65 years of age in both datasets (70.6% versus 81.1%, respectively), with a mean age of 56.7 years (SD = 10.3) in EORTC and 50.0 (SD = 9.3) in PDS trials. MBC patients (60.6%) were mainly over 65 years with a mean age of 66.2 years (SD = 15.0) in EORTC trials. In PDS trials, most MBC patients (81.2%) were 40–65 years of age, with a lower mean age of 53.3 years (SD = 9.7). Full details can be found in Table 2.

3.4. Main findings

The EBC and MBC RVs are presented in Tables 3 and 4.

3.4.1. Early breast cancer

From the EORTC trial, most EBC patients reported high mean levels of physical (M = 92.2, SD = 12.2) and social functioning (M = 92.2, SD = 15.9) with more than 53% of patients reporting the maximum levels and relatively low mean scores in emotional functioning (M = 69.5, SD = 24.0). Among all symptoms, EBC patients reported the lowest mean level of nausea/vomiting (M = 3.2, SD = 9.4) with 85.9% of patients reporting the minimum score at baseline. Insomnia was the most reported symptom (M = 27.5, SD = 28.5). The GHQ mean score was 76.9 (SD = 19.2). See also Table 3.

Similar results were found in PDS trials with 27.6% of patients reporting the maximum physical functioning score (M = 87.0, SD = 13.4). Moreover, high cognitive functioning levels (M = 85.6, SD = 18.8) were also reported. EBC patients from PDS trials reported having low mean levels of emotional functioning (M = 71.3, SD = 21.7) and low prevalence of nausea/vomiting (M = 3.8, SD = 11.1). A high proportion of patients (83.3%) reported the minimum level of this score. Insomnia was the most reported symptom (M = 29.6, SD = 29.5). The GHQ mean score was 72.4 (SD = 18.8). See also Table 3.

3.4.2. Metastatic breast cancer

EORTC trials showed that most patients reported the highest mean scores in cognitive functioning (M = 81.7, SD = 21.7) with 42.6% of patients reporting the maximum level in this scale, and lower scores in role functioning (M = 64.2, SD = 34.3). Among all symptoms, nausea/vomiting (M = 5.8, SD = 13.5) was the least reported scale for which 77.7% of patients reported the minimum score. Fatigue was the most reported symptom (M = 39.2, SD = 24.8). The GHQ mean score was 57.6 (23.1). See also Table 4.

Similar results were found in patients from PDS trials. Findings showed high levels of cognitive functioning (M = 83.5, SD = 21.7) and low mean scores in role (M = 73.1, SD = 28.5) and emotional functioning (M = 73.1, SD = 22.7). More than 45.5% of patients reported the maximum score in cognitive functioning. MBC patients reported low levels of nausea/vomiting (M = 7.7, SD = 16.4) but also diarrhea (M = 6.1, SD = 14.8) and high mean levels of fatigue (M = 33.7,

Table 2
Baseline demographic and clinical characteristics of patients from EORTC and PDS trials.

	EORTC		PDS	
	EBC patients (n = 4021)	MBC patients (n = 94)	EBC patients (n = 1065)	MBC patients (n = 341)
	No. (%)	No. (%)	No. (%)	No. (%)
Mean age *(SD)*	56.7 *(10.3)*	66.2 *(15.0)*	50 *(9.3)*	53.3 *(9.7)*
Range	24.0–87.0	30.0–89.0	27–74	30–82
Age				
<40 years	164 (4.1)	5 (5.3)	156 (14.6)	28 (8.2)
40–65 years	2840 (70.6)	32 (34.0)	864 (81.1)	277 (81.2)
>65 years	1017 (25.3)	57 (60.6)	45 (4.2)	36 (10.6)
WHO PS				
0	NA	22 (23.4)	1044 (98)	114 (33.4)
1	NA	50 (53.2)	21 [2]	146 (42.8)
2	NA	22 (23.4)	NA	10 (2.9)
Missing	NA	NA	NA	71 (20.8)
Comorbidities				
Not Present	NA	39 (41.5)	NA	NA
Present	NA	55 (58.5)	NA	NA
Country				
Southern Europe	639 (15.9)	56 (59.6)	NA	NA
Anglo-Saxon countries	168 (4.2)	24 (25.5)	NA	NA
Northern Europe	3131 (77.9)	1 (1.1)	NA	NA
Eastern Europe	83 (2.1)	13 (13.8)	NA	NA

NA: not available.

SD = 24.6). Over 77.7% of patients reported the minimum score for nausea/vomiting and diarrhea. The GHQ mean score was 54.6 (*SD* = 20.1). See also Table 4.

3.5. Secondary findings

The EBC and MBC RVs by covariates are presented in Tables 5–10.

3.5.1. Age

3.5.1.1. EBC. Across all groups, patients from the EORTC dataset reported the lowest mean levels in emotional functioning (<40: *M* = 63.8, *SD* = 23.1; 40–65: *M* = 68.9, *SD* = 20.8; and >65: *M* = 72.1, *SD* = 20.8). Physical functioning was highest in patients below 40 (*M* = 97.0, *SD*=7.5) and between 40 and 65 years old (*M* = 93.7, *SD* = 10.9), whereas social functioning was highest in patients older than 65 years of age(*M* = 94.1, *SD* = 14.6). All patients reported low mean scores in gastrointestinal symptoms [nausea/vomiting (<40: *M* = 4.1, *SD* = 10.1; 40–65: *M* = 3.3, *SD* = 9.7; and >65: *M* = 2.7, *SD* = 8.3), constipation (<40: *M* = 3.5, *SD* = 10.9; 40–65: *M* = 5.4, *SD* = 15.1; and >65: *M* = 7.1, *SD* = 18.2), and diarrhea (<40: *M* = 7.6, *SD* = 17.1; 40–65: *M* = 5.0, *SD* = 13.9; and >65: *M* = 4.9, *SD* = 13.5)]. A high prevalence of insomnia was observed (<40: *M* = 25.4, *SD* = 26.4; 40–65: *M* = 27.6, *SD* = 28.5; and >65: *M* = 27.6, *SD* = 28.9). The GHQ mean scores were similar across groups (<40: *M* = 75.3, *SD* = 19.5; 40–65: *M* = 77.4, *SD* = 19.0; and >65: *M* = 75.8, *SD* = 19.7) [16]. See also Table 5.

