

## REVIEW

# Quality-of-Life Measurement in Randomized Clinical Trials in Breast Cancer: An Updated Systematic Review (2001–2009)

Julie Lemieux, Pamela J. Goodwin, Louise J. Bordeleau, Sophie Lauzier, Valérie Théberge

Manuscript received August 18, 2009; revised November 2, 2010; accepted November 12, 2010.

**Correspondence to:** Julie Lemieux, MD, MSc, Santé des populations: Unité de recherche en santé des populations (URESP), Centre de recherche FRSQ du Centre hospitalier affilié universitaire de Québec (CHA), Service d'hémato-oncologie du CHA and Centre des Maladies du Sein Deschênes-Fabia du CHA, Département de Médecine, Université Laval, 1050 Chemin Ste-Foy, Rm JS1-01, Québec, Canada G1S 4L8 (e-mail: julie.lemieux@uresp.ulaval.ca).

**Background** Quality-of-life (QOL) measurement is often incorporated into randomized clinical trials in breast cancer. The objectives of this systematic review were to assess the incremental effect of QOL measurement in addition to traditional endpoints (such as disease-free survival or toxic effects) on clinical decision making and to describe the extent of QOL reporting in randomized clinical trials of breast cancer.

**Methods** We conducted a search of MEDLINE for English-language articles published between May–June 2001 and October 2009 that reported: 1) a randomized clinical trial of breast cancer treatment (excluding prevention trials), including surgery, chemotherapy, hormone therapy, symptom control, follow-up, and psychosocial intervention; 2) the use of a patient self-report measure that examined general QOL, cancer-specific or breast cancer-specific QOL or psychosocial variables; and 3) documentation of QOL outcomes. All selected trials were evaluated by two reviewers, and data were extracted using a standardized form for each variable. Data are presented in descriptive table formats.

**Results** A total of 190 randomized clinical trials were included in this review. The two most commonly used questionnaires were the European Organization for Research and Treatment of Cancer QOL Questionnaire and the Functional Assessment of Cancer Therapy/Functional Assessment of Chronic Illness Therapy. More than 80% of the included trials reported the name(s) of the instrument(s), trial and QOL sample sizes, the timing of QOL assessment, and the statistical method. Statistical power for QOL was reported in 19.4% of the biomedical intervention trials and in 29.9% of the nonbiomedical intervention trials. The percentage of trials in which QOL findings influenced clinical decision making increased from 15.2% in the previous review to 30.1% in this updated review for trials of biomedical interventions but decreased from 95.0% to 63.2% for trials of nonbiomedical interventions. Discordance between reviewers ranged from 1.1% for description of the statistical method (yes vs no) to 19.9% for the sample size for QOL.

**Conclusion** Reporting of QOL methodology could be improved.

J Natl Cancer Inst 2011;103:178–231

Health-related quality of life (QOL) is now commonly incorporated into the design of clinical trials as a primary or secondary outcome. In 1993, QOL was defined broadly by the World Health Organization as an “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the persons’ physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment” (1). In 1989, Moinpour et al. (2) suggested that QOL be included as an endpoint in randomized phase III clinical trials in the following circumstances: “protocols using adjuvant therapy for patients at risk of recurrence, disease sites with an extremely poor prognosis, protocols in which different modalities are compared, protocols in which treatment of different

intensities and/or durations are compared and protocols in which survival is expected to be equivalent but QOL is expected to show difference.” Data derived from QOL measured in clinical trials can be used to select the optimal intervention, describe a patient’s experience, or provide prognostic information (3). Previous studies (4,5) have shown that measuring QOL provides more information about symptoms than measuring adverse events alone.

In 2006, the Food and Drug Administration (FDA) introduced the term “patient-reported outcomes” as “a measurement of any aspect of a patient’s health status that comes directly from the patient” (6). The FDA proposed a series of criteria for selecting patient-reported outcome instruments when the effectiveness criteria for approval of medical product labeling claims are based on patient-reported outcomes. QOL is measured by patient-reported outcomes.

In breast cancer, patient-reported outcomes are rarely used for approval of a medical product. Most interventions are approved based on disease-free, progression-free, or overall survival outcomes. The incremental contribution of QOL measurement to clinical decision making beyond these traditional medical outcomes is unclear. However, for patients and clinicians, the effect of an intervention on QOL is of major interest.

The drawbacks of incorporating QOL outcomes into clinical trials include the additional resources needed to perform data collection and the challenges encountered in analyzing the data. Administering QOL questionnaires is labor intensive for the research team, and they take time and energy for patients to complete, which may be particularly precious when QOL assessment is conducted at the end of life. Administering and analyzing QOL questionnaires is also costly. Data analysis is a challenge because multiple questionnaires are often used, and missing data are frequently encountered. In addition, data analyses need to take into account the complexity of multiple assessments at different points in time with different questionnaires. Moreover, QOL data need to be presented so that the clinical significance of the results is clear. Ultimately, these results should also be made comprehensible for patients. Although QOL questionnaires are rarely included in the publications that describe their development and validity, many are accessible from the authors or from Web sites free of charge. Finally, QOL data are often reported either very briefly in the main publication or as a separate publication in a different journal and at a different time, potentially reducing the impact of these data on treatment decision making.

Despite these challenges, QOL outcomes are commonly used in oncology research. A systematic review published in 2003 by Goodwin et al. (3) (our group) found 66 randomized clinical trials in breast cancer that included at least one QOL outcome. We found that the contribution of information obtained by measuring QOL to clinical decision making (ie, to selecting the optimal treatment among those being studied) depended on the trial setting. In randomized clinical trials of adjuvant therapy, QOL data did not influence clinical decision making. By contrast, these data had more weight in trials of psychosocial interventions, in which QOL was often the primary outcome.

Other systematic reviews of QOL in oncology have been published since ours. For example, Efficace et al. (7) reviewed 24 randomized clinical trials in prostate cancer. They found that 74% reported some differences in QOL but only one-third had a robust QOL design and provided a “comprehensive picture of the whole treatment.” The trials that were considered to have a robust QOL design (ie, they met eight of 11 criteria from a checklist for QOL outcome) were exclusively in the metastatic setting. In 2006, Blazeby et al. (8) reviewed 33 randomized clinical trials in surgical oncology and found that in 22 of them, QOL measurement either influenced treatment recommendation from the authors or provided important information for patients to be fully informed of the impact of treatment on their QOL. In 2007, Joly et al. (9) reviewed trials in metastatic cancer that had a sample size of at least 150 patients. They concluded that reporting of QOL was poor. More recently, Montazeri (10) reviewed studies published from 1974 to 2007 that focused on QOL in breast cancer patients; the conclusions of the studies were summarized, but there was no assessment of the extent of QOL reporting.

## CONTEXT AND CAVEATS

### Prior knowledge

A previous systematic review of 66 randomized clinical trials in breast cancer published between 1981 and 2001 that incorporated quality-of-life (QOL) assessments found that the influence of QOL data on clinical decision making depend on the setting where it was used.

### Study design

Updated systematic review of 190 randomized clinical trials of interventions in breast cancer patients published from 2001 to 2009 to assess the incremental effect of QOL measurement in addition to traditional endpoints on clinical decision making and to describe the extent of QOL reporting.

### Contribution

The European Organization for Research and Treatment of Cancer QOL Questionnaire and the Functional Assessment of Cancer Therapy/Functional Assessment of Chronic Illness Therapy were the most commonly used instruments. Less than 30% of the trials reported the statistical power for QOL. For trials of biomedical interventions, the percentage of trials of biomedical interventions in which QOL findings influenced clinical decision making increased from 15.2% in the previous review to 30.1% in this updated review; for trials of nonbiomedical interventions, the percentage decreased from 95.0% to 63.2%.

### Implications

Reporting of QOL methodology could be improved.

### Limitations

Interpretation of the data, including whether or not QOL results influenced the study authors' decision to recommend the use of an intervention, was difficult in some cases. The search strategy may not have captured all relevant trials. Conclusions about the relevance of QOL to breast cancer relate to those studies in which QOL was measured not to breast cancer studies overall.

*From the Editors*

Because numerous randomized clinical trials in breast cancer have been published since our review in 2003 (3) (the literature search for that review was terminated in May–June 2001) and the quality and utility of QOL measurement and reporting have likely improved in recent studies, we have updated our review to examine if there has been any change in the effect of QOL on clinical decision making in randomized clinical trials in breast cancer. The objectives of this review were to assess the incremental effect of QOL measurement on clinical decision making over and above that of traditional trial endpoints and to describe the extent of QOL reporting in clinical trials.

## Methods

### Search Strategy and Inclusion Criteria

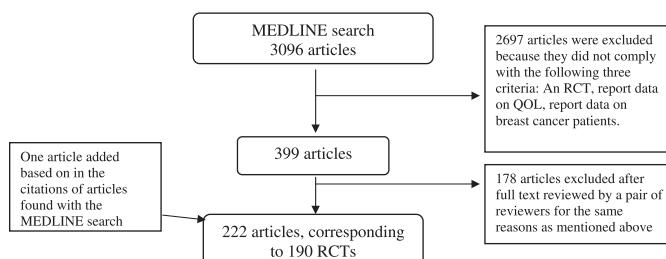
We searched for randomized clinical trials in breast cancer that had QOL as an outcome. Because our goal was to update our review published in 2003, we adopted the same search strategy (3). A search of MEDLINE was initially conducted in March 2006 and

updated in October 2009 using the following terms and restricting to English-language articles: breast cancer AND Hospital Anxiety and Depression Scale (HADS) OR Cancer Rehabilitation Scale (CARES) OR Functional Living Index for Cancer (FLIC) OR European Organization for Research and Treatment of Cancer QOL Questionnaire C-30 (EORTC QLQ-C30) OR Functional Assessment of Cancer Therapy (FACT) OR Breast Cancer Chemotherapy Questionnaire (BCQ) OR Profile of Mood States (POMS) OR Medical Outcomes Study—Short Form 36 (MOS SF-36) OR Symptom Distress Scale (SDS) OR Rotterdam Symptom Checklist (RSCL) OR State–Trait Anxiety Index (STAI) OR quality of life (QOL) OR QOL and instruments OR QOL and randomized trial OR QOL and clinical trial. Articles were required to meet the following criteria to be included in this review: 1) report a randomized clinical trial of breast cancer treatment (excluding prevention), including surgery, chemotherapy, hormone therapy, symptom control, follow-up, psychosocial intervention, or other setting (eg, survivorship); 2) use a patient self-report measure that examined general, cancer-specific, or breast cancer-specific QOL or psychosocial variables; and 3) have documentation of QOL outcomes. Trials that measured only utilities, toxic effects, or symptoms were excluded. We included additional articles that were identified based on citations in the articles found in the MEDLINE search.

We identified 3096 articles by using this search strategy (Figure 1). These articles were screened (title, abstract, and full text when necessary) by one author (J.L.) for inclusion in this review. Articles that included other types of cancer were excluded unless they reported data for breast cancer separately. From these 3096 articles, 399 were selected for full review by pairs of reviewers (March 2006 search: J.L. and P.J.G., and J.L. and L.J.B.; October 2009 update: J.L. and S.L., and L.J.B. and V.T.); 178 articles were excluded because they did not meet the inclusion criteria when the full text was reviewed. A total of 222 articles were included in this review, corresponding to 190 different randomized clinical trials published from May–June 2001 to October 2009. Data were extracted using a standard data collection form by pairs of authors (J.L. and P.J.G., J.L. and L.J.B., J.L. and S.L., and L.J.B. and V.T.). Disagreements were resolved by discussion.

## Data Extraction

We adopted the same criteria for QOL reporting as in our previous review (3) and added three variables: presence of power and/or sample size calculation for QOL outcome(s), documentation of missing data, and documentation of the clinical significance of QOL findings. A description of each criterion follows.



**Figure 1.** Flowchart of the literature search. QOL = quality of life; RCT = randomized clinical trial.

**Type of Intervention and Setting.** Articles were classified according to the type of intervention the trial evaluated and the clinical setting: biomedical intervention (for primary management, adjuvant treatment, metastatic disease, follow-up, or symptom control) or nonbiomedical intervention (psychosocial intervention in adjuvant [around the time of adjuvant treatment] or metastatic setting, symptom control, or other).

**Name and Type of the Trial.** Each randomized clinical trial was classified a superiority, a noninferiority, or an equivalence trial. When the standard arm was placebo-treated or a control group that received no treatment or usual care, the study was classified as a superiority trial. Pilot trials were identified as such.

**Description of the Intervention.** A brief description of the intervention (experimental vs standard arm) was produced for each trial.

**QOL as a Primary or Secondary Outcome.** We determined if QOL was the primary outcome of the trial (if an article reported specifically on QOL, but QOL was a secondary outcome of the original trial, it was classified as a secondary outcome even if it was the only outcome included in a separate report).

**QOL Instruments.** A set of questionnaires with documented validity was previously identified by the authors of the previous review (3) (European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire [EORTC QLQ], Functional Living Index-Cancer [FLIC], Functional Assessment of Cancer Therapy [FACT], Profile of Mood States [POMS], Hospital Anxiety and Depression Scale [HADS], Rotterdam Symptom Checklist [RSCL], Cancer Rehabilitation Evaluation System [CARES], Medical Outcome Study—Short Form-36 [MOS SF-36], Symptom Distress Scale [SDS], State-Trait Anxiety Inventory [STAI]). We noted other instruments that were not part of that list and that were used to measure QOL. For these other questionnaires, we conducted a search on MEDLINE or using the reference for the questionnaire in the article to find data on its validity, reliability, and responsiveness to change, and report those findings in the tables of results when available.

**Trial and QOL Sample Sizes.** We noted the total number of patients who were randomly assigned in the trial and the total number of patients who completed at least one QOL assessment, preferably the baseline assessment (this information was sometimes found in tables or a figure if not explicitly mentioned in the text).

**Statistical Power for QOL.** We noted whether we could identify a sample size calculation or statistical power for QOL outcome(s).

**Missing Data, General.** We noted if there was any mention in the article of the extent of missing data, even if missing data were limited to overall compliance (eg, the number of patients who completed questionnaires).

**Missing Data, Specific.** We noted whether the authors had explicitly discussed how missing data were handled (ie, missing questionnaires, not missing data within a questionnaire). If they

had, we required a description of the method(s) used to take into account missing data. Simply using available data for analyses without explicitly mentioning that they chose to use available data only did not satisfy this criterion.

**Statistical Method.** We noted whether the statistical method used to analyze QOL was reported in the article.

**Timing of QOL Assessment.** We noted whether the article reported when during the trial QOL was assessed.

**QOL Outcome(s).** We summarized the main QOL results according to the intervention arm.

**Clinical Significance of QOL Findings.** A study was classified as having clinical significance if it used either a distribution-based method (eg, effect size) or an anchor-based method (eg, if it used or referred to an article that asked patients if they improved or not and linked a change of the QOL score in the questionnaire to the whether the patients improved or not) to support a statement by the authors about the clinical significance of the results. A statement by the authors that the results were clinically significant that was not accompanied by the use of or reference to a recognized approach for defining clinical significance did not meet our criteria for this variable.

**Medical Outcome(s).** We summarized the medical outcomes according to the intervention arm.

**QOL Influence on Clinical Decision Making.** We determined whether QOL influenced the recommendation by the authors to use or not use the intervention over and above the information provided by the medical outcomes (including toxic effects) based on results of the trial and conclusions of the authors. We determined that it did if QOL results were used to select the optimal intervention while considering toxic effects or other medical outcomes. By default, for trials in which QOL was the primary outcome, this criterion was set to "yes." This criterion was used to assess the incremental impact of QOL measurement on decision making over and above that based on traditional endpoints.

Data were extracted independently by pairs of reviewers (J.L. and P.J.G., J.L. and L.J.B., J.L. and S.L., and L.J.B. and V.T.) and compared. A discrepancy between the two reviewers was considered to be discordance in the criterion. The percentage of discordance was calculated for each variable; for example, for the variable "clinical significance of QOL finding," there was discordance between the two reviewers for 25 (13.4%) of the 186 randomized clinical trials. Descriptive data are presented in tabular form.

## Results

### Summary of Questionnaires Used and Reporting by Criteria

A total of 190 randomized clinical trials were included in this review: 103 evaluated biomedical interventions and 87 evaluated nonbiomedical interventions. The QOL questionnaires that were used in these trials are shown in Table 1. Questionnaires not listed in Table 1 were used in less than 5% of the trials. For trials of biomedical interventions, the most commonly used questionnaire

**Table 1.** Summary of questionnaires used in randomized clinical trials of breast cancer treatment that included a quality-of-life measurement\*

Category	No. (%) of trials that used questionnaire											
	No. of trials	EORTC QLQ†	FACT/FACIT†	POMS	SF-12/SF-36	STAI	HADS	CES-D	IES	MAC	CARES	Others and novel‡
Biomedical interventions												
	First review (1983–2001)	46	12 (26.1)	0 (0)	2 (4.4)	2 (4.4)	6 (13.0)	0 (0)	0 (0)	0 (0)	0 (0)	17
Nonbiomedical interventions	Update (2001–2009)	103	42 (40.8)	26 (25.2)	5 (4.8)	11 (10.7)	4 (3.9)	11 (10.7)	3 (2.9)	0 (0)	1 (1.0)	64
	First review (1983–2001)	20	1 (5.0)	3 (15)	12 (60)	3 (15)	2 (10)	2 (10)	0 (0)	3 (15)	3 (15)	3
	Update (2001–2009)	87	11 (12.6)	15 (17.2)	19 (21.8)	14 (16.1)	15 (17.2)	14 (16.1)	13 (14.9)	11 (12.6)	7 (8.0)	1 (1.1)
												68

\* The first review (3) covered 1983–2001, and this update covers 2001–2009. CARES = Cancer Rehabilitation Evaluation System; CES-D = Center for Epidemiological Studies—Depression Scale; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire; FACT/FACIT = Functional Assessment of Cancer Therapy/Functional Assessment of Chronic Illness Therapy; HADS = Hospital Anxiety and Depression Scale; MAC = Mental Adjustment to Cancer; POMS = Profile of Mood States; SF-12/SF-36 = Short Form-12, short form-36; STAI = State-Trait Anxiety Index.

† When more than one module of the same "questionnaire" (eg, EORTC QLQ-C30 and BR23) was used, they were counted as only one questionnaire.

‡ Number of different questionnaires (percentage of each was not calculated).

was the EORTC QLQ, which was either used alone or with specific modules in 40% of the trials, followed by the FACT and Functional Assessment of Chronic Illness Therapy (FACIT) questionnaires, which were used in 25% of the trials. For nonbiomedical interventions, the most commonly used questionnaires were the POMS (21% of trials), FACT/FACIT (17.0% of trials), STAI (17.0% of trials), HADS (16%), and SF-12/SF-36 (16% of trials). Since our previous review (3), there was an increase in the percentage of trials of biomedical interventions that used the EORTC QLQ (from 26% to 40% of trials) and the FACT/FACIT (from 0% to 25% of trials). In trials of nonbiomedical interventions, the largest change in use was for the POMS: it was used in 60% of trials in the previous review but in only 21% of trials in this review. More than 80% of biomedical and nonbiomedical intervention trials reported the names of the QOL instruments, the trial sample size, the sample size for QOL outcome(s), the timing of QOL, and the statistical method for QOL analysis (Table 2). Statistical power for QOL was reported in 19.4% of the biomedical intervention trials and in 29.9% of the nonbiomedical intervention trials. Information on compliance or the number of patients who completed questionnaires was reported in 76.7% of biomedical intervention trials and in 89.7% of the nonbiomedical intervention trials, but only 30.1% and 24.1%, respectively, reported how missing data were handled. The percentage of trials in which QOL findings influenced clinical decision making increased from 15.2% in our previous review to 30.1% in this updated review for trials of biomedical interventions but decreased from 95.0% to 63.2% for trials of nonbiomedical interventions. Discordance between reviewers ranged from 1.1% for statistical method described (yes vs no) to 19.9% for sample size for QOL (Table 2).

Below we describe the main results for biomedical intervention trials (Table 3) and nonbiomedical intervention trials (Table 4).

# **QOL in Randomized Clinical Trials of Biomedical Interventions**

**Primary Management Setting.** Six clinical trials (11–17) involving various surgical procedures were reported; five trials (12–17) involved axillary interventions, reflecting the recent interest in reducing morbidity due to axillary assessment. Although no trial showed a difference in cancer outcomes between the treatment arms, in general, there was less arm morbidity with less extensive surgery. Overall, less aggressive surgical interventions had less of an effect on QOL outcomes: The effects on QOL were greatest shortly after surgery, and the differences between treatment arms disappeared over time. The International Breast Cancer Study Group (IBCSG) 10-93 (14) and Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) (15) trials clearly stated that QOL was the primary endpoint. The IBCSG 10-93 trial showed that axillary lymph node dissection was associated with more arm problems after surgery compared with no axillary lymph node dissection, but these differences disappeared over time. The ALMANAC trial showed better QOL with sentinel lymph node dissection than with standard axillary treatment, but no difference in anxiety between treatment arms.

