THE BREAST-Q UTILITY MODULE: A PREFERENCE-BASED MEASURE

THE BREAST-Q UTILITY MODULE: DEVELOPMENT OF A NEW PREFERENCE-BASED MEASURE FOR BREAST CANCER

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TITLE: The BREAST-Q Utility module: Development of a New Preference-Based Measure for Breast Cancer

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LAY ABSTRACT

The quality-adjusted life year (QALY) incorporates the impact of treatments on quantity and quality of life and is the preferred measure of health outcome for economic evaluation. A review of breast cancer literature concluded that generic preference-based measures (PBMs) are commonly used to estimate the "quality" of life (QOL) in QALYs and no breast cancer-specific PBM currently exists. Hence, the objectives of this thesis were to develop and refine a breast cancer-specific PBM. To do this, 57 women with breast cancer from two countries participated in in-depth interviews and rating exercise. The data were analyzed to understand the aspects of QOL that mattered most to women and develop the new PBM, called the BREAST-Q Utility module. The Utility module was refined through feedback from women and experts. Future studies will examine the measurement properties of the module and assign weights to the health states assessed by the module.

ABSTRACT

Preference-based measures (PBMs) of health-related quality of life (HRQOL) are used to generate health state utility values (HUVs). HUVs are then used to calculate quality-adjusted life years (QALYs) for use in cost-effectiveness analyses (CEAs) of healthcare interventions. Although generic PBMs have been commonly used to estimate QALYs in cancer, they omit aspects of HRQOL that matter to women with breast cancer. This thesis begins by setting the stage for the development of a new PBM (Chapter 1). In Chapter 2, the results of a systematic literature review of published HUVs in breast cancer are presented. This review highlighted the heterogeneity in the study population and utility estimation methods in the literature and found that most studies use EQ-5D, a generic PBM, to assess HUVs in breast cancer. No breast cancer-specific PBM exists. Consequently, this thesis delineates the development of the descriptive system of a new breast cancer-specific PBM called the BREAST-Q Utility module. The development of the Utility module adhered to best practice guidelines for development and validation of patient-reported outcome instruments; the protocol is included in Chapter 3. In Chapter 4, the results of the mixed methods, international study to develop the descriptive system of the Utility module are presented. Semi-structured interviews were conducted with 57 women diagnosed with breast cancer using an interpretive description approach. At the end of the interview, the women were asked to list their top five HRQOL concerns and rate the importance of each item on the BREAST-Q. The data were analyzed and used to develop the preliminary Utility module, which was refined with feedback from women with breast cancer (n=9) and a multidisciplinary group of experts (n=23). In the final chapter, the role

of the BREAST-Q Utility module in CEAs of breast cancer interventions is described, and the strengths and limitations of the work are reviewed.

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#pandemicthesis

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LIST OF ABBREVIATIONS

ABC	Advanced breast cancer
ALND	Axillary lymph node dissection
AOW	Avon Army of Women registry
AQOL-4D	Australian Quality of Life-4D
AQOL-8D	Australian Quality of Life-8D
BCS	Breast-conserving surgery
BCT	Breast-conserving therapy
BMI	Body Mass Index
CAD	Canadian Dollars
CDK	Cyclin-dependent kinase
CEA	Cost-effectiveness analysis
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments guidelines
CSPBM	Condition-specific preference-based measure
CT	Chemotherapy
DARE	Database of Abstracts of Reviews of Effectiveness
EBC	Early breast cancer

EORTC	European Organisation for Research and Treatment of Cancer Core
ER	Estrogen receptor
FACT	Functional Assessment of Cancer Therapy
FACT-B	breast cancer-specific module of the FACT-G
FACT-G	Functional Assessment of Cancer Therapy-General
FACT	Functional Assessment of Cancer Therapy
HALex	Health and Activities Limitation Index
HCP	Healthcare professional
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HRT	Hormone replacement therapy
HRQOL	Health-related quality of life
HSCS	Health state classification system
HTA	Health Technology Assessment
HUI	Health Utilities Index
HUI3	Health Utilities Index Mark 3
HUV	Health state utility value

IBR	Implant-based reconstruction
IQR	Interquartile range
IQOLA	International Quality of Life Assessment
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JCC	Juravinski Cancer Center
KT	Knowledge Translation
MAUI	Multi-Attribute Utility Instrument
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MSK	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network breast symptom index
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence, U.K.
NZ	New Zealand
PBM	Preference-based measure
PR	Progesterone receptor

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QOL	Quality of life
QOL-VAS	Quality of Life-Visual Analogue Scale
REDCap	Research Electronic Data Capture
RS	Rating scales
SD	Standard deviation
SG	Standard gamble
SF-6D	Short-Form 6D
SF-12	Short-Form 12
SHE	Subjective Health Estimation
SLNB	Sentinel lymph node biopsy
TGH	Toronto General Hospital
TMI	Testing Morbidities Index

TNM	Tumor, Nodes, Metastasis
TTO	Time trade-off
US	United States
US FDA	United States Food and Drug Administration
UK	United Kingdom
USD	United States Dollars
VAS	Visual Analogue Scale
VR-6D	Veterans RAND-6D

DECLARATION OF ACADEMIC ACHIEVEMENT

Chapter 1: This chapter is unpublished. MK is the sole author

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CHAPTER 1

Introduction

Breast cancer

Breast cancer is the most common malignancy in women globally. An estimated 2.08 million new cases of breast cancer are diagnosed annually, making it the second most common cancer.(1) In Canada, in 2019, an estimated 26,900 women were diagnosed with breast cancer, and 5000 women died from the disease.(2) Breast cancer is the second leading cause of death in Canadian women(2); however, advances in early detection and treatments have steadily improved the survival rate for breast cancer over the past two decades. The five-year survival rates of breast cancer vary by stage of breast cancer. For women diagnosed with Stage 0-IIA, the five-year survival rates range from 93 to 100%, whereas for women diagnosed with stage III and IV breast cancer, the five-year survival rate has been reported to be 72% and 22%, respectively.(2)

The pathophysiology of breast cancer is multidimensional and poorly understood, but certain risk factors have been associated with higher incidence rates. Advancing age (50 years and older), family history of breast cancer, and genetic predisposition are the most significant risk factors.(3) Other risk factors include early menarche (before age 13 years) or late menopause (after age 55 years), nulliparity or first birth at age greater than 30 years, family history of ovarian cancer, history of benign breast disease, and exposure to chest wall irradiation. The use of oral contraceptives at an early age (before 20 years) and hormone replacement therapy (i.e., combined progesterone and oestrogen), alongside lifestyle factors such as consuming high fat diet, higher body mass index, and alcohol consumption have also been proposed to increase the risk of breast cancer.(3)

A palpable lump or mass in the breast tissue is the most recognized symptom of breast cancer and is apparent in about 30% of women with breast cancer.(4) Other visible signs may include a lump in the axilla, changes in the shape or size of the breast, changes in breast skin or nipple (e.g., redness, thickening, blistering, dimpling), swelling, sanguineous nipple discharge, or nipple retraction.(5)

The recommended workup of breast cancer includes detailed history, physical examination and bilateral diagnostic mammography, and ultrasonography. Magnetic resonance imaging may be used for women with dense breasts, a history of breast cancer, and a high risk of breast cancer.(6) Once identified, a biopsy is performed to make a histological diagnosis of breast cancer according to standardized pathological criteria, and the grade (extent of difference between the cancer and healthy cells, and rate of cell growth) and stage (extent of spread) of tumor are established. The breast tumor is graded into three types: grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated). The most widely used method of clinical staging for breast cancer is the TNM (tumor, nodes, metastasis) system.(7, 8) The stages I and II are often referred to as early breast cancer, and Stages IIB and III are referred to as locally advanced breast cancer. Stage IV breast cancer is known as metastatic breast cancer. Locally advanced breast cancer and metastatic breast cancer combined are known as advanced breast cancer. The breast cancer grade and stage are the most important factors for prognosis. The TNM system has recently been updated to include important prognostic factors (biomarkers and grade).(7, 8)

Breast cancer is commonly classified by the type of the affected breast cells (i.e., ductal, lobular, or mixed) and whether cancer has spread to the surrounding tissue (in situ or invasive). Invasive ductal carcinoma (50-75% of patients) is the most common type of invasive breast cancer, followed by invasive lobular carcinoma (5-15% of patients). The other types of breast cancer include mixed ductal and lobular cancer and rare types of breast cancer such as medullary or metaplastic, mammary Paget's disease, and Phylloides tumors.(4, 9)

Breast cancer is also classified based on the presence of three biomarkers (a) estrogen receptor (ER), (b) progesterone receptor (PR), and (c) human epidermal growth factor 2 receptors (HER2). Hormone receptor (HR) positive breast cancer is amenable to hormone-blocking therapy. Approximately 80% of invasive breast cancers are ER+.(10, 11) HER2+ breast carcinomas constitute approximately 20% of breast cancers and are responsive to HER2 targeted therapies. Triple negative breast cancer refers to breast malignancies that are HR– and HER2-. About 12-15% of women diagnosed with breast cancer have triple negative disease.(11, 12) The triple negative breast tumors are prevalent in women who are younger, black, or Hispanic, whereas HR+ tumors are more likely in older, postmenopausal women.(12)

Management of breast cancer

Treatments for breast cancer can be classified into local and systemic therapy. For early and locally advanced breast cancer, the goal of therapy is to eradicate the tumor from the breast(s) and/or regional lymph nodes and prevent loco-regional and distant

recurrence(s).(13, 14) Local therapy for early breast cancer consists of surgical resection of the tumor and/or radiotherapy. Systemic treatment is driven by the receptor status and the stage of breast cancer and may include neoadjuvant or adjuvant chemotherapy, hormone-blocking therapy (for HR+ tumors), and HER2 targeted therapy (for HER2+ tumors). For metastatic breast cancer, the goal of therapy is to prolong life and palliation.(15) Treatments commonly used for advanced breast cancer may include neoadjuvant or adjuvant systemic therapy, with or without local therapy (i.e., surgery or radiation). Irrespective of the stage of breast cancer, as part of standard of care, patients should be offered personalized supportive services (psychological, social, or financial) and symptom management.

Local treatment

Surgery

Breast conserving surgery (local excision with negative margins) with or without radiation at diagnosis or post-systemic therapy is the preferred local treatment for most patients with early breast cancer. Oncoplastic techniques may be used as appropriate to ensure the best possible cosmetic outcome. In some patients, mastectomy (full excision of breast tissue) is considered based on the size of the tumor or multicentricity, inability of breast conserving surgery to achieve negative surgical margins, prior chest wall radiation or if adjuvant radiotherapy is contraindicated, and patient preference.(14) Mastectomy can be complete, skin-sparing, or nipple-sparing and is accompanied by sampling (sentinel lymph node biopsy (SLNB)) or removal of axillary lymph nodes (axillary lymph node dissection (ALND)). Some women may opt for immediate or delayed breast reconstruction post-

mastectomy using implants or autologous tissue to restore the appearance of breast(s) and associated health-related quality of life (HRQOL). The timing and approach of reconstruction is determined by the need for post-operative radiotherapy and patient preference. In patients with metastatic breast cancer, oncological breast surgery is not associated with prolonged survival but may be performed to improve quality of life in selected patients.

Radiation

Post-operative whole breast radiation is the "preferred" treatment per current guidelines post-breast conserving surgery.(14) Radiation reduces the 10-year risk of any first locoregional or distant recurrence by 15% and the 15-year risk of breast cancer-related mortality by 4%.(16) For patients with low risk of local recurrence, accelerated partial breast radiotherapy is considered an acceptable treatment option, whereas patients with high risk of local recurrence are treated with boost radiotherapy.(14) Postmastectomy radiotherapy is radiation to the chest wall either with or without a boost to the mastectomy scar. This approach is shown to reduce the 10-year risk of any locoregional or distant recurrence by 10% and the 20-year risk of breast cancer-related mortality by 8%.(17) Postmastectomy radiation may include regional nodal radiation for patients whose cancer was detected in lymph nodes. The timing, type of reconstruction, and radiation dosage in patients seeking reconstruction post-mastectomy are based on treatment and patient-factors. Treatment decisions are collaborative and involve input from the patient, reconstructive surgeons, and radiation oncologists. For patients with metastatic breast cancer, systemic therapy remains the first line of treatment. In cases where the tumor is

rendered resectable post-systemic therapy, (re)irradiation of all or part of the chest wall is considered.

Systemic therapy for breast cancer

Chemotherapy

Chemotherapy is recommended for high risk patients, including those with triple negative, locally advanced, HER2+/- breast cancer. For most patients with early breast cancer and locally advanced breast cancer, sequential anthracycline and/or a taxane-based regimen is the standard treatment.(14) For patients previously treated (in adjuvant or for metastatic cancer) with anthracycline and taxane, and who experience an early recurrence, single agent chemotherapy using capecitabine, vinorelbine, or eribulin is the preferred choice. When choosing the chemotherapy regime, the decision should be individualized by considering patient preferences, toxicity profiles, previous exposure, and the availability of the chemotherapy drug in the country. A range of side-effects have been documented with chemotherapy, including but not limited to infection, nausea or vomiting, diarrhea or constipation, stomatitis, dysgeusia, fatigue, alopecia, peripheral neuropathy, cardiomyopathy, leukemia, allergic reactions, and cognitive changes.

Endocrine therapy

Endocrine therapy is indicated in all patients with HR+ breast cancer, irrespective of HER2 status and use of chemotherapy.(18, 19) The choice of the anti-estrogen therapy is determined primarily by the patient's menopausal status (natural or medically or surgically induced), followed by the side-effect profiles of the endocrine regime(s). For premenopausal women, Tamoxifen (selective estrogen reception modulator) for 5 to 10

years is the standard of care. A switch to aromatase inhibitors for women who will be post-menopausal within 5 years of starting Tamoxifen is recommended, especially for women with a high risk of recurrence. Aromatase inhibitors (anastrozole, exemestane, and letrozole), which decrease the circulating estrogen levels by inhibiting conversion of androgens to estrogen, have been found to be most effective in post-menopausal women.(19, 20) In patients with advanced breast cancer, endocrine therapy, typically with incorporation of a cyclin-dependent kinase (CDK) 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib), is administered until the disease is endocrine resistant, following which the treatment regime is transitioned to another endocrine therapy or chemotherapy.(14) Typical side effects of endocrine therapy include, but are not limited to, menopause-like symptoms (hot flashes, vaginal dryness, or itching), muscle or joint pain, and, in rare cases, pulmonary embolism, endometrial cancer, or osteoporotic fractures.

Targeted therapy

(Neo)Adjuvant Trastuzumab combined with chemotherapy (concomitantly with taxanes or sequentially with anthracycline-based chemotherapy) is highly effective and is recommended for all patients with HER2+ early breast cancer. When tolerated, this regime halves the recurrence and mortality risk compared to chemotherapy alone. In most patients, one year of Trastuzumab remains a standard of care, except for selected low risk patients, where a duration of 6 months of treatment may be considered. In patients at high risk of recurrence, dual anti-HER2 therapy (pertuzumab + trastuzumab) is considered. Patients with residual disease post neo-adjuvant chemotherapy for HER2+ breast cancer can be considered for T-DM1. Similarly, for patients with HER+ metastatic breast cancer, anti-

HER2 therapy is recommended, but the optimal duration of treatment is currently unknown. The anti-HER2 therapy is generally well-tolerated; however, some patients may experience headache, diarrhea, nausea, insomnia, or rash. In certain cases, anti-HER2 therapy has been shown to reduce cardiopulmonary function, and hence, regular cardiac monitoring before and during the traztuzumab treatment is mandatory for patients receiving anti-HER2 therapy.(14)

Incorporating patient preferences in breast cancer treatment decision making

As is evident above, a range of treatment options and side-effect profiles exists within the management of breast cancer patients. Given the wide range of therapeutic options and the complexities of healthcare settings, the breast cancer treatment decision-making process remains complex and multi-layered. Consequently, research evidence on clinical effectiveness and safety of breast cancer treatment interventions is fundamental to the decision-making process, but not sufficient. Considering patients' perspectives, preferences, and values alongside the biopsychological context is crucial in informing the decision-making process.(21) Patient-centered, shared decision making in breast cancer has been shown to increase patients' willingness to accept treatment, set treatment expectations(22), and enhance treatment adherence and satisfaction, resulting in better short- and long-term HRQOL.(23, 24)

One approach to incorporating patients' perspectives in decision making is by measuring health-related quality of life (HRQOL) as part of standard clinical evaluation.

HRQOL is a multi-dimensional construct that is defined as "how well a person functions in their life and his or her perceived well-being in physical, mental, and social domains of health".(25) Functioning refers to an individual's ability to carry out pre-determined activities, while well-being refers to an individual's subjective feelings.(25, 26)

Several approaches have been proposed in the literature to measure HRQOL, including preference- and non-preference-based (often referred to as "psychometric") approaches. Non-preference-based approaches commonly use questionnaires or Likert-type rating scales to assess an individual's response to a series of statements measuring the overall HRQOL or its dimensions. Individual scores or weights are derived for each of the dimensions, which may or may not be summed to provide an overall score. This method is useful, but not designed for use in economic evaluation of health interventions. This is because HRQOL instruments for health economic evaluation should meet three requirements. The instrument should: (a) provide a single number that summarizes health change, (b) be able to compare different possible uses of scarce resources, and (c) be capable of being interpreted in terms of value.

Preference-based approaches to measuring HRQOL

Preferences are defined as an individual's evaluation of the desirability of a range of anticipated health status(es) or health outcome(s).(27) Health utility is defined as the strength of preference or desirability for a given health status or specific health outcome under conditions of uncertainty. Health utilities are measured on a cardinal numerical scale, where 1.0 represents full health, 0.0 represents death, and negative values represent states

worse than death.(28-30) Subsequently, the preference-based approach of measuring HRQOL includes not only a description of the health states of interest, but also utilities (or valuation) for those health states.(31)

Health utilities have several applications in healthcare, but they are primarily used to generate quality-adjusted life years (QALYs). QALYs represent the benefit of a health intervention in terms of time spent in a series of quality-weighted health states and incorporate impact of a treatment or intervention on the quantity of life (survival, longevity, or mortality) and quality of life (morbidity) within a single measure.(32) The QALYs are calculated by multiplying the number of years lived in each state of health by the health utility estimate for each respective state.(33-35) QALYs are the metric of choice in cost-utility analyses, which are a form of cost-effectiveness analyses that are increasingly being used by health technology assessment, pricing and reimbursement agencies in many countries to justify the costs of new interventions in terms of their expected health outcomes. As an example, the estimation of QALYs is integral to reference cases for economic evaluations submitted to the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom.(36) This model is increasingly being adopted by health agencies in many other countries, including Canada, Scotland and Germany.(37)

Several techniques have been proposed to estimate health utilities; however, the three "direct" methods that are most used include standard gamble (SG), time trade-off (TTO), and the visual analogue scale (VAS). The utilities can also be obtained "indirectly" by applying utility algorithms to generic or condition-specific preference-based measures (PBMs). The utility algorithms are obtained from members of the general population or

patients (or caregivers) who value the health states described by the questionnaire using one of the direct utility estimation methods described above (i.e., SG, TTO, or VAS). A PBM consists of a series of dimensions of health that are determinants of an individual's HRQOL and typically consist of one or two items per dimension.

Preference-based measures in breast cancer

The most frequently used PBMs in breast cancer include the EQ-5D(38, 39) and SF-6D(40). Other, less frequently used, PBMs in cancer research include the Finnish 15D(41), Health Utilities Index (HUI)(42), and AQOL-8D(43). All these PBMs are generic instruments designed to be used in population studies of cost-effectiveness of health interventions and programs. **Table 1** describes the descriptive system and valuation of these instruments. These generic PBMs do not incorporate the unique concerns of breast cancer patients, such as the impact of treatment on breast appearance, body image, psychosocial, or sexual well-being. Consequently, when generic PBMs are used in treatments evaluating cost-effectiveness of interventions, they may not be sensitive to the changes in HRQOL between specific groups of patients or within patients over time, resulting in flawed recommendations. Hence, to address this limitation of generic PBMs in breast cancer, a new breast cancer-specific PBM is needed.

Steps Involved in the Development of a Preference-Based Measure

The development of a PBM consists of three stages. The first stage is to develop a descriptive health state classification system consisting of a set of questions with response options. Health states are described by responses to the questions. The descriptive health state system is usually concise (typically 7 ± 2 dimensions) to be amenable to valuation

using established preference elicitation methods.(44) The health state classification system can be developed de novo or derived from an existing HRQOL instrument. When a de novo approach is used, qualitative interviews are conducted with the population of interest, and the conceptual framework and the instrument are developed. Psychometric methods are used to validate the instrument. This approach is patient driven, and hence, ensures that the dimensions included in the instrument are important and relevant to the patients; however, it requires time and is resource intensive. The use of existing measures to develop a PBM allows the developers to use existing datasets from clinical studies.(44) This approach is used when existing psychometric instruments have several items with multiple response levels, making them unsuitable for valuation. One or two item(s) per dimension are selected from the existing measure using traditional and psychometric methods for inclusion in the PBM such that the text is minimally altered.(44) This approach expands the scope of the new PBM for conducting economic evaluation of existing datasets, but carries forward the conceptual or measurement issues, if any, of the psychometric instrument.(44) Further, as the selection of dimensions occurs without patient input, the relevance and comprehensiveness of the PBM are not ensured.

In the second stage, the psychometric properties of the PBM, including reliability, validity, and responsiveness, are assessed.(44) For a condition-specific PBM, the psychometric properties are compared with an existing generic PBM to assess whether the condition-specific PBM is more sensitive to changes in HRQOL and can discriminate between patients based on the severity of their health condition. For PBMs derived using existing measures, the validity of the derived PBM is assessed in relation to the original

instrument, and the impact of item reduction on the instrument's psychometric properties is assessed.

The third and last stage in the development of a PBM is to construct an algorithm for assigning utility weights to each health state described by the measure (often described as a value set). Typically, these utility weights are obtained from randomly selected members of the public or patients for a subset of health states defined by the instrument via a direct utility estimation method (SG, TTO, or VAS).(44) The utility weights for the remaining health states are then derived using one of several established statistical or theoretical approaches.(45)

Rationale for developing a breast cancer-specific PBM de novo

The items from an existing HRQOL instrument can be used to develop a PBM if the existing instrument demonstrates face validity, content validity, and structural dependence (i.e. lack of correlation between the items and response levels). Many HRQOL instruments have been used in the breast cancer literature; however, the few that dominate the literature are: (1) European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ) C30 (generic cancer instrument) and its derivatives −BR45 (breast cancer-specific), MBC (metastatic breast cancer-specific), and BRECON-23 (breast reconstruction-specific); (2) Functional Assessment of Cancer Therapy (FACT) – General (generic cancer) and its derivatives – FACT-B (breast cancer-specific); (3) BREAST-Q (breast cancer surgery-specific). A brief description of these instruments is given below.

HRQOL instruments in breast cancer

***EORTC-QLQ – C30, BR45, BRECN-45*, *MBC*, 8D**

The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) is a 30-item generic HRQOL instrument designed for all types of cancer.(46) The 30 items are organized into nine scales and six single items. The scales are divided into five function scales (physical, role, cognitive, emotional, and social function), three symptom scales (fatigue, pain, nausea, or vomiting), one global health status and HRQOL scale, and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial impact of the disease). The scales have a recall period of the past week and are scored on a four-point Likert scale ("not at all" to "very much"), with the exception of the two global health status items that are scored on a seven-point Likert scale ("very poor" to "excellent"). The scales are linearly transformed into a 0 to 100 score, with 100 representing best global health status, functional status, or symptom status.

The BR45 (updated version of BR23)(47) includes breast-specific functional (body image, sexual functioning, future perspective, and sexual enjoyment) and symptom (arm symptoms, breast symptoms, side-effects of systemic therapy, and hair loss) items. The BRECON45 includes breast reconstruction-specific items (e.g. satisfaction with appearance of breasts, scars, and sensation).(48) The MBC, a metastatic breast cancer-specific EORTC-QLQ, is in development phases. The BR45, BRECON45, and MBC are designed to be used in conjunction with the C30 instrument.