All patients from PDS reported having high levels of physical (<40: *M* = 90.0, *SD* = 11.0; 40–65: *M* = 86.5, *SD* = 13.7; and >65: *M* = 84.8, *SD* = 14.2) and cognitive functioning (<40: *M* = 88.4, *SD* = 18.7; 40–65: *M* = 85.1, *SD* = 19.0; and >65: *M* = 86.0, *SD* = 16.4), and lower mean scores in emotional functioning (<40: *M* = 71.7, *SD* = 22.7; 40–65: *M* = 70.9, *SD* = 21.7; and >65: *M* = 79.0, *SD* = 17.5). Patients over 65 years of age also reported high mean scores in social functioning (*M* = 84.5, *SD* = 21.4) and low levels in role functioning (*M* = 78.0, *SD* = 23.5). All patients reported having low mean scores in nausea/vomiting (<40: *M* = 4.7, *SD* = 13.7; 40–65: *M* = 3.8, *SD* = 10.7; and >65: *M* = 2.3, *SD* = 6.9) and a high prevalence of insomnia (<40: *M* = 23.2, *SD* = 25.9; 40–65: *M* = 30.9, *SD* = 30.0; and >65: *M* = 26.4, *SD* = 28.7) and fatigue (<40: *M* = 23.7, *SD* = 17.3; 40–65: *M* = 25.4, *SD* = 19.7; and >65: *M* = 20.7, *SD* = 15.5). The GHQ mean scores presented some clinically MIDs (<40: *M* = 76.0, *SD* = 18.0; 40–65: *M* = 71.9, *SD* = 18.9; and >65: *M* = 70.3, *SD* = 20.0) [16]. See also Table 5.

3.5.1.2. MBC. Patients between 40 and 65 years old from EORTC trials reported the highest mean scores in cognitive functioning (*M* = 79.7, *SD* = 22.3) and lower scores in role functioning (*M* = 59.4, *SD* = 30.5). Although patients older than 65 years also reported high mean cognitive functioning scores (*M* = 83.9, *SD* = 20.6), they reported low levels of physical functioning (*M* = 65.5, *SD* = 29.1). Patients below 40 years of age reported higher levels of physical functioning (*M* = 84.0, *SD* = 21.4) and low cognitive functioning (*M* = 70.0, *SD* = 29.8). The least reported symptoms across all age groups were nausea/vomiting (<40: *M* = 6.7, *SD* = 9.1; 40–65: *M* = 10.4, *SD* = 19.7; and

Table 3
RVs, mean (SD) for EBC patients.

	EORTC trial (n = 4021)				PDS trials (n = 1065)			
	Total mean (SD)	Median	Floor effect (%)	Ceiling effect (%)	Total mean (SD)	Median	Floor effect (%)	Ceiling effect (%)
Physical functioning	**92.2 (12.2)**	100.0	0.0	53.0	**87.0 (13.4)**	93.3	0	27.6
Role functioning	91.9 (17.4)	100.0	0.4	76.4	77.0 (25.5)	83.3	2.0	40.7
Emotional functioning	*69.5 (24.0)*	75.0	0.7	8.7	*71.3 (21.7)*	75.0	1.4	12.2
Cognitive functioning	85.7 (19.0)	100.0	0.2	51.5	**85.6 (18.8)**	100.0	0.7	50.7
Social functioning	**92.2 (15.9)**	100.0	0.3	73.3	79.0 (23.2)	83.3	1.4	40.3
Global health status/ QoL	76.9 (19.2)	83.3	0.3	18.3	72.4 (18.8)	75.0	0.2	12.3
Fatigue	16.8 (19.0)	11.1	40.1	0.2	25.0 (19.2)	22.2	17.4	0.6
Nausea/vomiting	*3.2 (9.4)*	0	85.9	0.1	*3.8 (11.1)*	0.0	83.3	0.5
Pain	9.7 (17.0)	0	66.4	0.4	20.8 (21.8)	16.7	37.8	1.1
Dyspnea	7.5 (16.4)	0	80.2	0.3	8.5 (17.6)	0.0	76.9	0.5
Insomnia	**27.5 (28.5)**	33.3	42.1	4.5	**29.6 (29.5)**	33.3	37.8	6.6
Appetite loss	8.7 (18.6)	0	78.9	0.8	10.0 (19.3)	0.0	74.4	0.9
Constipation	5.8 (15.8)	0	85.3	0.5	10.2 (20.4)	0.0	74.8	1.3
Diarrhea	5.1 (14.0)	0	85.8	0.2	5.5 (13.9)	0.0	83.3	0.2
Financial problems	3.4 (13.5)	0	91.5	0.6	22.9 (30.3)	0.0	55.1	6.2

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.

>65: $M = 3.2$, $SD = 8.0$) and diarrhea (<40: $M = 0.0$, $SD = 0.0$; 40–65: $M = 7.3$, $SD = 14.0$; and >65: $M = 11.9$, $SD = 25.8$), whereas the most reported symptoms were fatigue (<40: $M = 48.9$, $SD = 23.0$; 40–65: $M = 44.8$, $SD = 22.8$; and >65: $M = 35.2$, $SD = 25.5$) and insomnia (<40: $M = 46.7$, $SD = 38.0$; 40–65: $M = 38.5$, $SD = 28.2$; and >65: $M = 30.4$, $SD = 34.4$). The GHQ mean scores varied significantly across age groups (<40: $M = 71.7$, $SD = 17.3$; 40–65: $M = 51.8$, $SD = 20.5$; and >65: $M = 59.7$, $SD = 24.3$) [16]. See also Table 6.

In PDS trials, although patients over 65 reported the highest scores in social functioning ($M = 77.8$, $SD = 27.0$), all patients reported high levels in cognitive

Table 4
RVs, mean (SD) for MBC.