Two trials (20,22) compared standard radiation with intensity-modulated radiation therapy. There was improved cosmesis and

**Table 2.** Summary of quality criteria for quality-of-life reporting\*

\* The first review (3) covered 1983–2001, and this update covers 2001–2009. QOL = quality of life; — = variable was not measured in the first review.

For trials of biomedical and nonbiomedical interventions in this update, there was missing information for discordance in four of the 190 trials included in this update.

**Table 3.** Trials of biomedical interventions\*

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on clinical decision making
de Haes, 2003 (11), EORTC 10850	Equivalence	Wide local excision + Tam vs MRM for women aged 70 y or older	Secondary	EORTC 36 items (R) based on HADS; novel Q (V,R) (body image, fear of recurrence, social support)	136 (6 of 11 centers participated in QOL study)/236	No	Yes	No	Yes	No difference except fewer arm problems in wide local excision + Tam group	No	No difference in PFS or OS	Yes
Tominaga, 2004 (12)	Superiority	ALND level III vs level II	Secondary	Novel Q on arm pain, motor function, and social functioning BDI; STAI; BS1; MAC; SF-36; VAS of QOL	783/1209	No	Yes	No	No	No difference	No	No difference in DFS or OS	No
Purushotham, 2005 (13)	Not stated; power was calculated for a difference in adverse effects	SLNB vs ALND	Unclear		nr/298	No	No	No	Yes	No difference in depressive symptoms or state or trait anxiety. Better physical functioning and QOL immediately after surgery.	No	Reduction in arm swelling, seroma formation, numbness, and loss of sensitivity	"Yes" if QOL considered a primary outcome and "No" if QOL considered a secondary outcome
Rudenstein, 2006 (14), IBCSG 10-93	Initially equivalence (then became a superiority trial)	No ALND vs ALND for women aged 60 y or older	Initially secondary but changed to primary because of slow recruitment	LASA scales (IBCSG approach) (V,R,Res)	394/473	Yes	Yes	No	Yes	More bothered by hand, arm, shoulder, or chest problems at the 1st postoperative period in ALND but return to baseline over time.	No	No difference in DFS or OS	Yes (QOL became primary endpoint)
Mansel, 2006 (15), ALMANAC	Superiority	SLNB vs standard axillary treatment	Primary	FACT-B + 4 items; STAI	829/1031	No	Yes	No	Yes	Better QOL but no difference in anxiety	Yes, anchor-based	Less arm and shoulder morbidity	Yes
Zavagno, 2008 (16) and Del Bianco, 2008 (17), Sentinel-GIVOM	Noninferiority	SLNB + ALND if SLN positive vs SNLB + ALND	Secondary	SF-36; Psychological Well-Being Index (V,R)	310 (QOL subprotocol)/749	No	Yes	No	Yes	No difference in QOL (SF-36). Better profile for anxiety and general index, but difference not statistically significant at 24 mo of follow-up	No	No difference in DFS, but study was underpowered (closed prematurely). At 6 mo, reduced arm morbidity. At 12 mo, less numbness and lymphedema. At 24 mo, only less numbness.	No

(Table continues)

Table 3 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on clinical decision making
Rayan, 2003 (18)	Noninferiority	Tam vs RT + Tam in women aged 50 y or older	Secondary EORTC QLQ-C30; EORTC BR-23; short form McGill questionnaire (V,R,Res)	86 (QOL subprotocol)/769	No	Yes	Only difference was better role functioning at 12 mo.	No	Decreased DFS with Tam alone but no difference in OS. No difference in pain (19).	No	
Donovan, 2007 (20)	Superiority	IMRT vs standard 2-D RT	Secondary EORTC QLQ-C30; EORTC-BR23; novel self-assessment questionnaire (breast hardness, pain, tenderness)	nr/306	No	Yes	No statistically significant difference.	No	Less change in breast appearance with IMRT	No	
Prescott, 2007 (21)	Superiority	Omission of RT vs standard postoperative breast irradiation in women aged 65 y or older, T0-2N0	Primary EORTC QLQ-C30; EORTC QLQ-BR23; HADS; Philadelphia Geriatric Center Morale Scale (V,R)	253/255	Yes	Yes, available case analysis using repeated-measures analyses	Yes	No difference in global QOL or depression and anxiety. Statistically significant differences within several QOL subscales: decreases in social functioning, insomnia, level of sexual functioning and systemic treatment side effects, increase in breast symptoms with RT.	No	Decrease in functional status and cosmetic result, increase in RT morbidities (mainly at 8 mo after surgery)	Yes
Pignol, 2008 (22)	Superiority	IMRT vs standard RT	Secondary Axillary padding after lymphadenectomy vs closed suction drainage	EORTC QLQ-C30; EORTC QLQ-BR23	nr/358	No	No	Yes	No difference in QOL.	No	Reduced moist desquamation.
Classe, 2006 (23)	Superiority		Secondary EORTC QLQ-C30	98/100	<b>Primary management: other</b> Yes	No	Yes	No difference in QOL.	No	Reduce length of hospital stay but no difference in arm or shoulder morbidity and pain.	No
IBCSG, 2002 (24) and Bernhard, 2004 (25), IBCSG Trial X de Haes, 2003 (26), ZEBRA	Superiority	CMF × 3 cycles → Tam vs Tam	Secondary LASA scales (V,R,Res)	1398/1715	No	Yes	Yes	Detrimental effect of CMF on QOL during chemotherapy but no difference after chemotherapy.	Yes, anchor-based	Increased DFS and OS in ER-negative but no difference in ER positive.	No
	Equivalence	Goserelin for 2 vs CMF	Secondary RSCL + VAS	1010 (QOL subprotocol)/11640	No	Yes	Yes	Better QOL in the first 6 mo since start of treatment but no difference after.	Yes, anchor-based	Equivalent DFS in ER positive. Goserelin inferior to CMF in ER-negative (27).	Yes

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on clinical decision making
Gronlund, 1990, DBCG-89	Superiority CMF vs ovarian ablation	Secondary HADS; DBCG 89 novel Q	ORTC QLQ-C30; the QOL subprotocol period	260/532 (340 in the QOL subprotocol period)	No	Yes, complete	Yes	Chemotherapy associated with more symptoms during the first 6 mo (except for hot flashes and sweats) and poorer overall QOL. More depressive symptoms but no difference in anxiety.	No	No difference in RFS or OS.	Yes
Bernhard, 2007 [29], IBCSG VIII	Superiority CMF vs goserelin	Secondary vs CMF → goserelin vs no adjuvant systemic therapy this arm was discontinued	IBCSG QOL core questionnaire	939/1065	No	Yes, imputation of last value carried forward	Yes	Goserelin alone: marked improvement or less deterioration in QOL during the first 6 mo. At 3 yr, no difference except for less hot flashes from compliant patients applied to non-compliant patients	No	ER-negative: better DFS with chemotherapy (+ goserelin). ER positive: CMF alone and goserelin alone had similar outcomes. Non-statistically significant improvement in DFS in CMF → goserelin.	Yes
The Adjuvant Breast Cancer Trials Collaborative Group, 2007 [30]	Superiority Ovarian ablation or suppression vs none in women with early-stage BC receiving 5 y of tam + chemotherapy	Secondary CEFF-14 + G-CSF vs CEF-21	nr (detailed QOL analysis to be reported elsewhere)	246/2144 (1290 from centers where QOL substudy was opened)	No	No	No	More menopausal symptoms.	No	No difference in RFS or OS.	No
Del Mastro, 2002 [31], MIG-1	Superiority Noninferiority CMF + Tam vs HCT	Secondary PDI (V,R)	363/392	No	Yes, single imputation using predicted means	Yes	Higher psychological distress in CEF-14 arm compared with CEF-21 arm during chemotherapy but no difference later.	No	No difference in recurrence or OS [32]	No	
Touraine, 2004 [33]		Novel	nr/136	No	Yes	No	Overall decline in QOL at 3 mo but no difference at 6 mo	No	No difference in OS or DFS.	No	
							6 mo expected for decline in social life in HCT.				

(Table continues)

**Table 3 (Continued).**

First author, year (reference, trial name)	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes(s)	QOL influence on clinical decision making
Brandberg, 2003 (34), Scandinavian Breast group study 9401	Superiority FEC × 3 cycles + high-dose chemotherapy + stem cell transplant vs tailored FEC × 9 cycles	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	408/525	No	Yes	No	No difference in QOL. Regarding BC-specific problems, high-dose chemotherapy arm had better body image but more arm symptoms.	No	No difference in OS but improved RFS in standard arm (35).	No
Lind, 2004 (36), NSABP B-23	Superiority AC+ placebo vs AC + Tam vs CMF + Tam vs CMF + placebo	Secondary	FACT-B; Symptom checklist (novel); MOS SF-36; Novel	151/2008 (332 for the QOL subprotocol)	Yes	Yes	Yes, repeated-measures modeling	No difference in overall QOL.	No	No difference in RFS, EFS, or OS (37)	No
Bottomley, 2005 (38); Efficace, 2004 (39); Therasse, 2003 (40)	Superiority EC + G-CSF (dose-intensive) vs CEF (standard)	Secondary	EORTC QLQ-C30	384/448 (one country did not participate in QOL assessment)	Yes	Yes	Yes, complete cases and last observation carried forward	Worse overall QOL in first 3 mo of treatment but no difference after 1 y.	Yes, anchor-based	No difference in PFS or OS.	No
Peppercorn, 2005 (41), CALGB 96102, SWOG 9114, NCIC CTG MA13	Superiority CAF → High-dose chemotherapy and autologous bone marrow transplant vs CAF → intermediate-dose chemotherapy	Secondary	FLIC; PAIS-SR; McCorkle symptoms distress scale	246/885	Yes	Yes	Yes, available case analysis (summary and repeated measures)	Worse QOL at 3 mo of treatment but no difference at 12 mo.	Yes	No difference in EFS or OS (42).	No
Nieboer, 2005 (43); van Buils, 2007 (44)	Superiority FE <sub>90</sub> C × 4 cycles → high-dose chemotherapy and peripheral stem cell reinfusion vs FE <sub>90</sub> C × 5 cycles	Secondary	RSCL; SF-36; VAS for overall QOL	804/885	No	Yes	Yes-linear mixed-effect models	After high-dose chemotherapy, QOL worse in all SF-36 subscales. One year after randomization, differences not clinically relevant and QOL comparable to that in the general population.	Yes, distribution-based + anchor-based	No difference in RFS.	No
Maitlin, 2005 (45)	Superiority TAC vs FAC	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	n/r/491	No	No	No	Greater decrease in QOL with TAC at the end of chemotherapy but no difference after.	Improved OS and DFS.	No	No

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes(s)	QOL influence on clinical decision making
Martini, 2009 (46), GEMINA 9805	Superiority	TAC vs FAC	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	854/1059	No	Yes	No	Yes	Greater decrease in QOL with TAC during chemotherapy but returned to baseline values after.	Yes, anchor-based	TAC more toxic than FAC. Other endpoints nr.	nr (no data on the primary outcome of the trial available)
Poole, 2006 (47), pooled analysis of NEAT and ER9601	Superiority	Epirubicin x 4 cycles → CMF x 4 cycles vs CMF x 6–8 cycles	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23; Women's Health Questionnaire (V,R)	511 (from the NEAT study)/2401	No	No	No	Yes	During chemotherapy, more severe symptoms with epirubicin → CMF. At 1 y after start of treatment, CMF, less improvement in global health or symptoms.	No	Improved RFS and OS.	No
Earl, 2008 (48), NEAT	Superiority	Epirubicin 100 mg/m <sup>2</sup> × 4 cycles → CMF × 4 cycles vs CMF × 6 cycles	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23; Women's Health Questionnaire (V,R,Res)	511 (substudy)/2021	No	Yes	No	Yes	At 2 y, no difference.	No	Improved OS and RFS.	No
Malinovszky, 2006 (49), Anglo-Celtic 1 Trial	Superiority	High-dose chemotherapy (+ autologous stem cells transplant) vs conventional-dose chemotherapy	Secondary	EORTC QLQ-C30; trialspecific checklist (menopausal symptoms); sexual activity questionnaire (V,R)	390 (substudy) but 302 completed the baseline Q/605	No	Yes	No	Yes	More symptoms on epirubicin → CMF during chemotherapy (systemic therapy side effects and upset by hair loss). At 1 y, greater improvement in epirubicin → CMF. No difference at 2 y.	No	Worsening of global QOL and social functioning, and decrease in sexual activity during chemotherapy but return to baseline after.	No difference in RFS or OS.

*(Table continues)*

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on clinical decision making
The Adjuvant Breast Cancer Trials Collaborative Group, 2007 (50)	Superiority	Standard chemotherapy vs no chemotherapy in women with early-stage BC who were receiving 5 y of tamoxifen; EQ5D	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23; HADS; sexual activity questionnaire (V,R); questions on menopausal symptoms (M) (novel); EQ5D	199/1991 (but 1178 in centers where QOL substudy was opened)	No	Yes, complete	Yes	More side effects during the first 9 mo of trial.	No difference	No	No difference in DFS, improved OS.
Bernhard, 2008 (51), IBCSG 15-95	Superiority	EC + filgrastim and stem cell support vs standard-dose anthracycline chemotherapy	Secondary	IBCSG QOL questionnaire; Trial-specific checklist	292/344	No	Yes	Yes, mixed-effects models	Overall, greater decrease in QOL during intensive chemotherapy but faster recovery at 3 mo following chemotherapy.	Yes, anchor-based	No difference in DFS.	No difference in DFS.
Marino, 2008 (52), PEGASSE 01	Not stated (but probably superiority)	FF <sub>100</sub> C × 4 cycles → HSCT vs FF <sub>100</sub> C × 4 cycles	Secondary	EORTC QLQ-C30	199/314 (199 in QOL substudy)	No	Yes	Yes, mixed model	After HSCT, worse QOL (all domains).	Yes, anchor-based	Better DFS (primary endpoint) but no difference in OS.	Yes
Watandee, 2009 (53)	Noninferiority	CMF × 6 cycles vs UFT for 2 y	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23; FACT-B	689/733	No	Yes	No	Better social functioning, less nausea, vomiting, constipation, systemic adverse effects, and upset with hair loss (EORTC) and better physical well-being and the breast cancer subscale (FACT-B) in favor of UFT.	No	No difference in RFS or OS.	Yes
<b>Adjuvant treatment: hormone therapy "X" vs hormone therapy "Y"</b>												
Nystedt, 2003 (54), ZPP	Superiority	Tam vs goserelin vs both vs neither	Secondary	HADS + PSPS (M)	293/408	No	Yes	Yes, last value carried forward	No effect on depression or anxiety in patients who did not receive chemotherapy.	Yes, anchor-based	Goserelin vs no goserelin, associated with better EFS and OS (54)	No
									more body image problems in goserelin + tam and goserelin vs neither. Also, more burdensome symptoms with goserelin.			

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes)	QOL influence on clinical decision making
Paganini, 2004 trials 12-33 and 14-33	Superiority	Toremifene vs tam	Secondary	LASA (V,R,Res)	697/1037	No	Yes	No	No difference	No	No difference in OS or DFS.	No
Fallowfield, 2004 [57, 58], and Cella, 2006 [59], ATAC	Superiority	Anastrozole vs tam vs anastrozole + tam	Secondary	FACT-B; additional endocrine subscale questionnaire	1021/9366 (1105 for the QOL subprotocol)	Yes	Yes	Repeated-measures models using MIXED procedure on SAS statistical software	No major impact on QOL. Some symptoms (diarrhea, vaginal dryness, decreased libido, dyspareunia) more common in anastrozole only group.	Yes, anchor-based	Anastrozole prolonged DFS (60)	No
Whelan, 2005 (61), Goss, 2007 [62], and Nauiss, 2008 (63), NCIC CTG MA.17	Superiority	Letrozole vs placebo after 5 y of tam	Secondary	SF-36; MENQOL	3612/5187; for the substudy according to age, 930 (aged 70 y or older)/5187 (1323 aged 70 y or older)	No	Yes	Yes	No difference in overall QOL but worse body pain and vasomotor symptoms. For women aged 70 y or older: at 6 mo, worse vitality score; at 12 mo, worse QOL body pain, physical pain, vasomotor symptoms; at 24 mo, only worse vasomotor symptoms.	Yes, distribution-based	Improved DFS (64, 65). For women aged 70 y or older, no interaction between age and treatment.	No
Francis, 2006 [66]	Superiority	Switch to exemestane vs continue tam after 2 yr of adjuvant tam.	Secondary	EORTC QLQ-C30	nr/60	No	No	Yes	No statistically significant difference between groups.	No	Decrease in fat mass, increase in bone mineral mass ratio, increase in the fat-free mass to fat ratio.	Decrease in fat mass.

(Table continues)

Table 3 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on clinical decision making
Jones, 2007 (67), TEAM	Superiority	5 y exemestane vs 2.5 y tam → exemestane	Secondary Menopausal symptoms questionnaire (modification of the Kupperman index)	1606/1614 (for the QOL substudy)	No	Yes, complete	Yes	No difference in mood. More vaginal dryness, less vaginal discharge, more bone and muscles aches, more decreased libido, more difficulty sleeping, fewer hot flashes.	No	No results for DFS.	No
Mamounas, 2008 (68), NSABP B-33	Superiority	Exemestane vs placebo after 5 y of tam	Secondary MENQOL	454/1598 (470 in QOL substudy)	Yes	Yes	No	No statistically significant difference.	No	Borderline statistically significant improvement in DFS ( $P = .07$ ).	
Leonard, 2001 (69)	Superiority	Mitofosine solution vs placebo (for cutaneous metastases)	Secondary RSCL; BIS (V,R,Res)	38/47	No	Yes	Yes	Lower psychological distress.	No	Increased TTF.	No
O'Shaughnessy, 2002 (70)	Superiority	Capecitabine + docetaxel vs docetaxel	Secondary EORTC QLQ-C30; EORTC BR-23	454/511	No	Yes	Yes, last observation carried forward	No difference	No	Superior TTP, OS, and RR.	No
Nabholtz, 2003 (71), TAX 306	Superiority	AT vs AC	Secondary EORTC QLQ-C30; EORTC QLQ-B23	nr/429	No	Yes	No	No difference	No	Superior TTP, TTF, and RR but no difference in OS.	No
Sledge, 2003 (72), E1193	Superiority	Doxorubicin + paclitaxel vs paclitaxel → doxorubicin → paclitaxel	Secondary FACT-B	687/739	No	Yes	No	No difference	No	Increased RR and TTF with combination but no difference in OS.	No
Fountzilas, 2004 (73)	Superiority	paclitaxel + epirubicin vs paclitaxel + carboplatin	Secondary EORTC QLQ-C30	98 (2 centers participated in QOL) /32	No	Yes	No	No difference	No	No difference in survival but improved TTF.	No
Cone, 2004 (74)	Noninferiority	Epirubicin → paclitaxel (sequential) vs Epirubicin + paclitaxel (concurrent)	Secondary EORTC QLQ-C30	82/202 (164 in centers participating in QOL)	No	Yes	No	No difference except improved emotional functioning in the concurrent arm.	No	Sequential not inferior.	No

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes)	QOL influence on clinical decision making
Bontonley, 2004 (75), EORTC 10961	Superiority	Doxorubicin + paclitaxel vs AC	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	219/275	Yes	Yes	Yes	No difference in QOL.	Yes, anchor-based	No PFS or median OS (76)	No difference in No RR or survival. No evidence of dose-response relationship among the three arms.
Winer, 2004 (77), CALGB 9342	Superiority	Paclitaxel 210 mg/m <sup>2</sup> vs 250 mg/m <sup>2</sup> vs 175 mg/m <sup>2</sup>	Secondary	FLIC; SDS (V,R)	451/474	No	Yes	Yes, available	No difference between arms except for stability in physical functioning in the 175 mg/m <sup>2</sup> arm.	No	No	No difference in No RR, response duration, or PFS, but statistically significantly superior OS for doxorubicin + DPPE. However, doxorubicin + DPPE was more toxic (gastro-intestinal + central nervous system)
Reyno, 2004 (78), NCIC MA.19	Superiority	Doxorubicin + DPPE vs doxorubicin	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	271/305	No	Yes	No	No difference except for nausea and vomiting (fewer patients worsened).	Yes, anchor-based	No	No difference in No RR, response duration, or PFS, but statistically significantly superior OS for doxorubicin + DPPE. However, doxorubicin + DPPE was more toxic (gastro-intestinal + central nervous system)
Liu, 2006 (24), NCIC CTG MA.16	Superiority	DPPE + doxorubicin vs doxorubicin	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23; trial-specific checklist (specific toxicities)	271/305	No	Yes	Yes, available-summary	Overall, doxorubicin alone had "fewer disease and treatment related adverse events and better QOL."	Yes, anchor-based	No	No difference in RR or PFS.
von Minckwitz, 2005 (80)	Superiority	BMF vs CMF	Secondary	EORTC QLQ-C30	nr/364	No	No	No	No difference	No	Improved OS but no difference in RR or PFS.	No
Jones, 2005 (81)	Superiority	Docetaxel vs paclitaxel	Secondary	FACT-B	212/449	No	Yes	No	No difference	No	Better OS and TTP but increased toxicity.	No
Karamouzis, 2007 (82)	Superiority	Chemotherapy vs supportive care	Primary	EORTC QLQ-C30; EORTC QLQ-BR23	200/210	No	Yes	Yes	Better QOL with chemotherapy	No	Yes	Yes
Cunha, 2008 (83)	Superiority	High-dose chemotherapy with stem cell support vs standard-dose chemotherapy	Secondary	FACT-BMT; trials-specific checklist	216/224	No	Yes	No	At first FU, worse physical function, social function, fatigue, dyspnea, and global QOL. At 6-9 mo FU, worse dyspnea and bruising and bleeding.	No	No difference in OS.	No