More recently, two cancer-specific PBMs have been derived from the C30. The EORTC-8D consists of eight dimensions and was derived from the C30 using an existing clinical trial dataset of 655 patients with multiple myeloma. A valuation study using time-trade off in the UK with members of the general public was conducted, and regression models with additive function were used to derive preference weights.(49) The EORTC QLU-C10D consists of 10 dimensions derived from secondary analysis of a diverse collection of cancer-related datasets consisting of 2,616 patients from 13 countries. Valuation studies for the QLU-C10D have been conducted in Australia and the UK in the general population using discrete choice experiments.(50, 51) In addition to the EORTC-8D and the EORTC-QLU-CD10, preference weights can be obtained directly from the C30 instrument using a published algorithm that maps responses from the C30 onto the EQ-5D(52-54), SF-6D(55), and 15D.(55)

FACT-G and FACT-B

The Functional Assessment of Cancer Therapy – General (FACT-G) version 4 is a 27-item instrument comprised of four subscales: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional wellbeing (7 items).(56) This instrument uses a 5-point Likert-type scale (“not at all” to “very much”) with a recall period of 7 days. The FACT-G and individual subscale scores are summed to produce a total score and calculated so that the higher score indicates better HRQOL. The FACT-B is a breast cancer-specific module of the FACT-G that includes 10 additional items that address concerns specific to women with breast cancer.(57) The FACT profile of measures also includes a breast cancer symptom index (8 items) and FACT/NCCN-breast symptom

index (16 items) that are derivatives of the FACT-G and FACT-B scales, as well as several cancer treatment-specific and symptom-specific modules. Mapping functions to estimate an EQ-5D score from FACT-G and FACT-B scores have been published in the literature.(54, 58, 59)

BREAST-Q

The BREAST-Q(60) was designed to evaluate outcomes of women undergoing different types of breast surgery. This instrument has three breast cancer surgery-specific modules: breast conserving surgery, mastectomy, and reconstruction. Each of these modules has independently functioning scales that measure satisfaction with breasts, outcome, and process of care, as well as HRQOL (physical well-being, psychosocial well-being, and sexual well-being). Each module has pre- and post-operative scales. The items in each scale are arranged in a clinically relevant hierarchy and have 3 to 5 response options. Each scale raw score is transformed to generate a 0 (worst) to 100 (best) using a Q score-program (version 1.0) or using tables (version 2.0).

The above-mentioned HRQOL instruments have been used extensively in the literature, validated in independent samples of women with breast cancer, and translated into many different languages. The instruments were developed using established PRO instrument development guidelines with their content generated from a combination of sources, including literature review, interviews with patients and/or healthcare providers, and a review of relevant existing instruments or item pools. However, there are important limitations that preclude the use of these tools to derive a breast cancer-specific PBM. None of these instruments were designed for measuring health utilities. The EORTC-QLQ and

FACT profile of measures were designed for a limited range of breast cancer patients (early stage breast cancer) and do not address concerns important to women with advanced or metastatic breast cancer. In addition, these instruments do not adequately measure breast cancer-specific concerns, including body image, breast appearance and breast sensation. The EORTC and FACT profile of measures were developed using traditional psychometric methods and hence, have no rank ordering of items in the scales to indicate the importance of the items to people in their lives. The BREAST-Q was designed for use in women undergoing breast cancer surgery and hence does not include the HRQOL impact of systemic therapies for breast cancer (i.e., chemotherapy, endocrine therapy, or targeted therapy). Each of these instruments (with their derivatives) is restricted to a subset of patients and does not have broad applicability to the full spectrum of women with breast cancer (stages 0-IV) in all phases of the treatment pathway.

The construction of a new breast cancer-specific PBM was motivated by the limitations in content validity of existing PBMs used with women with breast cancer. This project commenced with the hypothesis that the HRQOL of women diagnosed with breast cancer depends on both generic issues and issues specific to breast cancer and its treatments. We further hypothesized that with input from women with breast cancer and healthcare experts, a concise PBM could be designed to measure the most important concerns of women with breast cancer.

Thesis objectives

The objectives of this thesis were to:

1. Systematically review the literature to catalogue the health state utility values in breast cancer across stages of breast cancer and interventions.
2. Develop a conceptual framework identifying the dimensions that are important to the overall HRQOL of women with breast cancer.
3. Use the conceptual framework and input from women with breast cancer and healthcare providers to create a set of dimensions and response options for the breast cancer-specific PBM, BREAST-Q Utility module.

Thesis structure

This thesis is organized into the following chapters. *Chapter 2* presents a systematic literature review of breast cancer-related health utility values across different stages of breast cancer and treatment interventions. *Chapter 3* presents the protocol for a multi-phase, multi-center, mixed-methods study to develop and validate a descriptive health state classification system for the BREAST-Q Utility module. *Chapter 4* describes the results of a mixed-methods study to develop a conceptual framework covering dimensions important to the HRQOL of women with breast cancer. This chapter also describes the process used to select dimensions and response levels for the BREAST-Q Utility module based on patient and expert feedback. Finally, *Chapter 5* summarizes the main findings of this thesis and interprets them in the context of the existing literature. The implications of the results of this thesis for future research and clinical practice are described, as are the strengths and

limitations of the approach used to develop the Utility module. Next steps to assess the psychometric properties of the BREAST-Q Utility module and to refine the descriptive health state classification system and perform a valuation study to assign preference weights to the health states described by the BREAST-Q Utility module are outlined. The thesis concludes with a description of the knowledge translation approach adopted for the BREAST-Q Utility project and final conclusions for the research conducted.

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Table 1: Description of the five most used generic PBMs in breast cancer literature

	EQ-5D (38, 39)	SF-6D (40)	Finnish 15D (41)	HUI Mark 3 (42)	AQOL-8D (43)
Descriptive system – development	Review of HRQOL literature and EuroQol group consultation	Results from the International Quality of Life Assessment (IQOLA) project and consultation with multidisciplinary group of experts were used to shorten the Short form-36 (generic HRQOL instrument). SF-6D was derived from 11 items of SF-36 and 7 items of SF-12 (shortened version of SF-36).	Two patient surveys, feedback from instrument users, and factor analysis of empirical data from various patient groups	Developed to assess the health of children who had been in neonatal intensive care (HUI Mark 1), and later expanded to childhood cancer (HUI Mark 2) and general application (HUI Mark 3)	Focus groups with mental health patients, and factor analyses of empirical data using AQoL-4D and 6D version to create 8D
Number of dimensions	5	6	15	8	8
Response levels	3L - 3 5L – 5	4 - 6	5	5 - 6	4 - 6
Dimensions					
Physical well-being					

Pain/	+	+	+	+	+++
Vitality		+	+		+
Activities of daily living (self-care, mobility)	++	+	+	+	+++
Usual activities/	+	+	+		
Dexterity				+	+
Vision			+	+	+
Hearing			+	+	+
Breathing			+		
Sleeping			+		+
Eating			+		
Speech			+	+	
Excretion			+		
Communication					+
Psychological well-being					
Anxiety/depression	+	+	+++	+	++++
Anger					++
Feeling self-confident					+
Feeling worthless					+
Feelings of self-harm					+

Feeling happy/enthusiastic					+++++
Coping					++
Cognition				+	
Social well-being					
Social activities		+			+
Relationships					++++
Role in community					+
Sexual well-being					
Sexual activity			+		
Sexual relationships					+
Recall period	Today	Past four weeks (one week of acute SF-36)	Present health state	One, two, or four weeks	Past week
Preference elicitation method	VAS, TTO	SG	Variant of VAS	SG, VAS	VAS, TTO
MAUT regression model	Additive	Additive	Additive	Multiplicative	Multiplicative
Health states	3L –245 5L –3125	18,000	30 billion+	972,000	100 billion+

+ indicates the number of items measuring the dimension; VAS, Visual Analogue Scale; TTO, Time Trade-off; SG, Standard Gamble

CHAPTER 2

A Systematic Literature Review of Health Utility Values in Breast Cancer

Title: A Systematic Literature Review of Health Utility Values in Breast Cancer[1]

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Running head: Health State Utility in Breast Cancer

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Preliminary results of this review were presented as poster (Lee B. Lusted Finalist Student Competition - Poster) at the 39th Annual North American Meeting of the Society of Medical Decision-Making held in Pittsburgh, Pennsylvania, United States (October 22 – 25, 2017).

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ABSTRACT

Background: Health utility values are important inputs to the cost-utility analysis of breast cancer interventions.

Purpose: To provide a catalog of breast cancer-related published utility values across different stages of breast cancer and treatment interventions.

Data Sources: Systematic searches of MEDLINE, MEDLINE In-Progress, EMBASE, Web of Science, CINAHL, PsycINFO, EconLit, and Cochrane databases (2005-2017).

Study selection: Studies published in English that reported mean or median utility values using direct or indirect methods of utility elicitation for breast cancer were included.

Data extraction: Independent reviewers extracted data on a pre-established and piloted form; disagreements were resolved through discussion.

Data Synthesis: 79 studies were included in the review. Most articles (n=52, 66%) derived utilities using the EQ-5D. The utilities were obtained from patients with breast cancer in 72% of the studies (n=57). The utilities were reported for both local (surgery, range 0.48 to 0.91; radiation, range 0.46 to 0.90) and systemic (chemotherapy, range 0.28 to 0.96; endocrine therapy, range 0.52 to 0.95) treatments. The utilities for diagnostic or screening and allied health or complementary interventions ranged from 0.46 to 1.00 and 0.56 to 0.88, respectively. Patients with advanced-stage breast cancer (range -0.27 to 0.82) reported lower utility values as compared to early-stage breast cancer (range 0.58 to 0.99).

Limitations: Considerable heterogeneity in the study population, utility elicitation methods, and health states precluded the conduct of a meta-analysis.

Conclusion: This systematic review provides a breast cancer-related health state utility catalog that could be used to inform future cost-utility analyses. The review also highlights the substantial heterogeneity in the health utility studies in breast cancer literature, which translates to a considerable variation in the utility values.

INTRODUCTION

Patient-centered decisions about breast cancer treatments often involve trade-offs between the possible benefits and harms. Such trade-offs are personal judgments that may differ among individuals; some women may judge that the survival benefits of cancer treatment outweigh the potential toxicity, while others may place greater value on health-related quality of life (HRQOL) over survival. Quality-adjusted life years (QALY) is a measure that combines both survival and impact on HRQOL. The HRQOL impact (the "Q") in a QALY is measured by health utilities[1]. Health utilities are cardinal values that represent the strength of an individual's preferences for the health outcome or health state under consideration[2, 3]. Hence, a more desirable health outcome will have higher health utility value, and vice-versa. Health utilities are anchored at 0 for death and 1 for full health or the best possible outcome. Health states that are considered worse than death are indicated by negative values[3]. In breast cancer, health utilities have been measured using direct utility elicitation methods such as standard gamble (SG), time trade-off (TTO), or rating scales (RS) or indirect methods using self-reported, generic preference-based instruments such as the EQ-5D [4], the Short Form-6D (SF-6D)[5, 6], and the Health Utilities Index Mark 3 (HUI3)[7].

The health utility values for the same health outcome or health state can vary substantially depending on the method of health utility estimation, the population used to derive utility scores (patients, health professionals, or the general public), and the context (setting, method of administration, or description of health state). This heterogeneity in the health utility values makes it challenging for researchers to choose which values to use for

the calculation of QALY in cost-utility analyses. A previous systematic review by Peasgood et al.[8] summarized published utilities in breast cancer and pooled utilities for some breast cancer-related health states for peer-reviewed studies published up to 2007. Peasgood et al.[8] concluded that many utility values were available for similar breast cancer health states, making pooling of values problematic. To the best of our knowledge, no comprehensive systematic review of the breast cancer literature has been conducted since then. Hence, the objective of this systematic review of literature was to identify and descriptively summarize the published health utility values in breast cancer literature by the stage of breast cancer and type of intervention.

METHODS

Search strategy

A review of literature published between January 1, 2005, and August 2017 was conducted. This timeline was chosen to ensure that the included health utilities are relevant to the current diagnostic and treatment guidelines. The electronic databases of MEDLINE, MEDLINE In-Progress, EMBASE, Web of Science, CINAHL, PsycINFO, EconLit, and Cochrane databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), Cochrane Central Register of Clinical Trials, Health Technology Assessment (HTA), and NHS Economic Evaluation Database (NHS EED)) were searched. The electronic search strategy, designed with the help of a medical librarian, used health utility and utility elicitation method-specific terms, combined with breast cancer. The database search was complemented with a bibliographic hand search of

citations included in the articles that met the study inclusion criteria. The search strategy is provided in the **Supplementary material**.

Study eligibility

The studies were screened in two phases. In Phase 1, the titles and abstracts retrieved from the electronic databases search were reviewed by one author (MK). Studies where the title or the abstract clearly indicated that the health utility values were elicited for adult patients with breast cancer were included for the Phase 2 screening. We excluded literature reviews, meta-analyses, psychometric evaluations, editorials, comment letters, animal studies, conference abstracts, studies published in languages other than English, and studies where health utility values were obtained from the literature.

In Phase 2 screening, full texts of the studies that met the inclusion criteria in Phase 1 were reviewed by two independent reviewers (MK and PD, DP, or MS) using a pre-determined screening form which was piloted using five studies. Studies were included if they: (1) reported health utility values for adult breast cancer patients, including treatment-related and adverse events and (2) described methods of utility assessment. Inter-reviewer disagreements were resolved through discussion, and a senior author (FX) was consulted if the disagreement persisted.

Data Extraction and Management

The data from the included studies were extracted onto a predesigned data extraction form, which was piloted with five articles. The data extraction was completed by two reviewers independently (MK and PD, DP, or MS). The following variables were recorded: (1) first listed author, publication year, country, journal, and funding source; (2) study design; (3)

number and type of respondents from whom utilities were elicited (i.e., patients or non-patients); (4) method of utility elicitation (direct or indirect); for direct studies, data on whether pilot testing was completed, whether interview was trained, trained interviewer, and whether inconsistencies were assessed and recorded; for indirect studies, data on the country of scoring algorithm (where applicable) were recorded; (5) administration method; and (6) reported mean or median utility, with variance when provided.

A thematic approach was adopted for data management whereby the health utilities extracted from articles were classified into two main categories: (1) intervention-specific utilities and (2) breast cancer stage-specific utilities. Intervention-specific health utility values were further organized into: (1) screening/diagnosis, (2) local therapy (i.e. radiation and surgery), (3) systemic therapy (i.e., chemotherapy, endocrine therapy, targeted therapy), (4) allied health and complimentary medicine, and (5) adverse events and their treatments. Breast cancer stage-specific health utility values were organized into: (1) early breast cancer, (2) advanced breast cancer, and (3) non-specific breast cancer for when the stage of breast cancer was not specified or could not be ascertained from the article. Descriptive analyses were completed to summarize the results.

RESULTS

Review process

As shown in the PRISMA diagram (**Figure 1**), the electronic literature search yielded 21,444 records. Of these, 3,946 records were published in duplicate and were removed. After phase 1 screening, 17,158 records were excluded based on title and abstract

screening. The remaining 340 full-text articles were retrieved and reviewed for inclusion. Of these, 79 were included in the review.

Study characteristics

The study characteristics are shown in **Table 1**. Thirty-nine studies (49%) were published in oncology journals, followed by health economics and outcomes research journals (n=22, 28%), and the remaining articles in other medical or public health journals (n=18, 23%). Most articles received funding from not-for-profit or academic sources (n=37, 46.8%), 18 from for-profit sources (26.6%), and 3 from a combination of the two (3.8%). The remaining 21 articles did not receive funding or disclose a funding source. The number of articles published per year gradually increased since 2005, with the highest number of articles (n=12) published in 2017. The corresponding author(s) for most of the publications were based in the United States (n=23, 29.1%), the Netherlands (n=8, 10.1%), Australia (n=6, 7.6%), and Canada (n=6, 7.6%).

Indirect methods using multi-attribute utility instruments (MAUIs) were more common than direct methods of utility estimation. Direct methods of utility estimation were used in 18 studies (22.8%), where SG was the most common approach, followed by TTO and VAS. Indirect methods were used in 55 studies (66.6%), and a combination of direct and indirect methods in 6 studies (7.6%). Of 18 articles reporting on direct studies, 7 (38.9%) studies piloted the methods prior to administration, 9 (50%) reported on using trained interviewers, and 7 (38.9%) assessed inconsistencies in responses and adjusted their analyses accordingly. The health states to be assessed were identified and defined using literature review (n=10, 55.6%), consultation with health care professionals experienced in

treating women with breast cancer (n=8, 44.4%), interviews with women diagnosed with breast cancer (n=4, 22.2%), published guidelines or medical labelling information (n=3, 16.7%), epidemiological data (n=1, 5.6%), a previously developed questionnaire (n=1, 5.6%), and breast cancer web forums (n=1, 5.6%). Six (33.3%) studies did not specify how health states were developed.

Of 55 studies that used the indirect methods, the EQ-5D-3L was the most common preference-based measure (n=48, 87.2%), followed by the SF-6D (n=4, 7.3%). The remaining studies used the Finnish 15D[9], HUI3[10], or AQOL-4D[11]. Five studies mapped the data from EORTC-QLQ-C 30 to the EQ-5D-3L[12-16], and one study mapped the SF-12 to VR-6D[17] using published algorithms. Three studies used the 5L version of the EQ-5D[18-20]. Four studies (5.1%) compared direct and indirect methods[21-24], 6 (7.6%) compared one or more types of direct utility estimation methods[20, 21, 25-28], and 3 (3.8%) compared one or more types of indirect utility elicitation methods[9, 13, 29]. Three (5.4%) studies compared country-specific algorithms [19, 21, 30].

In terms of the respondents who completed the utility estimation exercise, the majority of the studies used women diagnosed with breast cancer (n=57, 72.1%), followed by members of the general public (n=14, 17.7%), a combination of the general public and women diagnosed with breast cancer (n=6, 7.6%), and healthcare professionals (n=2, 2.5%). The full-list of breast cancer-relevant health states and the utilities are provided in the Supplementary Material.

Intervention-specific health utility values

Screening or diagnostic interventions

Eight studies measured utility values for health states related to breast cancer screening or diagnostic interventions and are shown in **Figure 2a**. The mean values ranged from 0.46 to 1.00. Three mammography-related health states of false positive result on screening mammography, receiving diagnostic mammography, and true positive result on diagnostic mammography had lower mean utilities (range, 0.46 to 0.55) compared to the other health states (range, 0.72 to 1.00). Most of the health states were measured using either the EQ-5D or VAS, and others used Testing Morbidities Index and TTO. The values obtained from VAS were placed on the lower end of the 0-1 scale, the EQ-5D in the middle, and the TTO values fell on the higher end.

Local therapy

Eleven studies used direct (SG, TTO, VAS) and indirect (EQ-5D, VR-6D) methods to obtain health utilities for breast cancer surgery (Figure 2b). Breast cancer surgery-related mean utilities were found to have large variation; utilities for breast conserving surgery (range, 0.67 to 0.91) and mastectomy (range, 0.48 to 0.87) were found to be lower compared to utilities for mastectomy followed by breast conserving surgery (range, 0.75 to 0.89) and bilateral mastectomy (range, 0.70 to 0.86). Breast reconstruction-related utilities were found to be between 0.68 to 0.90. The mean utilities derived from VAS tended to be lower (range, 0.48 to 0.80) than those from other methods, which clustered between 0.67 and 0.91.

Three studies measured utilities for radiation as compared to no radiation. The sample size of the studies was similar, and the median utilities for no radiation were slightly

higher as compared to radiation. The utilities derived using VAS were found to be on the lower end, TTO in the middle, and the EQ-5D values on the higher end.

Four studies measured utilities related to breast cancer surgery and radiation combined. The values for mastectomy and radiation were lowest (range, 0.44 to 0.61), whereas the utilities for breast conserving surgery (with or without mastectomy) and radiation or repeat breast conserving surgery and radiation fell between 0.66 and 0.95. The utilities derived from VAS were at the lower end (range, 0.44 to 0.90) as compared to SG, TTO, and VR-6D. Most of the utilities in this category were derived from SG (range, 0.61 to 0.90).

Systemic therapy

The utilities associated with chemotherapy were categorised into when no drug was specified (n=8) or drugs were specified (n=8). When no drug was specified, the utilities for chemotherapy were found to be lower compared to those before and after chemotherapy (range, 0.73 to 0.96). The utilities derived from VAS were on the lower end. When the drug or drug combination for chemotherapy-related utilities was specified, substantial variation in the values was observed (Figure 2c). Utilities ranged from 0.28 to 0.92 and were measured using primarily self-reported instruments, the EQ-5D, Finnish 15D, HUI3, QOL-VAS, and Subjective Health Estimation.

Nine studies measured endocrine therapy-related utilities. The utilities for non-specific hormone replacement therapy ranged from 0.52 to 0.93, whereas for Tamoxifen the utilities were on the higher end and ranged from 0.75 to 0.95. One study with a sample size of 152 patients assessed the utility for Goserelin therapy using SG and reported a mean

utility value of 0.81. None of the identified studies reported utilities for targeted therapies for breast cancer.

Allied health and complimentary medicine

Seven studies assessed utilities associated with allied health and complimentary medicine-related health states (Figure 2d). Most of the studies used the EQ-5D, and the mean utility values ranged from 0.56 to 0.88.

Adverse events and their treatments

A total of 10 studies reported on a range of breast cancer treatment-related adverse events (**Figure 3**). Negative health utility values were reported for fatigue, diarrhea and vomiting, alopecia, febrile neutropenia, hand-foot syndrome, stomatitis, and moderate to severe hypercalcaemia, and most of these were derived using SG. Lower utilities (<0.5) were found to be associated with fractures, severe bone pain, local or distant recurrence that may or may not require treatment(s), lymphedema, pulmonary embolism, deep vein thrombosis, ischemic cerebrovascular events, endometrial or contralateral breast cancer, and cataracts and were derived predominantly from VAS or SG. VAS values were found to be lower as compared to SG. Many utilities in this category were derived using TTO or the EQ-5D, and TTO values tended to be lower than the EQ-5D derived values.

Breast cancer stage-specific utilities

A total of 4 and 11 studies assessed the utilities for early breast cancer and advanced breast cancer-related health states, respectively. As seen in Figure 4a, most of the studies for early breast cancer derived utilities using the EQ-5D. Studies with large sample sizes (>1000) consistently found the early breast cancer health states to be between 0.58 and 0.81. The

health utilities for advanced breast cancer states were mainly measured using direct methods (SG, TTO, and VAS). The utilities for local recurrence were found to be lower than early breast cancer without recurrence, but higher than advanced disease.

Figure 4b shows the utilities for when the stage of breast cancer was not specified (n=17) Several studies with small sample sizes found that the utilities for participants in mid- to long-term remission were lower as compared to loco-regional recurrence. The reported utilities from initial diagnosis of breast cancer to two years following primary or recurrent breast cancer were lower as compared to longer term (two years or more) follow-up.

DISCUSSION

There has been a continued interest in the measurement of health utilities for breast cancer since 2005. This systematic literature review identified the full range of published health utility values relevant to breast cancer from diagnostic or screening, local and systemic therapies, allied health or complementary medicine-related interventions, and treatment-related adverse events. Only one of the 79 identified studies in the review explicitly estimated the utility values for Indigenous women with breast cancer[11], which is concerning due to the higher incidence and mortality rates of cancer in this population[31].

We found that women undergoing screening mammography and MRI valued undergoing screening investigations as equivalent to being in full health. Also, women with false positive results on screening mammography and women with confirmed positive

results on diagnostic mammography were similar in terms of their health utility values, with values ranging from 0.40 to 0.60. This finding highlights the substantial drop in health utilities in women with potential breast cancer diagnosis and the need to provide psychosocial support to patients with breast cancer from the outset. For local interventions, we found that the utility values for breast cancer surgery (i.e., breast conserving surgery or mastectomy) were lower (range, 0.4-0.7) compared to women undergoing breast reconstruction post-cancer surgery (range, 0.6–0.9). This finding is corroborated by the evidence to-date that suggests that undergoing breast reconstructive surgery significantly improves health-related quality of life and satisfaction with breasts.[32-34] Health utility values were most assessed for chemotherapy-related health states, for which they ranged from 0.28-0.96. The high number of studies reporting on chemotherapy was conceivably due to the rapid turnover of research on new chemotherapeutic agents and possible drug combinations requiring health utility-relevant evidence prior to market entry. This may also have influenced the dominance of generic preference-based measures in this category. Substantial variation was noted between the different chemotherapy regimens; however, two trends were noted. First, patients who were on chemotherapy reported lower values as they progressed in their treatment, such that the values for the last treatment session were lower as compared to first session. Secondly, utilities for patients who were on chemotherapy were lower compared to patients who had completed chemotherapy, and utilities post-chemotherapy continued to increase. This has important implications when designing cost-effectiveness analyses, as the timeframe during which the costs and the benefits accrued may have been different. We did not identify studies estimating utility

values for patients on targeted therapies and identified few studies reporting on the utility values for specific HRT drugs. This lack of utility values in the HRT or targeted therapy literature was unforeseen due to the higher uptake of these interventions in breast cancer in recent years. In terms of breast cancer stage, predictable patterns were observed. We found that the utilities for early stage breast cancer states were higher compared to advanced stages. This finding is similar to Peasgood et al.[8], who reported higher values for EBC without recurrence and a sharp decline in progressive MBC health states. An interesting finding was that patients who were in remission (<2 years to ≥10 years) had lower utility values (range, -0.1 – 0.1), which indicates the long-term impacts of breast cancer and its associate treatments on the HRQOL. It also demonstrates the need to look beyond the treatment phase and assess the costs and HRQOL in patients in the survivor phase.