	EORTC trials (n = 94)				PDS trials (n = 341)			
	Total mean (SD)	Median	Floor effect (%)	Ceiling effect (%)	Total mean (SD)	Median	Floor effect (%)	Ceiling effect (%)
Physical functioning	68.5 (25.8)	80.0	1.1	11.7	77.1 (19.7)	80.0	0	13.2
Role functioning	*64.2 (34.3)*	66.7	8.5	35.1	*73.1 (28.5)*	83.3	5.0	37.5
Emotional functioning	72.0 (22.3)	75.0	1.1	14.9	*73.1 (22.7)*	75.0	1.5	16.1
Cognitive functioning	**81.7 (21.7)**	83.3	1.1	42.6	**83.5 (21.7)**	83.3	1.8	45.5
Social functioning	74.9 (30.4)	83.3	6.4	44.7	77.9 (26.5)	83.3	3.5	42.5
Global health status/ QoL	57.6 (23.1)	66.7	2.1	2.1	54.6 (20.1)[a]	50.0	0.6[a]	1.5[a]
Fatigue	**39.2 (24.8)**	33.3	7.4	1.1	**33.7 (24.6)**	33.3	12.6	4.1
Nausea/vomiting	*5.8 (13.5)*	0.0	77.7	0	*7.7 (16.4)*	0.0	73.3	0.9
Pain	26.8 (25.5)	16.7	35.1	0	30.4 (29.3)	16.7	28.4	5.9
Dyspnea	26.8 (30.6)	33.3	44.7	7.4	22.5 (26.4)	16.7	49.0	2.9
Insomnia	34.0 (32.6)	33.3	36.2	9.6	29.5 (30.5)	33.3	40.5	6.7
Appetite loss	19.9 (27.8)	0.0	58.5	4.3	18.9 (28.9)	0.0	62.2	5.6
Constipation	16.3 (28.4)	0.0	69.1	5.3	12.2 (24.1)	0.0	74.5	2.9
Diarrhea	9.7 (21.7)	0.0	77.7	3.2	*6.1 (14.8)*	0.0	82.7	0
Financial problems	13.3 (23.6)	0.0	70.2	2.1	27.3 (32.7)	33.3	49.0	8.8

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.
[a] Q29 and Q30 were missing in the Sanofi trial.

functioning (<40: $M = 86.4$, $SD = 17.9$; 40–65: $M = 84.3$, $SD = 21.2$; and >65: $M = 75.5$, $SD = 26.0$) and lower scores in role (<40: $M = 72.6$, $SD = 32.1$; 40–65: $M = 73.6$, $SD = 28.2$; and >65: $M = 70.4$, $SD = 28.2$) and emotional functioning (<40: $M = 71.8$, $SD = 24.2$; 40–65: $M = 73.4$, $SD = 22.4$; and >65: $M = 71.6$, $SD = 24.8$). Among symptoms, all groups reported a low prevalence of nausea/vomiting (<40: $M = 8.3$, $SD = 12.4$; 40–65: $M = 7.9$, $SD = 16.9$; and >65: $M = 6.0$, $SD = 15.5$) and diarrhea (<40: $M = 6.2$, $SD = 13.2$; 40–65: $M = 6.1$, $SD = 14.7$; and >65: $M = 5.6$, $SD = 16.9$) and high levels of fatigue (<40: $M = 37.1$, $SD = 30.8$; 40–65: $M = 32.5$, $SD = 23.8$; and >65: $M = 40.1$, $SD = 24.5$). The GHQ mean score differed across age groups (<40: $M = 45.8$, $SD = 13.2$; 40–65: $M = 56.0$, $SD = 20.3$; and >65: $M = 49.2$, $SD = 20.4$) [16]. See also Table 6.

3.5.2. Regions

3.5.2.1. EBC. Low mean scores in emotional functioning were reported across regions (Southern Europe: $M = 68.8$, $SD = 20.5$; Anglo-Saxon countries: $M = 71.8$, $SD = 21.8$; Northern Europe: $M = 69.6$, $SD = 20.9$; and Eastern Europe: $M = 65.8$, $SD = 23.9$). In all regions, except Northern Europe where physical ($M = 92.2$, $SD = 12.4$) and social functioning ($M = 92.4$, $SD = 15.5$) scored highest, role functioning had the highest scores (Southern Europe: $M = 94.7$, $SD = 12.5$; Anglo-Saxon countries: $M = 91.3$, $SD = 20.1$; and Eastern Europe: $M = 89.2$, $SD = 20.6$). In addition, patients from Eastern Europe reported high scores in physical functioning ($M = 89.2$, $SD = 13.9$). All groups reported nausea/vomiting (Southern Europe: $M = 2.7$, $SD = 8.6$; Anglo-Saxon countries: $M = 5.3$, $SD = 13.1$; Northern Europe: $M = 3.2$, $SD = 9.3$; and Eastern Europe: $M = 3.2$, $SD = 10.6$) as the least and insomnia (Southern Europe: $M = 26.7$, $SD = 25.4$; Anglo-Saxon countries: $M = 33.1$, $SD = 31.1$; Northern Europe: $M = 27.3$, $SD = 28.8$; and Eastern Europe: $M = 31.3$, $SD = 32.2$) as the most prevalent symptoms. In addition to the low prevalence of nausea/vomiting, Eastern European patients reported a lower mean score in diarrhea ($M = 2.8$, $SD = 10.7$). The GHQ mean scores varied significantly across regions (Southern Europe: $M = 70.6$, $SD = 21.0$; Anglo-Saxon countries: $M = 76.6$, $SD = 19.8$; Northern Europe: $M = 78.7$, $SD = 18.1$; and Eastern Europe: $M = 60.7$, $SD = 24.1$), with the lowest score observed in Eastern Europe [16]. See also Table 7.

3.5.2.2. MBC. Role functioning (Southern Europe: $M = 65.8$, $SD = 35.7$; Anglo-Saxon countries:

Table 5
RVs, mean (SD) for EBC by age group.