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes	QOL influence on clinical decision making
Cassier, 2008 (84), ERASME 3	Superiority	AT × 4 cycles → paclitaxel × 4 cycles vs AT × 4 cycles → docetaxel × 4 cycles (2 standard arms)	Primary	EORTC QLQ-C30	195/210	Yes	Yes	No	No difference in QOL.	Yes, anchor-based	No difference in RR, PFS, or OS, but differences in toxicities.	Yes
Hopwood, 2008 (85)	Superiority	Gemcitabine + paclitaxel vs paclitaxel alone	Secondary	RSCL; BPI	336/529 (but 366 in the QOL substudy)	No	Yes	Yes	Improved QOL but no difference in distress.	Yes, anchor-based	Improved OS.	No
Fountzilas, 2009 (86) and Maniadakis, 2009 (87)	Superiority	Paclitaxel + carboplatin vs docetaxel + gemcitabine vs weekly paclitaxel	Secondary	EQ-5D	325/437	No	Yes	No	No difference	No	Increased OS with weekly paclitaxel vs docetaxel + gemcitabine.	No
Osora, 2002 (88), Eiermann, 2001 (89), and Osora, 1999 (90)	Superiority	Chemotherapy + trastuzumab vs chemotherapy alone	Secondary	EORTC QLQ-C30	431/469	No	Yes	Yes, last observation carried forward	Improvement in global QOL.	Yes, anchor-based	Improved TTP, RR, OS (91)	No
Miller, 2005 (92)	Superiority	Bevacizumab + capcitabine vs capcitabine alone	Secondary	FACT-B	370/462	No	Yes	No	No difference	Yes, anchor-based	No difference in PFS or OS but increased RR.	No
Miller, 2007 (93), E2100	Superiority	Paclitaxel + bevacizumab vs paclitaxel alone	Secondary	FACT-B	631/722	No	Yes	Yes, pattern-mixture model analysis	No difference in QOL.	No	Prolongation of PFS and increased RR but no difference in OS.	No
Buzdar, 2001 (94)	Superiority	Letrozole 0.5 mg vs letrozole 2.5 mg vs megestrol acetate	Secondary	EORTC QLQ-C30	n/r/602	No	No	Yes	No difference	No	No difference	No
Howell, 2002 (95); Osborne, 2002 (96); Thomas, 2003 (97) and Thomas, 2004 (98)	Superiority	Fulvestrant vs Anastrozole	Secondary	FACT-B	n/r/451	No	No	Yes	No difference	No	No difference	No
	Superiority	Fulvestrant vs anastrozole	Secondary	FACT-B	n/r/400	No	No	Yes	No difference	No	No difference	No
	Superiority	Letrozole → anastrozole vs anastrozole → letrozole (each for 28 d in patients who did not tolerate tamoxifen or who had progressed within a trial)	Primary	FACT-B, FACT-ES	65/72	Yes	Yes	Yes, last value carried forward	QOL favors letrozole.	No	Fewer side effects with letrozole. Patients prefer letrozole.	Yes

(Table continues)

**Table 3 (Continued).**

First author, year (reference, trial name)	Trial type	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes(s)	QOL influence on clinical decision making
Aapro, 2008 (99), BRAVE study	Superiority	EPO 30000 IU weekly vs control	FACT-Tanemia	n/r/463	No	No	Yes	No difference in QOL.	No difference in OS.	No difference in TTP.	No difference in OS.
Chia, 2008 (100), EFFECT	Superiority	Fulvestrant vs exemestane	FACT-ES	571/693	No	Yes	No	No difference	No	6 mg: decrease grade 3 or higher adverse events.	No difference in OS.
Ellis, 2009 (101)	Superiority	6 mg estradiol vs 30 mg estradiol	FACT-B	n/r/66	No	No	Yes	No statistically significant difference	Yes, anchor-based	Similar clinical benefit rates.	No difference in OS.
Diel, 2004 (102)	Superiority	Ibandronate 2 mg vs ibandronate 6 mg vs placebo	EORTC QLQ-C30	419/466	No	Yes	Yes, last value carried forward	Better QOL in ibandronate.	Yes, anchor-based	Decrease in skeletal morbidity, pain and analgesic use (ibandronate 6 mg vs placebo) (103)	No difference in OS.
Scott, 2007 (104)	Superiority	Whole-brain RT + supplemental oxygen with etoposide vs Whole-brain RT alone	Spitzer QOL index (V,R,Res)	106/538 in the whole trial, 106 with breast and QOL data	No	Yes	Yes, generalized estimating equations	Better QOL in the first 6 mo after radiation.	Yes, distribution-based	Improved OS	No difference in OS.
Brown, 2002 (105)	Not stated if superiority or equivalence	Patient-initiated FU vs standard FU in patients with stage I BC	EORTC QLQ-C30; EORTC QLQ-BR23; HADS	61/61	No	Yes	No	No difference except lower arm and breast symptoms.	No	Two local recurrences in each study arm.	Yes
Wyatt, 2004 (106)	Not stated if superiority or equivalence	Agency nursing care (group B) or no nursing care (group C) vs in-home nursing protocol (group A) (after breast surgery)	Adaptation of Rand Health Insurance Experiment and Medical outcomes research and SF-36 (V,R); STAI; FACT-B	240/240	No	No	Yes	No difference	No	No increased risk of medical complication.	Yes
Kornberg, 2004 (107)	Not stated if superiority or equivalence	Nurse-led FU on demand vs regular FU visits with a physician after breast surgery.	HADS; SAAC (V,R)	264/400	Yes (a posteriori?)	No	Yes	No difference	No	No difference in time to LRR, distant metastasis, or death.	No difference in OS.
Sheppard, 2009 (108)	Superiority	Point of need access to specialist care vs routine 6-monthly clinical review	General Health Questionnaire-12; FACT-G; FACT-B; FACT-ES, 3 items on fear of recurrence (Novel)	237/237	Yes	Yes	No	No difference	No	No difference in recurrence	Yes

*Table continues*

Table 3 (Continued).

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Symptom control	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes(s)	QOL influence on clinical decision making
Pezella, 2001 (109)	Superiority	Paroxetine vs amitriptyline for depression	Primary	FLIC; MADRS (V,R,Res)	174/179	Yes	Yes, last value carried forward	Yes	No difference	No	No major difference in toxicities.	Yes	
O'Shaughnessy, S 2002 (110 and O'Shaugh- nessy, 2005)(111)	Superiority (pilot trial)	EPO vs placebo in adjuvant setting for cognitive dysfunction	Secondary	POMS; FACT-A; LASA for QOL (V)	94/100	No (pilot trial)	No	No	Less pronounced	No	Higher hemoglobin and improved executive function at cycle 4.	No	
Olsson, 2002 (112)	Unclear if superiority trial or not	Low-dose EPO weekly vs high- dose EPO (metastatic setting)	Primary	EORTC QLQ-C30 + novel module on tiredness	172/180	No	Yes	No	Yes	No difference in global QOL, but greater proportion if patients in high- dose arm had decrease in fatigue.	No difference in hemoglobin level or need for transfusion.	Yes	
Williams, 2002 (113)	Superiority	Manual lymphatic drainage vs single lymphatic drainage for lymphedema	Secondary	EORTC QLQ-C30	nr/31	No	No	Yes	Improvement in emotional function, dyspnea, and sleep with manual lymphatic drainage.	No	Reduced excess limb volume, dermal thickness, and pain with manual lymphatic drainage.	No	
Schmitz, 2002 (114)	Not stated if superiority topical or equivalence for RT-induced dermatitis		Secondary	SF-36; Skindex (V,R,Res)	17/23	No	Yes	No	Less embarrassment with topical steroids.	No	No reduction in RT-induced dermatitis but fewer symptoms with topical steroids.	No	
Carpenter, 2002 (115)	Not applicable, pilot trial	Magnets vs placebo for hot flashes	Secondary	Hot flash diary; Hot flash-related daily interference scale (V,R)	nr/15	No	No	Yes	Decrease in being bothered by hot flashes with placebo but no difference in overall QOL.	No	Decreased frequency of hot flashes with placebo.	Decreased frequency of hot flashes with placebo.	Does not apply (pilot trial)
Schneider, 2003 (116)	Not applicable, pilot trial	Virtual reality vs control	Secondary	RPFS (V,R); STA; SDS (V,R); Novel	16/16	No	No	Yes	Decrease in anxiety immediately after chemotherapy. No difference later.	Yes, distribution- based	Does not apply (pilot trial)	Does not apply (pilot trial)	
Nikander, 2003 (117)	Superiority	Phytosterogens vs placebo for hot flashes	Secondary	Work Ability Index (R); novel questionnaire for depression, anxiety, and self-confidence	nr/62	No	No	Yes	No difference	No	No difference in hot flashes.	No	
McKenzie, 2003 (118)	Not applicable, pilot trial	Exercise vs control for lymphedema	Secondary	SF-36	nr/14	No	No	Yes	No difference	No	No difference	No	Does not apply (pilot trial)

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes(s)	QOL influence on clinical decision making
Gothard, 2004 (119)	Superiority	Alpha-tocopherol acetate + pentoxifylline vs placebo for lymphedema	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	nr/68	No	No	No	No difference	No	No difference	No
Body, 2004 (120)	Superiority	Oral ibandronate vs placebo for bone metastases	Secondary	EORTC QLQ-C30	nr/564 (two trials combined)	No	No	Yes, last value carried forward	Yes	Statistically significantly less decline in global QOL over time and better physical and role functioning.	Reduction in bone pain. Smaller increase in analgesic use.	No
Semiglasov, 2004 (121)	Superiority	Mistletoe extract (10, 30 or 70 ng/mL by subcutaneous injection) vs placebo (during adjuvant chemotherapy)	Primary	QLQ-8 (V,R,Res); Spitzer uniscale (V,R,Res); EORTC QLQ-C30	261/272	Yes	Yes	No	For 30 ng/mL vs placebo, improvement in tiredness, sexuality (for the QLQ-8 items and Spitzer uniscale but not for EORTC QLQ-C30) and CD4/CD8 ratio.	Yes, distribution-based.	No difference in hematological parameters or analgesic or anti-emetic consumption. Dose-dependent increase in CD4 and CD4/CD8 ratio.	
Yates, 2005 (122)	Superiority	Individualized fatigue education + support program vs general cancer education	Primary	Novel; FACT-fatigue; RPS; EORTC QLQ-C30; HADS	110/110	Yes	Yes	No	Less worsening of fatigue between baseline and first FU. No other difference.	No	Does not apply	Yes
Lewland-Jones, 2005 (123)	Superiority	EPO vs placebo (metastatic setting)	Secondary	FACT-G; FACT-A fatigue, FACT-A nonfatigue; CLAS	nr/939	No	No	Yes, different assumptions used	No difference	No	Decreased survival in EPO group.	No
Wardley, 2005 (124)	Unclear if superiority or equivalence trial.	Zoledronic acid administered in the community setting vs in hospital setting (for bone metastases)	Primary	EORTC QLQ-C30; EORTC BR-23; BPI (V,R)	79/101	No	Yes	Yes, last value carried forward	Greater improvement in pain, and less interference with activity, mood, walking, role, and social functioning.	Yes, distribution-based	No difference in safety.	Yes
Rooze, 2005 (125)	Superiority	Acustimulation wristbands (appropriate location) vs acustimulation wristbands (inappropriate location) vs control (to prevent nausea)	Secondary	FACT-G	96/107	No	Yes	No	No difference	No	No difference	No

(Table continues)

Table 3 (Continued).

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes	QOL influence on clinical decision making	
Charg, 2000 (126)	Superiority	EPO vs standard of care (in adjuvant and metastatic settings)	Primary	FACT-A; CLAS (V,R)	338/354	Yes	Yes, last value carried forward	Better QOL.	Yes, anchor-based	Higher hemoglobin response and less transfusion.	Yes	No difference in toxicity.	
MacGregor, 2005 (127)	Superiority	Oral soy vs placebo for menopausal symptoms	Primary	EORTC QLQ-C30; EORTC BR-23; novel (Menopausal scale)	72/72	Yes	Yes	No difference	No	No difference in toxicity.	Yes	No difference in toxicity.	
Roscoe, 2005 (128)	Superiority	Paroxetine vs placebo	Primary	FSCL (V,R); MAF (V,R); POMS; CES-D	94/122	No	Yes, last value carried forward	Paroxetine effective in reducing depression but not fatigue.	Yes, anchor-based	No result on medical outcome.	Yes	No result on medical outcome.	
Jacobs, 2005 (129)	Not applicable, pilot trial	Individualized homeopathic single remedy vs homeopathic combination medicine vs placebo.	Secondary	SF-36	nr/83	No	No	Yes	Increase in general health score in homeopathic arms vs placebo.	No	No difference in severity of hot flashes.	Yes	No difference in severity of hot flashes.
Thompson, 2005 (130)	Not applicable, pilot trial	Homeopathic medicine vs placebo	Primary	Measure Yourself Outcome Profile (V,R,Res); menopausal symptom questionnaire (V); EORTC QLQ-C30; HADS; Novel; Glasgow homeopathic hospital outcome scale (V) outcome scale (V)	53/53	Yes	Yes	No	Yes	No difference in adverse events.	Yes	No difference in adverse events.	
Kinnick, 2006 (131)	Superiority	Sertraline vs placebo then crossover for hot flashes	Secondary	FACT-B; CES-D	59/62	No	Yes	No	No difference in QOL or mood.	Yes, anchor-based	Sertraline statistically significantly more effective than placebo	No	Sertraline statistically significantly more effective than placebo.
Semiglazov, 2006 (132)	Superiority	Standardized mistletoe extract PS76A2 vs placebo	Primary	FACT-G physical, emotional, and functional well-being subscales; GLQ-8 (Global QOL Scale); Spitzer uniscale	352/352	Yes	Yes	No	Better QOL (physical, emotional, and functional well-being)	No	Increased injection site reactions	Yes	Increased injection site reactions
Carpenter, 2007 (133)	Superiority	Venlafaxine vs placebo for hot flashes. Two crossovers: first with low dose (2.5 mg) and second with high dose (37.5 mg)	Secondary	MOS SF-36; POMS; PANAS; CES-D;	Low dose: 52/52; high dose: 18/18	Yes	Yes	No	No statistically significant difference.	Yes, anchor-based	Hot flashes decrease in very early and slow dose.	No	Hot flashes decrease in very early and slow dose.

(Table continues)

**Table 3 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs standard)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcomes)	QOL influence on clinical decision making
Roblo, 2007 (134)	Superiority	Transcutaneous electrical nerve stimulation vs Transcutaneous spinal electroanalgesia for chronic pain vs control (crossover trial)	Primary	HADS; BPI short form	49/49	No	Yes	Yes	No difference in anxiety or depression.	No	No difference in shoulder range of movement and pain. Well tolerated.	Yes
De Souza Fede, Superiority 2007 (135)		Multivitamins vs placebo during RT to prevent fatigue (crossover trial)	Primary	EORTC QLQ-C30; Chalder fatigue questionnaire (V,R)	40/40	No	Yes	Yes	With placebo, decreased fatigue and improvements in functional and symptoms score scales. No change on multivitamins.	No	Does not apply. Yes	Does not apply (trial closed prematurely due to slow accrual)
Mar Fan, 2008 (136)	Superiority	n-methylphenidate vs placebo during adjuvant chemotherapy	Primary	FACT-G; FACT-F; HADS	54/57	Yes	Yes	Yes	No difference	Yes, anchor-based	No difference in cognitive function.	Does not apply (trial closed prematurely due to slow accrual)
Navari, 2008 (137)	Not stated	Fluoxetine vs placebo in adjuvant setting for patients with depressive symptoms	Primary	FACT-G; brief Zung self-rated depression scale (V,R)	193/193	No	Yes	Yes	Improved QOL and depressive symptoms.	No	Higher completion rate of adjuvant therapy.	Yes
Yeo, 2009 (138)	Superiority	Ondansetron + dexamethasone + aperientant vs Ondansetron + dexamethasone for chemotherapy-induced nausea	Secondary	FLIE	124/127	No	Yes	Yes, complete	No difference except for worse QOL in the vomiting domain for patients in the ondansetron + dexamethasone arm.	No	No difference in complete responses.	No
Buijs, 2009 (139)	Superiority	Venlafaxine vs clonidine for hot flashes (crossover trial)	Secondary	MOS SF-36; Sexual activity questionnaire (V,R; Zung self-rated depression scale (V,R))	60/60	No	Yes	Yes	No difference except for improvement in the Zung self-rated depression scale on venlafaxine but not on clonidine.	No	No difference in hot flashes but increased side effects with venlafaxine.	No
Caprauer, 2009 (140)	Superiority	Acute tyrosine kinase and caspase inhibitors vs ondansetron + jer strength control drink and capsules for hot flashes	Secondary	POMS	27/36	No	Yes	No	No difference	No	Hot flashes not relieved by tyrosine kinase inhibitor.	No

*(Table continues)*

**Table 3 (Continued).**

\* The timing of QOL assessment was reported for all studies except for Classe et al. (23). AC = doxorubicin, cyclophosphamide; ALMANAC = axillary lymph node dissection; AT = doxorubicin, docetaxel; ATAC = Arimidex, Tamoxifen Alone or in Combination; BC = breast cancer; BCIRG = Breast Cancer International Research Group; BDI = Beck Depression Inventory; BMF = bendamustine, methotrexate, 5-fluorouracil; BIS = body image scale; BPI = Brief Pain Inventory; BRAVE = Breast cancer-Anemia and the Value of Erythropoietin; BSI = Brief Symptom Inventory; CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; CALGB = Cancer and Leukemia Group B; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CES-D = Center for Epidemiological Studies—Depression Scale; CLAS = cancer linear analog scale; CLOX 2 = clock drawing task; DBCG = Danish breast cancer cooperative group; DFS = disease-free survival; DPPE = N,N-diethyl-2-(4-phenylmethyl)phenoxylethanimine; EC = epirubicin, cyclophosphamide; EFFECT = Evaluation of Easidex versus Exemestane Clinical Trial; EFS = event-free survival; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire; EORTC = European Organization for Research and Treatment of Cancer; EPo = erythropoietin; EO5D = EuroQol Group 5-Dimension Self-Report Questionnaire score; ER = estrogen receptor; EXIT25 = executive interview; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; FACT-B = functional assessment of cancer therapy; FACT-ES = FACT endocrine subscale; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; FLIC = Functional Living Index—Cancer; FLSI = Functional Living Index—Emesis; FSCL = Fatigue Symptom Checklist; FU = follow-up; G-CSF = granulocyte colony-stimulating factor; GEICAM = Spanish Breast Cancer Research Group; GIM = Grupo Interdisciplinare Veneto di Oncologia Mammaria; GLO-8 = 8 linear analog self-assessment scales; HADS (SF) = Hospital Anxiety and Depression Scale (short form); HCFU = 1-hexylcarbamoyl-5-fluorouracil; HCT = 1-hexylcarbamoyl-5-fluorouracil + tamoxifen; HSCT = high-dose stem cell transplant; IBCSG = International Breast Cancer Study Group; IMRT = intensity-modulated radiotherapy; LASA = linear analog scale assessment; LRR = locoregional recurrence; MAC = mental adjustment to cancer; MADRS = Montgomery Asberg Depression Rating Scale; MAF = multidimensional assessment of fatigue; MENOQOL = menopause specific quality-of-life questionnaire; MG = Mammella inter gruppo; MOS SF-36 = Medical Outcomes Study 36-item Short Form; MRM = modified radical mastectomy; N = node; NEAT = National Epirubicin Adjuvant Trial; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCIC CTG = National Cancer Institute of Canada Clinical Trials group; nr = not reported; OS = overall survival; PAIS-SR = Psychosocial Adjustment to Illness Scale—Self-Report; PDI = Psychological Distress Inventory; PFS = progression-free survival; POEMS = Profile of Mood States; PSPS = physical symptom and problems; PSQI = Pittsburgh Sleep Quality Index; Q = questionnaire; R = reliable; Res = responsive; RFS = relapse-free survival; RR = response rate; RSCL = Rotterdam Symptom Checklist; RT = radiation therapy; SAAC = Satisfaction and Accessibility Scale; SAI = State-Anxiety Inventory for Adults; SCT = Symptom Checklist; SDS = Symptom Distress Scale; SF-36 = Short Form-36; SLN = sentinel lymph node biopsy; SWOG = Southwest Oncology Group; STAI = State-Trait Anxiety Inventory; T = tumor; TAC = docetaxel, doxorubicin, cyclophosphamide; Tam = tamoxifen; TEAM = Tamoxifen Exemestane Adjuvant Multicentre trial; TTF = time to treatment failure; TTP = time to progression; UFT = uracil-tegafur; V = validated; VAS = visual analog scale; ZEBRA = Zoledex Early Breast Cancer Research Association; ZIPP = Zoledex in Premenopausal Patients trial.