With respect to the methods used to assess utilities in the breast cancer population, a consistent observation was that utilities elicited using VAS were lower compared to other direct and indirect methods. VAS as a method of eliciting utilities is easy, inexpensive, and places minimal cognitive burden on the respondent. However, VAS frames the questions under certainty and does not offer any insight into the relative risk attitude or the trade-offs an individual is willing to make for a specific health state. This pattern of VAS-derived utilities being lower than other methods, and that VAS is not a good substitute for established direct and indirect methods of utility estimation[35-38], has been observed previously in the literature, but does raise the question of whether future studies should continue to use VAS to elicit preferences as a stand-alone method.

Our study has some limitations. To limit the scope of the study, we restricted our search to studies published in English, which may have limited the number of publications identified. Further, much heterogeneity was observed in the study population (i.e., stage of breast cancer, treatment type and phase, type of participant – patients vs general population vs healthcare providers, and demographic characteristics) and utility estimation methodology (i.e., anchors, administration method, tariffs), which precluded pooling of the results and limited us to presenting a qualitative description of the results. The search strategy for this review was designed with the help of a medical librarian and using published search strategies on this topic. Nonetheless, we identified many irrelevant articles through our electronic search, indicating that the search was highly sensitive but lacked precision. More recently, Arber et al[39, 40] conducted a study to assess and validate the sensitivity of OVID Medline search filters to identify studies reporting health utility values. In their paper, Arber et al[40] provide three different search strategies to maximize sensitivity, balance sensitivity and precision, and maximize precision. The latter two strategies reduce the number of articles that need to be evaluated and should be used in future reviews. We did not contact the authors for the articles where the data were insufficient or missing, and the study was excluded. This may have led to the exclusion of relevant literature and is an important consideration for the authors of future studies that report on health utility values, as the reporting of utility values takes minimal time or effort but enhances the uptake of the results in future economic evaluations. Lastly, we did not critically appraise the methodology or the reporting of the included studies.

CONCLUSION

This study provides a catalog of the published health utility values in breast cancer by the type of intervention and the stage of breast cancer. We found that even though a variety of utility estimation methods have been used in the breast cancer literature, EQ-5D is most commonly used. A higher proportion of studies identified in the review measured health utilities for interventions, more specifically for chemotherapy and treatment-related adverse events. Further, substantial variation was noted in the utility values among studies reporting on the same health state. This variation was larger for systemic interventions and treatment-related adverse events than for screening-, diagnostic-, local-, or allied health and complimentary medicine-related interventions. The utilities for early breast cancer-health states were higher compared to the advanced breast cancer health states.

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FIGURE LEGEND

Figure 1: PRISMA flow diagram for the systematic literature review of published health utility values in breast cancer

Figure 2: Health utility values in breast cancer, by treatment intervention

a. Screening or diagnostic interventions
b. Local interventions (surgery, radiation, surgery and radiation)
c. Systemic interventions (chemotherapy, endocrine therapy)
d. Allied health or complementary medicine interventions

Figure 3: Health utility values for adverse effects of breast cancer treatment interventions

Figure 4: Health utility values in breast cancer, by stage of breast cancer

a. Early and Advanced stage breast cancer
b. Non-specific breast cancer

Table 1: Characteristics of the studies included in the review (N=79)

Study (Author last name)	Country of corresponding author	Study design for preference elicitation study	Respondents	Health utility estimation method
Conner-Spady et al. (2005)[s][23]	Canada	Cohort - prospective	Patients	EQ-5D (UK), QOL VAS
Gordon et al. (2005)*[s][41]	Australia	Cohort - prospective	Patients	SHE
Hayman et al. (2005)*[s][42]	USA	Cross-sectional	Public (w), Patients	SG
Lloyd et al. (2006)*[43]	UK	Cross-sectional	Public	EQ-5D (UK), SG, VAS
Milne et al. (2006)[21]	New Zealand	Cross-sectional	Public (w)	EQ-5D (NZ, UK), TTO, VAS
Schleinitz et al. (2006)[s][44]	USA	Cross-sectional	Public (w)	SG, TTO
Shih et al. (2006)[45]	USA	Cross-sectional	Patients	SF-6D
Sullivan et al. (2006)[46]	USA	Cross-sectional	Patients	EQ-5D (US)

Lidgren et al. (2007)[24]	Sweden	Cross-sectional	Patients	EQ-5D (UK), TTO
Mansel et al. (2007)*[47]	UK	Cross-sectional	Patients	SG
Prescott et al. (2007)[s][48]	UK	RCT	Patients	EQ-5D (UK)
Yabroff et al. (2007)[49]	USA	Cross-sectional	Patients	HALex
Bernhard et al. (2008)*[s][50]	Switzerland	RCT	Patients	SHE, TTO
Bonomi et al. (2008)[51]	USA	Cross-sectional	Public (w)	VAS
Melnikow et al. (2008)[s][53]	USA	Cross-sectional	Public (w)	SG
Sherrill et al. (2008)*[54]	USA	RCT	Patients	EQ-5D (UK)
Wolowacz et al. (2008)*[12]	UK	Cross-sectional	Patients	EQ-5D^ (UK)
Dranitsaris et al. (2009)*[55]	Canada	Cross-sectional	HCP	TTO
Fountzilas et al. (2008)*[52]	Greece	RCT	Patients	EQ-5D (Europe)
Reed et al. (2009)*[10]	USA	RCT	Patients	HUI 3
Zhou et al. (2009)*[56]	USA	RCT	Patients	EQ-5D (UK)
Cheville et al. (2010)*[22]	USA	Cross-sectional	Patients	EQ-5D (US), TTO
De Kok et al. (2010)*[s][57]	The Netherlands	Cohort - prospective	Patients	EQ-5D (UK)

Domeyer et al. (2010)[58]	Greece	Cohort - prospective	Public (w)	EQ-5D (ES)
Freedman et al. (2010)*[59]	USA	Cohort - prospective	Patients	EQ-5D (UK)
Grann et al. (2010)*[s][60]	USA	Cross-sectional	Patients	TTO
Haines et al. (2010)*[s][61]	Australia	RCT	Patients	EQ-5D (UK)
Lux et al. (2010)*[62]	Germany	Cross-sectional	Patients	VAS
Kimman et al. (2011)*[s][63]	The Netherlands	RCT	Patients	EQ-5D (UK)
Matalqah et al. (2011)[64]	Malaysia	Cross-sectional	Public (w), Patients	EQ-5D (UK)
Sullivan et al. (2011)[65]	USA	Cross-sectional	Patients	EQ-5D (UK)
Shirowa et al. (2011)[66]	Japan	RCT	Patients	EQ-5D (UK)
Bastani et al. (2012)[s][13]	Iran	Cohort - prospective	Patients	EQ-5D^
Cheng et al. (2012)*[67]	Taiwan	Cohort - retrospective	Patients	SG
Oh et al. (2012)*[68]	Korea	Cross-sectional	Patients	EQ-5D (KR)
Robertson et al. (2012)*[s][69]	Sweden	Cross-sectional	Patients	EQ-5D (UK)
Serra et al. (2012)*[70]	USA	Cohort - prospective	Patients	EQ-5D

Shih et al. (2012)[s][28]	Singapore	Cross-sectional	HCP	SG, VAS
Frederix et al. (2013)[71]	UK	Cross-sectional	Public	VAS, TTO
Kuchuk et al. (2013)*[72]	Canada	Cross-sectional	Patients	SG
Moro-Valdezate et al. (2013)*[73]	Spain	Cohort - Prospective	Patients	EQ-5D (ES)
Postma et al. (2013)*[74]	The Netherlands	RCT	Patients	EQ-5D
Sinno et al. (2013)*[26]	Canada	Cross-sectional	Public	VAS, TTO, SG
Arving et al. (2014)*[s][14]	Sweden	RCT	Patients	EQ-5D^ (UK)
Farkkila et al. (2014)[9]	Finland	Cross-sectional	Patients	EQ-5D (UK), 15D
Humphrey et al. (2014)*[s][75]	USA	Cross-sectional	Public (w)	TMI
Min et al. (2014)[s][76]	Korea	Cross-sectional	Patients	EQ-5D
Moro-Valdezate et al. (2014)*[77]	Spain	Cohort - prospective	Patients	EQ-5D (ES)
Sinno et al. (2014)*[27]	USA	Cross-sectional	Public	VAS, TTO, SG
Songtish et al. (2014)[s][78]	Thailand	Cross-sectional	Public (w)	SG

Tan et al. (2014)[s][25]	Singapore	Cross-sectional	Patients	SG, VAS
Timmers et al. (2014)[s][79]	The Netherlands	RCT	Public (w)	EQ-5D (NL)
Tosteson at al. (2014)[s][80]	Lebanon	Cross-sectional	Public (w)	EQ-5D (US)
Dranitsaris et al. (2015)[81]	Canada	Cross-sectional	Patients	TTO
Eyles et al. (2015)*[s][82]	England	Cohort - prospective	Patients	EQ-5D
Hall et al. (2015)*[s][83]	UK	Cohort - prospective	Patients	EQ-5D (UK)
Kimman et al. (2015)[84]	Australia	Cross-sectional	Patients	EQ-5D (TH)
Swan et al. (2015)*[s][85]	USA	Cross-sectional	Public (w)	TMI
Tachi et al. (2015)[86]	Japan	Cohort - prospective	Patients	EQ-5D (JP)
Brown et al. (2016)[s][15]	USA	Cross-sectional	Public (w)	EQ-5D^ (US)
Garvey et al. (2016)[s][11]	Australia	Cohort - prospective	Patients	AQOL-4D
Pickard et al. (2016)[87]	USA	Cohort - retrospective	Patients	EQ-5D (US)
Shirowa et al. (2016)*[88]	Japan	RCT	Patients	EQ-5D (JP)
Trogdon et al. (2016)[s][16]	USA	Cross-sectional	Public, Patients	EQ-5D^ (US)
Wang et al. (2016)[89]	USA	Cross-sectional	Public, Patients	SF-6D^

Yagata et al. (2016)*[s][90]	Japan	RCT	Patients	EQ-5D (JP)
Yousefi et al. (2016)[s][29]	Iran	Cross-sectional	Patients	EQ-5D (UK), SF-6D
Ali et al. (2017)[s][17]	USA	Cohort - retrospective	Patients	SF-6D, VR-6D^
Enblom et al. (2017)*[s][91]	Sweden	Cross-sectional	Patients	EQ-5D (UK)
Gordon et al. (2017)*[s][92]	Australia	RCT	Patients	EQ-5D (AU)
Kim et al. (2017)[s][93]	South Korea	Cross-sectional	Public	SG, VAS
Knuttel et al. (2017)[20]	The Netherlands	Cross-sectional	Public (w), Patients	EQ-5D$^{\theta}$ (UK), TTO
Liu et al. (2017)[s][19]	China	Cross-sectional	Patients	EQ-5D$^{\theta}$ (UK, CHN, JP, KR)
May et al. (2017)[s][94]	The Netherlands	RCT	Patients	EQ-5D (NL)
Naik et al. (2017)[s][30]	Canada	Cross-sectional	Patients	EQ-5D (UK, CA, US)
Seferina et al. (2017)*[95]	The Netherlands	Cross-sectional	Patients	EQ-5D (UK)
The ACTION Study Group (2017)[96]	Australia, Netherlands	Cohort - prospective	Patients	EQ-5D (TH)

van Kampen et al. (2017)*[s][97]	The Netherlands	Cross-sectional	Patients	EQ-5D (UK)
Wallwiener et al. (2017)[18]	Germany	Cross-sectional	Patients	EQ-5D[θ]

[s]Received funding from not-for-profit sources; *Study published in Oncology journal; [θ]5-L version; ^mapping study; AU, Australia; CA, Canada; CHN, China; JP, Japan; KR, Korea; NL, the Netherlands; NZ, New Zealand; ES, Spain; TH, Thailand; UK, United Kingdom; US, United States of America; (w), women only; RCT, Randomized Controlled Trial; HCP, Health Care Provider; SHE, Subjective Health Estimation; SG, Standard Gamble; VAS, Visual Analogue Scale; TMI, Testing Morbidities Index; TTO, Time Trade Off; SF-6D, Short-form 6D; HALex, Health and Activity Limitation Index

Figure 1: PRISMA flow diagram for the systematic literature review of published health utility values in breast cancer

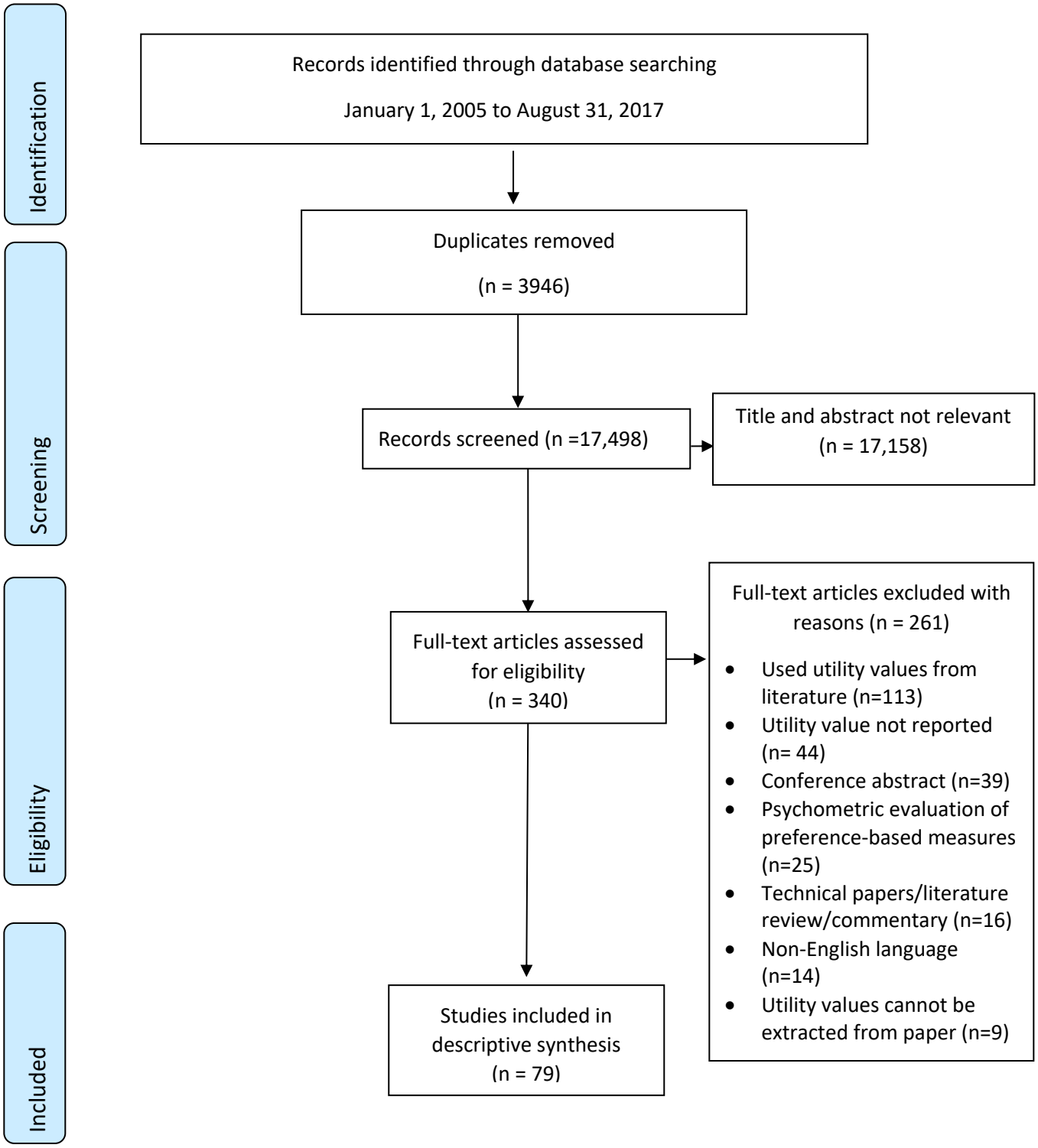
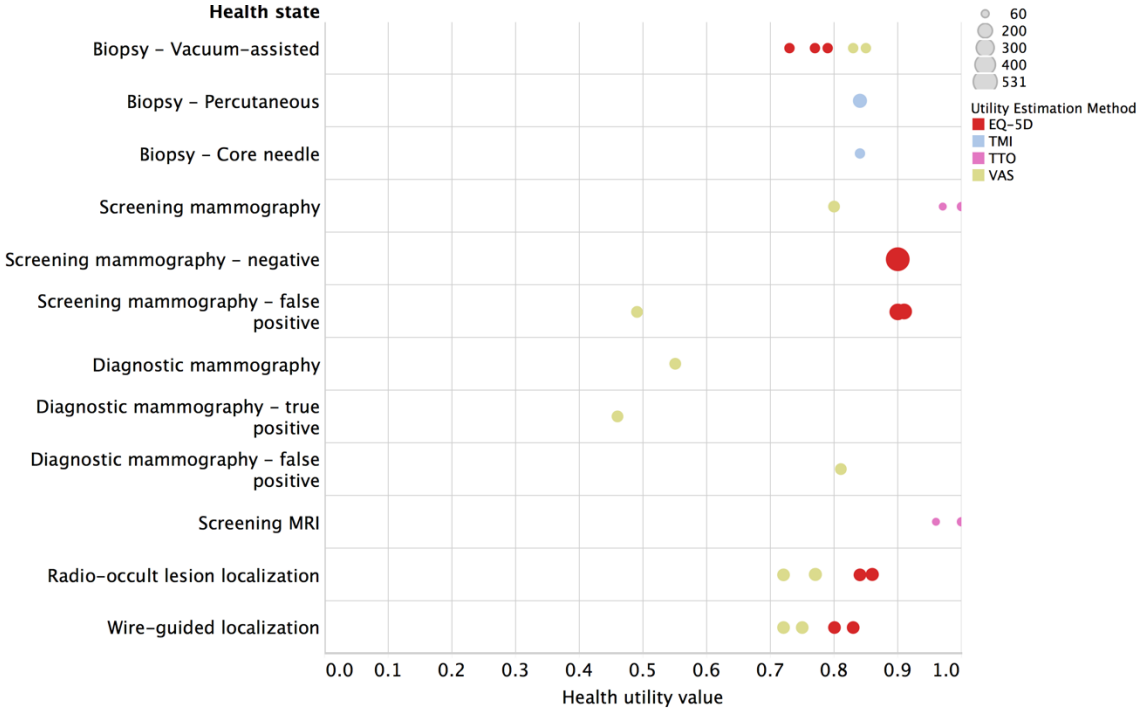


Figure 2: Health utility values by the type of breast cancer intervention[1]

[1]Circles represent mean or median value for each health state by study, size of the circle shows details about sample size and color of the circle shows details about the utility estimation method.

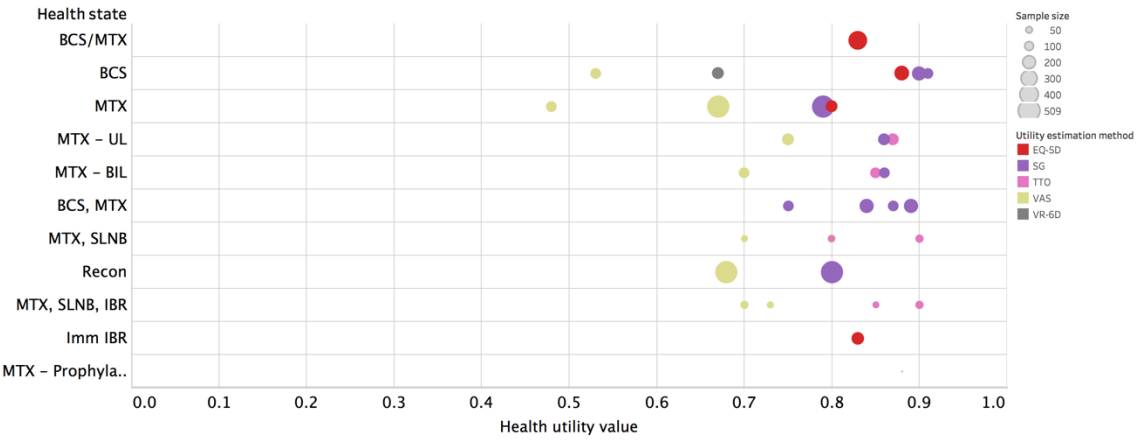
a. Screening or diagnostic interventions



MRI, Magnetic Resonance Imaging; TMI, Testing Morbidities Index; TTO, Time Trade-off; VAS, Visual Analogue Scale

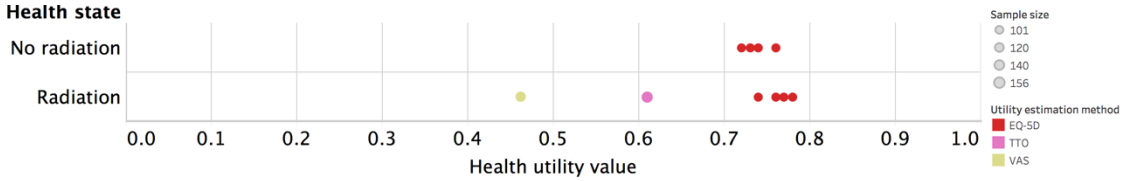
b. Local interventions

i. Surgery



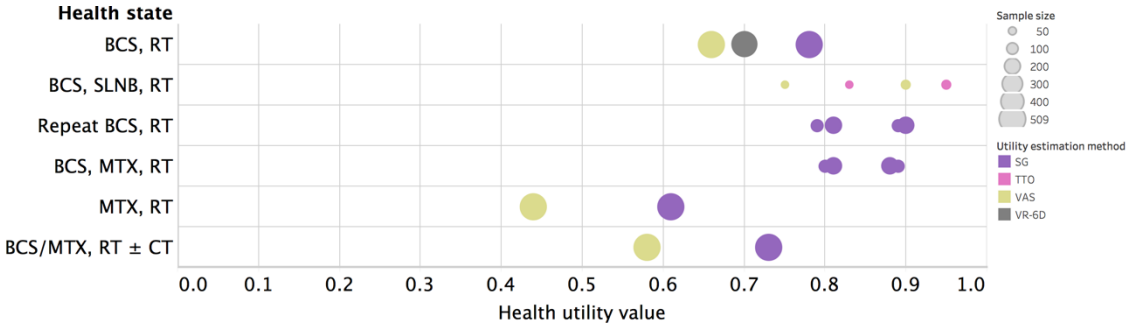
BCS, Breast Conserving Surgery; MTX, Mastectomy; UL, Unilateral; BL, Bilateral; SLNB, Sentinel Lymph Node Biopsy; Recon, Reconstruction; IBR, Implant-based Reconstruction; Imm, Immediate; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale; VR-6D, Veterans RAND-6D

ii. Radiation



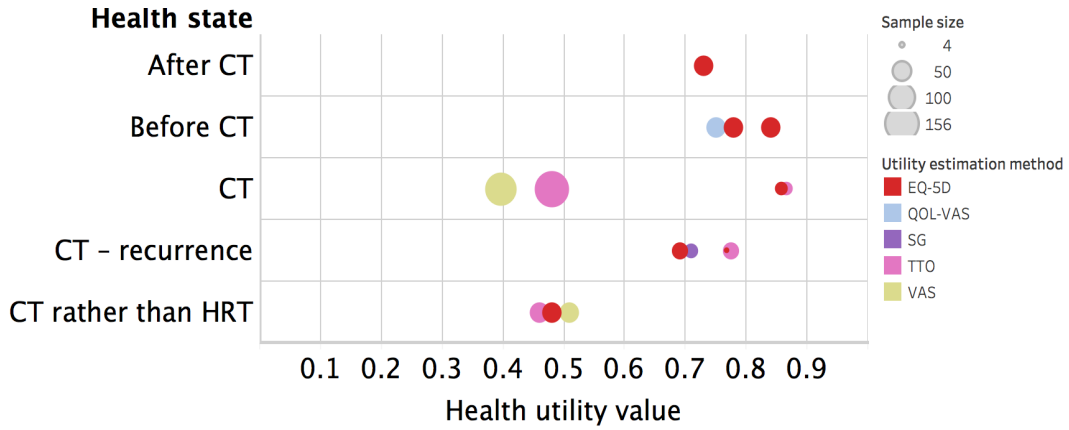
TTO, Time Trade-off; VAS, Visual Analogue Scale

iii. Surgery and Radiation

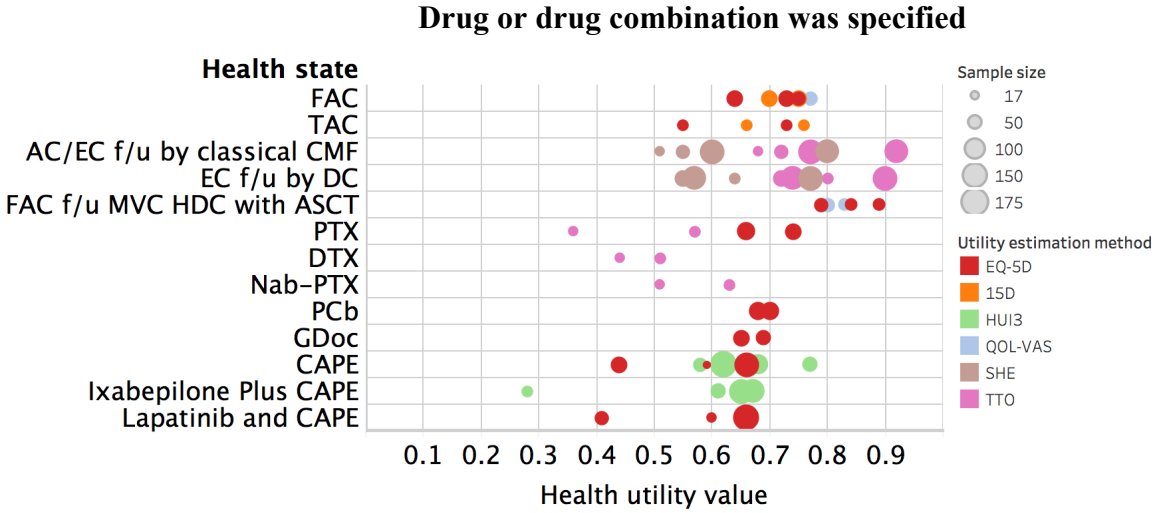


BCS, Breast Conserving Surgery; MTX, Mastectomy; SLNB, Sentinel Lymph Node Biopsy; RT, Radiation; CT, Chemotherapy; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale; VR-6D, Veterans Rand-6D

c. Systemic interventions
   i. Chemotherapy (when no drug was specified and when drug/drug combination was specified)