Age group	EORTC trials (n = 4021)			PDS trials (n = 1065)		
	<40	40–65	>65	<40	40–65	>65
N	164	2840	1017	156	864	45
Physical functioning	**97.0 (7.5)**[a]	**93.7 (10.9)**[c]	87.2 (14.6)[a,c]	**90.0 (11.0)**[a]	**86.5 (13.7)**[a]	**84.8 (14.2)**
Role functioning	88.2 (20.4)	92.1 (17.5)	92.0 (16.4)	76.0 (27.0)	77.1 (25.4)	*78.0 (23.5)*
Emotional functioning	*63.8 (23.1)*	*68.9 (20.8)*	*72.1 (20.8)*	*71.7 (22.7)*	*70.9 (21.7)*	*79.0 (17.5)*
Cognitive functioning	83.2 (20.5)[b]	85.2 (19.3)	87.4 (17.8)[b]	**88.4 (18.7)**[a]	**85.1 (19.0)**[a]	**86.0 (16.4)**
Social functioning	89.4 (19.2)	91.7 (16.0)	**94.1 (14.6)**	77.5 (25.2)[b]	79.0 (23.0)[c]	**84.5 (21.4)**[b,c]
Global health status/QOL	75.3 (19.5)	77.4 (19.0)	75.8 (19.7)	76.0 (18.0)[a,b]	71.9 (18.9)[a]	70.3 (20.0)[b]
Fatigue	20.5 (19.2)	16.7 (18.9)	16.4 (19.3)	**23.7 (17.3)**	**25.4 (19.7)**	**20.7 (15.5)**
Nausea/vomiting	*4.1 (10.1)*	*3.3 (9.7)*	*2.7 (8.3)*	*4.7 (13.7)*	*3.8 (10.7)*	*2.3 (6.9)*
Pain	10.3 (16.3)	9.1 (16.2)	11.2 (19.1)	17.7 (19.0)	21.5 (22.4)	18.6 (18.0)
Dyspnea	4.5 (13.1)	6.5 (15.3)[c]	10.6 (19.4)[c]	5.6 (13.6)[b]	9.0 (18.1)	9.8 (19.8)[b]
Insomnia	**25.4 (26.4)**	**27.6 (28.5)**	**27.6 (28.9)**	**23.2 (25.9)**[a]	**30.9 (30.0)**[a,c]	**26.4 (28.7)**[c]
Appetite loss	17.3 (26.2)[a,b]	8.9 (18.5)[a]	6.7 (16.9)[b]	8.4 (18.8)	10.4 (19.5)	8.3 (16.3)
Constipation	*3.5 (10.9)*	*5.4 (15.1)*	*7.1 (18.2)*	9.7 (20.4)	10.3 (20.3)	10.1 (21.3)
Diarrhea	*7.6 (17.1)*	*5.0 (13.9)*	*4.9 (13.5)*	6.7 (14.9)	5.3 (13.7)	5.4 (12.5)
Financial problems	4.1 (12.7)	3.8 (14.6)	2.2 (10.2)	26.2 (32.3)[a,d]	22.8 (30.3)[a,e]	11.4 (21.5)[d,e]

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.

The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.

[a] Small MID between mean scores in <40 and 40–65 years of age.
[b] Small MID between mean scores in <40 and >65 years of age.
[c] Small MID between mean scores in 40–65 and >65 years of age.
[d] Medium MID between mean scores in <40 and >65 years of age.
[e] Medium MID between mean scores in 40–65 and >65 years of age.

Table 6
RVs, mean (SD) for MBC by age group.

Age group	EORTC trials (n = 94)			PDS trials (n = 341)		
	<40	40–65	>65	<40	40–65	>65
N	5	32	57	28	277	36
Physical functioning	**84.0 (21.4)**[a,e]	71.5 (18.3)[a,c]	*65.5 (29.1)*[c,e]	78.8 (19.9)[b]	77.4 (19.9)	73.1 (17.9)[b]
Role functioning	73.3 (43.5)[a,b]	*59.4 (30.5)*[a,c]	66.1 (35.8)[b,f]	*72.6 (32.1)*	*73.6 (28.2)*	*70.4 (28.2)*
Emotional functioning	76.7 (14.9)	74.5 (20.2)	70.2 (24.0)	*71.8 (24.2)*	*73.4 (22.4)*	*71.6 (24.8)*
Cognitive functioning	**70.0 (29.8)**[b,d]	**79.7 (22.3)**[c,d]	**83.9 (20.6)**[b,f]	**86.4 (17.9)**[e]	**84.3 (21.2)**[c]	**75.5 (26.0)**[c,e]
Social functioning	73.3 (34.6)[a,b]	67.7 (24.3)[a,f]	79.2 (32.8)[b,f]	77.8 (28.9)	78.0 (26.3)	**77.8 (27.0)**
Global health status/QOL	71.7 (17.3)[e,g]	51.8 (20.5)[c,g]	59.7 (24.3)[c,e]	45.8 (13.2)[d]	56.0 (20.3)[c,d]	49.2 (20.4)[c]
Fatigue	**48.9 (23.0)**[e]	**44.8 (22.8)**[c]	**35.2 (25.5)**[c,e]	**37.1 (30.8)**	**32.5 (23.8)**[c]	**40.1 (24.5)**[c]
Nausea/vomiting	*6.7 (9.1)*[a,e]	*10.4 (19.7)*[a,c]	*3.2 (8.0)*[c]	*8.3 (12.4)*	*7.9 (16.9)*	*6.0 (15.5)*
Pain	23.3 (36.5)[b,d]	37.5 (23.2)[d,f]	21.0 (24.3)[f]	32.1 (30.1)	29.4 (28.2)[c]	36.6 (36.3)[c]
Dyspnea	33.3 (0.0)[a,b]	25.8 (28.2)[a]	26.8 (33.3)[b]	24.7 (30.1)[b]	21.4 (25.7)[c]	28.7 (28.9)[b,f]
Insomnia	**46.7 (38.0)**[a,e]	**38.5 (28.2)**[a,c]	**30.4 (34.4)**[c,e]	25.0 (26.6)[a]	30.6 (31.0)[a,c]	24.8 (29.5)[c]
Appetite loss	13.3 (18.3)[a,b]	18.7 (26.7)[a]	21.0 (29.3)[b]	19.0 (29.3)[b]	18.2 (28.1)[c]	24.1 (34.4)[b,c]
Constipation	33.3 (47.1)[d,e]	14.6 (28.0)[d]	15.8 (26.8)[e]	9.5 (23.8)[b]	12.2 (23.8)	14.8 (27.0)[b]
Diarrhea	*0.0 (0.0)*[d,e]	*7.3 (14.0)*[c,d]	*11.9 (25.8)*[c,e]	*6.2 (13.2)*	*6.1 (14.7)*	*5.6 (16.9)*
Financial problems	26.7 (27.9)[a,b,e]	20.8 (26.4)[a,f]	7.7 (20.1)[e,f]	34.6 (38.7)[a,e]	27.3 (32.8)[a,c]	21.3 (26.6)[c,e]

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.
[a] Small MID between mean scores in <40 and 40–65 years of age.
[b] Small MID between mean scores in <40 and >65 years of age.
[c] Small MID between mean scores in 40–65 and >65 years of age.
[d] Medium MID between mean scores in <40 and 40–65 years of age.
[e] Medium MID between mean scores in <40 and >65 years of age.
[f] Medium MID between mean scores in 40–65 and > 65 years of age.
[g] Large MID between mean scores in <40 and 40–65 years of age.