+ Only % compliance reported.

† Selected items.

§ QOL was associated with patient preferences.

less desquamation with intensity-modulated radiation therapy but no difference in QOL between treatment arms in either trial.

Two trials (18,21) compared radiation with no radiation in older women. One trial (18) compared tamoxifen with or without radiation therapy in women with good prognosis who were aged 50 years or older. A QOL and pain substudy conducted in the final 2 years of this trial found better role functioning at 12 months in the radiation arm. However, the clinical significance of this difference was not addressed. In the other trial (21), which addressed the benefit of adjuvant radiation therapy in women aged 65 years or older, there was no difference in global QOL, the primary endpoint.

**Adjuvant Treatment Setting.** There were 28 trials in this category (24–26,28–31,33,34,36,38–41,43–54,56–59,61–63,66–68), the majority of which were large multicenter trials in which QOL was measured for the whole population or in a subgroup of patients as a secondary endpoint. The majority of these trials used QOL questionnaires that were valid, reliable, and responsive to changes in QOL in a population of women with breast cancer. Power calculations for QOL outcomes were reported in a minority of these trials.

The QOL results influenced clinical decision making in five (26,28,29,52,53) of the 28 trials. Three trials (26,28,29) compared chemotherapy (cyclophosphamide–methotrexate–fluorouracil [CMF]) with ovarian ablation. In the Zoledex Early Breast Cancer Research Association (ZEBRA) equivalence trial (26), which compared goserelin with chemotherapy, disease-free survival was similar in the two treatment arms among hormone receptor-positive patients. In the Danish Breast Cancer Cooperative Group (DBCG)-89 trial (28), there was no difference between treatment arms in medical outcomes, but chemotherapy was associated with poorer QOL in the first 6 months. In the IBCSG VIII trial (29), similar medical outcomes were found for hormone receptor-positive patients in the two treatment arms, but QOL at 6 months was better with goserelin alone.

A trial of high-dose chemotherapy vs standard-dose chemotherapy (52), which identified no difference in overall survival between the study arms, balanced improved disease-free survival (the primary endpoint of the trial) against poorer QOL in the high-dose arm. A Japanese trial comparing CMF vs oral chemotherapy (53) showed no difference in overall survival but better QOL with oral chemotherapy.

The other trials in which QOL results did not influence clinical decisions are briefly reviewed here, according to the treatment arms that were compared.

**Hormone therapy vs hormone therapy plus chemotherapy.** The IBCSG trial IX compared CMF and tamoxifen with tamoxifen alone (24,25). Linear analog self-assessment scales were used to measure QOL. Patients who received CMF and tamoxifen reported worse QOL during chemotherapy administration but not after compared with those receiving tamoxifen alone, a finding that the authors considered clinically significant.

**Chemotherapy "X" vs chemotherapy "Y".** Sixteen trials (31,33,34,36,38–41,43–53) compared different chemotherapy regimens, of which six trials (34,41,43,44,49,51,52) evaluated autologous stem cell transplant and two trials (31,38–40) evaluated

**Table 4.** Trials of nonbiomedical interventions\*

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
<b>Psychosocial intervention: adjuvant setting</b>												
Simpson, 2001 (141)	Superiority	Group psychosocial intervention vs information package only	Primary	MAC; BDI; POMS; QLI (V,R,Res); DWI (R); SCL-90-R (V,R,Res)	89/89	No	Yes	No	Yes	Less depression and mood disturbance and better QOL.	No	Fewer psychiatric symptom and decreased health-care utilization.
Edgar, 2001 (142)	Superiority	Individual Nucare vs Nucare group format vs supportive unstructured group intervention vs no intervention control arm	Primary	POMS; FACT	187 (131 breast cancer, 56 colon cancer)/225 (146 breast cancer, 79 colon cancer)	No	Yes	No	Yes	Nucare-individual format had greater improvement in well-being compared with control and group arms.	No	Does not apply. None reported.
Hedgeson, 2001 (143)	Superiority	Education + peer discussion vs education vs peer discussion vs control	Primary	SF-36	258/312	No	Yes	No	Yes	Better vitality and social functioning, and less bodily pain in global test for the interventions vs control	No	Does not apply Yes
Gustafson, 2001 (144)	Superiority	Comprehensive health enhancement support system vs standard care	Primary	FACT-B; Social support scale; Information competence competence scale	246/295	Yes	Yes	No	Yes	No effect on QOL.	No	More competent at seeking information, more comfortable participating in care, greater confidence in doctor, and better social support.
Allan, 2002 (145)	Superiority	Problem-solving training vs cognitive behavioral power women	Primary	CARES; MHI (V,R); IES; SPSI-R (V,R); Novel Q for unmet need for assistance	164/164	No	Yes	No	Yes	At 4 mo, better mental health	No	Does not apply Yes

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Intervention (experimental vs control)	Instruments	sample size/trial	Power for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Kissane, 2003 (146)	Superiority	Group psychotherapy (cognitive-existential group therapy) + relaxation vs relaxation	Primary	ABS; HADS; MAC; FAD	303/303	No	Yes	Yes	No difference	Yes, distribution-based	No difference in OS (147)	Yes
Taylor, 2003 (148)	Not stated if superiority or equivalence	only in women with localized breast cancer	Psychoeducational support group vs control	POMS; IES; MHI (N/R)	73/93	No	Yes	No	Yes	Women with greater distress at baseline or lower income had improved mood.	Does not apply	Yes
Angelel, 2003 (149)	Not stated if superiority or equivalence	Workbook-journal + educational materials vs educational materials only	Primary	POMS; MAC; HADS; COPE; PCL-S	100/100	No	Yes	No	Yes	No main effect. No	No effect on posttraumatic stress disorder symptoms	Yes
Fukui, 2003 (150)	Superiority	Psychosocial group intervention vs waiting-list control	Primary	UCLA loneliness scale (N/R); SSQ; VAS (level of satisfaction)	50/50	No	Yes	No	Yes	Decreased loneliness, improved satisfaction with social support, and improved QOL (151)	nr	nr
Heiney, 2003 (152)	Superiority (pilot trial)	Therapeutic group therapy by telephone vs control (usual psychosocial care)	Primary	QOL scale of Ferrell modified; POMS	66/68	No (pilot trial)	Yes	No	Yes	No overall treatment effect. Differences seen between subscales only.	No difference in immune function	Not applicable (pilot)

(Table continues.)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Intervention (experimental vs control)	Instruments	sample size/trial	Power sample size for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Hack, 2003 (153)	Superiority	Consultation audiotaped but audiotape not given to patient, consultation audiotaped and audiotape given to patient, consultation audiotaped and patient offered choice vs standard care (no audiotape)	FACT-B; POMS	628/670	No	No	No	Yes	No difference in No mood or QOL.	Patients who received audiotape perceived they received more information.		
Sandgren, 2003 (154)	Superiority	Telephone intervention of emotional expression vs telephone intervention of cancer education vs standard care	POMS; FACT-B; Perceived stress scale; Cancer behavior inventory; 5 items on Social constraint	222/222	Yes	Yes	No	Yes	No difference in mood or QOL. Patients who received interventions perceived better control but felt more socially constrained.	Does not apply	Yes	
Andersen, 2004 (155) and Andersen, 2007 (156)	Superiority	Psychological group intervention (weekly for 4 mo) vs assessment only for patients with stage II or III breast cancer	POMS; IES; SNI; PSS (V,R); DAS (V,R)	227/227	Not clear	Yes	No	Yes	Decreased mood disturbance in patients with higher level of disturbance at baseline. Improvements in perceived social support.	Immune responses paralleled the psychological and behavioral improvements.	No	
Hiddeler, 2003 (157)	Not applicable, pilot trial	Autogenic training + home visit vs home visit alone in patients with early-stage breast cancer	HADS	31/31	No (pilot trial)	No	No	Yes	Improvement in anxiety and depression.	No difference for immune function parameters.	Not applicable (pilot)	

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Yoo, 2005 (158)	Superiority	Progressive muscle relaxation training and guided imagery vs neither	MAACL; FACT-B; Three Likert scales (extent to which vomited, felt anxious, nauseous)	60/60	Yes	No	Yes	Decreased anxiety, depression, and hostility after chemotherapy; improved emotional well-being	No	Decreased nausea and vomiting before chemotherapy	Yes
Owen, 2005 (159)	Superiority	Internet-based coping skills training vs waiting list	FACT-B: EuroQOL-5D (V,R,Res); IES; MSAS; Web Analysis and Measurement Inventory: Linguistic Inquiry and Word Count	62/62	No	Yes	Yes, complete	No difference	Yes, distribution-based peer	Does not apply	Yes
Walker, 2005 (160)	Superiority	Preparatory videotape vs pamphlet (on preparation for breast cancer treatment)	STAI; CES-D; FACT-G; Helpless-hopeless subscale of the Mini-MAC scale (V); Novel questions on satisfaction	79/95	No	Yes	No	No overall difference between groups but more vulnerable and underserved population may benefit.	No	Does not apply	Yes
Miyashita, 2005 (161)	Superiority	Support group vs control (nonmetastatic breast cancer survivors)	STAI; 1-item scale for life satisfaction (novel)	53/78	Yes	Yes	No	Overall no effect.	No	Does not apply	Yes
Antoni, 2006 (162)	Superiority	Group cognitive behavioral intervention vs control (1-day seminar)	Sickness Impact profile (V,R); Positive states of mind (V,R); ABS (R)	199/199	No	Yes	Yes	Positive effects on emotional well-being, positive states of mind, reduces social disruption	Yes	Improved positive life-style change	Yes

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Instruments	sample size/trial	Power for QOL general	Missing data, specific	Statistical method	QOL outcomes(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Svensk, 2009 (163)	Superiority	Weekly art therapy in individual session × 5 wk vs control	WHOQOL-BREF (V,R,Res); EORTC QLQ-BR23	41/42	No	Yes	No	Yes	At 6 mo, improved overall QOL, general health, and environment (WHOQOL-BREF) but no difference in the EORTC QLQ-BR23.	Does not apply	Yes
Classen, 2001 (164)	Superiority	Supportive-expressive group therapy vs self-directed education intervention	Secondary POMS; IES	102/125	No	Yes	No	Yes	No benefit on mood but greater decline in posttraumatic stress symptoms.	Yes, distribution-based	No difference in survival (165)
<b>Psychosocial intervention: metastatic setting</b>											
Bordelau, 2003 (166) and Lemieux, 2007 (167)	Superiority	Supportive-expressive group therapy vs standard psychosocial care	Secondary POMS; EORTC QLQ-C30; PAIS; PAIN VAS; MAC; IES	215/237 (166) Yes 218/235 (167) Yes	Yes	Yes, complete case analysis; available case	Yes, Yes	Yes, anchor-and distribution-based	Improved mood and reduced pain. No change in QOL.	Yes, anchor-and distribution-based	Yes survival difference, less pain in the intervention arm (168)

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Northouse, 2005 (169)	Superiority	Family-based intervention + usual care vs usual care	FACT-B; FACT-G; SF-36; AIS (V,R); MUS (V,R); BHS (V,R); Brief COPE (V)	Primary	134/189	No	Yes	No	No difference in QOL, but benefit in hopelessness and negative appraisal of illness at 3 mo (not sustained at 6 mo).	No	Does not apply	Yes
Aranda, 2006 (170)	Superiority	Brief nurse-delivered individual intervention (face to face and by telephone) to address the needs of women with advanced breast cancer	EORTC QLQ-C30	105/105	Yes	Yes	No	Yes	No difference in QOL.	Reduced "psychological and emotional needs of those with high initial needs."	No	No
Kissane, 2007 (171)	Superiority	Supportive-expressive group therapy vs control	EORTC QLQ-C30;IES; Mini-MAC	227/227	Yes	Yes	Yes, analysis of slopes with imputation of missing data	Yes, Yes	Prevention of depression, increased QOL and social functioning, decreased hopelessness and intrusive thoughts	No difference in OS.	Yes	No difference in OS.
Molassiotis, 2002 (172)	Superiority	Progressive muscle relaxation training vs control	Secondary POMS; STAI	71/71	No	Yes	No	Yes	Decrease mood No disturbance with but no effect on anxiety.	Decrease duration of nausea and vomiting	No	No
Williams, 2004 (173)	Superiority	Education (audiotapes on self-care behavior) vs control	Secondary STAI	nr/71	No	No	No	Yes	Greater decrease in anxiety in intervention arm.	Higher symptom improvement in intervention and greater use of recommended self-care behavior	No	No

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome (experimental vs control)	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Schneider, 2004 (174) (pilot trial)	Superiority	Virtual reality vs Primary no virtual reality (cross-over design for women receiving chemotherapy)	SDS (V,R); STAI; RPFs (V,R)	20/20	Yes	No	Yes	Decrease in symptom and distress and fatigue immediately after chemotherapy.	Yes, distribution-based	Does not apply	Yes (pilot supports a larger randomized controlled trial)	
Savard, 2005 (175,176)	Superiority	Cognitive behavioral therapy vs waiting-list control for insomnia	ISI; HADS; MFI; EORTC QLQ-C30	57/57	No	No	Yes	Decreased anxiety and depression and improved QOL.	No	Better sleep, lower frequency of medicated nights, higher secretion of interferon gamma, and less increase in lymphocytes.	Does not apply	Yes (supports a future randomized controlled trial)
Roscoe, 2005 (177)	Not applicable, pilot trial	Polarity therapy × 1 treatment vs polarity therapy × 2 treatments vs control (for radiotherapy-induced fatigue)	BFI (V,R); FACT-F; PFS	15/16	No (pilot trial)	Yes	No	Yes	Decreased fatigue and improvement in health-related QOL in both polarity therapy arms	No	Decreased nausea and anticipatory vomiting.	Yes (supports a future randomized controlled trial)
Raghavendra, 2007 (178)	Superiority	Integrated yoga program vs supportive-expressive therapy and coping preparation for nausea	STAI; BDI; FLLC; trialspecific checklist	69/98	No	Yes	No	Yes	Decreased anxiety, depression, distressful symptoms, and severity of symptoms.	Improved QOL.	Decreased nausea and anticipatory vomiting.	No difference in Not applicable (pilot trial) over time.
Crew, 2007 (179) (pilot)	Superiority	Immediate vs delayed acupuncture for musculoskeletal pain in women on aromatase inhibitors (cross-over after 6 weeks)	FACT-G; BPI-SF (V,R); WOMAC	n/r/21	Yes	No	No	Yes	Yes, anchored in joint pain and stiffness, physical function, and QOL at 6 weeks but no difference at 12 weeks.	Improvement in joint pain and stiffness.	No difference in Not applicable (pilot trial) over time.	

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Dirksen, 2008 (180)	Superiority	Group cognitive behavioral therapy for insomnia with many components vs control (sleep education and hygiene only).	POMS (fatigue/inertia subscale); STAI; CES-D; FACT-B; ISI (includes questionnaire about disturbance in function from insomnia) (V,R,Res)	72/81	Yes	Yes	No	Yes	Statistically significant time by group interaction for POMS fatigue, FACT-B and social well-being but no statistically significant differences between groups.	Yes, anchored distribution-based	Does not apply	Yes	
Elkins, 2008 (181)	Superiority	Hypnosis x 5 weeks (in person and audio-cassette) vs control for hot flashes	CESD; HADS (anxiety subscale); MOS (sleep scale); Hot Flash-Related Daily Interference Scale (V,R,Res)	nr/60	No	No	No	Yes: complete case analysis, imputation of group mean, last value carried forward, minimum and maximum value carried forward	Decreased anxiety, depression, and interference of hot flashes with daily activities or sleep.	Yes, anchored distribution-based	Decrease in hot flashes.		
Heidrich, 2009 (182)	Superiority (pilot)	Pilot 1: IRIS (Intervention to improve symptom management) vs usual care. Pilot 2: IRIS vs delayed IRIS	Secondary	Pilot 1: MOS-SF-36; Purpose in Life Scale; (V,R); CES-D; STAI-anxiety scale; Pilot 2: BPI; MOS-SF-12; Positive Relations Scale (V,R)	Pilot 1: nr/41 Pilot 2: nr/20	Yes	No	Yes	No difference	No	Pilot 1: More women changing self-care (pilot) Pilot 2: Less symptoms duration and more symptoms management behaviors.	Not applicable (pilot)	
Segal, 2001 (183)	Superiority	Self-directed exercise vs supervised exercise vs usual care	Primary	SF-36; FACT-G; FACT-B	123/123	Yes	Yes	Yes, last value carried forward	Increased physical functioning in the exercise groups.	No	No statistically significant difference in aerobic capacity.	Yes	

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	influence on decision
Courneyea, 2003 (184)	Superiority	Exercise training vs control in postmenopausal breast cancer survivors	Primary (along with change in peak oxygen consumption)	FACT-B; FACT-FS; Happiness Measure (V,R); Rosenberg self-esteem scale (V,R)	52/53	Yes	Yes	No	Yes	Improved QOL. Yes, anchor-and distribution-based	Increased peak oxygen consumption.	Yes	
Headley, 2004 (185)	Not applicable, pilot trial	Not applicable, 30-min seated exercise program 3 times/wk vs control	FACT-F	32/38	No (pilot trial)	Yes	No	Yes	"Slower decline in total and physical well-being and less increase in fatigue scores starting with the third cycle of chemotherapy"	No	Does not apply	Not applicable (pilot)	
Mustian, 2004 (186)	Not applicable, pilot trial	Primary exercise group vs psychosocial support group × 12 weeks	FACIT-F; Rosenberg self-esteem scale (V,R)	21/31	No (pilot trial)	Yes	No	Yes	Improved QOL. Improved self-esteem	No	Not applicable	Yes (supports a future randomized controlled trial)	
Sandel, 2005 (187)	Not applicable, pilot trial	Dance and movement program × 12 weeks vs waiting-list control	FACT-B; SF-36; BIS (V,R,Res)	37/38	No (pilot trial)	Yes	No	Yes	Improved QOL. Yes, distribution-based arm but no effect on body image.	Yes	No difference between groups for shoulder range of motion.	No difference between groups for shoulder range of motion.	
Pinto, 2005 (188)	Superiority	Home-based physical activity vs control group for women with localized breast cancer	Secondary POMS; Body esteem scale (V,R); LASA (fatigue)	82/86	No	Yes	No	Yes	Improved vigor and less fatigue. Trend in favor of improvement in mood and body self-esteem.	No physical activity but no difference in body mass index or decreased abdominal fat.	No		

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Campbell, 2005 (189)	Not applicable, pilot trial	Supervised group exercise vs control (during adjuvant therapy)	Primary	FACT-G; FACT-B; Satisfaction with life scale (V.R,Res); Perceived expectations and benefits of total care package (novel); RPFS (V.R); Scottish physical activity questionnaire (V.R)	19/22	No (pilot trial)	Yes	No	Higher QOL.	No	Higher physical functioning (12-min walking test) and activity	Yes (more study needed)
Ohira, 2006 (190)	Superiority	Weight training nr vs control in breast cancer survivors	Primary	CARES short form; CES-D	81/86	No	Yes	No	Yes	Yes	Increased muscle mass and decreased body fat.	
Herrero, 2006 (191)	Superiority (pilot)	Exercise training nr program (aerobic and resistance) vs control group (in breast cancer survivors)	Primary	EORTC QLQ-C30	16/20	No	Yes	No	Yes	Improved overall fitness.	Not applicable (pilot)	
Basen-Engquist, 2006 (192)	Superiority (pilot)	Lifestyle physical activity intervention vs standard care control group (in breast cancer survivors)	Primary	MOS-SF-36	60/60	No	Yes	Yes, imputation using regression models	Improved QOL, No general health, and body pain.	Improved 6-min walk test	Not applicable (pilot)	
Berurskens, 2007 (193)	Superiority	Standardized physiotherapy for arm and shoulder vs leaflet	Secondary	Sickness Impact profile -short version (V.R)	30/30	No	Yes	No	Improved QOL	No	Decreased functional shoulder impairments and pain in shoulder/arm at 3 mo and 6 mo.	
Banerjee, 2007 (194)	Superiority	Integrated yoga program vs supportive counseling	Primary	HADS; Perceived Stress scale (V.R)	58/68	No	Yes	No	Decreased anxiety and depression.	Slightly less DNA	Yes damage.	