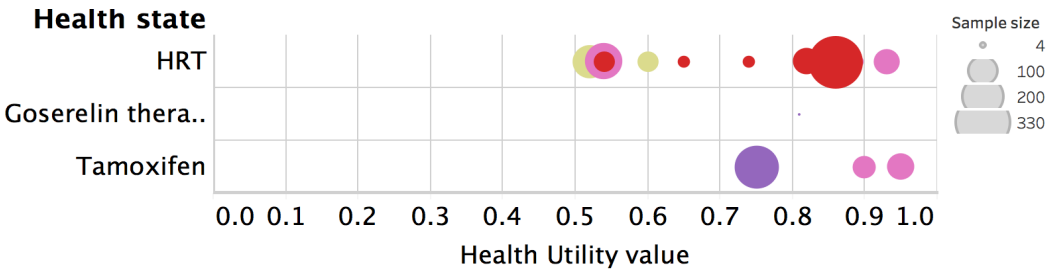


CT, Chemotherapy; HRT, Hormone Replacement Therapy; QOL-VAS, Quality of Life-Visual Analogue Scale; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale



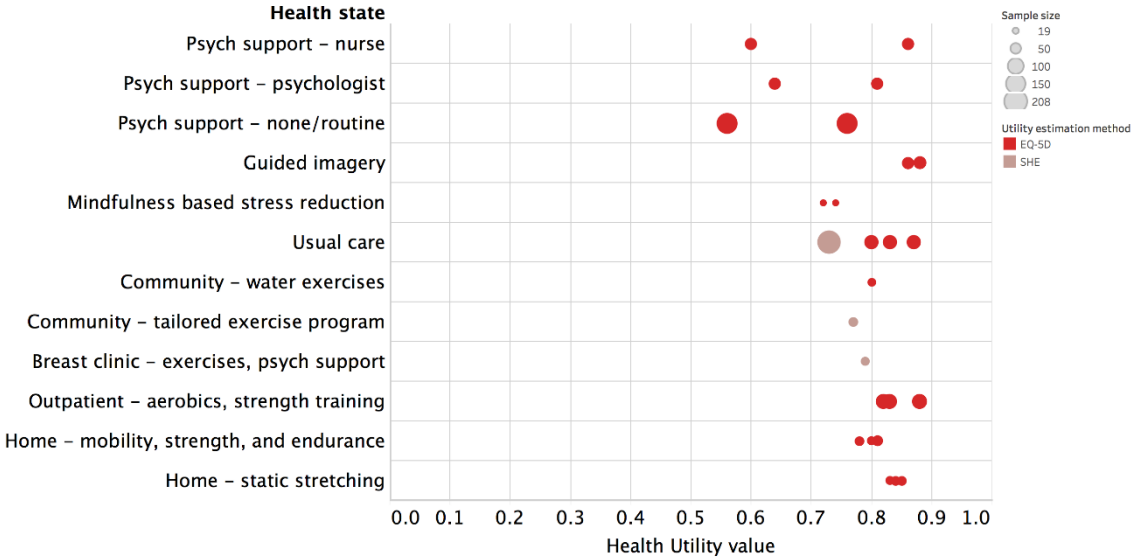
FAC, 5-Fluorouracil, Doxorubicin, Cyclophosphamide; TAC, Docetaxel with Doxorubicin and Cyclophosphamide; AC, Doxorubicin and Cyclophosphamide; EC, Epirubicin and Cyclophosphamide; HDC, High Dose Chemotherapy; PTX, Paclitaxel, DTX, Docetaxel; PcB, Paclitaxel and Carboplatin; GDoc, Gemcitabine and Docetaxel; CAPE, Capecitabine; HUI3, Health Utilities Index Mark 3; QOL-VAS, Quality of Life-Visual Analogue Scale; SHE, Subjective Health Estimation, TTO, Time Trade-off

ii. Endocrine therapy



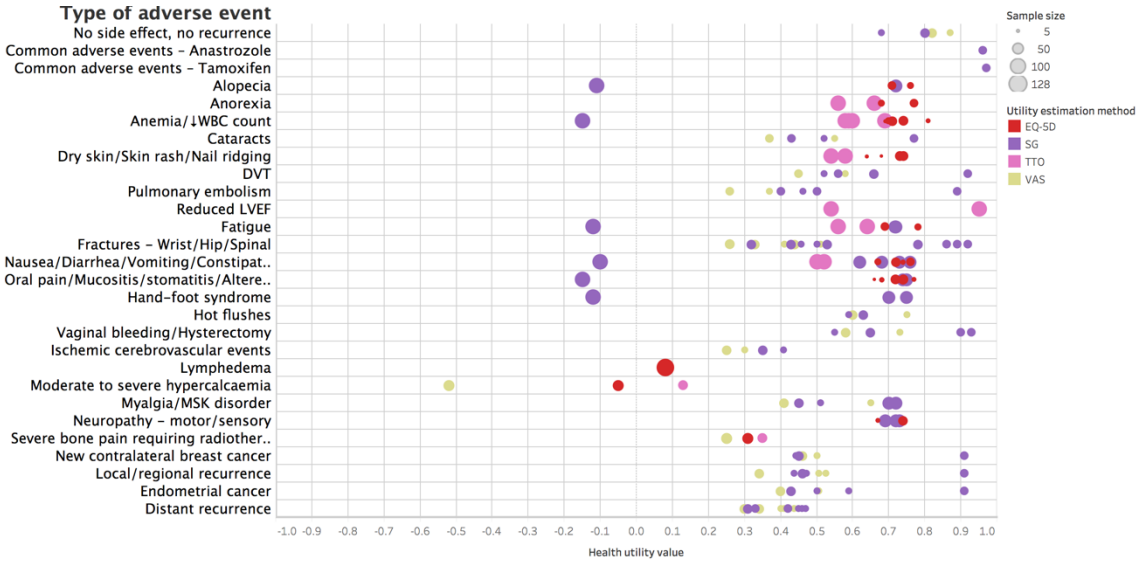
HRT, Hormone Replacement Therapy; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale

d. Allied health and complimentary medicine



SHE, Subjective Health Estimation

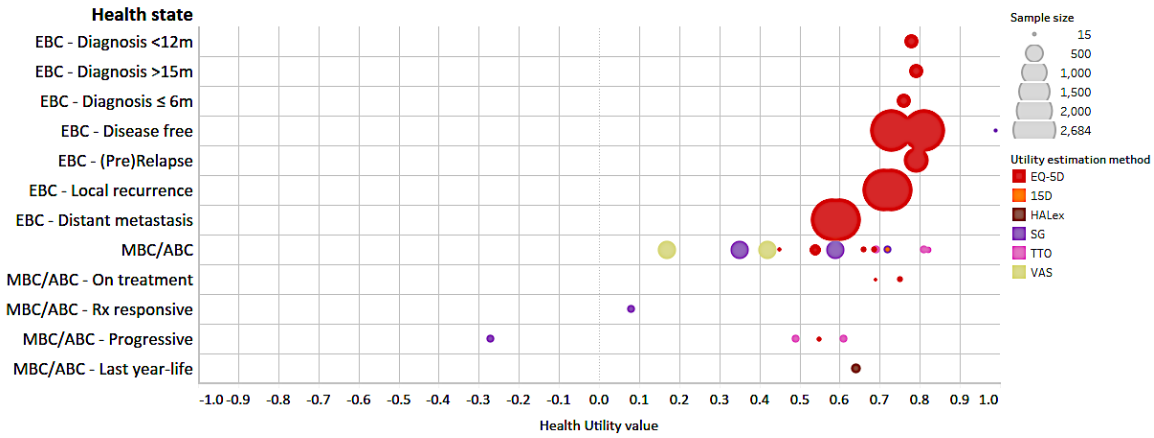
Figure 3: Health utility values by adverse events of breast cancer interventions



WBC, White Blood Cell; DVT, Deep Vein Thrombosis; LVEF, Left Ventricular Ejection Fraction; MSK, Musculoskeletal; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale

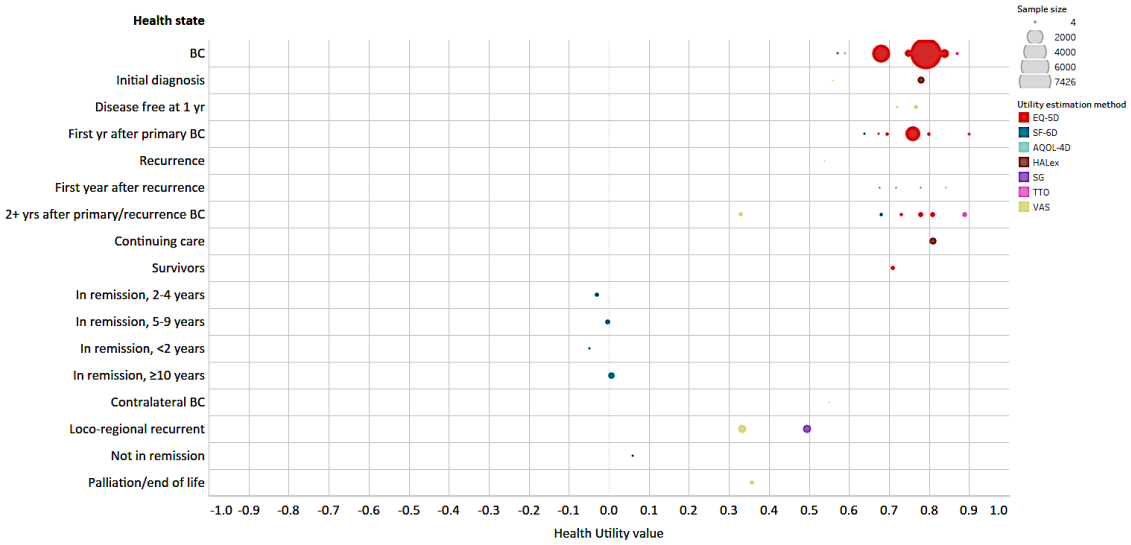
Figure 4: Health utility values by stage of breast cancer

a. Early breast cancer (EBC) vs. advanced or metastatic breast cancer (ABC/MBC)



EBC, Early Breast Cancer; ABC, Advanced Breast Cancer; MBC, Metastatic Breast Cancer; HALex, Health and Activities Limitation Index; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale

b. Non-specified breast cancer



BC, Breast Cancer; HALex, Health and Activities Limitation Index; SG, Standard Gamble; TTO, Time Trade-off; VAS, Visual Analogue Scale; SF-6D, Short form-6D; AQOL-4D, Australian Quality of Life-4D

Supplementary Material

Table 1: MEDLINE search strategy for the systematic review of literature of published health utility values in breast cancer

1. exp breast neoplasms/ or exp mammary neoplasms/
2. (breast$ adj5 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullary)).tw.
3. (mammar$ adj5 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullary)).tw.
4. or/1-3
5. (euroqol or euro QOL or eq5d or eq 5D).tw.
6. (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf6d or 6d or 6d or 6 dimension).
7. Health Utilities Index.mp. or health utilit$.tw. or hui.tw.
8. (Utility Based Questionnaire-Cancer or UBQC or UBQC or UBQ C).
9. (Qaly$ or quality adjusted life year$).tw.
10. (Hye$ or health$ year$ equivalent$).tw.
11. (quality of well being or quality of wellbeing).tw
12. (qald$ or qale$ or qtimes$ or (quality adjusted life day$ or quality adjusted life expectanc$ or quality adjusted survival$)).tw.
13. Standard gamble$.tw.
14. (time trade off or time tradeoff or tto).tw.
15. visual analog$ scale$.tw.
16. discrete choice experiment$.tw.
17. (health state$ utilit$ or health state$ value$ or health state$ preference$).tw.
18. (cost* adj2 (effective* or utilit* or benefit* or minimi* or evaluat* or analy*)).
19. or/5-18
20. 4 and 19
21. limit 20 to english language
22. limit 21 to yr="2005-Current"

Table 2: Health utility values by breast cancer intervention

a. Screening or Diagnosis-related health states

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Biopsy - Vacuum-assisted	Pre-biopsy	Public (w) - non-palpable lesions (BI-RADS 3/4)	102	51.3 ± 8.8	EQ-5D	0.73 ± 0.22	Domeyer et al. (2010)[58]
	Pre-biopsy	Public (w) - non-palpable lesions (BI-RADS 3/4)	102	51.3 ± 8.8	EQ-5D VAS	0.83 ± 0.08	Domeyer et al. (2010)[58]
	Post-Early	Public (w) - non-palpable lesions (BI-RADS 3/4)	102	51.3 ± 8.8	EQ-5D	0.79 ± 0.21	Domeyer et al. (2010)[58]
	Post-Early	Public (w) - non-palpable lesions (BI-RADS 3/4)	102	51.3 ± 8.8	EQ-5D VAS	0.85 ± 0.06	Domeyer et al. (2010)[58]
	Post-Late	Public (w) - non-palpable lesions (BI-RADS 3/4)	102	51.3 ± 8.8	EQ-5D	0.77 ± 0.23	Domeyer et al. (2010)[58]

	Post-Late	Public (w) - non-palpable lesions (BI-RADS 3/4)	102	51.3 ± 8.8	EQ-5D VAS	0.85 ± 0.09	Domeyer et al. (2010)[58]
Biopsy - Percutaneous		Public (w)	188	51.4	TMI	0.84 ± 0.06	Humphrey et al. (2014)[75]
Biopsy - Core needle		Public (w)	100	51	TMI	0.84 ± 0.07	Swan et al. (2015)[85]
Screening mammography		Public (w) (10% with history of BC)	131	65% <64	VAS	0.80 ± 0.14	Bonomi et al. (2008)[51]
		Public (w) – BRCA+	83	67.5% - 35-60	TTO	1.00 ± 0.00	Grann et al. (2010)[60]
		Public	60	43.1% - 18-34	TTO	0.97 ± 0.11	Grann et al. (2010)[60]
Screening mammography – negative[1]		Public (w) (10% with history of BC)	131	65% <64	VAS	0.89 ± 0.10	Bonomi et al. (2008)[51]
		Public (w)	531	48.7% - 50-64	EQ-5D	0.90 ± 0.13	Tosteson eat al. (2014)[80]
Screening mammography - false positive[1]		Public (w) (10% with history of BC)	131	65% <64	VAS	0.49 ± 0.21	Bonomi et al. (2008)[51]
	Unresolved	Public (w)	259	44% <50	EQ-5D	0.90 ± 0.13	Tosteson eat al. (2014)[80]
	Resolved	Public (w)	235	44% <50	EQ-5D	0.91 ±0.13	Tosteson eat al. (2014)[80]
Diagnostic mammography		Public (w) (10% with	131	65% <64	VAS	0.55 ± 0.20	Bonomi et al. (2008)[51]

		history of BC)					
Diagnostic mammography - true positive		Public (w) (10% with history of BC)	131	65% <64	VAS	0.46 ± 0.21	Bonomi et al. (2008)[51]
Diagnostic mammography - false positive		Public (w) (10% with history of BC)	131	65% <64	VAS	0.81 ± 0.15	Bonomi et al. (2008)[51]
Screening MRI		Public (w) – BRCA+	83	67.5% - 35-60	TTO	1.00 ± 0.01	Grann et al. (2010)[60]
		Public	60	43.1% - 18-34	TTO	0.96 ± 0.10	Grann et al. (2010)[60]
Radio-occult lesion localization	Baseline	Patients	162	60.5 ± 7.7	EQ-5D	0.86 ± 0.16	Postma et al. (2013)[74]
	Baseline	Patients	162	60.5 ± 7.7	EQ-5D VAS	0.77 ± 0.12	Postma et al. (2013)[74]
	12-months	Patients	151	60.5 ± 7.7	EQ-5D	0.84 ± 0.19	Postma et al. (2013)[74]
	12-months	Patients	151	60.5 ± 7.7	EQ-5D VAS	0.72 ± 0.13	Postma et al. (2013)[74]
Wire-guided localization	Baseline	Patients	152	61.1 ± 9.7	EQ-5D	0.83 ± 0.18	Postma et al. (2013)[74]
	Baseline	Patients	152	61.1 ± 9.7	EQ-5D VAS	0.75 ± 0.15	Postma et al. (2013)[74]
	12-months	Patients	141	61.1 ± 9.7	EQ-5D	0.80 ± 0.20	Postma et al. (2013)[74]
	12-months	Patients	141	61.1 ± 9.7	EQ-5D VAS	0.72 ± 0.14	Postma et al. (2013)[74]
Diagnostic follow-up*	With general practitioner	Public (w)	91	57	EQ-5D	0.89	Timmers et al. (2014)[79]

	– pre-workup						
	With general practitioner – post-workup	Public (w)	91	57	EQ-5D	0.91	Timmers et al. (2014)[79]
	With radiologist – pre-workup	Public (w)	245	57	EQ-5D	0.85	Timmers et al. (2014)[79]
	With radiologist – post-workup	Public (w)	245	57	EQ-5D	0.89	Timmers et al. (2014)[79]

[1]Baseline values are shown; values for one year after baseline are not shown as similar to baseline values; *not a diagnostic intervention but a follow-up strategy; (w), women only; BI-RADS, Breast Imaging Reporting and Data System; BRCA, Breast Cancer gene; VAS, Visual Analogue Scale; TMI, Testing Morbidity Index; TTO, Time trade-off

b. Local therapy

i. Surgery

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Oncological surgery (ç)	1-year	Patients	364	59 ± 13	EQ-5D	0.83**	Moro-Valdezate et al.(2014)[77]
Breast conserving surgery		Patients	146	76.64 ± 7.09	VR-6D	0.67 ± 0.13	Ali et al. (2017) [17]
		Public (w) (10% with history of BC)	131	65% <64	VAS	0.53 ± 0.21	Bonomi et al. (2008)[51]
		Patients	120	61 ± 10	SG	0.91 ± 0.15	Hayman et al (2005) [42]
		Public (w)	210	50 ± 14	SG	0.90 ± 0.15	Hayman et al. (2005) [42]
	1-year	Patients	227	59 ± 13	EQ-5D	0.88**	Moro-Valdezate et al.(2014)[77]
	EBC	Public (w)	110	26 – 60	SG	0.76	Songtish et al.(2014) [78]
	EBC, with lymphedema	Public (w)	110	26 – 60	SG	0.59	Songtish et al.(2014) [78]
Mastectomy		Public (w) (10% with	131	65% <64	VAS	0.48 ± 0.22	Bonomi et al. (2008)[51]

		history of BC)					
		Public	509	45.7 ± 14.1	VAS	0.67 ± 0.20	Kim et al. (2017)[93]
		Public	509	45.7 ± 14.1	SG	0.79 ± 0.27	Kim et al. (2017)[93]
	1-year	Patients	137	59 ± 13	EQ-5D	0.80**	Moro-Valdezate et al.(2013)[73]
Mastectomy – unilateral		Public	140	23.6 ± 7.0	VAS	0.75 ± 0.17	Sinno et al. (2014)[27]
		Public	141	23.6 ± 7.0	TTO	0.87 ± 0.14	Sinno et al. (2014)[27]
		Public	142	23.6 ± 7.0	SG	0.86 ± 0.18	Sinno et al. (2014)[27]
Mastectomy – bilateral		Public	120	24.8 ± 8.4	VAS	0.70 ± 0.18	Sinno et al. (2013)[26]
		Public	120	24.8 ± 8.4	TTO	0.85 ± 0.16	Sinno et al. (2013)[26]
		Public	120	24.8 ± 8.4	SG	0.86 ± 0.17	Sinno et al. (2013)[26]
Mastectomy with sentinel lymph node biopsy		Patients	71	60.1 ± 9.4	VAS	0.80 (0.70-0.90) **	Knuttel et al. (2017)[20]
		Patients	71	60.1 ± 9.4	TTO	0.90 (0.80-0.95) **	Knuttel et al. (2017)[20]
		Public	50	56.1 ± 9.4	VAS	0.70 (0.60-0.80) **	Knuttel et al. (2017)[20]
		Public	50	56.1 ± 9.4	TTO	0.80 (0.80-0.95) **	Knuttel et al. (2017)[20]
Mastectomy after breast conserving surgery	Recurrence-DCIS	Patients	120	61 ± 10	SG	0.87 ± 0.21	Hayman et al. (2005) [42]
		Public (w)	210	50 ± 14	SG	0.89 ± 0.15	Hayman et al. (2005) [42]

	Recurrence – IBC	Patients	120	61 ± 10	SG	0.75 ± 0.29	Hayman et al. (2005) [42]
		Public (w)	210	50 ± 14	SG	0.84 ± 0.18	Hayman et al. (2005) [42]
Breast conserving surgery or mastectomy with sentinel lymph node biopsy		Public (w)	110	26 - 60			
Mastectomy followed by reconstruction	Stage 0	Public	509	45.7 ± 14.1	SG	0.80 ± 0.26	Kim et al. (2017)[93]
		Public	509	45.7 ± 14.1	VAS	0.68 ± 0.20	Kim et al. (2017)[93]
Mastectomy with sentinel lymph node biopsy and implant-based reconstruction		Patients	71	60.1 ± 9.4	VAS	0.70 (0.60-0.85) **	Knuttel et al. (2017)[20]
		Patients	71	60.1 ± 9.4	TTO	0.90 (0.75-0.95) **	Knuttel et al. (2017)[20]
		Public	50	56.1 ± 9.4	VAS	0.73 (0.64-0.85) **	Knuttel et al. (2017)[20]
		Public	50	56.1 ± 9.4	TTO	0.85 (0.70-0.95) **	Knuttel et al. (2017)[20]
Immediate implant-based reconstruction		Patients	164	50	EQ-5D	0.83	Robertson et al. (2012)[69]
Mastectomy – Prophylactic		Public (w) - BRCA+	83	67.5% - 35-60	TTO	0.88 ± 0.22	Grann et al. (2010)[60]
		Public (w)	60	40% - 35-50	TTO	0.88 ± 0.17	Grann et al. (2010)[60]