$M = 59.7$, $SD = 33.7$; and Eastern Europe: $M = 62.8$, $SD = 30.5$) was the lowest and cognitive functioning (Southern Europe: $M = 84.2$, $SD = 20.4$; Anglo-Saxon countries: $M = 75.4$, $SD = 26.5$; and Eastern Europe: $M = 82.0$, $SD = 17.3$) the highest functioning scale in all regions. Nausea/vomiting (Southern Europe: $M = 3.9$, $SD = 9.5$; Anglo-Saxon countries: $M = 9.0$, $SD = 14.7$; and Eastern Europe: $M = 9.0$, $SD = 23.2$) were the least prevalent symptoms in regions, whereas diarrhea was also rarely reported in patients from Anglo-Saxon countries ($M = 5.8$, $SD = 12.9$) and Eastern Europe ($M = 5.1$, $SD = 12.5$). Fatigue was the most prevalent symptom across all regions (Southern Europe: $M = 35.3$, $SD = 25.8$; Anglo-Saxon countries: $M = 47.0$, $SD = 23.4$; and Eastern Europe: $M = 42.7$, $SD = 20.7$). The GHQ mean score presented some clinically MIDs [16]. See also Table 8.

3.5.3. Performance status

Performance status scores were available for MBC patients only. For EORTC trials, patients with WHO PS 1 and 2 reported the highest mean scores in cognitive functioning (WHO PS 1: $M = 82.3$, $SD = 21.4$ and WHO PS 2: $M = 78.0$, $SD = 26.9$) and low scores in role (WHO PS 1: $M = 64.3$, $SD = 32.5$) and physical functioning (WHO PS 2: $M = 36.4$, $SD = 20.5$). Patients with WHO PS 0 reported high levels of social functioning scores ($M = 91.7$, $SD = 15.2$) and low emotional functioning ($M = 80.7$, $SD = 12.7$). Overall, low levels of nausea/vomiting (WHO PS 0: $M = 0.8$, $SD = 3.5$; WHO PS 1: $M = 6.7$, $SD = 14.7$; and WHO PS 2: $M = 9.1$, $SD = 16.0$) and a high presence of fatigue were reported (WHO PS 0: $M = 22.7$, $SD = 19.8$; WHO PS 1: $M = 40.3$, $SD = 21.9$; and WHO PS 2: $M = 53.0$, $SD = 26.8$). A clinically significant decrease in GHQ mean scores was observed between WHO PS 0 ($M = 72.3$, $SD = 19.6$) and 2 ($M = 45.8$, $SD = 23.4$). See also Table 9.

For PDS trials, all patients reported high levels of cognitive functioning (WHO PS 0: $M = 87.5$, $SD = 17.0$; WHO PS 1: $M = 82.8$, $SD = 20.4$; and WHO PS 2: $M = 63.3$, $SD = 29.2$). While patients with WHO PS 1 and 2 reported low levels in role functioning score (WHO PS 1: $M = 69.3$, $SD = 27.7$; WHO PS 2: $M = 35.0$, $SD = 33.7$), patients with WHO PS 0 reported low mean scores in emotional functioning ($M = 78.0$, $SD = 20.5$). Among symptom scales, patients with WHO PS 0 and 1 reported low levels of nausea/vomiting (WHO PS 0: $M = 4.9$, $SD = 9.6$ and WHO PS 1: $M = 7.4$, $SD = 16.5$), whereas patients with WHO PS 2 reported the lowest

Table 7
RVs, mean (SD) presented for EBC by region.

Region	EORTC trials (n = 4021)			
	Southern Europe	Anglo-Saxon	Northern Europe	Eastern Europe
N	639	168	3131	83
Physical functioning	92.8 (9.8)	90.8 (15.0)	**92.2 (12.4)**	**89.2 (13.9)**
Role functioning	**94.7 (12.5)**	**91.3 (20.1)**	91.5 (17.9)	**89.2 (20.6)**
Emotional functioning	*68.8 (20.5)*	*71.8 (21.8)*	*69.6 (20.9)*	*65.8 (23.9)*
Cognitive functioning	87.8 (17.2)[a,c]	82.0 (20.8)[a,d]	85.5 (19.1)[d]	82.7 (23.1)[c]
Social functioning	93.4 (14.1)[a,c]	87.8 (22.6)[a]	**92.4 (15.5)**[f]	85.8 (23.3)[c,f]
Global health status/QOL	70.6 (21.0)[a,b,c]	76.6 (19.8)[a,g]	78.7 (18.1)[b,h]	60.7 (24.1)[c,g,h]
Fatigue	15.6 (16.8)	16.4 (18.4)	16.9 (19.4)	20.5 (20.3)
Nausea/vomiting	*2.7 (8.6)*	*5.3 (13.1)*	*3.2 (9.3)*	*3.2 (10.6)*
Pain	7.7 (13.6)	13.6 (20.3)	9.8 (17.4)	11.4 (17.3)
Dyspnea	7.5 (15.5)	8.0 (16.4)	7.4 (16.5)	11.2 (19.7)
Insomnia	**26.7 (25.4)**[a,c]	**33.1 (31.1)**[a,d]	**27.3 (28.8)**[d,f]	**31.3 (32.2)**[c,f]
Appetite loss	6.4 (15.2)[a,c]	12.6 (23.9)[a]	8.8 (18.7)	13.3 (23.2)[c]
Constipation	10.8 (20.1)[b]	6.6 (16.9)[e]	4.5 (14.2)[b,f]	13.3 (21.4)[e,f]
Diarrhea	5.1 (13.1)	6.6 (17.7)[e]	5.1 (14.0)	*2.8 (10.7)*[e]
Financial problems	4.3 (14.4)	5.6 (18.2)	3.0 (12.9)[f]	7.4 (17.5)[f]