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	sample size/trial	Power for QOL	Missing data, general	Statistical specific method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Baileya, 2007 (195)	Superiority	Telephone interpersonal counseling vs self-managed exercise vs attention control (patients and partners)	Primary	CES-D; Anxiety: a total of 8 items from PANAS, SF-12, and Index of Clinical Stress (V,R)	96 women and 96 partners/96 dyads	No	Yes	No	Telephone counseling group: decreased symptoms of depression. Telephone counseling and self-managed exercise groups: decreased anxiety. For partners: no difference between groups. Statistically significant time effect for depression and anxiety.	Does not apply. Yes	QOL mood, and well-being, social support, spirituality
Hemm, 2007 (196)	Superiority	Structured physical training program (+ muscle and aerobic exercises) vs standard rehabilitation programme for fatigue	Primary	FACT-G; FACT-F; HADS; MFI	63/unclear	No	Yes	No	Better QOL. Less fatigue.	No difference in aerobic capacity. Trend toward higher muscular strength.	QOL mood, and well-being, social support, spirituality
Moade, 2007 (197)	Superiority	Yoga vs standard Primary care (wait-list control) (twice as many patients randomly assigned to yoga vs standard care)	Primary	FACT-G; FACT-Spiritual; FACIT-F; POMS	164/164	Yes	Yes	No	Yes	In whole population, yes, anchor-based and distribution-based no difference except better social functioning. Among women not receiving chemo-motherapy, better mood, better锚定，更好的情绪，更好的锚定，更好的情绪	QOL mood, and well-being, social support, spirituality

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size	Power for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Courneya, 2007 (198) and Courtney, 2007 (199)	Superiority	Supervised exercise resistance exercise program vs supervised aerobic exercise program vs standard care	FACT-anemia; Rosemberg self-esteem scale; CES-D; STAI	Primary	223/242	Yes	Yes	Yes, mixed model	Interventions: Yes, anchor-better self-esteem, but no other statistically significant change.	Interventions: Yes, anchor-better self-esteem and distribution-based	Aerobic exercise Yes	Aerobic exercise superior to usual care for aerobic fitness and % body fat. Resistance exercise superior to usual care for muscular strength, lean body mass, and chemotherapy completion rate.	
Vallance, 2007 (200) and Vallance, 2008 (201)	Superiority	Printed materials vs step pedometer vs both vs standard public recommendation (control)	FACT-B; FACT-F	377/377	No	Yes	Yes	Yes, linear mixed model	In combined group: increased QOL and decreased fatigue but differences disappeared at 6 mo of follow-up.	Yes, anchor-and distribution-based	All intervention groups: increased brisk walking minutes (self-reported). Step pedometer and combined group: decreased self-reported moderate to vigorous physical activity. Differences disappeared at the 6-mo follow-up.		
Mutrie, 2007 (202)	Superiority	12-wk supervised group exercise vs usual care during treatment, for early stage breast cancer	FACT-G; FACT-B; FACT-F; FACT-ES; BDI; PANAS (N, R)	Primary	201/203	Yes	Yes	No	Yes	No difference	No	Less use of health services, improved 12-item walk test and shoulde mobility	

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Intervention (experimental vs control)	Instruments	sample size/trial	Power sample size for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Lee, 2007 [203]	Superiority	Pectoral stretching program vs control for women receiving radiation therapy	Secondary	EORTC QLQ-C30; EORTC QLQ-BR23	61/61	No	Yes	Yes, complete cases	No difference	No	No difference in No shoulder movement.	
Daley, 2007 [204]	Superiority	Supervised aerobic exercise therapy vs exercise placebo vs usual care (12–26 mo after treatment for breast cancer)	Primary	FACT-G; FACT-B; RPFs; BDI-II; Physical Self-Perception Profile (VR)	108/108	Yes	Yes	No	Yes	Aerobic exercise: Improved QOL at 8 weeks of intervention (global, functional/social/family well-being and specific breast cancer concerns), increased physical conditioning competence (8 and 24 weeks of intervention).Exercise and placebo: improved physical self-worth scores (8 weeks) and decreased depression (8 and 24 weeks)	Yes, anchor-based	Aerobic exercise Yes and exercise placebo: improved aerobic fitness (8 weeks), improved physical activity (8 and 24 weeks)
Demark-Wahnefried, 2008 [205]	Feasibility (Pilot)	Calcium + exercise vs calcium + exercise + high-fiber and vegetable, low-fat diet vs calcium-rich control (women receiving adjuvant chemotherapy)	Not specified, pilot	HADS; FACT-B	90/90	No	Yes	No	Yes	No difference in No anxiety, depression, or QOL.	No difference in Not physical activity. Increased calcium intake and higher fruit and lower fat intakes in the diet arm. Less body fat in diet arm.	applicable (pilot)

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Mustian, 2008 (206)	pilot trial	Not applicable, Tai Chi Chuan vs psychosocial support therapy (control)	Not specified, pilot	FACIT-fatigue	21/21	No (pilot trial)	Yes	No	Better QOL.	No	Statistically significant improvement in walked distance, hand-grip strength, functional capacity, and flexibility.	Not applicable (pilot)
Milne, 2008 (207)	Superiority	Combined aerobic and resistance exercise program vs control (and crossover at 12 weeks)	Primary	FACT-B; Schwartz physique anxiety scale (V,R)	58/58	Yes	Yes	Yes, imputation of the last value carried forward	Yes, anchor-and less fatigue.	Improved QOL Yes, anchor-and less fatigue.	Improved aerobic fitness and strength with time over course of intervention but no time-group interaction reported.	Yes
Fillion, 2008 (208)	Superiority	Group stress management, psychoeducation, and physical activity vs control	Primary	MOS-SF12; POMS (vigor subscale); MFI (general/fatigue subscale); MENQOL; BPI; POMS (anxiety/depression subscale)	87/94	Yes	Yes	No	Yes	Improved physical QOL (based and energy, less fatigue. Less distress.)	No difference in fitness level.	Yes
Hwang, 2008 (209)	Superiority	Exercise vs control (shoulder exercise only) in patients receiving radiation	nr	WHOQOL-BREF; BFI	37/40	No	Yes	No	Yes	Improved QOL No (overall QOL, overall health, physical, psychological, and social).	Improved shoulder motion range and decreased pain.	Decreased fatigue.

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Missing data, specific method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Rogers, 2009 (210) and Rogers, 2009 (211)	Superiority (pilot)	Physical activity behavior change intervention vs usual care in breast cancer survivors	Secondary	FACT-G; FACT-B; FACT-F; FACT-ES; FACT-cognitive	41/41	No	Yes	No	No difference except for im-and distribution- proved social based.	Yes, anchor- except for im-and distribution- proved social based.	Immediately and 3 mo after intervention:	Yes (pilot results support further physical activity behavior, muscle search)
Danhauser, 2009 (212)	Superiority (pilot)	Restorative Yoga vs wait-list control group in women with breast cancer undergoing treatment or not	Secondary	FACT-B; FACT-F; SF-12; FACIT-Spirituality; CES-D; PSQI (V,R); PANAS	44/44	No	Yes	Yes, available cases-repeated measures using the MIXED procedure on the SAS statistical software	Improved mental health, less depression, improved positive affect, and greater spirituality	No	Does not apply	Not applicable (pilot)
Tang, 2002 (213)	Not clear if a superiority or equivalence trial	Group support + complementary and alternative medicine support interventions vs group support x 12 wk	Primary	FACIT; FACIT-Spiritual; POMS; Principles of Living Survey (R)	167/181	No	Yes	No	Differences only statistically significant for increases in measures of spiritual integration.	None reported	Yes	Yes, distribution-based

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Intervention (experimental vs control)	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Roberts, 2003 (214)	Not stated if superiority or equivalence	Oral diet vs total parenteral nutrition after bone marrow transplant	Secondary POMS	n/r/55	No	No	No	Yes	No difference	No	No difference in length of stay, engraftment, infection, survival, hand-grip strength.	No difference in weight and anthropometrics were better maintained in total parenteral nutrition group.	No
Wells, 2004 (215)	Superiority	Nurse-led intervention of early discharge (3 days) vs conventional hospital stay (6 days) after axillary lymph node dissection	Primary FACT-B; EQ-5D (V,R,Res)	108/108	Yes	Yes	No	No	Yes	No difference	No difference in pain or arm volume.	Yes	No difference in pain or arm volume.
van Roosmalen, 2004 (216)	Superiority	First randomization: decision aid vs control. Second randomization: shared decision-making intervention vs control in <i>BRCA1</i> and <i>BRCA2</i> mutation carriers (affected and unaffected)	Secondary State anxiety subscale of STA; CES-D; IES; Scale 0–10 general health	Decision aid: No 35/390. Shared decision-making intervention: 87/89	Yes	Yes, available	Yes	Yes, available	Decision aid: no effect on well-being (217). Shared decision-making intervention: no short-term effect. At 9 months, better general health and less intrusive thoughts.	Decision aid: no effect on distribution-based	Decision aid: considered prophylactic surgery more frequently and were better informed.	Decision aid: no effect on well-being (217). Shared decision-making intervention: improved decision-making in unaffected mutation carriers (unpublished data).	Decision aid: considered prophylactic surgery more frequently and were better informed.

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	QOL Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size for QOL	Power statistical method	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Scheier, 2005 (2018)	Superiority	Educational intervention vs nutritional intervention vs control	Primary CESD; SF-36; IES; Self efficacy (home-based questionnaire); Profile of Con- cerns about breast cancer scale; Self concept (novel); COPE	224/252	Yes	Yes	No	Yes	Participants in the two intervention arms had less depressive symptoms and better physical functioning at 13 mo of follow-up	No	nr	Yes
Stanton, 2005 (2019)	Superiority	Standard print material + peer-modeling video + two sessions with a trained can- cer educator (EDU) and informational workbook vs standard print material + peer-modeling video (VID) vs control (standard Na- tional Cancer Institute print material)	Primary SF-36; IES-R; CES- D; PTGI; Perceived preparedness for re-entry (novel)	558/679 consented	Yes	Yes	Yes, multiple imputa- tions	Yes, multiple imputa- tions	At 6 mo: VID vs control had greater improvement in vitality, and EDU vs control had less cancer- specific dis- tress in those less prepared for reentry. No difference at 12 mo.	Yes	Not applicable	Yes
Cho, 2006 (2020)	Superiority	Comprehensive group reha- bilitation 3 times/week for 10 weeks vs wait-list control group in women with early- stage breast cancer	Not clear Novel QOL questionnaire (V.R); Novel psy- chological adjust- ment (R)	55/65	Yes	Yes	No	Yes	Improved QOL No and psycho- logical adjust- ment.	Increased range of shoulder motion.	Increased range Yes	

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome	Intervention (experimental vs control)	Instruments	QOL sample size/trial	Power for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Meneses, 2007 (221) and Loerzel, 2008 (222)	Superiority	Breast cancer education intervention (face to face, telephone, written, and audiotaped reinforcement)	Primary	QOL-BC survivors (V,R)	256/261; Subgroup analysis of women ≥65 y. 50/50	No	Yes	Yes, GEE	Yes	Improved overall, psychological, and social QOL. No difference in physical or spiritual well-being. No difference in QOL in population ≥65 y.	Does not apply	Yes
Sandgren, 2007 (223)	Superiority	Health education Primary therapy vs emotional expression therapy vs control (telephone-delivered) (1–3 mo after diagnosis)	Primary	FACT-G; POMS; FACT-B (9 items); Coping Responses Indices-Revised (avoidance subscale); Perceived Stress scale (V,R) (4 items)	218/218	No	Yes	No	Yes	No statistically significant difference except for decreased stress with the health education therapy.	Better knowledge.	Yes
Meneses, 2009 (224)	(pilot)	Breast cancer education intervention vs wait-list control	Secondary	QOL-BC survivors (V,R)	53/53	No	Yes	No	Yes	Statistically significant effect on overall QOL and in mean psychological QOL score and maintained over time.	Does not apply (pilot)	Does not apply (pilot)
Low, 2006 (225)	Superiority	Writing about deepest thoughts and feelings vs writing about positive thoughts vs writing about facts regarding career and treatment (control)	nr	POMS	55/63	No	Yes	No	Yes	No difference except for difference in negative mood and the three groups.	Fewer symptoms and fewer cancer-related symptoms (total interview time groups)	No

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	QOL primary or secondary outcome (experimental vs control)	Instruments	sample size/trial	Power sample size for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Arving, 2007 (226) and Arving, 2006 (227)	Superiority	Individual psychosocial support by oncology nurses vs by psychologists vs standard care in breast cancer patients receiving adjuvant therapy	EORTC QLQ-C30; EORTC QLQ-BR23; HADS; IES; STAI-State Psychologist: 82/120	171/179; for comparison of nurse vs psychologist: 82/120	No	Yes	No	Intervention (both); improved global QOL, health status, less nausea/vomiting, systemic therapy side effects, dyspnea, insomnia, pain, financial difficulties.	Yes, anchored-based	Does not apply	Yes
Dagani, 2007 (228)	Superiority	Multicomponent Unclear nutritional tools diet (arm A) vs control (arm B)	FACT-G; FACT-B; additional items	Arm A: 17/17; No Arm B: nr/17	Yes, partial	No	Yes	Difference in physical and functional well-being	Decreased body mass index and increased hydrosoluble anti-oxidant.	Decreased oxidative stress.	No
Bilhuri, 2007 (229)	Superiority	Massage therapy Secondary therapy (visit by hospital staff) to prevent nausea and associated with chemotherapy	HADS; VAS for anxiety (Y)	39/39	No	Yes	Yes	No statistically significant difference in anxiety and depression.	Decreased nausea.	Decreased nausea.	(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial	Power sample size for QOL	Missing data, general	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Hartmann, 2007 (230)	Superiority (pilot)	Step-by-step inpatient rehabilitation program vs conventional rehabilitation program	Primary	EORTC QLQ-C30	197/200	Yes	Yes	No	No	No statistically significant difference but statistically significant benefits for emotional and cognitive function observed in subgroup with cognitive impairments.	Does not apply	Does not apply (pilot)
Gottay, 2007 (231)	Superiority	Brief telephone intervention vs standard care	Primary	CARES-SF; CES-D	305/305	Yes	Yes	No	Yes	At 3 mo: no difference in distress or depression	Does not apply	Yes
Titeca, 2007 (232)	Superiority	Cosmetic care vs control	Primary	VQ-Dermato (V,R)	26/27	No	Yes	No	Yes	Increased mood state and self-perception of the disease.	Does not apply	Yes
Fenlon, 2008 (233)	Superiority	Individual relaxation training + instructions for home + audiotape vs control (discussion with a nurse about menopause management)	Secondary	FACT-ES; STAI; Hunter menopause scale	150/150	No	Yes	Yes, no imputation	Yes	No difference except for improvement in distress from hot flashes at 1 mo but not at 3 mo	Decrease in the number of hot flashes at 1 mo	No incidence, severity, and distress from hot flashes.
Bilhult, 2008 (234)	Superiority	Massage vs control	Secondary	HADS; Life satisfaction questionnaire; STAI	22/22	No	No	No	Yes	No difference	No	No difference in No lumune function.
Lindemann, 2008 (235)	Superiority	Support group intervention vs control	Primary	HADS; Norwegian Fatigue Questionnaire (V,R)	41 for this	No	No	No	Yes	No difference	No	No difference in fatigue findings.

(Table continues)

Table 4 (Continued).

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	sample size/trial	Power sample size for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Campos, 2009 (236)	Superiority (pilot)	Two trials. Trial 1: Home-based exercise program vs usual care (newly diagnosed survivors). Trial 2: Combined supervised and home-based exercise intervention vs usual care (during or recently completed adjuvant radiation of chemotherapy).	FACT-B; MOS-SF-36; Trial 1: 50/50; No Fordyce Happiness Measure (V,R,Res); Rosenberg self-esteem scale; CES-D; STAI (only State anxiety scale)	Trial 1: 74/75 Trial 2: 74/75	Yes	Yes, last value carried forward	Yes	No difference	No	Women in the intervention group (Trial 2) increased their average number of pedometer steps (237).	Does not apply (pilot)	
Berger, 2009 (238) and Berger, 2009 (239)	Superiority	Individualized sleep promotion plan vs healthy eating control	HADS; MOS-SF-36; Piper Fatigue Scale; PSQI (V,R)	203/219	Yes	Yes	Yes, mixed-model analysis	Yes	Improvement in sleep quality.	Improvement in Yes sleep quality.	Improvement in sleep quality, fatigue unchanged.	
Dohbeau, 2009 (240)	Superiority	Psychoeducational group intervention vs waiting-list control	EORTC QLQ-C30; EORTC QLQ-BR23; POMS; STAI; MAC	188/203	No	Yes	Yes, method of data allocation [from Jöreskog and Sörbom (241)]	Yes	Intervention group: reduction in anxiety, anger, depression, and fatigue; improvement in vigor and interpersonal relationships, emotional and role functioning, and health status	Does not apply. Yes		

(Table continues)

**Table 4 (Continued).**

First author, year (reference), trial name	Trial type	Intervention (experimental vs control)	QOL primary or secondary outcome	Instruments	QOL sample size/trial sample size for QOL	Power for QOL general	Missing data, specific	Statistical method	QOL outcome(s)	Clinical significance of QOL finding	Medical outcome(s)	QOL influence on decision
Poppelreuter, 2009 (242)	Superiority	Computer-based training vs neuropsychological training group vs control (control group not randomly assigned)	EORTC QLQ-C30; MFI; HADS	96/96	No	Yes	Yes, complete	Yes	No result for intervention except for EORTC cognitive functioning scale showing no difference between groups.	No	No difference in cognitive function.	No
Nidich 2009 (243)	Superiority	Transcendental meditation program vs control group	FACT-B; MOS-SF-36 (mental health and vitality subscale); FACT-SP	130/130	Yes	Yes	Yes, single imputation	Yes	Significant improvement in the FACT-B and SF-36 mental health subscale.	Yes, Yes, distribution-based	No difference in survival.	Yes

\* The timing of QOL was reported for all studies. ABS = Appraisal of Illness Scale; AIS = Affect Balance Scale; BIS = Beck Hopelessness Scale; BIS = Body Image Scale; CARES = Cancer Rehabilitation Evaluation System; CES-D = Center for Epidemiological Studies—Depression Scale; COPE = Coping Operation Preference Inventory; DAS = Dyadic Adjustment Scale; DWI = Dealing With Illness Inventory; EQ-5D = EuroQol-5D; ES = effect size; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire; FACIT-(F) = Functional Assessment of Chronic Illness Therapy—(Fatigue); FACIT-SP = FACIT—Spiritual Well-Being; FACT-G = Functional Assessment of Cancer Therapy—General; FACT-B = FACT-G + a breast cancer (revised); ISI = Insomnia Severity Index; HADS = Hospital Anxiety and Depression Scale; LASA = Linear Analog Self-Assessment; MAACL = Multiple Affect Adjective Checklist; MAC = Mental adjustment to cancer; MFI = Multidimensional Fatigue Inventory; MSAS = Memorial Symptom Assessment Scale; MHI = Mental Health Inventory-5; MOS SF-12 = Medical Outcomes Study 12-item Short Form; MOS SF-36 = Medical Outcomes Study 36-item Short Form; MUIS = Mishel Uncertainty in Illness Scale; nr = not reported; PANAS = Positive and Negative Affect Scale; PALS = Profile of Mood States; PSS = Perceived Social Support Scale; PCL-S = Posttraumatic Stress Checklist—Specific Version; PFS = Pittsburgh Sleep Quality Inventory; PSQI = Pittsburg Sleep Quality Inventory; RLI = Quality of life Index; R = reliable; Res = responsive; RPFS = Revised Piper Fatigue Scale; SCL-90-R = Symptom Checklist; SDS = Symptom Distress Scale; SF-36 = Short Form-36; SNI = Social Network Index; SPSI-R = Social Problem-Solving Inventory—Revised; SSQ = social support questionnaire; STAI = State-Trait Anxiety Index; VAS = visual analog scale for the level of satisfaction; UCLA = University of California Los Angeles Loneliness scale; V = valid; VAS = visual analog scale; WHOQOL = World Health Organization Quality of Life; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index.

dose-intensive vs standard-dose chemotherapy. All of these trials showed either no difference or a transient decline in QOL during treatment administration in the dose-intensive chemotherapy arm with subsequent improvement over time.

**Hormone therapy "X" vs hormone therapy "Y".** The Zoladex in Premenopausal Patients trial (54) was conducted in premenopausal women and compared tamoxifen with ovarian ablation. Six trials were conducted in postmenopausal women and compared tamoxifen with toremifene [IBCSG trials 12-93 and 14-93 (56)] or with aromatase inhibitors [ie, anastrozole (57-59), exemestane (66,68), or letrozole (61-63)].

QOL in the Zoladex in Premenopausal Patients trial was assessed in 72% of the participants of the whole trial using the HADS and the Physical Symptom and Problem Scale; missing data were imputed using the last value carried forward. In the large trials involving aromatase inhibitors, there was no overall effect of any treatment on QOL; however, symptoms differed according to the type of hormone therapy received.

**Metastatic Disease Setting.** Twenty-nine trials (69-75, 77-90,92-102,104,244) tested a biomedical intervention in the metastatic disease, of which only three (82,84,97,98) had QOL as a primary endpoint. The QOL instruments used in this setting were quite uniform, mainly the EORTC QLQ-C30 plus or minus the EORTC QLQ-BR23 or the FACT-B. For trials in the metastatic setting, QOL was often reported only in brief in the main article (eg, most reported only summary results but no subscale results or subscales results were reported in tables only). Other trials reported QOL data in a separate article or stated that QOL outcomes would be reported separately (data not shown).