**median values; BC, Breast Cancer; (w), women only; BRCA, BReast CAncer gene; EBC, Early breast cancer; VAS, Visual Analogue Scale; TTO, Time Trade Off; SG, Standard Gamble; VR-6D, Veterans RAND-6D

ii. Surgery and radiation

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Breast conserving surgery and radiation	Stage 0	Public	509	45.7 ± 14.1	SG	0.78 ± 0.26	Kim et al. (2017)[93]
		Public	509	45.7 ± 14.1	VAS	0.66 ± 0.20	Kim et al. (2017)[93]
		Patients	472	72.53 ± 5.41	VR-6D	0.70 ± 0.12	Ali et al. (2017)[17]
	Stage 0-II, 1 year	Patients	482	57% - 45-64	EQ-5D	0.87	Freedman et al (2010)[59]
	Stage 0-II, 5 years	Patients	171	57% - 45-64	EQ-5D	0.89	Freedman et al (2010)[59]
	Stage 0-II, 10 years	Patients	64	57% - 45-64	EQ-5D	0.90	Freedman et al (2010)[59]
	Stage 0-II, 15 years	Patients	21	57% - 45-64	EQ-5D	0.90	Freedman et al (2010)[59]
Breast conserving surgery with sentinel lymph node biopsy and whole breast radiation		Patients	71	60.1 ± 9.4	VAS	0.90 (0.8-0.90)**	Knuttel et al.(2017)[20]
		Patients	71	60.1 ± 9.4	TTO	0.95 (0.90–1.00) **	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	VAS	0.75 (0.65-0.90) **	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	TTO	0.83 (0.80-0.95) **	Knuttel et al.(2017)[20]
Breast conserving surgery or	Stages I, II	Public	509	45.7 ± 14.1	SG	0.73 ± 0.26	Kim et al.(2017)[93]

mastectomy, radiation, and/or chemotherapy		Public	509	45.7 ± 14.1	VAS	0.58 ± 0.20	Kim et al.(2017)[93]
Mastectomy and radiation	Stages IIIA, IIIB	Public	509	45.7 ± 14.1	SG	0.61 ± 0.26	Kim et al.(2017)[93]
		Public	509	45.7 ± 14.1	VAS	0.44 ± 0.18	Kim et al. (2017)[93]
Breast conserving surgery followed by mastectomy and radiation	Recurrence-DCIS	Patients	120	61 ± 10	SG	0.89 ± 0.16	Hayman et al. (2005)[42]
		Public (w)	210	50 ± 14	SG	0.88 ± 0.16	Hayman et al. (2005)[42]
	Recurrence – IBC	Patients	120	61 ± 10	SG	0.80 ± 0.27	Hayman et al. (2005)[42]
		Public (w)	210	50 ± 14	SG	0.81 ± 0.19	Hayman et al. (2005)[42]
Repeat breast conserving surgery and radiation	Recurrence-DCIS	Patients	120	61 ± 10	SG	0.89 ± 0.19	Hayman et al. (2005)[42]
		Public (w)	210	50 ± 14	SG	0.90 ± 0.15	Hayman et al. (2005)[42]
	Recurrence – IBC	Patients	120	61 ± 10	SG	0.79 ± 0.26	Hayman et al. (2005)[42]
		Public (w)	210	50 ± 14	SG	0.81 ± 0.19	Hayman et al. (2005)[42]

**median values; DCIS, Ductal Carcinoma In-situ; IBC, Invasive Breast Cancer; (w), women only; VAS, Visual Analogue Scale; TTO, Time Trade Off; SG, Standard Gamble; VR-6D, Veterans RAND-6D

iii. Radiation therapy

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Radiation		Public (10% history of BC)	131	50-79	VAS	0.46 ± 0.23	Bonomi et al. (2008)[51]
		Public (w)	156	46.2% ≥ 50	TTO	0.61	Schleinitz et al. (2006)[44]
	baseline	Patients	102	72.3 ± 5.0	EQ-5D	0.77*	Prescott et al. (2007)[48]
	3.5m	Patients	102	72.3 ± 5.0	EQ-5D	0.78*	Prescott et al. (2007)[48]
	9m	Patients	102	72.3 ± 5.0	EQ-5D	0.76*	Prescott et al. (2007)[48]
	15m	Patients	102	72.3 ± 5.0	EQ-5D	0.74*	Prescott et al. (2007)[48]
No radiation	baseline	Patients	101	72.8 ± 5.2	EQ-5D	0.74*	Prescott et al. (2007)[48]
	3.5m	Patients	101	72.8 ± 5.2	EQ-5D	0.76*	Prescott et al. (2007)[48]
	9m	Patients	101	72.8 ± 5.2	EQ-5D	0.72*	Prescott et al. (2007)[48]
	15m	Patients	101	72.8 ± 5.2	EQ-5D	0.73*	Prescott et al. (2007)[48]
Radiofrequency ablation preceded by		Patients	71	60.1 ± 9.4	VAS	0.80*	Knuttel et al.(2017)[20]

SLNB and followed by whole breast radiotherapy^^		Patients	71	60.1 ± 9.4	TTO	0.90*	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	VAS	0.78*	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	TTO	0.80*	Knuttel et al.(2017)[20]
Magnetic resonance guided high intensity focused ultrasound preceded by SLNB followed by whole breast radiotherapy^^		Patients	71	60.1 ± 9.4	VAS	0.80*	Knuttel et al.(2017)[20]
		Patients	71	60.1 ± 9.4	TTO	0.88*	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	VAS	0.80*	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	TTO	0.85*	Knuttel et al.(2017)[20]
Ablative tumor radiation (single dose) preceded by SLNB^^		Patients	71	60.1 ± 9.4	VAS	0.77*	Knuttel et al.(2017)[20]
		Patients	71	60.1 ± 9.4	TTO	0.85*	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	VAS	0.80*	Knuttel et al.(2017)[20]
		Public	50	56.1 ± 9.4	TTO	0.88*	Knuttel et al.(2017)[20]

^^techniques that use heat (i.e., ultrasound) with or without radiation – included here for classification purposes; *median values; BC, Breast Cancer; (w), women only; VAS, Visual Analogue Scale; TTO, Time Trade Off

c. Systemic therapy

i. Chemotherapy – drug not specified

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Before chemotherapy		Patients	52	44.7 ± 8.5	EQ-5D	0.78 ± 0.18	Conner-Spady et al. (2005)[23]
		Patients	52	44.7 ± 8.5	QOL-VAS	0.75 ± 0.04	Conner-Spady et al. (2005)[23]
		Patients	47	59.6 ± 12.2	EQ-5D	0.84 ± 0.10	Tachi et al. (2015)[86]
Chemotherapy		Public (10% with history of BC)	131	50-79	VAS	0.40 ± 0.21	Bonomi et al. (2008)[51]
	First year post-diagnosis	Patients	23	28 - 93	EQ-5D	0.86	Lidgren et al. (2007)[24]
	First year post-diagnosis	Patients	22	28 - 93	TTO	0.87	Lidgren et al. (2007)[24]
		Patients	30	45 ± 6	EQ-5D	0.92 ± 0.09	Min et al. (2014)[76]
		Public (w)	156	46.2% ≥ 50	TTO	0.48 ± 0.06	Schleinitz et al. (2006)[44]
Chemotherapy – recurrence	Loco-regional and/or contralateral recurrence	Patients	4	28 - 93	EQ-5D	0.77	Lidgren et al. (2007)[24]

	Distant/metastatic	Patients	26	68	SG	0.71 ± 0.25	Mansel et al. (2007)[47]
		Patients	38	28 - 93	EQ-5D	0.69	Lidgren et al. (2007)[24]
		Patients	35	28 - 93	TTO	0.78	Lidgren et al. (2007)[24]
After chemotherapy		Patients	47	59.6 ± 12.2	EQ-5D	0.73 ± 0.18	Tachi et al. (2015)[86]
Chemotherapy rather than HRT		Public (w)	46	46	TTO	0.46*	Milne et al. (2006)[21]
		Public (w)	50	46	EQ-5D	0.48*	Milne et al. (2006)[21]
		Public (w)	50	46	VAS	0.51*	Milne et al. (2006)[21]

Tachi et al. (2015)[86] - values are not given by type of chemotherapy regimen. 36.4% of patients were administered a regimen of epirubicin plus cyclophosphamide, 53% of participants had adjuvant chemotherapy; Mansel et al (2007)[47] - most patients were on Tamoxifen;

**indicates median (interquartile range); ABC, Advanced Breast Cancer; EBC, Early Breast Cancer; HRT, Hormone Replacement Therapy; BC, Breast Cancer; (w), women only; VAS, Visual Analogue Scale; TTO, Time Trade Off; SG, Standard Gamble; QOL-VAS, Quality of Life-Visual Analogue Scale

ii. Chemotherapy – drug specified

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
5-Fluorouracil, Doxorubicin, Cyclophosphamide (FAC)	Third cycle	Patients	48	44.7 ± 8.5	EQ-5D	0.75 ± 0.18	Conner-Spady et al. (2005)[23]
	Third cycle	Patients	48	44.7 ± 8.5	QOL-VAS	0.77 ± 0.04	Conner-Spady et al. (2005)[23]
	Last session	Patients	68	49.29 ± 11.59	15D	0.70	Bastani et al. (2012)[13]
	Last session	Patients	68	49.29 ± 11.59	EQ-5D	0.64	Bastani et al. (2012)[13]
	4 months post	Patients	68	49.29 ± 11.59	15D	0.75	Bastani et al. (2012)[13]
	4 months post	Patients	68	49.29 ± 11.59	EQ-5D	0.73	Bastani et al. (2012)[13]
Docetaxel with Doxorubicin and Cyclophosphamide (TAC)	Last session	Patients	32	46.71 ± 8.23	15D	0.66	Bastani et al. (2012)[13]
	Last session	Patients	32	46.71 ± 8.23	EQ-5D	0.55	Bastani et al. (2012)[13]
	4 months post	Patients	32	46.71 ± 8.23	15D	0.76	Bastani et al. (2012)[13]
	4 months post	Patients	32	46.71 ± 8.23	EQ-5D	0.73	Bastani et al. (2012)[13]
Standard dose chemotherapy -	During CT	Patients	149	25% < 40	SHE	0.60	Bernhard et al. (2008)[50]

Doxorubicin or Epirubicin and Cyclophosphamide followed by classical CMF	During CT	Patients	149	25% < 40	TTO	0.77	Bernhard et al. (2008)[50]
	Toxicity from adjuvant treatment	Patients	27	25% < 40	SHE	0.51	Bernhard et al. (2008)[50]
	Toxicity from adjuvant treatment	Patients	27	25% < 40	TTO	0.68	Bernhard et al. (2008)[50]
	No adverse events	Patients	140	25% < 40	SHE	0.80	Bernhard et al. (2008)[50]
	No adverse events	Patients	140	25% < 40	TTO	0.92	Bernhard et al. (2008)[50]
	Relapse	Patients	51	25% < 40	SHE	0.55	Bernhard et al. (2008)[50]
	Relapse	Patients	51	25% < 40	TTO	0.72	Bernhard et al. (2008)[50]
Dose-intensive Epirubicin Cyclophosphamide followed by dose intensive Doxorubcin and Cyclophosphamide	During CT	Patients	135	25% < 40	SHE	0.57	Bernhard et al. (2008)[50]
	During CT	Patients	135	25% < 40	TTO	0.74	Bernhard et al. (2008)[50]
	Toxicity from adjuvant treatment	Patients	69	25% < 40	SHE	0.55	Bernhard et al. (2008)[50]
	Toxicity from adjuvant treatment	Patients	69	25% < 40	TTO	0.72	Bernhard et al. (2008)[50]
	No adverse events	Patients	152	25% < 40	SHE	0.77	Bernhard et al. (2008)[50]

	No adverse events	Patients	152	25% < 40	TTO	0.90	Bernhard et al. (2008)[50]
	Relapse	Patients	34	25% < 40	SHE	0.64	Bernhard et al. (2008)[50]
	Relapse	Patients	34	25% < 40	TTO	0.80	Bernhard et al. (2008)[50]
FAC followed by MVC HDC with ASCT support	6 months	Patients	45	44.7 ± 8.5	EQ-5D	0.79 ± 0.19	Conner-Spady et al. (2005)[23]
	6 months	Patients	45	44.7 ± 8.5	QOL-VAS	0.80 ± 0.04	Conner-Spady et al. (2005)[23]
	12 months	Patients	40	44.7 ± 8.5	EQ-5D	0.84 ± 0.19	Conner-Spady et al. (2005)[23]
	12 months	Patients	40	44.7 ± 8.5	QOL-VAS	0.83 ± 0.04	Conner-Spady et al. (2005)[23]
	24 months	Patients	37	44.7 ± 8.5	EQ-5D	0.89 ± 0.13	Conner-Spady et al. (2005)[23]
	24 months	Patients	37	44.7 ± 8.5	QOL-VAS	0.89 ± 0.03	Conner-Spady et al. (2005)[23]
Paclitaxel	3 cycles	Patients	75	42.7% - 50-<60	EQ-5D	0.78	Shirowa et al. (2011) [66]
	5 cycles	HCP	24	44.9	TTO	0.36**	Dranitsaris et al. (2009)[55]
	5 cycles	Patients	28	50	TTO	0.57**	Dranitsaris et al. (2015)[81]
	Post-treatment	Patients	83	60.5*	EQ-5D	0.66 ± 0.25	Fountzilas et al. (2009)[52]
	6 months	Patients	72	60.5*	EQ-5D	0.74 ± 0.22	Fountzilas et al. (2009)[52]
	1 year (8 cycles)	Patients	75	42.7% - 50-<60	EQ-5D	0.80	Shirowa et al. (2011) [66]

Docetaxel	3 cycles	Patients	75	37.3% - 50-<60	EQ-5D	0.80	Shirowa et al. (2011) [66]
	6 cycles	HCP	24	44.9	TTO	0.44**	Dranitsaris et al. (2009)[55]
	6 cycles	Patients	28	50	TTO	0.51**	Dranitsaris et al. (2015)[81]
	1 year (8 cycles)	Patients	75	37.3% - 50-<60	EQ-5D	0.79	Shirowa et al. (2011) [66]
Nab-paclitaxel	6 cycles	HCP	24	44.9	TTO	0.51**	Dranitsaris et al. (2009)[55]
	6 cycles	Patients	28	50	TTO	0.63**	Dranitsaris 2015
Paclitaxel+ carboplatin (PCb)	Post-treatment	Patients	78	60**	EQ-5D	0.68 ± 0.22	Fountzilas et al. (2009)[52]
	6 months	Patients	74	60**	EQ-5D	0.70 ± 0.27	Fountzilas et al. (2009)[52]
Gemcitabine+ docetaxel (GDoc)	Post-treatment	Patients	73	60**	EQ-5D	0.65 ± 0.21	Fountzilas et al. (2009)[52]
	6 months	Patients	62	60**	EQ-5D	0.69 ± 0.23	Fountzilas et al. (2009)[52]
Capecitabine	Treatment response	Patients	54	52**	HUI3	0.77	Reed et al. (2009)[10]
	Stable disease	Patients	175	52**	HUI3	0.62	Reed et al. (2009)[10]
	Grade 3/4 toxicity prior to disease progression	Patients	17	51**	EQ-5D	0.59	Sherrill et al. (2008)[54]
	Time spent with grade3/4 toxicity	Patients	157	51**	EQ-5D	0.66	Sherrill et al. (2008)[54]

	Disease progression	Patients	102	52** (25-79)	HUI3	0.68	Reed et al. (2009)[10]
	Relapse	Patients	67	51**	EQ-5D	0.44	Sherrill et al. (2008)[54]
	Unknown response	Patients	46	52** (25-79)	HUI3	0.58	Reed et al. (2009)[10]
		Patients	168	51	EQ-5D	0.64 ± 0.26	Zhou et al. (2009)[56]
Ixabepilone Plus Capecitabine	Treatment response	Patients	130	53 (25-76)**	HUI3	0.67	Reed et al. (2009)[10]
	Stable disease	Patients	155	53 (25-76)**	HUI3	0.65	Reed et al. (2009)[10]
	Disease progression	Patients	58	53 (25-76)**	HUI3	0.61	Reed et al. (2009)[10]
	Unknown response	Patients	32	53 (25-76)**	HUI3	0.28	Reed et al. (2009)[10]
Lapatinib and Capecitanib	Grade 3/4 toxicity prior to disease progression	Patients	27	54 (26-80)**	EQ-5D	0.60	Sherrill et al. (2008)[54]
	Time spent with grade 3/4 toxicity	Patients	168	54 (26-80)**	EQ-5D	0.66	Sherrill et al. (2008)[54]
	Relapse	Patients	50	54 (26-80)**	EQ-5D	0.41	Sherrill et al. (2008)[54]
		Patients	163	54	EQ-5D	0.66 ± 0.24	Zhou et al. (2009)[56]

** median values; HCP, Health Care Professionals; VAS, Visual Analogue Scale; TTO, Time Trade Off; SG, Standard Gamble; QOL-VAS, Quality of Life-Visual Analogue Scale; HUI3, Health Utilities Index Mark 3; SHE, Subjective Health Estimation

iii. Endocrine therapy

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
On Hormone replacement therapy		Public (w) - ABC	46	46	TTO	0.54	Milne et al. (2006)[21]
		Public (w) - ABC	50	46	VAS	0.60	Milne et al. (2006)[21]
		Public (w) - ABC	50	46	EQ-5D (UK)	0.54	Milne et al. (2006)[21]
		Public (w) - ABC	40	46	EQ-5D(NZ)	0.65	Milne et al. (2006)[21]
		Public (w)	156	46.2% ≥ 50	TTO	0.54	Schleinitz et al. (2006)[44]
		Patients	330	65**	EQ-5D	0.86	Yagata et al. (2016) [90]
		Public (w)	131	50-79	VAS	0.52 ± 0.22	Bonomi et al. (2008)[51]
	First year after primary diagnosis	Patients	17	56	EQ-5D	0.74	Lidgren et al. (2007)[24]
		Patients	17	56	TTO	0.89	Lidgren et al. (2007)[24]
	At least 1 recurrence within 1 year of primary BC	Patients	4	59	EQ-5D	0.82	Lidgren et al. (2007)[24]
		Patients	4	59	TTO	0.86	Lidgren et al. (2007)[24]

	Second and following years after primary BC	Patients	79	58	EQ-5D	0.82	Lidgren et al. (2007)[24]
		Patients	76	58	TTO	0.93	Lidgren et al. (2007)[24]
	For distant recurrence	Patients	16	56	EQ-5D	0.65	Lidgren et al. (2007)[24]
		Patients	17	56	TTO	0.86	Lidgren et al. (2007)[24]
		Patients	23	68	SG	0.88 ± 0.11	Mansel et al. (2007)[47]
Goserelin therapy		Patients		42.6 ± 7.3	SG	0.81 ± 0.17	Cheng et al. (2012)[67]
Tamoxifen		Public (w) - BRCA+	83	67.5% - 35-60	TTO	0.95 ± 0.14	Grann et al. (2010)[60]
		Public (w)	60	43.1% - 18-34	TTO	0.90 ± 0.16	Grann et al. (2010)[60]
		Public (w)	219	43.8% - 65-74	SG	0.75 ± 0.31	Melnikow et al. (2008)[53]

BC, breast cancer; (w), women only; BRCA, BReast CAncer gene; ABC, advanced breast cancer; VAS, Visual Analogue Scale; TTO, Time Trade Off; SG, Standard Gamble; VR-6D, Veterans RAND-6D

Table 3. Health utility values for allied health and complementary medicine

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Psychological support - by oncology nurse	Baseline	Patients	55	55	EQ-5D	0.60 ± 0.24	Arving et al. (2014)[14]
	24m	Patients	55	55	EQ-5D	0.86 ± 0.16	Arving et al. (2014)[14]
Psychological support - by psychologists	Baseline	Patients	57	55	EQ-5D	0.64 ± 0.23	Arving et al. (2014)[14]
	24m	Patients	57	55	EQ-5D	0.81 ± 0.23	Arving et al. (2014)[14]
Psychological support - standard care ± referral to psychiatrist/social worker if deemed necessary	Baseline	Patients	168	55	EQ-5D	0.56 ± 0.25	Arving et al. (2014)[14]
	24m	Patients	168	55	EQ-5D	0.76 ± 023	Arving et al. (2014)[14]
Exercise program – face-to-face or phone - 16 sessions by a trained	Before	Patients	67	52 ± 8	EQ-5D	0.79	Gordon et al (2017)[92]
	6 months	Patients	67	52 ± 8	EQ-5D	0.83	Gordon et al (2017)[92]
	12 months	Patients	67	52 ± 8	EQ-5D	0.86	Gordon et al (2017)[92]

and qualified exercise physiologist							
Guided imagery	Before	Patients	64	57	EQ-5D	0.88 ± 0.12	Serra et al. (2012)[70]
	After	Patients	54	57	EQ-5D	0.86 ± 0.10	Serra et al. (2012)[70]
Mindfulness based stress reduction	Baseline	Patients	19	37-65	EQ-5D	0.74	Eyles et al. (2015)[82]
	Week 24	Patients	19	37-65	EQ-5D	0.72	Eyles et al. (2015)[82]
Usual care/maintain habitual activity		Patients	208	55 ± 10.3	SHE	0.73 ± 0.17	Gordon et al. (2005) [41]
	Baseline	Patients	78	49.4 ± 7.6	EQ-5D	0.87 ± 0.13	May et al. (2017)[94]
	First 18 weeks	Patients	78	49.4 ± 7.6	EQ-5D	0.83 ±0.12	May et al. (2017)[94]
	Last 18 weeks	Patients	78	49.4 ± 7.6	EQ-5D	0.80 ± 0.14	May et al. (2017)[94]
	Before	Patients	60	52 ± 8	EQ-5D	0.83	Gordon et al (2017)[92]
	6 months	Patients	60	52 ± 8	EQ-5D	0.81	Gordon et al (2017)[92]
	12 months	Patients	60	52 ± 8	EQ-5D	0.85	Gordon et al (2017)[92]
Water exercising - community	Baseline	Patients	29	42 - 82	EQ-5D	0.80 (0.73-1.0)**	Enblom et al. (2017)[91]
Shoulder mobility, education, tailored exercise		Patients	36	59 ± 10.7	SHE	0.77 ± 0.19	Gordon et al. (2005) [41]

program – community							
Shoulder mobility, education, psychosocial issues – breast clinics		Patients	31	54 ± 11.3	SHE	0.79 ± 0.18	Gordon et al. (2005) [41]
Aerobic and strength program – outpatient clinic	Baseline	Patients	87	50 ± 7.9	EQ-5D	0.88 ± 0.13	May et al. (2017)[94]
	First 18 weeks	Patients	87	50 ± 7.9	EQ-5D	0.83 ± 0.14	May et al. (2017)[94]
	Last 18 weeks	Patients	87	50 ± 7.9	EQ-5D	0.82 ± 0.13	May et al. (2017)[94]
Multimedia instructional package and home-based strength, balance, shoulder mobility, and cardiovascular endurance program - home	Baseline	Patients	45	55.9 ± 10.5	EQ-5D	0.81 ± 0.14	Haines et al. (2010)[61]
	3 months	Patients	36	55.9 ± 10.5	EQ-5D	0.78 ± 0.19	Haines et al. (2010)[61]
	6 months	Patients	35	55.9 ± 10.5	EQ-5D	0.80 ± 0.21	Haines et al. (2010)[61]
Multimedia instructional package and static stretching program - home	Baseline	Patients	42	54.2 ± 11.5	EQ-5D	0.85 ± 0.19	Haines et al. (2010)[61]
	3 months	Patients	37	54.2 ± 11.5	EQ-5D	0.84 ± 0.17	Haines et al. (2010)[61]
	6 months	Patients	34	54.2 ± 11.5	EQ-5D	0.83 ± 0.18	Haines et al. (2010) [61]

Others* - Not shown in figures							
Short-stay admission program	One day before surgery	Patients	127	56.1 ± 10.8	EQ-5D	0.84 ± 0.02	de Kok et al. (2010)[57]
Usual length of stay	One day before surgery	Patients	135	55.3 ± 11.6	EQ-5D	0.08 ± 0.02	de Kok et al. (2010)[57]
Follow-up after breast cancer treatment completed – usual care		Patients	74	57.2 ± 9.8	EQ-5D	0.74 ± 0.23	Kimman et al (2011)[63]
Follow-up after breast cancer treatment completed with nurse		Patients	76	55.5 ± 9.0	EQ-5D	0.73 ± 0.21	Kimman et al (2011)[63]
Follow-up as usual after breast cancer treatment completed and educational group program		Patients	75	55.3 ± 11.5	EQ-5D	0.80 ± 0.18	Kimman et al (2011)[63]
Follow-up after breast cancer treatment completed with nurse and		Patients	74	55.4 ± 9.2	EQ-5D	0.73 ± 0.23	Kimman et al (2011)[63]

educational group program							

**median values (interquartile range); SHE, Subjective Health Estimation

Table 4: Health state utility values by adverse events

Type of adverse event	Severity grade++ (when available)	Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
No side effect, no recurrence		HCP	20	33.2 ± 6	VAS	0.87	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.68	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.82 ± 0.14	Tan et al. (2014)[25]
		Patients	33	50.1 ± 8.2	SG	0.80 ± 0.22	Tan et al. (2014)[25]
Common adverse events – Tamoxifen		Patients	26	68	SG	0.97 ± 0.04	Mansel et al. (2007)[47]
Common adverse events – Anastrozole		Patients	26	68	SG	0.96 ± 0.06	Mansel et al. (2007)[47]
Fatigue		Public - Sweden	100	48% - 18-29	TTO	0.64 ± 0.30	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.56 ± 0.27	Frederix et al. (2013)[71]
	Grade 1-2	Patients	69	54 ± 10.7	SG	0.72 ± 0.21	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.72 ± 0.18	Kuchuk et al. (2013)[72]
		General public	100	40.16 ± 13.59	SG	-0.12	Lloyd et al. (2006)[43]