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.
[a] Small MID between mean scores in Southern Europe and Anglo-Saxon countries.
[b] Small MID between mean scores in Southern and Northern Europe.
[c] Small MID between mean scores in Southern and Eastern Europe.
[d] Small MID between mean scores in Anglo-Saxon countries and Northern Europe.
[e] Small MID between mean scores in Anglo-Saxon countries and Eastern Europe.
[f] Small MID between mean scores in Northern and Eastern Europe.
[g] Large MID between mean scores in Anglo-Saxon countries and Eastern Europe.
[h] Large MID between mean scores in Northern and Eastern Europe.

prevalence of diarrhea ($M = 16.7$, $SD = 23.6$). All patients reported a high prevalence of fatigue (WHO PS 0: $M = 25.1$, $SD = 19.2$; WHO PS 1: $M = 37.4$, $SD = 22.4$; and WHO PS 2: $M = 54.4$, $SD = 28.4$). The GHQ mean scores differed between WHO PS 0 ($M = 61.7$, $SD = 19.1$) and 2 ($M = 52.8$, $SD = 12.7$) [16]. See also Table 9.

3.5.4. Comorbidity

Comorbidity scores were available for MBC patients only from EORTC trials. All MBC patients reported having high levels of cognitive functioning (not present: $M = 86.0$, $SD = 19.6$ and present: $M = 78.8$, $SD = 22.8$), whereas mean score was lowest for role functioning in patients with comorbidities ($M = 53.9$, $SD = 34.4$); patients with no other diseases reported low emotional functioning ($M = 71.3$, $SD = 23.6$). Both groups reported low levels of nausea/vomiting (not present: $M = 3.0$, $SD = 7.5$ and present: $M = 7.9$, $SD = 16.3$) and high scores in fatigue (not present: $M = 32.3$, $SD = 26.2$ and present: $M = 44.0$, $SD = 22.7$). The GHQ of patients without comorbidities ($M = 65.1$, $SD = 23.4$) was clinically relevantly higher compared to those with comorbidities ($M = 52.4$, $SD = 21.6$) [16]. See also Table 10.

4. Discussion

4.1. Main findings

EORTC EBC RVs, supported by the PDS dataset, showed high functioning and low prevalence of symptoms. These results also support prior findings showing high mean levels of physical functioning and low emotional functioning scores with nausea/vomiting and insomnia as the least and most reported symptoms at baseline [4]. Current baseline values showed clinically significantly higher mean scores in most scales [4,16] relative to the prior RVs and normative data [4,25]. These better HRQoL scores relative to normative data might be explained by the healthier nature of patients generally enrolled in RCTs [26].

MBC RVs, also supported by the comparison dataset, had lower HRQoL baseline values than EBC. These findings were similar to prior RVs showing the highest mean scores in cognitive functioning and low levels of role functioning. In addition, trends in symptom scales were similar: MBC patients reported a low prevalence of nausea/vomiting and diarrhea and a high prevalence of fatigue and pain [4]. Not surprisingly, HRQoL was

Table 8
RVs, mean (SD) for MBC by region.

Region	EORTC trials (n = 94)		
	Southern Europe	Anglo-Saxon	Eastern Europe
N	56	24	13
Physical functioning	66.7 (28.8)[b]	69.7 (21.7)	72.8 (19.5)[b]
Role functioning	*65.8 (35.7)*[a]	*59.7 (33.7)*[a]	*62.8 (30.5)*
Emotional functioning	71.9 (23.1)	74.3 (18.1)	71.1 (26.0)
Cognitive functioning	**84.2 (20.4)**[a]	**75.4 (26.5)**[a,c]	**82.0 (17.3)**[b]
Social functioning	78.6 (32.8)[d]	66.7 (28.9)[c,d]	75.6 (18.8)[c]
Global health status/QOL	59.1 (23.3)[b]	57.2 (24.1)[c]	51.3 (22.0)[b,c]
Fatigue	**35.3 (25.8)**[a,b]	**47.0 (23.4)**[a]	**42.7 (20.7)**[b]
Nausea/vomiting	*3.9 (9.5)*[a,b]	*9.0 (14.7)*[a]	*9.0 (23.2)*[b]
Pain	20.8 (24.7)[d,e]	34.7 (26.9)[d]	35.9 (21.3)[e]
Dyspnea	29.7 (32.5)[a,b]	23.2 (27.4)[a]	23.1 (28.5)[b]
Insomnia	29.1 (32.1)[d]	45.8 (33.8)[d,f]	30.8 (28.7)[f]
Appetite loss	21.4 (29.4)[b]	20.8 (27.5)[c]	12.8 (21.7)[b,f]
Constipation	16.1 (27.0)	16.7 (31.1)	17.9 (32.2)
Diarrhea	12.5 (25.9)[d,e]	*5.8 (12.9)*[d]	*5.1 (12.5)*[e]
Financial problems	8.9 (19.6)[a,e]	17.4 (22.2)[a,c]	25.6 (36.4)[c,e]

Northern Europe was excluded from the analysis because of the low sample size (one patient only).

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.
[a] Small MID between mean scores in SE and AS.
[b] Small MID between mean scores in SE and EE.
[c] Small MID between mean scores in AS and EE.
[d] Medium MID between mean scores in SE and AS.
[e] Medium MID between mean scores in SE and EE.
[f] Medium MID between mean scores in AS and EE.

more impaired in MBC patients relative to the healthy general population [4,25], showing an impact of the disease on the patients' HRQoL before treatment.

Our findings also demonstrated the presence of floor effect in symptom scales and ceiling effects in functioning scales for EBC, but not for MBC. This observation is consistent with the fact that, similar to the healthy general population, EBC patients generally report good functioning and less symptoms at baseline [4].