The majority of the trials of biomedical interventions in the metastatic disease setting did not report differences in QOL between study arms. However, trials that compared combination chemotherapy with a single agent reported increased toxicity with the combinations [eg, (70,244)]. Trials that tested adding a taxane to an anthracycline-based chemotherapy reported no differences in QOL between study arms (71,75). For example, in a trial that compared doxorubicin-docetaxel with doxorubicin-cyclophosphamide, doxorubicin-docetaxel demonstrated longer time to progression and time to treatment failure but no difference in QOL and overall survival (71); a second trial that used paclitaxel instead of docetaxel reported no difference in efficacy and no difference in QOL (75).

Among the trials of hormone therapy for metastatic disease, a small crossover trial of anastrozole vs letrozole assessed QOL and drug tolerance (97,98); QOL was the primary endpoint, and a sample size of 66 patients was needed to show an 8.1-point difference between study arms on the FACT questionnaire. QOL outcomes favored letrozole, but with a mean difference of only 5.1 points between study arms, which was statistically significant (clinical significance was not addressed). The other five trials (94-96,101) that tested hormone therapy in the metastatic setting showed no differences in QOL or medical outcomes between the study arms.

QOL was a useful adjunct for clinical decision making in a noninferiority trial. Conte et al. (74) compared sequential with concurrent administration of epirubicin and paclitaxel in the

metastatic setting. In this trial, QOL (a secondary endpoint) was measured using the EORTC QLQ-C30. QOL was evaluated in only 50% of the patients. There was a non-statistically significant trend for better functioning and better symptom control in the concurrent arm.

**Follow-up Setting.** Previous studies have shown that most breast cancer recurrences are detected between doctors' appointments (245). Three trials compared standard follow-up with patient-initiated (105,108) or nurse-led (107) follow-up. In the latter trial (107), the statistical power was 90% to detect a 10-point increase in anxiety in nurse-led follow-up (although these calculations seem to have been made a posteriori). A total of 135 of the 400 randomly assigned patients from one center were excluded post hoc because the two intervention arms at that center were considered too similar by the study authors. Overall, these studies showed no differences in QOL between the study arms; however, in one study (105), subjects in the patient-initiated follow-up arm reported fewer arm and breast symptoms compared with those in the standard follow-up arm. There were no differences in recurrence between study arms. These trials suggest that patient-initiated follow-up or nurse-led follow-up on demand could be an alternative to standard clinic follow-up.

**Symptom Control Setting.** Three trials evaluated the effect of antidepressants on depression and fatigue: one compared paroxetine with placebo (128), one compared paroxetine with amitriptyline (109), and one compared fluoxetine with placebo (137). Only one trial (109) reported a sample size calculation. Two of these trials identified a statistically significant difference in depression (128,137) but not in fatigue (128).

Erythropoietin (EPO) was studied in the adjuvant treatment (111,126) and metastatic disease (112,123,126) settings, with the goal of improving three outcomes: transfusion requirements, QOL, and, more recently, cognitive dysfunction. These trials used widely accepted instruments: EORTC QLQ-C30, FACT-anemia, and POMS. In a pilot trial that assessed the feasibility of administering neurocognitive assessment tests (111), QOL was better in the EPO group than in the placebo group; however, no formal statistical testing was conducted. QOL was the primary endpoint in the other two trials. One trial (112) compared two different doses of EPO and found no difference in transfusion rates. The second trial (126) compared EPO with standard care and found fewer transfusions with EPO. QOL was improved in the EPO arm compared with standard care (126), but there was no difference in global QOL between the high and low doses of EPO (112). Responder-type analysis at the patient level was used in one study (112). The largest trial (>900 patients) (123) had QOL as a secondary endpoint and compared EPO with placebo. The area under the curve from baseline to 12 months of follow-up was analyzed, enabling the use of all data collected even if there were missing assessments. The authors conducted sensitivity analyses for missing data using different assumptions (but did not detail the approach used). QOL did not differ between study arms; however, overall survival was decreased in the EPO arm, leading to early stoppage of the trial. The measurement of QOL in these trials was important because EPO was not associated with improved cancer outcomes and could potentially have been associated with worse outcomes.

Hot flashes and other menopausal symptoms are common complaints among women with breast cancer. Because hormonal replacement therapy is not recommended for women with a history of breast cancer, other interventions for these symptoms are needed. We identified trials that tested phytoestrogens (117,127), homeopathic medicine (129,130), magnets (115), and antidepressants (131,133,139) for controlling menopausal symptoms in breast cancer patients. These trials were small (ie, 15–83 patients), and three (115,129,130) were pilot trials. A variety of questionnaires were used to assess hot flashes and QOL associated with menopausal symptoms. None of these trials reported a QOL benefit for any intervention; however, one trial (129) reported better general health using the SF-36 questionnaire among subjects who received homeopathic medicines.

We identified three trials that evaluated lymphatic drainage (113), exercise (118), or vitamin E plus pentoxifylline (119) for the treatment of lymphedema. In all of these trials, reduction in arm volume was the primary endpoint and QOL was a secondary endpoint. Only one study (119) used a questionnaire with specific questions about arm symptoms (EORTC QLQ-BR23) and that trial did not identify differences in QOL between the study arms. One trial (113) showed a statistically significant beneficial effect of lymphatic drainage on reducing arm volume and for QOL. In that trial, 31 women were randomly assigned to manual lymphatic drainage or simple lymphatic drainage using a crossover design. Manual lymphatic drainage was associated with improved emotional functioning and with reduced dyspnea and sleep disturbances; however, there was no difference in physical or role functioning between the study arms.

Bisphosphonates are recommended by the American Society of Clinical Oncology for patients with bone metastases to decrease skeletal events and pain (246). A trial reported by Body et al. (120) confirmed that a bisphosphonate improved pain and QOL compared with a placebo. Another trial (124) compared administration of zoledronic acid in a community setting with administration in a hospital setting. The primary endpoints included bone pain, QOL, performance status, resource utilization, and patient satisfaction, but no formal composite endpoint was defined; power calculations were not provided. Only 79 of the 101 patients enrolled had usable QOL data. Missing data were replaced by the last observation carried forward. Patients who received community-administered zoledronic acid had better QOL compared with patients who received hospital-administered zoledronic acid. The authors reported that improvements in global QOL and physical, social, and emotional functioning were greater than 5% and were, therefore, clinically significant but provided no justification for this conclusion.

Two randomized placebo-controlled clinical trials evaluated mistletoe extract for improving QOL in women receiving adjuvant chemotherapy for breast cancer (121,132). QOL benefits (improvement in tiredness, sexuality, physical, emotional, and functional well-being) were identified in the mistletoe arm.

## **QOL in Randomized Clinical Trials of Nonbiomedical Interventions**

**Psychosocial Interventions in the Adjuvant Setting.** Twenty trials belong to this category (141–146,148–150,152–163) (Table 4). QOL was a primary study outcome in all but two (153,155,156) of

these 20 trials. Power calculations were presented in only four of the 20 trials. The absence of power calculation could have been, at least in part, overcome by addressing the clinical significance of the results. However, few trials reported the clinical significance of their findings (or stated a priori what would be considered clinically significant): Three trials (146,159,162) used effect sizes to address clinical significance. Many questionnaires were used; the most common were the POMS and FACT (each was used in seven of the 20 trials). QOL influenced the conclusions because it was the primary outcome in the majority of these trials. However, it is not clear to what extent the interventions reported as being beneficial are available and currently used in clinical practice.

## **Psychosocial Interventions in the Metastatic Disease Setting.**

**Setting.** We identified only four trials of psychosocial interventions in the metastatic disease setting (164,166,167,169,170); one report (166) focused on analysis of missing data in a randomized clinical trial (168) that was published before the cutoff for inclusion in this review.

Clasen et al. (164) conducted a trial designed to replicate earlier findings (247) of survival benefits associated with supportive-expressive group therapy in the metastatic setting. The POMS and IES questionnaires were used. Interpretation of the QOL data was based on the effect sizes. The intervention had no effect on mood but was associated with a greater decline in posttraumatic stress symptoms compared with the control. Given the absence of survival benefit (164), it is unclear to what extent this study would change clinical practice.

Another report (166) was an analysis focusing on missing data of a randomized clinical trial that was included in our first review (3) using results for responsiveness to change from a randomized clinical trial of supportive-expressive group therapy that was published in 2001 (168), which was also designed to replicate survival benefits found by Spiegel et al. (247). A variety of approaches were used to impute missing data. The main QOL results did not differ according to the approaches used to account for missing data.

Northouse et al. (169) examined the effects of a family-based intervention on QOL. The intervention had no effect in QOL, but reduced hopelessness and negative appraisal of illness at 3 months; however, these effects were not sustained at 6 months.

Aranda et al. (170) compared a nurse-delivered intervention to address the needs of women with advanced breast cancer with usual care. There were no differences in QOL between the study arms.

**Symptom Control.** There were 10 trials (172–182) that examined symptom control and they all had a small sample size (16–98 patients). All of these trials used well-validated instruments to assess QOL and described the statistical methods used, but only one (181) considered missing data. The trials focused on interventions to manage nausea (172,178), treatment side effects (173,174), insomnia (175,176), and radiotherapy-induced fatigue (177). All of trials showed that the study intervention improved these outcomes as well as some aspects of QOL. Four trials (174,177,179,182) were pilot studies.

**Other Nonbiomedical Interventions.** Since our previous review in 2003 (3), many trials that evaluated exercise and included a QOL endpoint have been published. The majority used FACT/FACIT questionnaires to assess QOL. QOL was the primary outcome in 16 of these trials (183,184,186,187,189,190,192,194–199,202,204,207,208), and eight reported sample size or power calculations (183,184,197–199,202,204,207,208). Ten trials (185–187,189,191,192,205,206,210–212) were pilot studies that did not include sample size calculations for the QOL outcomes. Most of the exercise intervention trials reported improvements in some aspects of QOL. However, the degree of uptake of these interventions in routine clinical practice is unclear.

One trial compared standard group support with an alternative medicine support intervention that included meditation, affirmation, imagery, and ritual (213). QOL improved in both study arms, and the only statistically significant difference was increased spiritual integration in the alternative medicine arm.

Twenty five trials tested education and support interventions (213–216,218–236,238–240,242,243), substantially more than were included in our previous review. Nine trials (216,218,219,221–223,230,231,238–240) included 200 patients or more. Among 14 trials in which QOL was the primary endpoint (213,215,218,219,221–223,226,227,230–232,235,238–240,243), only five reported the clinical significance of the QOL finding (213,216,219,226,227,243).

One study tested the benefit of shared decision making. Van Roosmalen et al. (216) reported a randomized clinical trial of a shared treatment decision-making intervention among *BRCA1* and *BRCA2* mutation carriers. Women were first randomly assigned to receive a decision aid or no decision aid; they were then randomly assigned to receive shared decision making or no shared decision making. The primary outcome was decision uncertainty. QOL was measured using the STAI, CES-D, and IES questionnaires. The group using the decision aid had most frequently considered prophylactic surgery and was better informed. For those included in the second randomization and receiving the shared decision making intervention, decision making was improved in unaffected mutation carriers but not in mutation carriers with breast cancer. Those receiving the shared decision-making intervention had better general health and less intrusive thoughts at 9 months, but overall QOL did not differ between the study arms.

Only one study looked at nutrition. A randomized clinical trial comparing an oral diet with parenteral nutrition at the time of autologous bone marrow transplant was conducted with 55 breast cancer patients (214). The POMS questionnaire was used to measure the patients' sense of well-being at hospital admission, at discharge, and at 30 days after the transplant. There was no difference in POMS scores between the study arms at any time point. Given the lack of effect of autologous bone marrow transplant on breast cancer outcomes (248), these results are unlikely to influence decisions about use of parenteral nutrition for breast cancer patients.

## Discussion

This systematic review is an update of our earlier review published in 2003 (3). The earlier review reported 66 trials published between 1983 and 2001, and this update reports 190 trials pub-

lished from 2001 to 2009. In the earlier review, we concluded that caution was needed before including QOL assessment in newly planned randomized clinical trials unless treatment equivalency was expected or the "QOL question targets unique or specific questions that can only be assessed through patient self-report" (3).

The objectives of this updated review were to assess the incremental influence of QOL findings on clinical decision making over and above that of traditional trial endpoints and to describe the extent and quality of QOL reporting in clinical trials. For trials of biomedical interventions, QOL influenced decisions about use of the intervention studied in 30.1% of the trials in this review compared with 15.2% of the trials in the previous review. Corresponding numbers for trials of nonbiomedical interventions were 63.2% and 95%, respectively. However, it must be noted that there were only 20 trials testing nonbiomedical interventions in the previous review, and there were 89 such trials in this update. Also, studies used a greater variety of interventions in this update, including, for example, many trials of physical activity interventions. Despite the fact that in many trials, QOL findings were taken into consideration by the study authors in their conclusions about the benefit of the intervention, the extent to which the interventions tested in the trials included in this review are used in routine clinical practice and to which the QOL results influenced uptake of apparently beneficial interventions, remain unclear. Kazdin (249) has postulated that the gap between the uptake of psychosocial interventions shown to be beneficial in clinical trials and their use in routine clinical practice might be explained by the selection of patients in trials based on a specific symptom or condition and the unknown true impact on patients' daily life.

In the previous review, the most common questionnaire used was the POMS followed by the EORTC QLQ. In this updated review, the two most commonly used questionnaires were the EORTC QLQ and the FACT/FACIT. However, there were numerous other questionnaires used, the majority of which were valid and reliable.

There were no major differences between the previous review and this update regarding the quality of QOL reporting. In more than 80% of the trials included in the review, the sample size of the trial and of the number of patients who completed questionnaires was reported, as well as the timing of questionnaire administration and the statistical method used. Three criteria were not evaluated in the previous review but were assessed in this update: whether power and sample size calculations for QOL outcomes were reported, a description of how missing data were handled, and whether the clinical significance of expected or obtained results was reported. Adherence to all of these criteria was poor, and less than one-third of articles reported on them. It is surprising that sample size calculations were not always reported, even in trials in which QOL was a primary endpoint.

The main strength of this updated review is that it included a large number of randomized clinical trials. In addition, because we used mostly same criteria in this review as were used in the previous review, we were able to compare results of both reviews.

This review has several limitations. First, interpretation of the data was difficult in some cases, especially determining whether or not QOL results influenced the study authors' decision to recommend the use of an intervention. In addition, because QOL results

were, in some cases, very detailed (eg, when the assessment was multidimensional), it was difficult to extract the key elements. This complexity is reflected in the percentages of discordance between the reviewers, which ranged from 1.1% to 19.9%. It must be noted, however, that a difference in only one element of the variable between reviewers was sufficient to consider a variable discordant (eg, if a trial used six QOL instruments but one reviewer entered only five instruments, the name-of-instruments variable was considered discordant for that trial). Second, it is possible that we did not capture all relevant trials with our search strategy (eg, studies not published in English were excluded). Third, our search was limited to randomized clinical trials in breast cancer that included QOL as an outcome. Therefore, our conclusions about the relevance of QOL to breast cancer relate to those studies in which QOL was measured, not to breast cancer studies overall. Fourth, we did not weight the quality of the report based on whether or not the focus in the article was on QOL results. For example, in large adjuvant therapy trials, QOL was often reported succinctly in one paragraph in the results section of the article. Finally, we cannot exclude the possibility that some trials with negative QOL findings were not published or did not publish the QOL outcomes. We were not able to evaluate if there was such publication bias because we did not have the protocols of the published trials. However, given that we were not measuring the strength of an effect in this review, this limitation is minor.

In summary, QOL data tend to be most useful for clinical decision making in trials of nonbiomedical interventions, in which QOL is often the primary outcome. In randomized clinical trials testing adjuvant treatments, QOL data provided additional information on the effect of new treatments; however, QOL data rarely affected the decision to use or not to use these new interventions. In regard to reporting of QOL, we found that handling of missing data, QOL-specific power calculations, and assessment of the clinical significance of QOL findings were frequently not reported.

In conclusion, results obtained from the previous review and this updated review leads us to make the following suggestions about including QOL in the design of randomized clinical trials in breast cancer and about reporting QOL. First, QOL should only be included as a secondary endpoint in a trial of adjuvant therapy if the trial is an equivalence or noninferiority trial (where QOL may play a greater role in decision making) or if it focuses on a vulnerable population (eg, elderly) or is testing very different modalities or is testing a new intervention and descriptive information needs to be obtained about the effect on QOL. Second, in the metastatic setting, QOL should be measured in trials in which the incremental benefit of traditional medical endpoints is expected to be small (eg, a 1-month improvement in overall survival) or the treatments have different tolerability profiles or if the trial is testing a new intervention and information about its effect on QOL needs to be obtained. Third, QOL-specific sample size calculations should be performed and QOL should be measured only in the subset defined by these calculations. Finally, when QOL is not the primary endpoint of a trial, QOL results should ideally appear in a companion article published at the same time as the traditional medical outcomes article so that a full view of the risks and benefits of the intervention can be presented at the same time to clinicians.

## References

- WHOQOL group. Study protocol for the World Health Organization project to develop a Quality of Life assessment instrument (WHOQOL). *Qual Life Res*. 1993;2(2):153–159.
- Moinpour CM, Feigl P, Metch B, Hayden KA, Meyskens FL Jr., Crowley J. Quality of life end points in cancer clinical trials: review and recommendations. *J Natl Cancer Inst*. 1989;81(7):485–495.
- Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer—taking stock [review] [93 refs]. *J Natl Cancer Inst*. 2003;95(4):263–281.
- Huschka MM, Mandrekar SJ, Schaefer PL, Jett JR, Sloan JA. A pooled analysis of quality of life measures and adverse events data in north central cancer treatment group lung cancer clinical trials. *Cancer*. 2007;109(4):787–795.
- Paul N, Pater J, Whitehead M, Sadura A. Methods of toxicity data collection: an evaluation of the relative effectiveness of the case report flow sheet (FS), the patient symptom diary (SD), and the quality of life questionnaire (QLQ). *Control Clin Trials*. 1991;12(5):648.
- US Department of Health and Human Services FaDA. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>. Accessed December 2009.
- Efficace F, Bottomley A, van Andel G. Health related quality of life in prostate carcinoma patients: a systematic review of randomized controlled trials. *Cancer*. 2003;97(2):377–388.
- Blazey JM, Avery K, Sprangers M, Pikhart H, Fayers P, Donovan J. Health-related quality of life measurement in randomized clinical trials in surgical oncology. *J Clin Oncol*. 2006;24(19):3178–3186.
- Joly F, Vardy J, Pintilie M, Tannock IF. Quality of life and/or symptom control in randomized clinical trials for patients with advanced cancer. *Ann Oncol*. 2007;18(12):1935–1942.
- Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *J Exp Clin Cancer Res*. 2008;27:32.
- de Haes JC, Curran D, Aaronson NK, Fentiman IS. Quality of life in breast cancer patients aged over 70 years, participating in the EORTC 10850 randomised clinical trial. *Eur J Cancer*. 2003;39(7):945–951.
- Tominaga T, Takashima S, Danno M. Randomized clinical trial comparing level II and level III axillary node dissection in addition to mastectomy for breast cancer. *Br J Surg*. 2004;91(1):38–43.
- Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol*. 2005;23(19):4312–4321.
- Rudenstam CM, Zahrieh D, Forbes JF, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93 [see Rudenstam CM, Zahrieh D, comment]. *J Clin Oncol*. 2006;24(3):337–344.
- Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst*. 2006;98(9):599–609.
- Zavagno G, De Salvo GL, Scalco G, et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg*. 2008;247(2):207–213.
- Del Bianco P, Zavagno G, Burelli P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. *Eur J Surg Oncol*. 2008;34(5):508–513.
- Rayan G, Dawson LA, Bezjak A, et al. Prospective comparison of breast pain in patients participating in a randomized trial of breast-conserving surgery and tamoxifen with or without radiotherapy [see comment]. *Int J Radiat Oncol Biol Phys*. 2003;55(1):154–161.
- Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med*. 2004;351(10):963–970.