	Grade 0	Patients	21	59.6 ± 12.2	EQ-5D	0.78 ± 0.14	Tachi et al. (2015)[86]
	Grade 1-3	Patients	26	59.6 ± 12.2	EQ-5D	0.69 ± 0.21	Tachi et al. (2015)[86]
Anorexia		Public - Sweden	100	48% - 18-29	TTO	0.56 ± 0.30	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.66 ± 0.24	Frederix et al. (2013)[71]
	Grade 0	Patients	27	59.6 ± 12.2	EQ-5D	0.77 ± 0.16	Tachi et al. (2015)[86]
	Grade 1-3	Patients	20	59.6 ± 12.2	EQ-5D	0.68 ± 0.21	Tachi et al. (2015)[86]
Nausea	Grade 1-2	Patients	69	54 ± 10.7	SG	0.73 ± 13.0	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.62 ± 22.2	Kuchuk et al. (2013)[72]]
	Grade 0	Patients	35	59.6 ± 12.2	EQ-5D	0.72 ± 0.20	Tachi et al. (2015)[86]
	Grade 1-3	Patients	12	59.6 ± 12.2	EQ-5D	0.74 ± 0.12	Tachi et al. (2015)[86]
Diarrhea		Public - Sweden	100	48% - 18-29	TTO	0.52 ± 0.31	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.50 ± 0.25	Frederix et al. (2013)[71]
	Grade 1-2	Patients	69	54 ± 10.7	SG	0.76 ± 16.8	Kuchuk et al. (2013)[72] et al (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.68 ± 22.1	Kuchuk et al. (2013)[72]
Diarrhea and vomiting		Public	100	40.16 ± 13.59	SG	-0.10	Lloyd et al. (2006)[43]
Constipation	Grade 0	Patients	31	59.6 ± 12.2	EQ-5D	0.76 ± 0.14	Tachi et al. (2015)[86]

	Grade 1-3	Patients	16	59.6 ± 12.2	EQ-5D	0.67 ± 0.24	Tachi et al. (2015)[86]
Oral pain	Grade 0	Patients	42	59.6 ± 12.2	EQ-5D	0.74 ± 0.19	Tachi et al. (2015)[86]
	Grade 1-3	Patients	5	59.6 ± 12.2	EQ-5D	0.66 ± 0.15	Tachi et al. (2015)[86]
Altered taste	Grade 0	Patients	39	59.6 ± 12.2	EQ-5D	0.72 ± 0.19	Tachi et al. (2015)[86]
	Grade 1-3	Patients	8	59.6 ± 12.2	EQ-5D	0.77 ± 0.12	Tachi et al. (2015)[86]
Alopecia		Patients	69	54 ± 10.7	SG	0.72 ± 22.5	Kuchuk et al. (2013)[72]
		Public	100	40.16 ± 13.59	SG	-0.11	Lloyd et al. (2006)[43]
	Grade 0	Patients	16	59.6 ± 12.2	EQ-5D	0.76 ± 0.18	Tachi et al. (2015)[86]
	Grade 1-3	Patients	31	59.6 ± 12.2	EQ-5D	0.71 ± 0.19	Tachi et al. (2015)[86]
Lymphedema		Patients	128	16-89	EQ-5D	0.08 ± 0.02	Cheville (2010)[22]
Anemia		Public - Sweden	100	48% - 18-29	TTO	0.69 ± 0.29	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.59 ± 0.26	Frederix et al. (2013)[71]
	Grade 0	Patients	29	59.6 ± 12.2	EQ-5D	0.74 ± 0.16	Tachi et al. (2015)[86]
	Grade 1-3	Patients	18	59.6 ± 12.2	EQ-5D	0.70 ± 0.22	Tachi et al. (2015)[86]
Febrile neutropenia		Public	100	40.16 ± 13.59	SG	-0.15	Lloyd et al. (2006)[43]
	Grade 0	Patients	40	59.6 ± 12.2	EQ-5D	0.74 ± 0.19	Tachi et al. (2015)[86]

	Grade 1-3	Patients	7	59.6 ± 12.2	EQ-5D	0.69 ± 0.21	Tachi et al. (2015)[86]
Reduced WBC count	Grade 0	Patients	37	59.6 ± 12.2	EQ-5D	0.71 ± 0.19	Tachi et al. (2015)[86]
	Grade 1-3	Patients	10	59.6 ± 12.2	EQ-5D	0.81 ± 0.14	Tachi et al. (2015)[86]
		Public - Sweden	100	48% - 18-29	TTO	0.58 ± 0.31	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.60 ± 0.26	Frederix et al. (2013)[71]
Skin rash		Public - Sweden	100	48% - 18-29	TTO	0.58 ± 0.31	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.54 ± 0.27	Frederix et al. (2013)[71]
Nail ridging	Grade 0	Patients	42	59.6 ± 12.2	EQ-5D	0.73 ± 0.19	Tachi et al. (2015)[86]
	Grade 1-3	Patients	5	59.6 ± 12.2	EQ-5D	0.68 ± 0.15	Tachi et al. (2015)[86]
Dry skin	Grade 0	Patients	40	59.6 ± 12.2	EQ-5D	0.74 ± 0.18	Tachi et al. (2015)[86]
	Grade 1-3	Patients	7	59.6 ± 12.2	EQ-5D	0.64 ± 0.16	Tachi et al. (2015)[86]
Decrease in left ventricular ejection fraction		Public - Sweden	100	48% - 18-29	TTO	0.54 ± 0.29	Frederix et al. (2013)[71]
		Public - Netherlands	100	51% - 50-59	TTO	0.95 ± 0.25	Frederix et al. (2013)[71]
Hand-foot syndrome	Grade 1-2	Patients	69	54 ± 10.7	SG	0.75 ± 16.7	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.70 ± 18.9	Kuchuk et al. (2013)[72]

		Public	100	40.16 ± 13.59	SG	-0.12	Lloyd et al. (2006)[43]
Mucositis	Grade 0	Patients	35	59.6 ± 12.2	EQ-5D	0.74 ± 0.19	Tachi et al. (2015)[86]
	Grade 1-3	Patients	12	59.6 ± 12.2	EQ-5D	0.68 ± 0.17	Tachi et al. (2015)[86]
Stomatitis		Public (w)	100	40.16 ± 13.59	SG	-0.15	Lloyd et al. (2006)[43]
Mucositis/stomatitis	Grade 1-2	Patients	69	54 ± 10.7	SG	0.75 ± 17.9	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.74 ± 17.9	Kuchuk et al. (2013)[72]
Sensory neuropathy	Grade 1-2	Patients	69	54 ± 10.7	SG	0.73 ± 18.9	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.69 ± 19.1	Kuchuk et al. (2013)[72]
	Grade 0	Patients	38	59.6 ± 12.2	EQ-5D	0.74 ± 0.18	Tachi et al. (2015)[86]
	Grade 1-3	Patients	9	59.6 ± 12.2	EQ-5D	0.67 ± 0.18	Tachi et al. (2015)[86]
Motor neuropathy	Grade 1-2	Patients	69	54 ± 10.7	SG	0.72 ± 14.5	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.73 ± 15.1	Kuchuk et al. (2013)[72]
Deep vein thromboembolism		Patients - Tamoxifen	26	68	SG	0.92 ± 0.11	Mansel et al. (2007)[47]
		Public (w) - no history of BC	32	43.8% - 65-74	SG	0.66 ± 0.42	Melnikow et al. (2008)[53]
		HCP	20	33.2 ± 6	VAS	0.58	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.52	Shih et al. (2012)[28]

		Patients	31	50.1 ± 8.2	VAS	0.45 ± 0.20	Tan et al. (2014)[25]
		Patients	29	50.1 ± 8.2	SG	0.56 ± 0.25	Tan et al. (2014)[25]
Pulmonary embolism		Patients - Tamoxifen	26	68	SG	0.89 ± 0.17	Mansel et al. (2007)[47]
		Public (w) - no history of BC	30	43.8% - 65-74	SG	0.50 ± 0.39	Melnikow et al. (2008)[53]
		HCP	20	33.2 ± 6	VAS	0.37	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.46	Shih et al. (2012)[28]
		Patients	31	50.1 ± 8.2	VAS	0.26 ± 0.27	Tan et al. (2014)[25]
		Patients	29	50.1 ± 8.2	SG	0.40 ± 0.40	Tan et al. (2014)[25]
Myalgia	Grade 1-2	Patients	69	54 ± 10.7	SG	0.72 ± 14.5	Kuchuk et al. (2013)[72]
	Grade 3-4	Patients	69	54 ± 10.7	SG	0.70 ± 13.8	Kuchuk et al. (2013)[72]
Musculoskeletal disorder		HCP	20	33.2 ± 6	VAS	0.65	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.51	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.41 ± 0.34	Tan et al. (2014)[25]
		Patients	34	50.1 ± 8.2	SG	0.45 ± 0.38	Tan et al. (2014)[25]
Osteoporotic fracture		Public (w) - no history of BC	33	43.8% - 65-74	SG	0.78 ± 0.28	Melnikow et al. (2008)[53]
Wrist fracture		Patients - Tamoxifen	26	68	SG	0.92 ± 0.10	Mansel et al. (2007)[47]

		HCP	20	33.2 ± 6	VAS	0.51	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.53	Shih et al. (2012)[28]
		Patients	36	50.1 ± 8.2	VAS	0.44 ± 0.23	Tan et al. (2014)[25]
		Patients	33	50.1 ± 8.2	SG	0.53 ± 0.18	Tan et al. (2014)[25]
Spinal fracture		Patients - Tamoxifen	26	68	SG	0.89 ± 0.19	Mansel et al. (2007)[47]
		HCP	20	33.2 ± 6	VAS	0.41	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.46	Shih et al. (2012)[28]
		Patients	40	50.1 ± 8.2	VAS	0.26 ± 0.51	Tan et al. (2014)[25]
		Patients	37	50.1 ± 8.2	SG	0.32 ± 0.29	Tan et al. (2014)[25]
Hip fracture		Patients - Tamoxifen	26	68	SG	0.86 ± 0.20	Mansel et al. (2007)[47]
		HCP	20	33.2 ± 6	VAS	0.51	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.50	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.33 ± 0.23	Tan et al. (2014)[25]
		Patients	34	50.1 ± 8.2	SG	0.43 ± 0.36	Tan et al. (2014)[25]
Cataracts		Public (w) - no history of BC	31	43.8% - 65-75	SG	0.77 ± 0.31	Melnikow et al. (2008)[53]
		HCP	20	33.2 ± 6	VAS	0.55	Shih et al. (2012)[28]

		HCP	20	33.2 ± 6	SG	0.52	Shih et al. (2012)[28]
		Patients	31	50.1 ± 8.2	VAS	0.37 ± 0.39	Tan et al. (2014)[25]
		Patients	28	50.1 ± 8.2	SG	0.43 ± 0.32	Tan et al. (2014)[25]
Hot flushes		HCP	20	33.2 ± 6	VAS	0.75	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.59	Shih et al. (2012)[28]
		Patients	36	50.1 ± 8.2	VAS	0.60 ± 0.19	Tan et al. (2014)[25]
		Patients	33	50.1 ± 8.2	SG	0.63 ± 0.21	Tan et al. (2014)[25]
Vaginal bleeding		Patients - Tamoxifen	26	68	SG	0.93 ± 0.10	Mansel et al. (2007)[47]
		HCP	20	33.2 ± 6	VAS	0.73	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.55	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.58 ± 0.23	Tan et al. (2014)[25]
		Patients	33	50.1 ± 8.2	SG	0.65 ± 0.25	Tan et al. (2014)[25]
Hysterectomy		Patients - Tamoxifen	26	68	SG	0.90 ± 0.10	Mansel et al. (2007)[47]
Severe bone pain requiring radiotherapy		Public (w) - no history of BC	50	46	VAS	0.25	Milne et al. (2006)[21]
		Public (w) - no history of BC	50	46	EQ-5D (UK)	0.31	Milne et al. (2006)[21]
		Public (w) - no history of BC	45	46	EQ-5D (NZ)	0.45	Milne et al. (2006)[21]

		Public (w) - no history of BC	46	46	TTO	0.35	Milne et al. (2006)[21]
Moderate to severe hypercalcaemia		Public (w) - no history of BC	50	46	VAS	-0.52	Milne et al. (2006)[21]
		Public (w) - no history of BC	50	46	EQ-5D (UK)	-0.05	Milne et al. (2006)[21]
		Public (w) - no history of BC	50	46	EQ-5D (NZ)	-0.17	Milne et al. (2006)[21]
		Public (w) - no history of BC	46	46	TTO	0.13	Milne et al. (2006)[21]
Ischemic cerebrovascular events		HCP	20	33.2 ± 6	VAS	0.30	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.41	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.25 ± 0.30	Tan et al. (2014)[25]
		Patients	34	50.1 ± 8.2	SG	0.35 ± 0.26	Tan et al. (2014)[25]
Endometrial cancer		Patients - Tamoxifen	26	68	SG	0.91 ± 0.10	Mansel et al. (2007)[47]
		Public(w) - no history of BC	20	43.8% - 65-74	SG	0.59 ± 0.39	Melnikow et al. (2008) [53]
		HCP	20	33.2 ± 6	VAS	0.51	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.50	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.40 ± 0.22	Tan et al. (2014)[25]
		Patients	34	50.1 ± 8.2	SG	0.43 ± 0.40	Tan et al. (2014)[25]
New contralateral breast cancer		Patients - Tamoxifen	26	68	SG	0.91 ± 0.10	Mansel et al. (2007)[47]

		HCP	20	33.2 ± 6	VAS	0.50	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.44	Shih et al. (2012)[28]
		Patients	35	50.1 ± 8.2	VAS	0.46 ± 0.25	Tan et al. (2014)[25]
		Patients	34	50.1 ± 8.2	SG	0.45 ± 0.32	Tan et al. (2014)[25]
Local/regional recurrence with no adverse events		Patients - Tamoxifen	26	68	SG	0.91 ± 0.10	Mansel et al. (2007)[47]
		HCP	20	33.2 ± 6	VAS	0.56	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.47	Shih et al. (2012)[28]
		Patients	37	50.1 ± 8.2	VAS	0.34 ± 0.21	Tan et al. (2014)[25]
		Patients	35	50.1 ± 8.2	SG	0.46 ± 0.30	Tan et al. (2014)[25]
Local/regional recurrence with adverse events		HCP	20	33.2 ± 6	VAS	0.51	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.44	Shih et al. (2012)[28]
Distant recurrence with no adverse effects		HCP	20	33.2 ± 6	VAS	0.44	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.47	Shih et al. (2012)[28]
		Patients	32	50.1 ± 8.2	VAS	0.34 ± 0.19	Tan et al. (2014)[25]
		Patients	31	50.1 ± 8.2	SG	0.42 ± 0.28	Tan et al. (2014)[25]
Distant recurrence with adverse		Patients	38	50.1 ± 8.2	VAS	0.30 ± 0.30	Tan et al. (2014)[25]

effects ± chemotherapy		Patients	34	50.1 ± 8.2	SG	0.31 ± 0.40	Tan et al. (2014)[25]
		HCP	20	33.2 ± 6	VAS	0.40	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.46	Shih et al. (2012)[28]
Distant recurrence with adverse effects ± hormonal therapy		Patients	31	50.1 ± 8.2	VAS	0.30 ± 0.24	Tan et al. (2014)[25]
		Patients	29	50.1 ± 8.2	SG	0.33 ± 0.28	Tan et al. (2014)[25]
		HCP	20	33.2 ± 6	VAS	0.41	Shih et al. (2012)[28]
		HCP	20	33.2 ± 6	SG	0.45	Shih et al. (2012)[28]

++For definition of the severity grade, please refer to the published article; BC, Breast Cancer; HCP, Health Care Provider; VAS, Visual Analogue Scale; SG, Standard Gamble; TTO, Time Trade Off

Table 5: Health utility values by the stage of breast cancer

a. Early breast cancer

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Diagnosis ≤ 6m		Patients	297	56 ± 10.7	EQ-5D	0.76	Hall et al. (2015)[83]
Diagnosis <12m		Patients	297	57 ± 10.7	EQ-5D	0.78	Hall et al. (2015)[83]
Diagnosis >15m		Patients	297	57 ± 10.7	EQ-5D	0.79	Hall et al. (2015)[83]
Disease free	no adverse events	Patients	26	68	SG	0.99 ± 0.01	Mansel et al. (2007)[47]
	first year	Patients	2684	-	EQ-5D	0.73	Seferina et al. (2017)[95]
	> first year	Patients	2684	-	EQ-5D	0.81	Seferina et al. (2017)[95]
Remission/Pre-relapse		Patients	929	49**	EQ-5D	0.79	Wolowacz et al. (2008)[12]
Local recurrence	first year	Patients	2684	-	EQ-5D	0.73	Seferina et al. (2017)[95]
	> first year	Patients	2684	-	EQ-5D	0.71	Seferina et al. (2017)[95]
Distant metastasis	first year	Patients	2684	-	EQ-5D	0.58	Seferina et al. (2017)[95]

	> first year	Patients	2684	-	EQ-5D	0.60	Seferina et al. (2017)[95]

**median values; SG, Standard Gamble

b. Advanced/Metastatic breast cancer

Health state		Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Advanced/Metastatic breast cancer		Patients	27	66 ± 10.4	15D	0.72 ± 0.14	Farkkila et al. (2014)[9]
		Patients	27	66 ± 10.4	EQ-5D	0.45 ± 0.37	Farkkila et al. (2014)[9]
	Sweden	Public	100	18-29 - 48%	TTO	0.81 ± 0.23	Frederix et al. (2013)[71]
	The Netherlands	Public	100	50-59 - 51%	TTO	0.69 ± 0.25	Frederix et al. (2013)[71]
	Stage 4	Public	509	45.7 ± 14.10	VAS	0.17 ± 0.22	Kim et al. (2017)[93]
	Stage 4	Public	509	45.7 ± 14.10	SG	0.35 ± 0.28	Kim et al. (2017)[93]
	Stage 3C	Public	509	45.7 ± 14.10	VAS	0.42 ± 0.17	Kim et al. (2017)[93]
	Stage 3C	Public	509	45.7 ± 14.10	SG	0.59 ± 0.26	Kim et al. (2017)[93]
		Public	100	40.16 ± 13.59	SG	0.72	Lloyd et al. (2006)[43]
		Patients	67	56	TTO	0.82	Lidgren et al. (2007)[24]
		Patients	65	56	EQ-5D	0.69	Lidgren et al. (2007)[24]

		Patients	188	49.8 ± 9.89	EQ-5D	0.54 - 0.62	Oh et al. (2012)[68]
		Patients	58	62 (36-85)**	EQ-5D	0.66	van Kampen (2017)[97]
		Patients	24	46.7± 9.97	SF-6D	0.59 ± 0.13	Yousefi et al. (2016)[29]
		Patients	24	46.7 ± 9.97	EQ-5D	0.55 ± 0.23	Yousefi et al. (2016)[29]
On treatment		Patients	52	54 ± 11.20	EQ-5D	0.75 ± 0.17	Pickard et al. (2016)[87]
		Patients	15	56.9 ± 14	EQ-5D	0.69 ± 0.26	Wallwiener et al. (2017)[18]
Responding to treatment		Public	100	40.16 ± 13.59	SG	0.08	Lloyd et al. (2006)[43]
Progressive disease		Public - Sweden	100	18-29 - 48%	TTO	0.61 ± 0.34	Frederix et al. (2013)[71]
		Public - Netherlands	100	50-59 - 51%	TTO	0.49 ± 0.31	Frederix et al. (2013)[71]
		Public	100	40.16 ± 13.59	SG	-0.27	Lloyd et al. (2006)[43]
	Local recurrence	Public (w)	110	26 – 60	SG	0.61	Songtish et al.(2014) [78]
	Local recurrence with lymphedema	Public (w)	110	26 – 60	SG	0.39	Songtish et al.(2014) [78]
	Regional recurrence	Public (w)	110	26 – 60	SG	0.60	Songtish et al.(2014) [78]
	Regional recurrence with lymphedema	Public (w)	110	26 – 60	SG	0.45	Songtish et al.(2014) [78]

		Patients	38	62 (36-85)**	EQ-5D	0.55	van Kampen et al. (2017)[97]
Last year of life		Patients	150	65+ - 49.2%	HALex	0.64	Yabroff et al. (2007)[49]

**median values; SG, Standard Gamble; TTO, Time Trade Off; VAS, Visual Analogue Scale; HALex, Health Activity Limitations Index

c. Non-specific breast cancer

Health state	Respondents	Sample size	Age in years (mean, mean ± standard deviation is provided when available)	Health utility estimation method	Health Utility value (mean, mean ± standard deviation when available	Study
Breast cancer	Public (w)	259	18-44	EQ-5D (US)	0.89	Brown et al (2016)[15]
	Public (w)	7174	≥ 45	EQ-5D (US)	0.82	Brown et al (2016)[15]
	Patients	41	51.6	AQOL-4D	0.59	Garvey et al. (2016)[11]
	Public (w) - BRCA+	83	67.5% between 35-60	TTO	0.87 ± 0.20	Grann et al. (2010)[60]
	Public (w)	160	43.1% 18-34	TTO	0.84 ± 0.18	Grann et al. (2010)[60]
	Patients	2445	51.8	EQ-5D	0.68 ± 0.18	Kimman et al. (2015)[84]
	Patients	608	48 ± 9.6	EQ-5D	0.84 ± 0.15	Liu et al. (2017)[19]
	Patients	608	48 ± 9.6	EQ-5D (China)	0.83 ± 0.18	Liu et al. (2017)[19]
	Patients	608	48 ± 9.6	EQ-5D (Korea)	0.83 ± 0.14	Liu et al. (2017)[19]
	Patients	608	48 ± 9.6	EQ-5D (Japan)	0.80 ± 0.16	Liu et al. (2017)[19]
	Public (w)	45	43.1% - 18-34	SG	0.57 ± 0.38	Melnikow et al. (2008)[s][53]

	Patients	287	59	EQ-5D	0.76 ± 0.24	Naik et al. (2017)[30]
	Patients	287	59	EQ-5D (CAN)	0.80 ± 0.17	Naik et al. (2017)[30]
	Patients	287	59	EQ-5D (US)	0.82 ± 0.17	Naik et al. (2017)[30]
	Patients	59	51	SF-6D	0.81 ± 0.12	Shih et al. (2006)[45]
	Patients	201	64	EQ-5D	0.80	Sullivan et al. (2006)[46]
	Patients	385	64.2	EQ-5D	0.75	Sullivan et al. (2011)[65]
	Patients	7426	85% ≥45	EQ-5D	0.79 ± 0.18	Trogdon et al. (2016)[16]
Initial diagnosis	Patients	14	-	VAS	0.56	Lux et al. (2010)[62]
	Patients	389	49.2% ≥ 65	HALex	0.78	Yabroff et al. (2007)[49]
Disease free at 1 year/Unremarkable in follow-up	Public	131	65% < 64	VAS	0.77 ± 0.13	Bonomi et al. (2008)[51]
	Patients	42	-	VAS	0.72	Lux et al. (2010)[62]
First year after primary breast cancer	Patients	1654	52	EQ-5D	0.76 ± 0.21	The ACTION Study Group (2017)[96]
	Patients	72	56	TTO	0.90	Lidgren et al. (2007)[24]
	Patients	72	56	EQ-5D	0.70	Lidgren et al. (2007)[24]
	Patients	104	59	EQ-5D	0.80	Naik et al. (2017)[30]
	Patients	48	46.7 ± 9.97	EQ-5D	0.67 ± 0.20	Yousefi et al. (2016)[29]

	Patients	48	46.7 ± 9.97	SF-6D	0.64 ± 0.13	Yousefi et al. (2016)[29]
First year after recurrence	Patients	21	59	EQ-5D	0.78	Lidgren et al. (2007)[24]
	Patients	21	59	TTO	0.84	Lidgren et al. (2007)[24]
	Patients	15	46.7 ± 9.97	EQ-5D	0.72 ± 0.14	Yousefi et al. (2016)[29]
	Patients	15	46.7 ± 9.97	SF-6D	0.68 ± 0.06	Yousefi et al. (2016)[29]
Second and following years post primary breast cancer or recurrence	Public	131	50-79	VAS	0.33 ± 0.19	Bonomi et al. (2008)[51]
	Patients	185	58	TTO	0.89	Lidgren et al. (2007)[24]
	Patients	177	58	EQ-5D	0.78	Lidgren et al. (2007)[24]
	Patients	179	59	EQ-5D	0.81	Naik et al. (2017)[30]
	Patients	71	46.7 ± 9.97	EQ-5D	0.73 ± 0.22	Yousefi et al. (2016)[29]
	Patients	71	46.7 ± 9.97	SF-6D	0.68 ± 0.13	Yousefi et al. (2016)[29]
Recurrence	Patients	17	-	VAS	0.54	Lux et al. (2010)[62]
Survivors	Patients	150	52.8 ± 11.1	EQ-5D	0.71 ± 0.25	Matalqah et al. (2011)[64]
In remission, <2 years	Patients	66	14.1% ≥ 80	SF-6D	-0.05	Wang et al. (2016)[89]
In remission, 2-4 years	Patients	129	14.1% ≥ 80	SF-6D	-0.03	Wang et al. (2016)[89]
In remission, 5-9 years	Patients	190	14.1% ≥ 80	SF-6D	-0.002	Wang et al. (2016)[89]

In remission, ≥10 years	Patients	315	14.1% ≥ 80	SF-6D	0.006	Wang et al. (2016)[89]
Not in remission	Patients	48	14.1% ≥ 80	SF-6D	0.06	Wang et al. (2016)[89]
Continuing care	Patients	381	49.2% ≥ 65	HALex	0.81	Yabroff et al. (2007)[49]
Loco-regional recurrent	Public	509	45.7 ± 14.1	SG	0.50 ± 0.26	Kim et al. (2017)[93]
	Public	509	45.7 ± 14.1	VAS	0.33 ± 0.18	Kim et al. (2017)[93]
Contralateral breast cancer	Patients	4	-	VAS	0.55	Lux et al. (2010)[62]
Palliation/end of life	Public	131	50-79	VAS	0.36 ± 0.27	Bonomi et al. (2008)[51]

**median values; SG, Standard Gamble; TTO, Time Trade Off; VAS, Visual Analogue Scale; HALex, Health Activity Limitations Index; SF-6D, Short-form-6D; AQOL-4D, Australian Quality of Life-4D; CAN, Canada; US, United States

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CHAPTER 3

International Phase 1 Study Protocol to Develop a Health State Classification System for a Preference-Based Measure for Women with Breast Cancer: The BREAST-Q Utility Module

Title: International Phase 1 Study Protocol to Develop a Health State Classification System for a Preference-Based Measure for Women with Breast Cancer: The BREAST-Q Utility Module

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Keywords: health utility, preference-based measure, breast cancer, qualitative, protocol, patient-reported outcomes, health state value

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ABSTRACT

Introduction: Concerns unique to women with breast cancer can include impact of cancer on body image, sexual wellbeing, and changes in breast appearance and sensation. These important issues are not captured by existing generic preference-based measures (PBM), and no breast cancer-specific PBM currently exists. This Phase 1 protocol describes a mixed methods study to develop and validate the descriptive health state classification system (HSCS) for a breast cancer-specific PBM, called the BREAST-Q Utility module.