4.2. Secondary findings

Using Cocks' thresholds [16], covariates such as disease stage, PS, and comorbidities seemed to demonstrate clinically MIDs in some HRQoL domains in BC.

Supporting differences found among disease stages in previous RVs [4], a clear trend was found involving more impaired functioning and higher symptomatology in MBC relative to EBC. Similarly, for PS, MBC patients with WHO PS 2 had worse functioning and GHQ and more symptoms than patients with PS 0, demonstrating that the QLQ-C30 reflects the differences found in PS. Finally, MBC patients with comorbidities had worse functioning and GHQ and more symptoms, similar to the literature [27–29].

The impact of age and region was less clear. Comparing patients in different groups, older patients with EBC reported worse scores for physical functioning only, which was supported by PDS data. Although these findings support Quinten *et al.*'s [30] results, they also contradicted prior results showing that younger women report worse physical functioning after BC diagnosis [31]. In MBC patients, mean scores varied among groups and trials, supporting the idea that impacted domains vary by age [30]. Moreover, most symptoms in MBC showed, surprisingly, a tendency toward a lower level with increasing age. The impact of age on EBC is supported by the literature [29,30,32–34]. Even though regional trends were difficult to establish, many cross-cultural differences were reported supporting prior results that found differences in HRQoL scores between European and Rest of the World, and among European countries [25,34,35]. These differences might be

Table 9
RVs (SD) for MBC by performance status.

Performance status	EORTC trials (n = 94)			PDS trials (n = 341)		
	WHO PS 0	WHO PS 1	WHO PS 2	WHO PS 0	WHO PS 1	WHO PS 2
N	22	50	22	112	167	10
Physical functioning	89.4 (10.6)[d,h]	73.5 (18.7)[d,i]	*36.4 (20.5)*[h,i]	85.4 (12.3)[a,h]	74.2 (16.9)[a,i]	49.3 (24.4)[h,i]
Role functioning	89.4 (20.9)[d,h]	*64.3 (32.5)*[d,f]	38.6 (31.0)[f,h]	83.6 (20.8)[a,h]	*69.3 (27.7)*[a,i]	*35.0 (33.7)*[h,i]
Emotional functioning	*80.7 (12.7)*	70.6 (22.8)	66.7 (26.7)	*78.0 (20.5)*	75.1 (21.9)	60.0 (23.8)
Cognitive functioning	84.1 (16.6)[b]	**82.3 (21.4)**[c]	**78.0 (26.9)**[b,c]	**87.5 (17.0)**[a,h]	**82.8 (20.4)**[a,i]	**63.3 (29.2)**[h,i]
Social functioning	**91.7 (15.2)**[g,h]	75.5 (27.7)[g,i]	56.8 (37.7)[h,i]	84.7 (21.7)[a,h]	76.3 (26.6)[a,i]	46.7 (39.1)[h,i]
Global health status/QOL	72.3 (19.6)[g,h]	**56.3 (21.2)**[f,g]	**45.8 (23.4)**[f,h]	61.7 (19.1)[b,d]	50.1 (19.7)[d]	52.8 (12.7)[b]
Fatigue	**22.7 (19.8)**[d,h]	40.3 (21.9)[c,d]	53.0 (26.8)[f, h]	**25.1 (19.2)**[a,h]	**37.4 (22.4)**[a,f]	**54.4 (28.4)**[f,h]
Nausea/vomiting	*0.8 (3.5)*[a,e]	*6.7 (14.7)*[a]	*9.1 (16.0)*[e]	*4.9 (9.6)*[h]	*7.4 (16.5)*[f]	21.7 (30.5)[f,h]
Pain	16.7 (21.8)[d,e]	29.7 (25.0)[d]	30.3 (28.5)[e]	21.2 (21.8)[a,e]	34.1 (31.5)[a]	36.7 (36.7)[e]
Dyspnea	12.7 (19.6)[d,h]	26.0 (28.8)[d,i]	42.9 (36.7)[h,i]	16.1 (20.6)[a,h]	24.9 (26.2)[a,i]	40.0 (30.6)[h,i]
Insomnia	22.7 (29.8)[d,e]	37.3 (32.7)[d]	38.1 (33.8)[e]	21.8 (25.7)[a,b]	30.6 (31.5)[a]	33.3 (38.5)[b]
Appetite loss	6.1 (13.2)[a,h]	17.3 (25.4)[a,f]	39.4 (33.5)[f,h]	11.9 (20.4)[a,h]	22.6 (31.5)[a,f]	44.4 (23.6)[f,h]
Constipation	6.1 (19.6)[a,h]	14.7 (25.3)[a,f]	30.3 (37.0)[f,h]	8.8 (20.9)[e]	11.0 (22.5)[c]	23.3 (35.3)[c,e]
Diarrhea	4.5 (11.7)[a,b]	10.9 (23.0)[a]	12.1 (26.3)[b]	6.0 (14.3)[e]	5.5 (14.7)[f]	*16.7 (23.6)*[e,f]
Financial problems	10.6 (18.9)[a]	16.3 (26.5)[a,c]	9.1 (21.0)[c]	24.1 (33.2)[e]	29.9 (32.0)[f]	50.0 (39.3)[e,f]

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.
[a] Small MID between mean scores in WHO PS 0 and 1.
[b] Small MID between mean scores in WHO PS 0 and 2.
[c] Small MID between mean scores in WHO PS 1 and 2.
[d] Medium MID between mean scores in WHO PS 0 and 1.
[e] Medium MID between mean scores in WHO PS 0 and 2.
[f] Medium MID between mean scores in WHO PS 1 and 2.
[g] Large MID between mean scores in WHO PS 0 and 1.
[h] Large MID between mean scores in WHO PS 0 and 2.
[i] Large MID between mean scores in WHO PS 1 and 2.

explained by the inequalities across regions in terms of resources, support, and access to cancer care, which could impact HRQoL [36] or cross-cultural differences related to patients' perception of illness [35].

When HRQoL data are collected in a future sample of BC patients, the availability of these RVs will provide one potential reference point that could be used to compare the new HRQoL scores with the RVs that were derived from a similar group of patients. For example, the RVs will be useful in interpreting whether the new HRQoL scores are better, worse, or relatively similar. Having a collection of these RVs from different samples will improve not only the representativeness, but also our understanding of the distribution of the scores of the various QLQ-C30 domains among BC patients [4].