20. Donovan E, Bleakley N, Denholm E, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiat Oncol.* 2007;82(3):254–264.
21. Prescott RJ, Kunkler IH, Williams IJ, et al. A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. *Health Technol Assess.* 2007;11(31):1.
22. Pignol J-P, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol.* 2008;26(13):2085–2092.
23. Classe JM, Berchery D, Campion L, Pioud R, Dravet F, Robard S. Randomized clinical trial comparing axillary padding with closed suction drainage for the axillary wound after lymphadenectomy for breast cancer. *Br J Surg.* 2006;93(7):820–824.
24. International Breast Cancer Study G. Endocrine responsiveness and tailoring adjuvant therapy for postmenopausal lymph node-negative breast cancer: a randomized trial [see comment] [erratum appears in *J Natl Cancer Inst* 2002 Sep 4;94(17):1339]. *J Natl Cancer Inst.* 2002;94(14):1054–1065.
25. Bernhard J, Zahrieh D, Coates AS, et al. Quantifying trade-offs: quality of life and quality-adjusted survival in a randomised trial of chemotherapy in postmenopausal patients with lymph node-negative breast cancer. *Br J Cancer.* 2004;91(11):1893–1901.
26. de Haes H, Olschewski M, Kaufmann M, et al. Quality of life in goserelin-treated versus cyclophosphamide + methotrexate + fluorouracil-treated premenopausal and perimenopausal patients with node-positive, early breast cancer: the Zoledex Early Breast Cancer Research Association Trialists Group [see comment]. *J Clin Oncol.* 2003;21(24):4510–4516.
27. Jonat W, Kaufmann M, Sauerbrei W, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoledex Early Breast Cancer Research Association Study. *J Clin Oncol.* 2002;20(24):4628–4635.
28. Groenvold M, Fayers PM, Petersen MA, Mouridsen HT. Chemotherapy versus ovarian ablation as adjuvant therapy for breast cancer: impact on health-related quality of life in a randomized trial. *Breast Cancer Res Treat.* 2006;98(3):275–284.
29. Bernhard J, Zahrieh D, Castiglione-Gertsch M, et al. Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients—the International Breast Cancer Study Group Trial VIII. *J Clin Oncol.* 2007;25(3):263–270.
30. The Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial. *J Natl Cancer Inst.* 2007;99(7):516–525.
31. Del Mastro L, Costantini M, Morasso G, et al. Impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients. *Eur J Cancer.* 2002;38(3):359–366.
32. Venturini M, Del Mastro L, Aitini E, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. *J Natl Cancer Inst.* 2005;97(23):1724–1733.
33. Tominaga T, Kimura M, Asaga T, et al. 1-hexylcarbamoyl-5-fluorouracil + cyclophosphamide + tamoxifen versus CMF + tamoxifen in women with lymph node-positive breast cancer after primary surgery: a randomized controlled trial. *Oncol Rep.* 2004;12(4):797–803.
34. Brandberg Y, Michelson H, Nilsson B, et al. Quality of life in women with breast cancer during the first year after random assignment to adjuvant treatment with marrow-supported high-dose chemotherapy with cyclophosphamide, thiotapec, and carboplatin or tailored therapy with fluorouracil, epirubicin, and cyclophosphamide: Scandinavian Breast Group Study 9401 [see comment]. *J Clin Oncol.* 2003;21(19):3659–3664.
35. Bergh J, Wiklund T, Erikstein B, et al. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. Scandinavian Breast Group 9401 study. *Lancet.* 2000;356(9239):1384–1391.
36. Land SR, Kopec JA, Yothers G, et al. Health-related quality of life in axillary node-negative, estrogen receptor-negative breast cancer patients undergoing AC versus CMF chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel Project B-23. *Breast Cancer Res Treat.* 2004;86(2):153–164.
37. Fisher B, Anderson S, Tan-Chiu E, et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. *J Clin Oncol.* 2001;19(4):931–942.
38. Bottomley A, Therasse P, Piccart M, et al. Health-related quality of life in survivors of locally advanced breast cancer: an international randomised controlled phase III trial [see comment]. *Lancet Oncol.* 2005;6(5):287–294.
39. Efficace F, Therasse P, Piccart MJ, et al. Health-related quality of life parameters as prognostic factors in a nonmetastatic breast cancer population: an international multicenter study. *J Clin Oncol.* 2004;22(16):3381–3388.
40. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study [review] [33 refs]. *J Clin Oncol.* 2003;21(5):843–850.
41. Peppercorn J, Herndon J II, Kornblith AB, et al. Quality of life among patients with Stage II and III breast carcinoma randomized to receive high-dose chemotherapy with autologous bone marrow support or intermediate-dose chemotherapy: results from Cancer and Leukemia Group B 9066. *Cancer.* 2005;104(8):1580–1589.
42. Peters WP, Rosner GL, Vredenburgh JJ, et al. Prospective, randomized comparison of high-dose chemotherapy with stem-cell support versus intermediate-dose chemotherapy after surgery and adjuvant chemotherapy in women with high-risk primary breast cancer: a report of CALGB 9082, SWOG 9114, and NCIC MA-13. *J Clin Oncol.* 2005;23(10):2191–2200.
43. Nieboer P, Buijs C, Rodenhuis S, et al. Fatigue and relating factors in high-risk breast cancer patients treated with adjuvant standard or high-dose chemotherapy: a longitudinal study [see comment]. *J Clin Oncol.* 2005;23(33):8296–8304.
44. Buijs C, Rodenhuis S, Seynaeve CM, et al. Prospective study of long-term impact of adjuvant high-dose and conventional-dose chemotherapy on health-related quality of life. *J Clin Oncol.* 2007;25(34):5403–5409.
45. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352(22):2302–2313.
46. Martin M, Lluch A, Segui MA, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. *Ann Oncol.* 2006;17(8):1205–1212.
47. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med.* 2006;355(18):1851–1862.
48. Earl HM, Hiller L, Dunn JA, et al. NEAT: National Epirubicin Adjuvant Trial—toxicity, delivered dose intensity and quality of life. *Br J Cancer.* 2008;99(8):1226–1231.
49. Malinovszky KM, Gould A, Foster E, et al. Quality of life and sexual function after high-dose or conventional chemotherapy for high-risk breast cancer. *Br J Cancer.* 2006;95(12):1626–1631.
50. The Adjuvant Breast Cancer Trials Collaborative Group. Polychemotherapy for early breast cancer: results from the international adjuvant breast cancer chemotherapy randomized trial. *J Natl Cancer Inst.* 2007;99(7):506–515.
51. Bernhard J, Zahrieh D, Zhang JJ, et al. Quality of life and quality-adjusted survival (Q-TwIST) in patients receiving dose-intensive or standard dose chemotherapy for high-risk primary breast cancer. *Br J Cancer.* 2008;98(1):25–33.
52. Marino P, Roché H, Biron P, et al. Deterioration of quality of life of high-risk breast cancer patients treated with high-dose chemotherapy: the PEGASE 01 Quality of Life Study. *Value Health.* 2008;11(4):709–718.
53. Watanabe T, Sano M, Takashima S, et al. Oral uracil and tegafur compared with classic cyclophosphamide, methotrexate, fluorouracil as post-operative chemotherapy in patients with node-negative, high-risk breast

- cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. *J Clin Oncol.* 2009;27(9):1368–1374.
54. Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol.* 2003;21(9):1836–1844.
  55. Baum M, Hackshaw A, Houghton J, et al. Adjuvant goserelin in premenopausal patients with early breast cancer: Results from the ZIPP study. *Eur J Cancer.* 2006;42(7):895–904.
  56. Pagani O, Gelber S, Price K, et al. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. *Ann Oncol.* 2004;15(12):1749–1759.
  57. Fallowfield L, Celli D, Cuzick J, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol.* 2004;22(21):4261–4271.
  58. Buzdar AU. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial: an update [review] [23 refs]. *Clin Breast Cancer.* 2004;5(suppl 1):S6–S12.
  59. Celli D, Fallowfield L, Barker P, Cuzick J, Locker G, Howell A. Quality of life of postmenopausal women in the ATAC (“Arimidex”, tamoxifen, alone or in combination) trial after completion of 5 years’ adjuvant treatment for early breast cancer. *Breast Cancer Res Treat.* 2006;100(3):273–284.
  60. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. *Lancet.* 2005;365(9453):60–62.
  61. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. *J Clin Oncol.* 2005;23(28):6931–6940.
  62. Goss PE. Letrozole in the extended adjuvant setting: MA.17. *Breast cancer research and treatment.* 2007;105(suppl 1):45–53.
  63. Muss HB, Tu D, Ingle JN, et al. Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. *J Clin Oncol.* 2008;26(12):1956–1964.
  64. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med.* 2003;349(19):1793–1802.
  65. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* 2005;97(17):1262–1271.
  66. Francini G, Petrioli R, Montagnani A, et al. Exemestane after tamoxifen as adjuvant hormonal therapy in postmenopausal women with breast cancer: effects on body composition and lipids. *Br J Cancer.* 2006;95(2):153–158.
  67. Jones SE, Cantrell J, Vukelja S, et al. Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: report of a Tamoxifen Exemestane Adjuvant Multicenter trial substudy. *J Clin Oncol.* 2007;25(30):4765–4771.
  68. Mamounas EP, Jeong J-H, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol.* 2008;26(12):1965–1971.
  69. Leonard R, Hardy J, van Tienhoven G, et al. Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol.* 2001;19(21):4150–4159.
  70. O’Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002;20(12):2812–2823.
  71. Nabholz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemo-therapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial [see comment] [erratum appears in J Clin Oncol. 2003 May 15;21(10):2048]. *J Clin Oncol.* 2003;21(6):968–975.
  72. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193) [see comment]. *J Clin Oncol.* 2003;21(4):588–592.
  73. Fountzilas G, Kalofonos HP, Dafni U, et al. Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol.* 2004;15(10):1517–1526.
  74. Conte PF, Guarneri V, Bruzzi P, et al. Concomitant versus sequential administration of epirubicin and paclitaxel as first-line therapy in metastatic breast carcinoma: results from the Gruppo Oncologico Nord Ovest randomized trial. *Cancer.* 2004;101(4):704–712.
  75. Bottomley A, Biganzoli L, Cufer T, et al. Randomized, controlled trial investigating short-term health-related quality of life with doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: European Organization for Research and Treatment of Cancer Breast Cancer Group, Investigational Drug Branch for Breast Cancer and the New Drug Development Group Study. *J Clin Oncol.* 2004;22(13):2576–2586.
  76. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. *J Clin Oncol.* 2002;20(14):3114–3121.
  77. Winer EP, Berry DA, Woolf S, et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: cancer and leukemia group B trial 9342. *J Clin Oncol.* 2004;22(11):2061–2068.
  78. Reyno L, Seymour L, Tu D, et al. Phase III study of N, N-diethyl-2-[4-(phenylmethyl) phenoxy]ethanamine (BMS-217380-01) combined with doxorubicin versus doxorubicin alone in metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA.19. *J Clin Oncol.* 2004;22(2):269–276.
  79. Lin C-C, Chang A-P, Chen M-L, Cleeland CS, Mendoza TR, Wang XS. Validation of the Taiwanese version of the Brief Fatigue Inventory. *J Pain Symptom Manage.* 2006;32(1):52–59.
  80. von Minckwitz G, Chernozemsky I, Sirakova L, et al. Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. *Anticancer Drugs.* 2005;16(8):871–877.
  81. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol.* 2005;23(24):5542–5551.
  82. Karamouzis MV, Ioannidis G, Rigatos G. Quality of life in metastatic breast cancer patients under chemotherapy or supportive care: a single-institution comparative study. *Eur J Cancer Care.* 2007;16(5):433–438.
  83. Crump M, Gluck S, Tu D, et al. Randomized trial of high-dose chemotherapy with autologous peripheral-blood stem-cell support compared with standard-dose chemotherapy in women with metastatic breast cancer: NCIC MA.16. *J Clin Oncol.* 2008;26(1):37–43.
  84. Cassier PA, Chabaud S, Trillet-Lenoir V, et al. A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. *Breast Cancer Res Treat.* 2008;109(2):343–350.
  85. Hopwood P, Watkins J, Ellis P, Smith I. Clinical interpretation of quality-of-life outcomes: an investigation of data from the randomized trial of gemcitabine plus paclitaxel compared with paclitaxel alone for advanced breast cancer. *Breast J.* 2008;14(3):228–235.
  86. Fountzilas G, Dafni U, Dimopoulos MA, et al. A randomized phase III study comparing three anthracycline-free taxane-based regimens, as first line chemotherapy, in metastatic breast cancer: a Hellenic Cooperative Oncology Group study. *Breast Cancer Res Treat.* 2009;115(1):87–99.
  87. Maniadakis N, Dafni U, Fragoulakis V, et al. Economic evaluation of taxane-based first-line chemotherapy in the treatment of patients with

- metastatic breast cancer in Greece: an analysis alongside a multicenter, randomized phase III clinical trial. *Ann Oncol.* 2009;20(2):278–285.
88. Osoba D, Slamon DJ, Burchmore M, Murphy M. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. *J Clin Oncol.* 2002;20(14):3106–3113.
  89. Eiermann W, International Herceptin Study G. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: pivotal trial data. *Ann Oncol.* 2001;12(suppl 1):S57–S62.
  90. Osoba D, Burchmore M. Health-related quality of life in women with metastatic breast cancer treated with trastuzumab (Herceptin). *Semin Oncol.* 1999;26(4 Suppl. 12):84–88.
  91. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over-expresses HER2. *N Engl J Med.* 2001;344(11):783–792.
  92. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol.* 2005;23(4):792–799.
  93. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357(26):2666–2676.
  94. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate [see comment]. *J Clin Oncol.* 2001;19(14):3357–3366.
  95. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment [see comment]. *J Clin Oncol.* 2002;20(16):3396–3403.
  96. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial [see comment]. *J Clin Oncol.* 2002;20(16):3386–3395.
  97. Thomas R. Examining quality of life issues in relation to endocrine therapy for breast cancer. *Am J Clin Oncol.* 2003;26(4):S40–S44.
  98. Thomas R, Godward S, Makris A, Bloomfield D, Moody AM, Williams M. Giving patients a choice improves quality of life: a multi-centre, investigator-blind, randomised, crossover study comparing letrozole with anastrozole. *Clin Oncol (R Coll Radiol).* 2004;16(7):485–491.
  99. Aapro M, Leonard RC, Barnadas A, et al. Effect of once-weekly epoetin beta on survival in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy: results of the Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) study. *J Clin Oncol.* 2008;26(4):592–598.
  100. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior non-steroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol.* 2008;26(10):1664–1670.
  101. Ellis MJ, Gao F, Dehdashti F, et al. Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: a phase 2 randomized study. *JAMA.* 2009;302(7):774–780.
  102. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *Eur J Cancer.* 2004;40(11):1704–1712.
  103. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol.* 2003;14(9):1399–1405.
  104. Scott C, Suh J, Stea B, Nabid A, Hackman J. Improved survival, quality of life, and quality-adjusted survival in breast cancer patients treated with efaproxiral (Efaproxy) plus whole-brain radiation therapy for brain metastases. *Am J Clin Oncol.* 2007;30(6):580–587.
  105. Brown L, Payne S, Royle G. Patient initiated follow up of breast cancer. *Psychooncology.* 2002;11(4):346–355.
  106. Wyatt GK, Donze LF, Beckrow KC. Efficacy of an in-home nursing intervention following short-stay breast cancer surgery. *Res Nurs Health.* 2004;27(5):322–331.
  107. Koinberg IL, Fridlund B, Engholm GB, Holmberg L. Nurse-led follow-up on demand or by a physician after breast cancer surgery: a randomised study. *Eur J Oncol Nurs.* 2004;8(2):109–117.
  108. Sheppard C, Higgins B, Wise M, Yianguo C, Dubois D, Kilburn S. Breast cancer follow up: a randomised controlled trial comparing point of need access versus routine 6-monthly clinical review. *Eur J Oncol Nurs.* 2009;13(1):2–8.
  109. Pezzella G, Moslinger-Gehmair R, Contu A. Treatment of depression in patients with breast cancer: a comparison between paroxetine and amitriptyline. *Breast Cancer Res Treat.* 2001;70(1):1–10.
  110. O'Shaughnessy JA. Effects of epoetin alfa on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant chemotherapy [review]. *Clin Breast Cancer.* 2002;3(suppl 3):S116–S120.
  111. O'Shaughnessy JA, Vukelja SJ, Holmes FA, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clin Breast Cancer.* 2005;5(6):439–446.
  112. Olsson AM, Svensson JH, Sundstrom J, et al. Erythropoietin treatment in metastatic breast cancer—effects on Hb, quality of life and need for transfusion. *Acta Oncologica.* 2002;41(6):517–524.
  113. Williams AF, Vadgama A, Franks PJ, Mortimer PS. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *Eur J Cancer Care.* 2002;11(4):254–261.
  114. Schmuth M, Wimmer MA, Hofer S, et al. Topical corticosteroid therapy for acute radiation dermatitis: a prospective, randomized, double-blind study. *Br J Dermatol.* 2002;146(6):983–991.
  115. Carpenter JS, Wells N, Lambert B, et al. A pilot study of magnetic therapy for hot flashes after breast cancer. *Cancer Nurs.* 2002;25(2):104–109.
  116. Schneider SM, Ellis M, Coombs WT, Shonkwiler EL, Folsom LC. Virtual reality intervention for older women with breast cancer. *Cyberpsychol Behav.* 2003;6(3):301–307.
  117. Nikander E, Kilkkinen A, Metsa-Heikkila M, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol.* 2003;101(6):1213–1220.
  118. McKenzie DC, Kalda AL. Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: a pilot study. *J Clin Oncol.* 2003;21(3):463–466.
  119. Gothard L, Cornes P, Earl J, et al. Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer. *Radiother Oncol.* 2004;73(2):133–139.
  120. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain.* 2004;111(3):306–312.
  121. Semiglavov VF, Stepula VV, Dudov A, Lehmanner W, Mengs U. The standardised mistletoe extract PS76A2 improves QoL in patients with breast cancer receiving adjuvant CMF chemotherapy: a randomised, placebo-controlled, double-blind, multicentre clinical trial. *Anticancer Res.* 2004;24(2C):1293–1302.
  122. Yates P, Aranda S, Hargraves M, et al. Randomized controlled trial of an educational intervention for managing fatigue in women receiving adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol.* 2005;23(25):6027–6036.
  123. Leyland-Jones B, Semiglavov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study [see comment]. *J Clin Oncol.* 2005;23(25):5960–5972.
  124. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. *Br J Cancer.* 2005;92(10):1869–1876.
  125. Roscoe JA, Matteson SE, Morrow GR, et al. Acustimulation wrist bands are not effective for the control of chemotherapy-induced nausea in women with breast cancer. *J Pain Symptom Manage.* 2005;29(4):376–384.
  126. Chang J, Couture F, Young S, McWatters KL, Lau CY. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion

- in breast cancer patients receiving chemotherapy [see comment] [erratum appears in *J Clin Oncol*. 2005 Aug 1;23(22):5276]. *J Clin Oncol*. 2005;23(12):2597–2605.
127. MacGregor CA, Canney PA, Patterson G, McDonald R, Paul J. A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. *Eur J Cancer*. 2005;41(5):708–714.
  128. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat*. 2005;89(3):243–249.
  129. Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial [see comment]. *J Altern Complement Med*. 2005;11(1):21–27.
  130. Thompson EA, Montgomery A, Douglas D, Reilly D. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors [see comment]. *J Altern Complement Med*. 2005;11(1):13–20.
  131. Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB. Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast J*. 2006;12(2):114–122.
  132. Semiglazov VF, Stepula VV, Dudov A, Schnitker J, Mengs U. Quality of life is improved in breast cancer patients by standardised mistletoe extract PS76A2 during chemotherapy and follow-up: a randomised, placebo-controlled, double-blind, multicentre clinical trial. *Anticancer Res*. 2006;26(2B):1519–1529.
  133. Carpenter JS, Storniolo AM, Johns S, et al. Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. *Oncologist*. 2007;12(1):124–135.
  134. Robb KA, Newham DJ, Williams JE. Transcutaneous electrical nerve stimulation vs. transcutaneous spinal electroanalgesia for chronic pain associated with breast cancer treatments. *J Pain Symptom Manage*. 2007;33(4):410–419.
  135. de Souza Fede AB, Bensi CG, Trufelli DC, et al. Multivitamins do not improve radiation therapy-related fatigue: results of a double-blind randomized crossover trial. *Am J Clin Oncol*. 2007;30(4):432–436.
  136. Mar Fan HG, Clemons M, Xu W, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer*. 2008;16(6):577–583.
  137. Navari RM, Brenner MC, Wilson MN. Treatment of depressive symptoms in patients with early stage breast cancer undergoing adjuvant therapy. *Breast Cancer Res Treat*. 2008;112(1):197–201.
  138. Yeo W, Mo FKF, Suen JJS, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. *Breast Cancer Res Treat*. 2009;113(3):529–535.
  139. Buijs C, Mom CH, Willemse PHB, et al. Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study. *Breast Cancer Res Treat*. 2009;115(3):573–580.
  140. Carpenter JS, Yu M, Wu J, et al. Evaluating the role of serotonin in hot flashes after breast cancer using acute tryptophan depletion. *Menopause*. 2009;16(4):644–652.
  141. Simpson JS, Carlson LE, Trew ME. Effect of group therapy for breast cancer on healthcare utilization [see comment]. *Cancer Pract*. 2001;9(1):19–26.
  142. Edgar L, Rosberger Z, Collet JP. Lessons learned: outcomes and methodology of a coping skills intervention trial comparing individual and group formats for patients with cancer. *Int J Psychiatry Med*. 2001;31(3):289–304.
  143. Helgeson VS, Cohen S, Schulz R, Yasko J. Long-term effects of educational and peer discussion group interventions on adjustment to breast cancer [see comment]. *Health Psychol*. 2001;20(5):387–392.
  144. Gustafson DH, Hawkins R, Pingree S, et al. Effect of computer support on younger women with breast cancer. *J Gen Intern Med*. 2001;16(7):435–445.
  145. Allen SM, Shah AC, Nezu AM, et al. A problem-solving approach to stress reduction among younger women with breast carcinoma: a randomized controlled trial. *Cancer*. 2002;94(12):3089–3100.
  146. Kissane DW, Bloch S, Smith GC, et al. Cognitive-existential group psychotherapy for women with primary breast cancer: a randomised controlled trial. *Psychooncology*. 2003;12(6):532–546.
  147. Kissane DW, Love A, Hatton A, et al. Effect of cognitive-existential group therapy on survival in early-stage breast cancer. *J Clin Oncol*. 2004;22(21):4255–4260.
  148. Taylor KL, Lamdan RM, Siegel JE, Shelby R, Moran-Klimi K, Hrywna M. Psychological adjustment among African American breast cancer patients: one-year follow-up results of a randomized psychoeducational group intervention. *Health Psychol*. 2003;22(3):316–323.
  149. Angell KL, Kreshka MA, McCoy R, et al. Psychosocial intervention for rural women with breast cancer: the Sierra-Stanford Partnership. *J Gen Intern Med*. 2003;18(7):499–507.
  150. Fukui S, Koike M, Ooba A, Uchitomi Y. The effect of a psychosocial group intervention on loneliness and social support for Japanese women with primary breast cancer. *Oncol Nurs Forum*. 2003;30(5):823–830.
  151. Fukui S, Kugaya A, Okamura H, et al. A psychosocial group intervention for Japanese women with primary breast carcinoma. *Cancer*. 2000;89(5):1026–1036.
  152. Heiney SP, McWayne J, Hurley TG, et al. Efficacy of therapeutic group by telephone for women with breast cancer. *Cancer Nurs*. 2003;26(6):439–447.
  153. Hack TF, Pickles T, Bultz BD, et al. Impact of providing audiotapes of primary adjuvant treatment consultations to women with breast cancer: a multisite, randomized, controlled trial. *J Clin Oncol*. 2003;21(22):4138–4144.
  154. Sandgren AK, McCaul KD. Short-term effects of telephone therapy for breast cancer patients. *Health Psychol*. 2003;22(3):310–315.
  155. Andersen BL, Farrar WB, Golden-Kreutz DM, et al. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. *J Clin Oncol*. 2004;22(17):3570–3580.
  156. Andersen BL, Farrar WB, Golden-Kreutz D, et al. Distress reduction from a psychological intervention contributes to improved health for cancer patients. *Brain Behav Immun*. 2007;21(7):953–961.
  157. Hidderley M, Holt M. A pilot randomized trial assessing the effects of autogenic training in early stage cancer patients in relation to psychological status and immune system responses. *Eur J Oncol Nurs*. 2004;8(1):61–65.
  158. Yoo HJ, Ahn SH, Kim SB, Kim WK, Han OS. Efficacy of progressive muscle relaxation training and guided imagery in reducing chemotherapy side effects in patients with breast cancer and in improving their quality of life. *Support Care Cancer*. 2005;13(10):826–833.
  159. Owen JE, Klapow JC, Roth DL, et al. Randomized pilot of a self-guided internet coping group for women with early-stage breast cancer. *Ann Behav Med*. 2005;30(1):54–64.
  160. Walker MS, Podbilewicz-Schuller Y. Video preparation for breast cancer treatment planning: results of a randomized clinical trial. *Psychooncology*. 2005;14(5):408–420.
  161. Miyashita M. A randomized intervention study for breast cancer survivors in Japan: effects of short-term support group focused on possible breast cancer recurrence. *Cancer Nurs*. 2005;28(1):70–78.
  162. Antoni MH, Lechner SC, Kazi A, et al. How stress management improves quality of life after treatment for breast cancer. *J Consult Clin Psychol*. 2006;74(6):1143–1152.
  163. Svensk AC, Oster I, Thyme KE, et al. Art therapy improves experienced quality of life among women undergoing treatment for breast cancer: a randomized controlled study. *Eur J Cancer Care*. 2009;18(1):69–77.
  164. Classen C, Butler LD, Koopman C, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. *Arch Gen Psychiatry*. 2001;58(5):494–501.
  165. Spiegel D, Butler LD, Giese-Davis J, et al. Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer: a randomized prospective trial. *Cancer*. 2007;110(5):1130–1138.
  166. Bordeleau L, Szalai JP, Ennis M, et al. Quality of life in a randomized trial of group psychosocial support in metastatic breast cancer: overall effects

- of the intervention and an exploration of missing data. *J Clin Oncol.* 2003;21(10):1944–1951.
167. Lemieux J, Beaton DE, Hogg-Johnson S, Bordeleau LJ, Hunter J, Goodwin PJ. Responsiveness to change due to supportive-expressive group therapy, improvement in mood and disease progression in women with metastatic breast cancer. *Qual Life Res.* 2007;16(6):1007–1017.
  168. Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med.* 2001;345(24):1719–1726.
  169. Northouse L, Kershaw T, Mood D, Schafenacker A. Effects of a family intervention on the quality of life of women with recurrent breast cancer and their family caregivers. *Psychooncology.* 2005;14(6):478–491.
  170. Aranda S, Schofield P, Weih L, Milne D, Yates P, Faulkner R. Meeting the support and information needs of women with advanced breast cancer: a randomised controlled trial. *Br J Cancer.* 2006;95(6):667–673.
  171. Kissane DW, Grabsch B, Clarke DM, et al. Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. *Psychooncology.* 2007;16(4):277–286.
  172. Molassiotis A, Yung HP, Yam BM, Chan FY, Mok TS. The effectiveness of progressive muscle relaxation training in managing chemotherapy-induced nausea and vomiting in Chinese breast cancer patients: a randomised controlled trial. *Support Care Cancer.* 2002;10(3):237–246.
  173. Williams SA, Schreier AM. The effect of education in managing side effects in women receiving chemotherapy for treatment of breast cancer [online]. *Oncol Nurs Forum.* 2004;31(1):E16–E23.
  174. Schneider SM, Prince-Paul M, Allen MJ, Silverman P, Talaba D. Virtual reality as a distraction intervention for women receiving chemotherapy [online]. *Oncol Nurs Forum.* 2004;31(1):81–88.
  175. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: immunologic effects. *J Clin Oncol.* 2005;23(25):6097–6106.
  176. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol.* 2005;23(25):6083–6096.
  177. Roscoe JA, Matteson SE, Mustian KM, Padmanaban D, Morrow GR. Treatment of radiotherapy-induced fatigue through a nonpharmacological approach. *Integr Cancer Ther.* 2005;4(1):8–13.
  178. Raghavendra RM, Nagarathna R, Nagendra HR, et al. Effects of an integrated yoga programme on chemotherapy-induced nausea and emesis in breast cancer patients. *Eur J Cancer Care.* 2007;16(6):462–474.
  179. Crew KD, Capodice JL, Greenlee H, et al. Pilot study of acupuncture for the treatment of joint symptoms related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients. *J Cancer Surviv.* 2007;1(4):283–291.
  180. Dirksen SR, Epstein DR. Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. *J Adv Nurs.* 2008;61(6):664–675.
  181. Elkins G, Marcus J, Stearns V, et al. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J Clin Oncol.* 2008;26(31):5022–5026.
  182. Heidrich SM, Brown RL, Egan JJ, et al. An individualized representational intervention to improve symptom management (IRIS) in older breast cancer survivors: three pilot studies. *Oncol Nurs Forum.* 2009;36(3):E133–E143.
  183. Segal R, Evans W, Johnson D, et al. Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. *J Clin Oncol.* 2001;19(3):657–665.
  184. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes [see comment]. *J Clin Oncol.* 2003;21(9):1660–1668.
  185. Headley JA, Ownby KK, John LD. The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer [online]. *Oncol Nurs Forum.* 2004;31(5):977–983.
  186. Mustian KM, Katula JA, Gill DL, Roscoe JA, Lang D, Murphy K. Tai Chi Chuan, health-related quality of life and self-esteem: a randomized trial with breast cancer survivors. *Support Care Cancer.* 2004;12(12):871–876.
  187. Sandel SL, Judge JO, Landry N, Faria L, Ouellette R, Majczak M. Dance and movement program improves quality-of-life measures in breast cancer survivors. *Cancer Nurs.* 2005;28(4):301–309.
  188. Pinto BM, Frierson GM, Rabin C, Trunzo JJ, Marcus BH. Home-based physical activity intervention for breast cancer patients. *J Clin Oncol.* 2005;23(15):3577–3587.
  189. Campbell A, Mutrie N, White F, McGuire F, Kearney N. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. *Eur J Oncol Nurs.* 2005;9(1):56–63.
  190. Ohira T, Schmitz KH, Ahmed RL, Yee D. Effects of weight training on quality of life in recent breast cancer survivors: the Weight Training for Breast Cancer Survivors (WTBS) study. *Cancer.* 2006;106(9):2076–2083.
  191. Herrero F, San Juan AF, Fleck SJ, et al. Combined aerobic and resistance training in breast cancer survivors: a randomized, controlled pilot trial. *Int J Sports Med.* 2006;27(7):573–580.
  192. Basen-Engquist K, Taylor CLC, Rosenblum C, et al. Randomized pilot test of a lifestyle physical activity intervention for breast cancer survivors. *Patient Educ Couns.* 2006;64(1–3):225–234.
  193. Beurskens CHG, van Uden CJT, Strobbe LJA, Oostendorp RAB, Wobbes T. The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomized controlled study. *BMC Cancer.* 2007;7:166.
  194. Banerjee B, Vadiraj HS, Ram A, et al. Effects of an integrated yoga program in modulating psychological stress and radiation-induced genotoxic stress in breast cancer patients undergoing radiotherapy. *Integr Cancer Ther.* 2007;6(3):242–250.
  195. Badger T, Segrin C, Dorros SM, Meek P, Lopez AM. Depression and anxiety in women with breast cancer and their partners. *Nurs Res.* 2007;56(1):44–53.
  196. Heim ME, v dM, Niklas A. Randomized controlled trial of a structured training program in breast cancer patients with tumor-related chronic fatigue. *Onkologie.* 2007;30(8–9):429–434.
  197. Moadel AB, Shah C, Wylie-Rosett J, et al. Randomized controlled trial of yoga among a multiethnic sample of breast cancer patients: effects on quality of life. *J Clin Oncol.* 2007;25(28):4387–4395.
  198. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multi-center randomized controlled trial. *J Clin Oncol.* 2007;25(28):4396–4404.
  199. Courneya KS, Segal RJ, Gelmon K, et al. Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy. *Cancer Epidemiol Biomarkers Prev.* 2007;16(12):2572–2578.
  200. Vallance JK, Courneya KS, Plotnikoff RC, Yasui Y, Mackey JR. Randomized controlled trial of the effects of print materials and step pedometers on physical activity and quality of life in breast cancer survivors. *J Clin Oncol.* 2007;25(17):2352–2359.
  201. Vallance JK, Courneya KS, Plotnikoff RC, Dinu I, Mackey JR. Maintenance of physical activity in breast cancer survivors after a randomized trial. *Med Sci Sports Exerc.* 2008;40(1):173–180.
  202. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. *BMJ.* 2007;334(7592):517.
  203. Lee TS, Kilbreath SL, Refshauge KM, Pendlebury SC, Beith JM, Lee MJ. Pectoral stretching program for women undergoing radiotherapy for breast cancer. *Breast Cancer Res Treat.* 2007;102(3):313–321.
  204. Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A. Randomized trial of exercise therapy in women treated for breast cancer. *J Clin Oncol.* 2007;25(13):1713–1721.
  205. Demark-Wahnefried W, Case LD, Blackwell K, et al. Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. *Clini Breast Cancer.* 2008;8(1):70–79.
  206. Mustian KM, Palesh OG, Flecksteiner SA. Tai Chi Chuan for breast cancer survivors. *Med Sport Sci.* 2008;52:209–217.
  207. Milne HM, Wallman KE, Gordon S, Courneya KS. Effects of a combined aerobic and resistance exercise program in breast cancer survivors: a randomized controlled trial. *Breast Cancer Res Treat.* 2008;108(2):279–288.

208. Fillion L, Gagnon P, Leblond F, et al. A brief intervention for fatigue management in breast cancer survivors. *Cancer Nurs.* 2008;31(2):145–159.
209. Hwang JH, Chang HJ, Shim YH, et al. Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. *Yonsei Med J.* 2008;49(3):443–450.
210. Rogers LQ, Hopkins-Price P, Vicari S, et al. A randomized trial to increase physical activity in breast cancer survivors. *Med Sci Sports Exerc.* 2009;41(4):935–946.
211. Rogers LQ, Hopkins-Price P, Vicari S, et al. Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects. *Cancer Epidemiol Biomarkers Prev.* 2009;18(5):1410–1418.
212. Danhauer SC, Mihalko SL, Russell GB, et al. Restorative yoga for women with breast cancer: findings from a randomized pilot study. *Psychooncology.* 2009;18(4):360–368.
213. Targ EF, Levine EG. The efficacy of a mind-body-spirit group for women with breast cancer: a randomized controlled trial. *Gen Hosp Psychiatry.* 2002;24(4):238–248.
214. Roberts S, Miller J, Pineiro L, Jennings L. Total parenteral nutrition vs oral diet in autologous hematopoietic cell transplant recipients. *Bone Marrow Transplant.* 2003;32(7):715–721.
215. Wells M, Harrow A, Donnan P, et al. Patient, carer and health service outcomes of nurse-led early discharge after breast cancer surgery: a randomised controlled trial. *Br J Cancer.* 2004;91(4):651–658.
216. van Roosmalen MS, Stalmeier PF, Verhoef LC, et al. Randomized trial of a shared decision-making intervention consisting of trade-offs and individualized treatment information for BRCA1/2 mutation carriers. *J Clin Oncol.* 2004;22(16):3293–3301.
217. van Roosmalen MS, Stalmeier PF, Verhoef LC, et al. Randomised trial of a decision aid and its timing for women being tested for a BRCA1/2 mutation. *Br J Cancer.* 2004;90(2):333–342.
218. Scheier MF, Helgeson VS, Schulz R, et al. Interventions to enhance physical and psychological functioning among younger women who are ending nonhormonal adjuvant treatment for early-stage breast cancer. *J Clin Oncol.* 2005;23(19):4298–4311.
219. Stanton AL, Ganz PA, Kwan L, et al. Outcomes from the Moving Beyond Cancer psychoeducational, randomized, controlled trial with breast cancer patients. *J Clin Oncol.* 2005;23(25):6009–6018.
220. Cho O-H, Yoo Y-S, Kim N-C. Efficacy of comprehensive group rehabilitation for women with early breast cancer in South Korea. *Nurs Health Sci.* 2006;8(3):140–146.
221. Meneses KD, McNees P, Loerzel VW, Su X, Zhang Y, Hassey LA. Transition from treatment to survivorship: effects of a psychoeducational intervention on quality of life in breast cancer survivors. *Oncol Nurs Forum.* 2007;34(5):1007–1016.
222. Loerzel VW, McNees P, Powel LL, Su X, Meneses K. Quality of life in older women with early-stage breast cancer in the first year of survivorship. *Oncol Nurs Forum.* 2008;35(6):924–932.
223. Sandgren AK, McCaul KD. Long-term telephone therapy outcomes for breast cancer patients. *Psychooncology.* 2007;16(1):38–47.
224. Meneses K, McNees P, Azuero A, Loerzel VW, Su X, Hassey LA. Preliminary evaluation of psychoeducational support interventions on quality of life in rural breast cancer survivors after primary treatment. *Cancer Nurs.* 2009;32(5):385–397.
225. Low CA, Stanton AL, Danoff-Burg S. Expressive disclosure and benefit finding among breast cancer patients: mechanisms for positive health effects. *Health Psychol.* 2006;25(2):181–189.
226. Arving C, Sjoden P-O, Bergh J, et al. Individual psychosocial support for breast cancer patients: a randomized study of nurse versus psychologist interventions and standard care. *Cancer Nurs.* 2007;30(3):E10–E19.
227. Arving C, Sjoden P-O, Bergh J, et al. Satisfaction, utilisation and perceived benefit of individual psychosocial support for breast cancer patients—a randomised study of nurse versus psychologist interventions. *Patient Educ Couns.* 2006;62(2):235–243.
228. Dragan S, Nicola T, Ilina R, et al. Role of multi-component functional foods in the complex treatment of patients with advanced breast cancer. *Rev Med Chir Soc Med Nat Iasi.* 2007;111(4):877–884.
229. Billhult A, Bergbom I, Stener-Victorin E. Massage relieves nausea in women with breast cancer who are undergoing chemotherapy. *J Altern Complement Med.* 2007;13(1):53–57.
230. Hartmann U, Muche R, Reuss-Borst M. Effects of a step-by-step inpatient rehabilitation programme on quality of life in breast cancer patients. A prospective randomised study. *Onkologie.* 2007;30(4):177–182.
231. Gotay CC, Moinpour CM, Unger JM, et al. Impact of a peer-delivered telephone intervention for women experiencing a breast cancer recurrence. *J Clin Oncol.* 2007;25(15):2093–2099.
232. Titeca G, Poot F, Cassart D, et al. Impact of cosmetic care on quality of life in breast cancer patients during chemotherapy and radiotherapy: an initial randomized controlled study. *J Eur Acad Dermatol Venereol.* 2007;21(6):771–776.
233. Fenlon DR, Corner JL, Haviland JS. A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer. *J Pain Symptom Manage.* 2008;35(4):397–405.
234. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of massage on cellular immunity, endocrine and psychological factors in women with breast cancer—a randomized controlled clinical trial. *Auton Neurosci.* 2008;140(1–2):88–95.
235. Lindemalm C, Mozaffari F, Choudhury A, et al. Immune response, depression and fatigue in relation to support intervention in mammary cancer patients. *Support Care Cancer.* 2008;16(1):57–65.
236. Cadmus LA, Salovey P, Yu H, Chung G, Kasl S, Irwin ML. Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. *Psychooncology.* 2009;18(4):343–352.
237. Irwin ML, Cadmus L, Alvarez-Reeves M, et al. Recruiting and retaining breast cancer survivors into a randomized controlled exercise trial: the Yale Exercise and Survivorship Study. *Cancer.* 2008;112(11):2593–2606.
238. Berger AM, Kuhn BR, Farr LA, et al. Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. *Psychooncology.* 2009;18(6):634–646.
239. Berger AM, Lockhart K, Agrawal S. Variability of patterns of fatigue and quality of life over time based on different breast cancer adjuvant chemotherapy regimens. *Oncol Nurs Forum.* 2009;36(5):563–570.
240. Dolbeault S, Cayrou S, Brédart A, et al. The effectiveness of a psycho-educational group after early-stage breast cancer treatment: results of a randomized French study. *Psychooncology.* 2009;18(6):647–656.
241. Joreskog K, Sorbom D. *PRELIS 2: User's Reference Guide.* Chicago, IL: Scientific software international Inc; 1996.
242. Poppelreuter M, Weis J, Bartsch HH. Effects of specific neuropsychological training programs for breast cancer patients after adjuvant chemotherapy. *J Psychosoc Oncol.* 2009;27(2):274–296.
243. Nidich SI, Fields JZ, Rainforth MV, et al. A randomized controlled trial of the effects of transcendental meditation on quality of life in older breast cancer patients. *Integr Cancer Ther.* 2009;8(3):228–234.
244. Liu J, Tu D, Dancey J, et al. Quality of life analyses in a clinical trial of DPPE (tesmilifene) plus doxorubicin versus doxorubicin in patients with advanced or metastatic breast cancer: NCIC CTG Trial MA.19. *Breast Cancer Res Treat.* 2006;100(3):263–271.
245. Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol.* 2006;24(31):5091–5097.
246. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol.* 2003;21(21):4042–4057.
247. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet.* 1989;2(8668):888–891.
248. Berry DA, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous stem-cell support versus standard-dose chemotherapy: meta-analysis of individual patient data from 15 randomized adjuvant breast cancer trials. *Br Cancer Res Treat.* 2007;106(suppl 1):S5.
249. Kazdin AE. Evidence-based treatment and practice: new opportunities to bridge clinical research and practice, enhance the knowledge base, and improve patient care. *Am Psychol.* 2008;63(3):146–159.

## Funding

The authors received no external funding for this study. S.L. was supported by a Postdoctoral Fellowship Award, CIHR-funded Strategic Training Initiative in Health Research Psychosocial Oncology Research Training program.

## Notes

The authors take full responsibility for the design of the study; the collection, analysis, or interpretation of the data; the writing of the article; and the decision to submit the article for publication.

**Affiliations of authors:** Santé des populations: Unité de recherche en santé des populations (URESP), Centre de recherche FRSQ du Centre

hospitalier affilié universitaire de Québec (CHA), Service d'hémato-oncologie du CHA and Centre des Maladies du Sein Deschênes-Fabia du CHA, Quebec City, QC, Canada (JL); Département de Médecine, Université Laval, Quebec City, QC, Canada (JL, VT); Samuel Lunenfeld Research Institute, Marvella Koffler Chair in Breast Research, University of Toronto, Toronto, ON, Canada (PJG); Department of Oncology, McMaster University and Juravinski Cancer Centre, Hamilton, ON, Canada (LJB); Formerly of School of Nursing, McGill University, Montreal, QC, Canada (SL); Faculté de pharmacie, Université Laval, Quebec City, QC, Canada (SL); Formerly of Department of Radiation Oncology, McMaster University and Juravinski Cancer Centre, Hamilton, ON, Canada (VT); Centre Hospitalier Universitaire de Québec, Quebec City, QC, Canada (VT).