Methods and analysis: A heterogeneous sample of women aged 18 years and older diagnosed with breast cancer who are undergoing or have had treatment for breast cancer will be invited to participate in qualitative interviews. Participants will be asked to describe impact of their diagnosis and treatment(s) on their health-related quality of life (HRQOL). Interviews will be audio-recorded, transcribed verbatim, and coded using a line-by-line approach. At the end of each interview, based on each participant's cancer treatment history, patients will complete the mastectomy, breast-conserving therapy, or reconstruction module of BREAST-Q, with modified 5-point Likert scale to measure importance of the BREAST-Q concepts. Both sources of data will be analyzed to identify the most important HRQOL concerns.

A conceptual framework and item pool will be developed from the qualitative dataset. Preliminary version of the BREAST-Q Utility module will be created and refined at an in-person meeting of multidisciplinary experts. Content validity of the Utility Module

will be examined (cognitive debriefing, expert feedback). Psychometric properties of Utility module will be evaluated in a large sample of women with breast cancer.

Ethics and dissemination: The study has been approved by Hamilton Integrated Research Ethics Board, Canada. Results of this study will be presented at international conferences and published in peer-reviewed journals.

ARTICLE SUMMARY

Strengths and limitations of this study

- The BREAST-Q Utility module will be the first, rigorously developed, and validated breast cancer-specific preference-based measure.
- Phase 1 involves input from a large, international sample of women with breast cancer and multidisciplinary experts, which will ensure that the utility module measures concerns important and relevant to women with breast cancer across stage (Stage 0-4) and treatment (surgical and non-surgical).
- The BREAST-Q Utility module will facilitate clinical and cost-effectiveness studies of breast cancer interventions and programs.

BACKGROUND

Annual spending on cancer care in the United States has exceeded $125 billion and is expected to increase exponentially.(1) Breast cancer was responsible for the largest share of cancer-related spending (13%) in 2010.(1) Past data demonstrate that the rate of growth in spending for breast cancer has exceeded that observed for lung, colorectal, or prostate cancer.(2, 3) Breast cancer is the most commonly diagnosed malignancy in women worldwide and the leading cause of cancer-related deaths among women.(4) The survival rate for breast cancer varies by stage of breast cancer and treatments received. Non-invasive (stage 0) and early-stage invasive breast cancer (stages I and II) have higher survival rates than later stage cancers (stages III and IV). (5) For early-stage breast cancer, the median survival can be many years, if not decades. As survival increases, healthcare resource consumption and costs associated with breast cancer can accrue years after diagnosis.

Cost-effectiveness analyses (CEA) are used to identify the optimal allocation of healthcare resources and set funding priorities.(6-9) In CEA, the costs and outcomes of a new intervention (e.g., diagnostic or interventional, surgical or non-surgical) are compared with the costs and outcomes of an alternate, usually standard, intervention for the same health condition.(6, 8) The incremental outcome of the new health intervention in CEA is described in terms of gains in quantity (i.e., life expectancy) or quality of life.(10) The measure that combines these attributes (i.e., quality and quantity of life) into a single index is called quality-adjusted life-year (QALY). A QALY is the most commonly used metric in CEA and is defined as the value of living one year in full or perfect health.(9, 10) Several

approaches exist for estimating the "Q" (i.e., health-related quality of life (HRQOL)) in the QALY, namely, rating scales, time trade-off, standard gamble, or generic preference-based measures (PBMs), such as the EQ-5D, Short Form-6D (SF-6D), or Health Utilities Index Mark 3 (HUI3). The use of generic PBMs is recommended by health agencies in Australia (Pharmaceutical Benefits Advisory Committee) (11), Canada (Canadian Agency for Drugs and Technologies in Health) (12), United Kingdom for England and Wales (National Institute for Health and Clinical Excellence) (13), Scotland (Scottish Medicines Consortium) (14), and other countries in Asia, Africa, Europe, and Latin America.(15) Generic PBMs are intended to be applicable to all interventions and patient groups allowing for intra- and inter-population comparisons. However, for conditions such as breast cancer, most existing generic PBMs fail to capture the unique concerns of patients, such as body image and sexual wellbeing.

A systematic review of studies of breast cancer interventions published between 2005 and 2017 identified no breast cancer-specific PBM (Kaur M et al. (2019). Health State Utility Values in Breast Cancer: A Systematic Review of Literature). Our program of research addresses this gap by developing a condition-specific PBM for breast cancer. The development of this PBM will occur in two consecutive phases: (1) Phase 1 - development and validation of a breast cancer-specific health state classification system (HSCS); and (2) Phase 2 – valuation survey and modeling to produce values for health states described by the HSCS. An overview of the components of each phase is shown in **Figure 1**. This protocol describes the Phase 1 mixed-methods study to develop and validate the HSCS for

the breast cancer-specific PBM. This breast cancer-specific PBM will form a new module of the BREAST-Q (hereby referred to as the BREAST-Q Utility module).

METHODS AND ANALYSIS

The first phase of developing a PBM instrument is to develop a descriptive HSCS (also called "measurement system" or "descriptive system"). A HSCS consists of several dimensions (or attributes), where each dimension refers to an aspect of health-related quality of life (HRQOL) (e.g., appearance, physical symptoms, social function).(16) In a PBM, the number of dimensions is typically limited to 7 ± 2, with each dimension usually measured by one item. The limited number of dimensions in a PBM makes it amenable to valuation using methods such as standard gamble, time-trade off, or discrete choice experiments.(16) The valuation exercise (Phase 2) is used to develop the preference weights that are needed for generating health utilities.

There are two main approaches to developing a HSCS: (1) the top-down approach, where existing literature, instruments, and surveys are used to generate an item pool which is then reduced by classical test theory or item response theory; and (2) bottom-up approach, where qualitative methods are used to identify dimensions based on patient input. The bottom-up approach will be used in this study. This approach is endorsed by the USA Food and Drug Administration in the development of patient-reported outcome measures (PROMs) as patient perspective is considered to be of paramount importance.(17)

An interpretive descriptive qualitative study will be conducted. Interpretive description is an inductive, analytic approach that assumes prior clinical knowledge of a health event or phenomenon being studied.(18) This approach allows for an in-depth and systematic description of a health event or phenomenon to be explored in the context of clinical knowledge and expertise to inform and guide future practice and research.(18, 19)

Establishing the construct being measured

We will start with the conceptual framework of patient satisfaction and HRQOL in breast surgery that informed the development of the BREAST-Q.(20) The BREAST-Q is a PROM comprised of independently functioning scales that measure outcomes and patient's experience of care (i.e., satisfaction with the surgeon, information, and medical team).(20) The BREAST-Q has become the gold standard measure of HRQOL for breast surgery and has three breast cancer surgery modules – mastectomy, breast-conserving therapy, and reconstruction. The BREAST-Q conceptual framework, shown in **Figure 2**, consists of two overarching domains: HRQOL and satisfaction with outcome. The HRQOL domain consists of three subdomains: physical, psychosocial, and sexual well-being. The satisfaction with outcome domain also consists of three subdomains: satisfaction with breasts, satisfaction with overall outcome, and satisfaction with care. This framework was developed from patient interviews (n= 48) and refined from patient input obtained in focus groups (n= 58), cognitive debriefing interviews (n= 30), and from expert feedback (n=17). As such, the BREAST-Q is grounded in the patient's voice and experiences.

Health technology assessments and health policy decisions are focused on the health benefit gained from an intervention. Therefore, for a PBM to be used in QALY calculations and subsequently in CEAs, it should be able to describe and assess the health or HRQOL gain from an intervention(s). Hence, the BREAST-Q Utility module will be designed to measure the impact of breast cancer or its intervention(s) on the HRQOL of women with a diagnosis of breast cancer.

Generating an item pool

Participants, setting, and recruitment

A heterogeneous sample of women with a diagnosis of breast cancer aged 18 years or older will be recruited from two breast cancer centers in Ontario, Canada (Juranvinski Cancer Center, Hamilton; and Toronto General Hospital (TGH), Toronto) and one in the USA (Memorial Sloan Kettering Cancer Center(MSK), New York). Women undergoing diagnostic or prophylactic interventions for breast cancer, or women unable to participate due to language barriers, cognitive, or neurological deficit will be excluded from this study.

Potential study participants will be approached to participate in the study at the hospital during their clinical visit or via telephone call by a member of the clinical team within their circle of care. Patients will be provided with the study information sheet (in-person or e-mail). After the patient has had time to review the information sheet and ask study-specific questions, their contact information will be shared with a member of the research team. Potential participants will be contacted to describe the study further and to

set up a time and preferred place for the interview. Participants will be asked to sign a consent form and provide verbal consent at the start of the interview.

Sampling

We will aim to recruit a maximum variation sample (21) of women who vary by age, pathological stage of breast cancer (Stage 0-4), and type and stage of surgical (i.e., mastectomy, breast-conserving therapy, or reconstruction) or non-surgical (i.e., adjuvant or neoadjuvant therapy) breast cancer treatment. Recruitment will continue until the investigators determine that sufficient data to understand the experiences of women diagnosed with breast cancer has been obtained. According to Thorne, in interpretive description, data saturation is not the desired outcome and can be "problematic." (18) This is because theoretically the experiences of patients can represent an infinite number of variations.(18) Hence, the focus in interpretive description is on obtaining a deeper understanding of the patient's perspective while acknowledging that outliers may exist. For this study, we established a stopping criterion for data saturation as the point at which redundancy is achieved in the domains at the level of minor themes (i.e., no new information is obtained). This approach is in line with the PROM development methodology.

Data collection

The BREAST-Q conceptual framework (20) will be used to develop the interview guide. (**Table 1**). Semi-structured interviews (22) will be conducted in-person either at participants' homes, at the hospital in a private space, or over the telephone. During the

interview, we will explore the HRQOL issues most important and relevant to the participant's experience of breast cancer. Probes will be used to elicit detailed information where appropriate (e.g., appearance, body image, sexual wellbeing). New concepts that arise will be added to the guide as the interview progress. The choice of location of the interview will depend on a patient's preference and study logistics. This will ensure that the inclusion in the study is not limited due to accessibility.

The semi-structured interviews will be conducted by two experienced qualitative interviewers across the three sites. Each interview will be audio-recorded and transcribed verbatim by a professional transcriptionist and identifying information will be removed. At the end of the interview, participants will be asked to describe five most important HRQOL concerns. The interviews are anticipated to last 60 to 90 minutes.

After the semi-structured interview, participants will complete the most appropriate BREAST-Q module based on their surgical treatment, where the response options for the BREAST-Q scales will be replaced with a 5-point Likert scale to measure the importance of the items to the participant's experience of breast cancer (not important, slightly important, moderately important, important, and very important). As the goal of our study is to develop a PBM, the BREAST-Q experience of care scales will not be completed. Participants will also be asked to nominate any items (i.e., concepts) important to them that are missing from the BREAST-Q. Finally, non-identifying demographics (age, body mass index, racial or ethnic group, education level, annual income) and clinical (stage of breast cancer, type of treatments received/planned) information will be collected.

Analysis

We will use a combination of inductive (new codes developed from the data) and deductive (application of existing codes from the BREAST-Q conceptual framework) (23) to code the data. Each interview will be coded within Microsoft word using a line-by-line coding approach. (24, 25) The participant quote alongside the codes will be transferred to a Microsoft Excel spreadsheet. We will also include specific participant (e.g., age, country), clinical, and treatment characteristics in the Microsoft Excel spreadsheet. Constant comparison of codes will be used to refine and finalize the codes, i.e., codes that have common elements will be merged to form minor themes (e.g., codes about intensity, frequency, type, location, and impact of pain be coded in a "pain" category). The minor themes with common elements will be combined to form major themes (e.g., pain, swelling and bruising will be grouped under "symptoms"). The related major themes will be combined to form the top-level domain (e.g., symptoms and physical function will be grouped under "physical well-being" domain). The interview guide and codebook will be revised throughout the study as new concepts emerge. Regular team meetings will be held to review changes to the codebook. The item pool developed from the codes will be analyzed to identify concepts of importance across patient, clinical, and treatment characteristics. The quantitative data on the BREAST-Q item ratings of importance will be analyzed descriptively using SPSS®, version 25.0 (IBM Corporation, Armonk NY, USA for Windows®/Apple Mac®). Subgroup analyses using analysis of variance tests or equivalent non-parametric tests will be conducted to explore if the differences in item

ratings differ by patient demographics (e.g., age), clinical (e.g., stage of breast cancer), or treatment (e.g., type of treatment) characteristics.

The item pool will be used to draft the HSCS that contains concepts that are common across surgical and non-surgical breast cancer treatments. We will retain the language used by the participants in the wording of the items and response options. We will ensure that the item and response options are worded clearly, are easy to understand, relevant, and appropriate to Grade 6 reading level. Double-barreled, negatively worded, or vague quantifiers will be avoided. Decisions regarding the type (e.g., frequency or severity) and the number of response options to include will be guided by how the concepts are described in the qualitative data.

Credibility

To enhance credibility, several techniques will be used as follows: (a) use of audio-recording and verbatim transcription by a professional transcriptionist: this will ensure errors in transcription; (b) pilot coding: the first 10 interviews (or as many as necessary) will be coded independently by two members of the research team who have experience in qualitative data analysis. The two coders will meet to review their codes, establish consensus on the definition of codes, and to create a codebook. Once consistency in coding is achieved, the remaining interviews will be coded by one team member; (c) ongoing feedback: the transcribed interviews will be reviewed by a senior team member (AK) who will provide feedback on maintaining or improving quality of data collection by improving questions, altering probes, or providing strategies to pursue specific aspects in greater detail; (d) member checking: the concepts elicited during the interviews will be confirmed

in subsequent interviews by the interviewer; (e) debriefing: the results of the data analysis will be discussed with team members routinely via teleconference; and (f) triangulation: the conceptual framework, qualitative, and quantitative data, and review of the literature will be used to develop the HSCS for the Utility module.

Determining the format for measurement and response options

Once the interviews are analyzed and saturation is determined to be reached, an international group of multidisciplinary experts will be invited to a one day, in-person meeting to review the sample characteristics, codes, item pool, and draft the Utility module that covers key aspects of the preliminary conceptual framework. Feedback on attributes to be included in the Utility module, and suggestions for scale items and response options will be obtained. The wording of the items and response options and the ordering of the items of the existing generic PBMs used in breast cancer research will be also reviewed. (Kaur M et al. (2019). Health State Utility Values in Breast Cancer: A Systematic Review of Literature)

Refining the preliminary scales

A draft of the Utility module will be shown to patients and experts knowledgeable in the content area. This step will ensure that the content validity of the scale is maximized.

Cognitive debriefing interviews – Patients

Participants who took part in qualitative interviews and consented to ongoing participation in the study will be invited to participate in cognitive interviews. Feedback will be obtained on the module's instructions, items, and response options using the "Think

Aloud" approach. (26,27) In the think-aloud approach, participants are asked to complete each item and describe their thinking process behind choosing their response. Participants will also be asked to describe the item in their own words, what the item (i.e., attribute) means to them, and to provide examples from their daily activities pertinent to the item. Feedback will be obtained on the clarity and readability of the overall instrument and participants will be asked to nominate items that are missing from the Utility module. The cognitive interviews (anticipated to last 60 minutes) will be conducted by two experienced qualitative interviewers over phone or in-person. Interviews will be audio-recorded and transcribed verbatim.

We will use the line-by-line coding approach to extract data relevant to the instructions, items, and response options. The participant quote and the feedback will be transferred to Microsoft Excel worksheet for analysis. The feedback will be used to refine the instructions and response options and to decide whether to keep, modify, or delete each item.(28-30) Two or three rounds of cognitive interviews will be conducted with 5 to 15 participants per round. Changes will be made to the Utility module after each round. The endpoint of the cognitive interviews will be when three consecutive patients do not recommend any new changes to the items in the Utility module.

Expert input

Once cognitive interviews are completed, a group of international multidisciplinary experts in the field of HRQOL and/or breast cancer research who are known to the investigators (medical and radiation oncologists, oncoplastic surgeons, allied health professionals, health

economics and outcomes researchers, and patient advocates) will be invited to review the Utility module using REDCap (Research Electronic Data Capture),(31) a secure web-based data collection system. Feedback on the scale instructions, items, and response options will be sought, and experts will be invited to nominate items that should be added or removed. Feedback will be summarized descriptively and used to make changes to the module.

PRE-TESTING OF THE BREAST-Q UTILITY MODULE

The BREAST-Q Utility module will be completed by a large sample of women with breast cancer (Stage 0-4, any treatment). Items will be analyzed in relation to demographic and clinical variables to identify the best subset of items to include in the final set of items.

Participants and recruitment

We will use the AVON Army of Women (AOW) registry to recruit women (18 years or older) who have been diagnosed with breast cancer and are fluent in English. Women undergoing prophylactic treatments for breast cancer or who have language barriers or cognitive impairments that limit participation in the study will be excluded.

Data collection

All research participants on the AOW registry will be sent an e-blast with the link to the study information sheet. Women who agree to participate will be directed to a REDCap survey to complete the BREAST-Q Utility module and a set of comparison measures (**Table 2**). Demographic and clinical information (e.g., stage of breast cancer, type of

treatments to-date/ planned) will be collected. Participants who consent to ongoing participation will be invited to complete the BREAST-Q Utility module 1 week later to assess test-retest reliability. This time interval is sufficiently long to minimize recall bias and sufficiently short to reduce the possibility of change in responses as a result of the participant's health condition.(32) Patients will be asked if their health status is "better", "the same", or "worse" since the initial administration of questionnaires.

Data analysis

The data from REDCap will be exported to SPSS®, version 25.0 (IBM Corporation, Armonk NY, the USA for Windows®/Apple Mac®) for analysis. The demographic and clinical characteristics of the participants will be analyzed descriptively – mean (with standard deviation) or medians (with interquartile range) will be used for continuous variables, and percentages and frequencies will be used for categorical variables.

Psychometric evaluation of the Utility module will be performed according to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines.(31) We will evaluate reliability (test-retest reliability), and construct (hypothesis testing and known-groups) validity. We will also evaluate distribution of responses by items, stage of cancer and type of treatment, and floor and ceiling effects (≥15% of the responses on either end of the scale (32)). Further, we will consider missing items (and reasons for missing data), descriptive feedback from participants, and clinical considerations to finalize the descriptive HSCS of the BREAST-

Q Utility module. **Table 3** describes the psychometric tests and criteria that will be used in the evaluation of the BREAST-Q Utility module.

FINAL COGNITIVE DEBRIEFING (POST-FIELD TEST) – PATIENTS

A new set of cognitive interviews will be conducted, and participants will be shown the refined version of the Utility module based on the field-test results. Feedback will be obtained on the final set of items. The procedure outlined in the cognitive debriefing section will be repeated, and the Utility module will be refined and finalized.

LIMITATIONS

A limitation of our study is that the interviews and field-test study will involve women who are fluent in English and live in Canada or the United States. Another limitation is that participants will be drawn from a small number of cancer centers. Consequently, the results of our study may not be generalizable to women diagnosed with breast cancer in other non-English speaking countries (mainly middle and low-income countries). Future research will be needed to translate the Breast-Q Utility module for use in different contexts and languages.

SUBSEQUENT PHASES

Valuation survey and modeling to produce values for health states

Once the descriptive health-state classification system of the BREAST-Q Utility module is finalized, utility weights for the health states will be developed using established methods such as standard gamble, time-trade off, or discrete choice experiments. The design of the valuation study will be determined once the health-state classification system of the Utility module is validated.

PATIENT AND PUBLIC INVOLVEMENT

Our patient-centered approach engages women with breast cancer and healthcare providers in all stages of our research as experts and research team members. The use of qualitative methods ensures that the issues most important to women with breast cancer are included in the BREAST-Q Utility module. Ongoing engagement of patients in this research is ensured by inviting women who participated in the initial interviews to take part in scale refinement interviews to ensure that the Utility module is easy is understand, relevant, and comprehendible. Furthermore, healthcare providers will be involved in the stages of protocol development, recruitment, data analysis, and dissemination of study findings.

ETHICS AND DISSEMINATION

This study is approved by the Hamilton Integrated Research Ethics Board, Hamilton, Canada. Ethics approval for the study (Project no. 2078) and data sharing agreement is also obtained from the ethics review boards and legal department of TGH (Project no. 16-5934)

and MSK (Project no. 17-147A(1)) respectively. The ethical aspects of this research will comply with the guidelines of the national granting councils (The Canadian Institutes of Health Research) as outlined in the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans.

The patients will be invited to participate by a member of the clinical team, but the consent will be obtained by the research coordinator to ensure there is no coercion to participation. Participation in this research is voluntary. As no intervention will be provided in the course of the study, there is no direct risk to participants. However, talking about experiences with breast cancer can evoke negative feelings and unwanted recollections. If a participant feels distressed or is determined to be at risk to self or others post-interview, they will be put in touch with a skilled therapist. Participants will be made aware that they do not need to answer any question(s) that make them uncomfortable and can choose to end the interview or withdraw from the study at any time. There is no direct benefit to the participant for participating in the study except for the opportunity to contribute to improving treatment outcomes in breast cancer research. Participants in the interviews and cognitive interviews will be given a $50 gift card as a thank you for their time.

Participants will be informed of the steps taken to protect their identity and maintain confidentiality. Any written document (e.g., notes, interview transcripts, demographic forms, questionnaires) will be de-identified to ensure confidentiality. Electronic data will be stored in secure, password-protected servers, and hardcopy files will be stored in a locked cabinet at the senior researcher's office at McMaster University, Canada.

The results of this study will be published in a series of articles in peer-reviewed scientific journals and presented at local, national, and international conferences or meetings. Once developed, the BREAST-Q Utility module will be made available free-of-cost to non-profit users (e.g., clinicians, researchers, and students). Information on use, scoring, and interpretation of BREAST-Q Utility module will be posted on the Q-portfolio webpage (www.qportfolio.org).