The availability of the reference data allows for the development of a more plausible hypothesis on HRQoL in cancer clinical research [4]. For example, EBC patients tend to have high physical functioning before treatment, with several patients scoring a 100 in a 0–100 scale in the QLQ-C30 physical functioning scale. Such high levels of functioning could show less responsiveness to demonstrate improvement [37]. Because these scores cannot go beyond 100, rather than hypothesizing an improvement in physical functioning scores over time, it is more plausible to expect that the scores of EBC patients will not worsen (or will be maintained) over time. If, however, an improvement in physical functioning is to be expected, then these RV findings would encourage the use of the Computer Adaptive Testing (CAT) version of the QLQ-C30, which will allow the measurement of higher levels of physical functioning relative to the QLQ-C30 [38].

The EORTC dataset presents some limitations. It is difficult to draw conclusions in MBC because of the small sample size and not representativeness of the whole MBC population differing between the trials. These limitations may have impacted differences in HRQoL scores and therefore this study's conclusions. To counter this, PDS data were used to support most trends found in EORTC trials. However, some concerns were raised regarding the data available in the platform (e.g. not reporting data

Table 10
RVs, mean (SD) for MBC by presence of comorbidities.

Comorbidity	EORTC trials (n = 94)	
	Not present	Present
N	55	39
Physical functioning	76.9 (26.5)[b]	62.6 (23.7)[b]
Role functioning	78.6 (28.8)[b]	*53.9 (34.4)*[b]
Emotional functioning	*71.3 (23.6)*	72.6 (21.5)
Cognitive functioning	**86.0 (19.6)**[a]	**78.8 (22.8)**[a]
Social functioning	86.0 (28.1)[c]	67.3 (29.7)[c]
Global health status/QoL	65.1 (23.4)[b]	52.4 (21.6)[b]
Fatigue	**32.3 (26.2)**[a]	**44.0 (22.7)**[a]
Nausea/vomiting	*3.0 (7.5)*[a]	*7.9 (16.3)*[a]
Pain	19.7 (24.4)[a]	31.8 (25.3)[a]
Dyspnea	25.4 (29.4)	27.8 (31.6)
Insomnia	28.1 (36.8)[a]	38.2 (29.0)[a]
Appetite loss	17.9 (28.5)	21.2 (27.5)
Constipation	12.8 (23.7)[a]	18.8 (31.3)[a]
Diarrhea	7.9 (19.7)[a]	10.9 (23.2)[a]
Financial problems	9.6 (25.6)[a]	15.8 (22.1)[a]

A high score for a functional scale represents a high level of functioning, whereas a high score for a symptom scale/single item represents a high level of symptomatology.
The highest and lowest mean scores for both the functioning and symptom scales were identified. The functioning scale with the highest score is in bold, whereas the functioning score with the lowest value is in italics. The symptom scale with the highest value is in bold, whereas the symptom scale with the lowest value is in italics.
[a] Small MID between scores in patients without and with comorbidities.
[b] Medium MID between scores in patients without and with comorbidities.
[c] Large MID between scores in patients without and with comorbidities.

from all scales and treatment arm). Second, RVs were generated with baseline data obtained from diagnosed and randomised patients. Although they were not treated, the announcement of the diagnosis could impact some specific domains such as emotional functioning. Moreover, it is widely recognised that BC predominately affects females. The literature is, however, less clear for the male population. As gender has been found to impact HRQoL [31], male BC patients' HRQoL may be important to be further evaluated [39].

These RVs allow clinically relevant interpretation of HRQoL in BC female patients and subgroups and are of benefit to EORTC tools users, regulators, clinicians, and patients. These outcomes can help contextualize individual data and provide interpretation guidelines for patient-reported outcomes in the evaluation of new therapies [33].

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Conflict of Interest

Prof. Velikova reports personal fees from Roche, EISAI, Genentech, and Novartis; grants from NIHR UK Government, Breast Cancer NOW, and EORTC, outside the work in question. Dr. Ignatiadis reports grants from Roche, Menarini Silicon Biosystems, Janssen Diagnostics, Pfizer; honoraria from Celgene, Novartis, Pfizer, Seattle Genetics, and Tesaro and travel grants from Pfizer; he is a board member in EORTC board of directors. Dr. Bottomley reports unrestricted educational grants for the EORTC from Boehringer Ingelheim International GmBH, Germany, Genentech, Merck, BMS, Celgene, RWS Life Sciences, and the EORTC Quality of Life Group for work outside the topic of this work. All other authors report no disclosure.

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Appendix

Table A1
EORTC QLQ-C30 scales and questions

Scales	Questions
Functional scale	
Physical function	1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
	2. Do you have any trouble taking a long walk?
	3. Do you have any trouble taking a short walk outside of the house?
	4. Do you need to stay in bed or a chair during the day?
	5. Do you need help with eating, dressing, washing yourself, or using the toilet?
Role function	6. Were you limited in doing either your work or other daily activities?
	7. Were you limited in pursuing your hobbies or other leisure time activities?
Cognitive function	20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?
	25. Have you had difficulty remembering things?
Emotional function	21. Did you feel tense?
	22. Did you worry?
	23. Did you feel irritable?
	24. Did you feel depressed?
Social function	26. Has your physical condition or medical treatment interfered with your family life?
	27. Has your physical condition or medical treatment interfered with your social activities?
Symptom scale	
Fatigue	10. Did you need to rest?
	12. Have you felt weak?
	18. Were you tired?
Nausea/vomiting	14. Have you felt nauseated?
	15. Have you vomited?
Pain	9. Have you had pain?
	19. Did pain interfere with your daily activities?
Dyspnea	8. Were you short of breath?
Insomnia	11. Have you had trouble sleeping?
Appetite loss	13. Have you lacked appetite?
Constipation	16. Have you been constipated?
Diarrhea	17. Have you had diarrhea?
Financial difficulties	28. Has your physical condition or medical treatment caused you financial difficulties?
Global health status/QOL scale	29. How would you rate your overall health during the past week?
	30. How would you rate your overall quality of life during the past week?

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