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FIGURE LEGEND

Figure 1: An overview of the multiphase, mixed methods approach used in the development of the BREAST-Q Utility module

Figure 2: Conceptual framework of the BREAST-Q (19)

Table 1: Semi-structured Guide for Qualitative Interviews in Phase 1

Experience of care

- Can you tell me about the events leading up to and including your breast cancer diagnosis?
- Can you tell me what being a breast cancer survivor/breast cancer patient has been like for you?
- What kinds of treatments have you had/are currently on/will have in the future?

Appearance

- How would you describe the appearance of your breast(s)/breast area of the chest? (Probe: with clothes, with/without bra, symmetry, contour)
- How did breast cancer and/or its treatment change the appearance of your breast(s)/breast area of the chest? (Probe: scarring, color)
- Is there anything about your breast(s)/nipple(s)/breast area of the chest that you would like to change? (Probe: size, location, shape)
- Of the changes in your appearance, can you tell me what changes have had the most impact on you and why?

Physical function

- Do you experience any difficulty in your daily activities as a result of breast cancer/its treatment? (Probe: driving, self-care, dressing, transfers, toileting)
- Do you have any trouble moving your arm as a result of breast cancer/its treatments? (Probe: reaching objects, lifting heavy objects)
- Do you have any trouble with fine movements involving your fingers or toes? (Probe: cooking, threading a needle, typing)
- Of the physical function limitations, can you tell me which ones have had the most impact on you and why?

Physical symptoms

- Do you experience any symptoms related to breast cancer/its treatments? (e.g., pain, tightness, numbness, heaviness, fatigue)
- Of the symptoms you mentioned, can you tell me which ones have had the most impact on you and why?

Psychological function

- How does breast cancer diagnosis/treatments make you feel? (Probe: upset, angry, depressed, anxious)
- How does the appearance of your breast(s)/breast area of the chest make you feel about yourself? (Probe: self-conscious, less attractive)
- Out of the emotions you mentioned, can you tell me which ones have had the most impact on you and why?

Social function

- How has breast cancer/its treatment impacted your participation in social roles? (Probe: parent, spouse, work, recreation/leisure, sports)
- Out of the social concerns you mentioned, can you tell me which ones have had the most impact on you and why?

Sexual function

- How has your sex life changed after breast cancer/its treatments? (Probe: satisfaction, feeling sexually attractive)
- Do you try to cover/hide your breasts during sex?
- Out of the sexual concerns you mentioned, can you tell me which ones have had the most impact on you and why?

Others

- Are there any other concerns or issues you experienced that we have not already covered? (e.g., spiritual, coping, etc.)

Most/least important aspects of HRQOL

- Thinking back over what you have talked about in this interview, what would you say are the top five most important aspects of your quality of life impacted by breast cancer and/or its treatment.

After Completion of the BREAST-Q

- Thinking about the content of the BREAST-Q you just completed, can you tell me if there are any questions that are currently missing from the BREAST-Q that you feel are important.

Table 2: Comparison measures used in the psychometric evaluation of the BREAST-Q Utility module

Measure	Characteristics
EQ-5D-5L (33-35)	• Generic preference-based measure • Consists of a descriptive system and the EQ-VAS. The descriptive system comprises of 5 HRQOL dimensions with five levels each - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. • Most common utility instrument used in breast cancer research (Kaur M, et al (2019). Health State Utility Values in Breast Cancer: A Systematic Review of Literature)
EORTC-QLQ-C30 (36)	• Cancer-specific HRQOL instrument that consists of nine multi-item scales - five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. • Used to derive EORTC-8D (37), a preference-based single index measure that consists of eight dimensions - physical functioning, role functioning, pain, emotional functioning, social functioning, nausea, fatigue, sleep disturbance, and constipation and diarrhea, with four levels each (except physical functioning which has five levels).
SF-12 (38)	• Generic HRQOL instrument that consists of 12 questions and 8 domains - pain, mental health, physical functioning, social functioning, role limitations due to physical and emotional problems, vitality and general health. • Used to derive SF-6D (39), generic preference-based measure that comprises of 6 domains – pain, mental health, physical functioning, social functioning, role limitations, and vitality, with 4-6 response levels each.

Table 3: Psychometric tests and criteria used in the evaluation of the BREAST-Q Utility module

Psychometric property	A priori hypothesis	Tests and criteria
Reliability The extent to which a measurement is consistent and free from error		
Test-retest reliability – the degree to which repeated measurements in stable individuals (i.e. no clinical/life change) provides similar answers (32) *Measurement error* – the systematic and random error of a patient's score that is not due to true changes in the construct to be measured.(32)	The BREAST-Q Utility module will demonstrate high test-retest reliability, i.e. the responses between the first and second administration (1 week later) will be similar.	Weighted kappa ≥ 0.70 (32, 40) Percentage of positive and negative agreement
Construct validity The degree to which scores of an instrument are consistent with the hypotheses, if the new instrument validly measures the construct of interest		
Hypothesis testing – the degree to which the scores of an item/scale are consistent with a priori hypothesis. (32)	*Direction and magnitude of the correlation between BREAST-Q Utility module and the comparison instruments* – We hypothesize that - The BREAST-Q Utility module score will show positive (≥0.3) correlation with similar domains on EQ-5D-5L, EORTC-QLQ-C30, and SF-12. *Known – groups validity* – Based on published evidence on HRQOL outcomes in breast cancer (41-44), we hypothesize	ANOVA or Kruskal-Wallis depending on the distribution of the data for differences in mean scores ($p < 0.05$) Pearson's r or Spearman's rho depending on the distribution of the data: ≥0.5 will be considered strong correlation, 0.3-0.49, moderate, and 0.10-0.29 small. (32, 45, 46)

	that the BREAST-Q Utility module score will be: - higher (i.e., worse HRQOL) in women currently undergoing (neo)adjuvant treatment(s) compared to women who have not had/ had neoadjuvant treatment(s) in the past for breast cancer. - lower for women who are had breast cancer surgery alone as compared to women who had breast cancer surgery and (neo)adjuvant treatments. - lower for women diagnosed with early versus advanced stage breast cancer.	
Acceptability and data quality		
Response distributions of the instruments and missing data *Floor and ceiling effects* - >15% of (32) respondents scoring the lowest or highest possible score	We hypothesize that the Utility module will have less than 15 percent missing data. We hypothesize that the responses of the Utility module will be evenly distributed across the response categories (i.e., no floor or ceiling effect).	Distribution of responses by instrument, item-level, stage of cancer and type of treatment will be summarized using descriptive statistics (mean, standard deviation, % of item-level missing data)

Author statement

- MK, AK, SC and AP were responsible for conceptualizing the project, designing the study, and drafting of the manuscript. and approved the version that is submitted.
- FX, LB, SC, and TZ were responsible for designing the study, and providing intellectual feedback on the manuscript.
- All listed authors approved the manuscript to be submitted.

Data statement

There are no data in this work.

Figure 1: An overview of the multiphase, mixed methods approach used in the development of the BREAST-Q Utility module

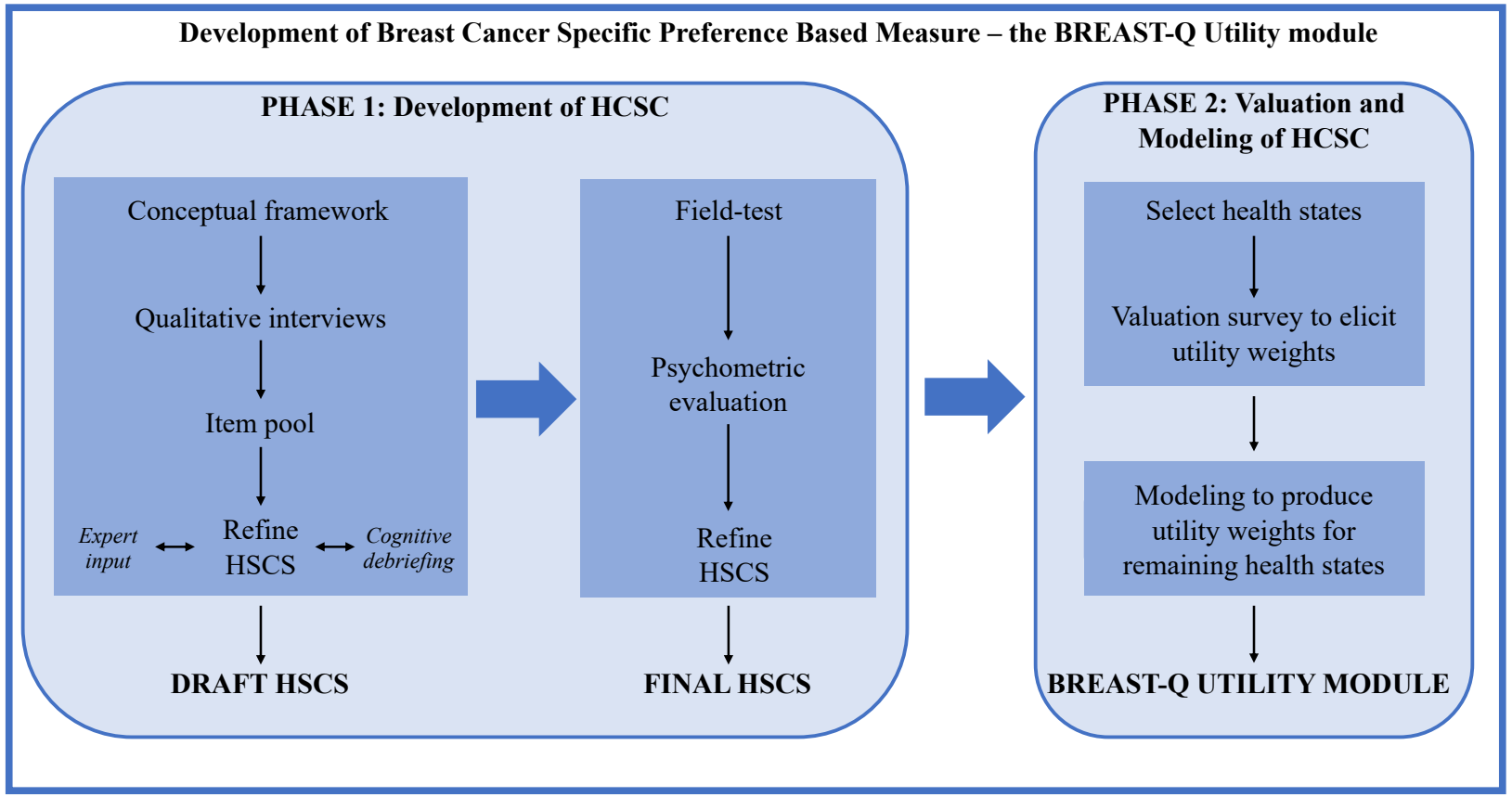

Figure 2: Conceptual framework of the BREAST-Q (19)

CHAPTER 4

An International Mixed-Methods Study to Develop a Descriptive Health State Classification System for a New Preference-Based Measure for Women with Breast Cancer: The BREAST-Q Utility Modules

Title: An International Mixed-Methods Study to Develop a Descriptive Health State Classification System for a New Preference-Based Measure for Women with Breast Cancer: The BREAST-Q Utility Module

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ABSTRACT

Background: Generic preference-based measures (PBM), though commonly used, may not be optimal for use in economic evaluations of breast cancer interventions. No breast cancer-specific PBM currently exists, and the generic PBMs fail to capture the unique concerns of women with breast cancer (e.g., body image, appearance, treatment-specific adverse effects). Hence, the objective of this study was to develop a breast cancer-specific PBM, the BREAST-Q Utility module.

Methods: Women diagnosed with breast cancer (stage 0-4, any treatment) were recruited from two tertiary hospitals in Canada and one in the USA. The study followed a mixed-methods approach using a convergent design. Semi-structured interviews were conducted using an interpretive description approach. At the end of the interview, participants were asked to list their top five health-related quality of life (HRQOL) concerns and to rate the importance of each item on the BREAST-Q. Interviews were audio-recorded, transcribed verbatim, and coded. Constant comparison was used to refine the codes and develop a conceptual framework. Qualitative and quantitative data were triangulated to develop the content of the Utility module, which was refined through 2 rounds of cognitive debriefing interviews with women diagnosed with breast cancer and feedback from experts.

Results: Interviews were conducted with 57 women aged 55 ± 10 years. A conceptual framework was developed from 3948 unique codes specific to breasts, arms, abdomen, and cancer experience. Five top-level domains were: HRQOL (i.e., physical, psychological, social, and sexual well-being) and appearance. Data from the interviews, top 5 HRQOL

concerns, and BREAST-Q item ratings were used to inform dimensions for inclusion in the Utility module. Feedback from women with breast cancer (n=9) and a multidisciplinary group of experts (n=23) was used to refine the module. The field-test version of the HSCS consists of 10 unique dimensions. Each dimension is measured with 1 or 2 candidate items that have 4-5 response levels each.

Conclusion: The field-test version of the BREAST-Q Utility module was derived from extensive patient and expert input. This comprehensive approach ensured that the content of the Utility module is relevant and comprehensive and includes concerns that matter the most to women diagnosed with breast cancer.

KEYWORDS

health utility, preference-based measure, breast cancer, qualitative, patient-reported outcomes, economic evaluation, cost-effectiveness, cost-utility, interviews

BACKGROUND

In women, breast cancer is the most common cancer and the second leading cause of death from cancer globally.(1) In the United States, for example, an estimated 276,480 new cases of invasive and 48,530 new cases of non-invasive breast cancer will be diagnosed in 2020. (1, 2) Fortunately, breast cancer incidence rates in the United States and other developed countries have been in decline since 2000 due to improvement in early diagnosis and advancement in therapy.(1, 3) Consequently, the number of breast cancer survivors is on the rise. There are more than 3.1 million women with a history of breast cancer in the United States. As the number of breast cancer survivors increases, the focus of breast cancer interventions has expanded from survival to include improvements in health-related quality of life (HRQOL).

HRQOL is defined as the subjective perception of the impact of disease or its treatment(s) on an individual's daily life (e.g., physical, psychological, and social well-being).(4) HRQOL data can be used to understand the burden of cancer and its treatments on patients and their caregivers. Further, HRQOL data provide unique information from patients' perspectives on the persistent or late-onset effects of cancer treatments, such as the impact on social or sexual well-being, lymphedema, or fatigue on daily activities.(5-7) As such, the data about HRQOL can be used to improve how breast cancer care is planned, organized, and delivered.

A common approach to collecting HRQOL data is by means of patient-reported outcome measures (PROMs). There are several different types of PROMs, including generic measures that capture the core dimensions of health across conditions and

condition-specific measures. Another type of PROM generates a profile of dimension scores or a single index that is based on either a summation of item scores or preference weights obtained from patients or the general public (known as preference-based measures (PBM) or multi-attribute utility measures).

The use of PBMs in the economic evaluation of healthcare interventions has increased markedly in recent years, and their use has been formalized in many countries. The index (or utility) value obtained from a PBM can be used to calculate quality-adjusted life-years, which is the metric of choice in economic evaluation of healthcare interventions.(8)

In breast cancer, due to the lack of condition-specific PBMs, generic measures such as the EQ-5D(9, 10), the Short Form-6D (SF-6D)(11, 12), and the Finnish 15D(13, 14) are frequently used. Research has shown that when generic PBMs are used for certain conditions, they may fail to evaluate outcomes relevant to the specific patient group, and hence, over- or under-estimate the cost-effectiveness of the interventions examined. In breast cancer, generic PBMs do not include unique concerns of women, such as breast appearance, body image, or sexual well-being. Hence, the objective of this mixed-methods study was to develop the descriptive health state classification system for a new breast cancer-specific PBM module of the BREAST-Q(15), called the BREAST-Q Utility module.

METHODS

The development of the BREAST-Q Utility module adhered to recommended methods for PROM instrument development.(16-21) The study followed a mixed-methods approach

using a convergent study design, where quantitative data were collected to supplement the qualitative study.(22) An overview of the steps involved in the development of the health state classification system of the Utility module is shown in **Figure 1**. The detailed study protocol is published elsewhere.(23)

Study setting and recruitment

Purposive sampling was used to recruit women with a confirmed diagnosis of breast cancer (Stage 0-4, any treatment) from three tertiary healthcare centers – Juravinski Cancer Centre, Hamilton; Toronto General Hospital (TGH), Ontario, Canada; and Memorial Sloan Kettering Cancer Center (MSK), New York, United States. A heterogeneous sample was targeted to include women who varied by age (18 years and older), stage of breast cancer, and type of treatments for breast cancer. Women seeking prophylactic or diagnostic interventions for breast cancer and women who were cognitively impaired or unable to speak English were excluded. Ethics approval for the study was obtained from the Hamilton Integrated Research Ethics Board, Ontario, Canada, and research ethics boards of TGH and MSK.

Eligible patients were invited to participate either during routine hospital visits or by phone with a member of the clinical team within their circle of care. Patients who expressed interest in participation were contacted by a member of the research team who reviewed the study objectives and terms of participation. Written consent was obtained, and the interview was scheduled at a time and location convenient to the participant.

Qualitative phase

We used an applied qualitative health research approach known as interpretive description. This inductive approach was inspired by grounded theory, naturalistic inquiry, ethnography, and phenomenology.(24) Interpretive description allows healthcare professionals to gain new insights from the clinical field while taking into consideration existing knowledge regarding the clinical phenomenon.(25)

Conceptual framework

The conceptual framework of the BREAST-Q was used to inform the study interview guide.(15) The BREAST-Q is a PROM designed to measure breast cancer surgery outcomes (breast-conserving therapy (BCT), mastectomy, and reconstruction). The BREAST-Q conceptual framework was developed from interviews with patients seeking breast surgery (n=48) and was refined using focus groups with patients (n=58), cognitive interviews (n=30), and expert feedback (n=17).(26) As such, the conceptual framework of the BREAST-Q includes the domains that are most meaningful and relevant to women with breast cancer.

Data collection

Semi-structured interviews (in-person or by telephone) were conducted. Probes were used to elicit in-depth information about HRQOL domain(s). At the end of the interview, women were asked to nominate the top five concerns most important to their experience of breast cancer and its treatment(s). The interviews were audio-recorded and transcribed verbatim.

Analysis

The interview data were analyzed concurrently to allow findings to inform changes to the interview guide and to inform probing of new content in subsequent interviews. The transcripts were coded using a combination of inductive (generation of new codes) and deductive (application of existing BREAST-Q codes) approaches. Constant comparison was used to develop a codebook and refine codes. The language used by participants was retained as much as possible. New top-level domains and subdomains were created to capture content missing from the BREAST-Q conceptual framework. The top-level codes were kept broad to prevent pre-mature redundancy of concepts elicited during interviews. The conceptual framework was refined throughout the study. Interviews were conducted until researchers felt redundancy was achieved in the domains at the level of minor themes (i.e., no new information was elicited). The data on the top five HRQOL concerns were summarized descriptively.

Credibility

To ensure credibility, the first ten transcripts were coded by two independent researchers, with consensus established through discussion. The codebook and the conceptual framework were reviewed by a senior author (AK) who provided ongoing feedback on the quality of the interviews, interview questions, and probes. The concepts elicited during the interviews were confirmed in subsequent interviews. The results of the data analysis were routinely reviewed with research team members.

Quantitative phase

To understand the importance of current BREAST-Q scales' content to the breast cancer experience, women were asked to complete four scales (i.e., Satisfaction with Breasts and Psychosocial, Sexual, and Physical Well-being) within the most appropriate BREAST-Q Version 2.0 module (27) based on their surgical treatment (BCT, mastectomy, or reconstruction).

Data collection

At the end of the interview, women were asked to indicate how important (not important, slightly important, moderately important, important, and very important) each item on the BREAST-Q scale was to them. Completion of the BREAST-Q took place at the end of the interview on paper for in-person interviews or electronically for telephone interviews.

Analysis

BREAST-Q data were entered into IBM© SPSS Statistics version 25 for analysis. Using descriptive statistics, the BREAST-Q item rankings were summarized to identify the highest scoring items.

Developing the BREAST-Q Utility module

Data from the qualitative interviews, including the top five HRQOL concerns, and the BREAST-Q item ranking exercise were triangulated to identify items for inclusion in the BREAST-Q Utility module. A draft of the Utility module was developed according to the following PROM development principles(19, 20): (1) domains should be relevant to the patient experience, (2) negatively worded and double-barrelled items should be avoided,

(3) items should be easy to understand and not use slang or technical terms, (4) item wording should be easy to translate, (5) items and response options should retain participants' words where possible, and (6) items should measure concepts that are likely to change with treatment or over time to enhance responsiveness. The qualitative data were used to inform the choice of response options (e.g., severity versus frequency) and the wording of the item. The number of response options was limited to five to capture the range of health states experienced while reducing cognitive burden. The content of the Utility module was compared with existing instruments identified through a systematic literature review of published breast cancer utility values.(28)

The results of the mixed-methods study and the draft of the Utility module were reviewed at a one-day, in-person meeting with quality of life researchers, healthcare professionals (breast surgeons, nurse), and a health economist. Feedback was sought on the content of the Utility module and the wording of the instructions, items, and response options. The draft Utility module was also emailed to an international group of oncologists (medical, radiation, and surgical) and one psychometrician known to the investigators for feedback.

Refining the BREAST-Q Utility module

Input from patients and healthcare professionals (HCPs) was used to refine and ensure the content validity of the BREAST-Q Utility module.

Patient input

Women who took part in qualitative interviews and newly recruited participants were invited to take part in a cognitive interview to ensure that the items of the Utility module were relevant, comprehensive, and comprehensible.(18, 20) We used the "think aloud" technique (29-31) to obtain feedback on the instructions, items, and response options. Participants were asked to rephrase the item in their own words and identify missing items. The interviews were conducted in-person or over the telephone, audio-recorded, and transcribed verbatim. The data from the cognitive interviews were analyzed concurrently using line-by-line coding, and the Utility module was revised using feedback between two rounds of interviews. Interviews continued until no further changes were recommended by the three consecutive participants at the level of the items.

Expert input

An international multi-disciplinary group of experts (oncologists, breast surgeons, allied health professionals, health economics and outcomes researchers, and patient advocates) was identified through the research team's professional network and invited to review the Utility module using REDCap (Research Electronic Data Capture), a secure web-based data collection system.(32) Feedback was sought on the wording of the instructions, items, and response options. The experts were also asked to rate the importance of the items on a 5-point Likert scale and to identify items that were missing. One reminder email was sent two weeks later. The expert feedback was examined, and the Utility module was revised.

RESULTS

A total of 57 qualitative interviews were conducted between January 2017 and June 2018. Interviews lasted 80 ± 34 minutes (range 30 to 162 minutes). The mean age of the sample was 55 ± 10 years (range, 22 to 75 years) and mean Body Mass Index (BMI) was 26 ± 5 (range, 18 to 42). Participant demographic and clinical characteristics are shown in **Table 1**.

Qualitative Phase

The BREAST-Q Utility conceptual framework was developed from 3948 unique codes. Five top level domains were identified: physical, psychological, social, and sexual well-being (health-related quality of life) and appearance (**Figure 2**). **Figure 3** highlights the subdomains. The domains, sub-domains, and themes are described in detail below.

Health-related quality of life

Physical well-being

This domain was used to capture symptoms and mobility-related issues specific to breast cancer surgery and the (neo)adjuvant treatments.

Physical symptoms

Fatigue

Breast cancer treatment-related fatigue was the most disabling symptom experienced by women actively receiving treatment or in survivorship. Women described the experience of fatigue as, “I was tired no matter”, “I was wiped out”, “I was lethargic”, “I was completely depleted of energy”, “I felt drained”, “I was exhausted”, and “I had a lot of

fatigue". Women also equated the feeling of fatigue with feeling physically weak or unwell. Frequent napping during the day and unrestful sleep at night were common complaints: "I laid down so much", "I had to have an afternoon nap during chemotherapy", "I didn't want to get out of bed", and "I felt lousy in the night".

Women also described the impact that fatigue had on their physical, psychosocial, and sexual well-being. Feeling tired was described as interfering with their ability to do daily activities in a timely fashion (i.e., "took longer"). Not being able to appropriately care for self or dependents due to fatigue caused substantial distress. Fatigue interfered with women's ability to participate in hobbies, social activities ("I missed the church picnic as I felt really lousy", "I tried playing golf and I was toast"), and work ("I could not go back to work due to tiredness"). Women also reported reduced interest in sexual activities ("not on my mind", "too tired to have sex") because of fatigue.

Pain and discomfort

Women who were receiving treatment(s) commonly reported experiencing pain or discomfort that varied by type (dull, sharp, ache, shooting), intensity (mild, moderate, severe), frequency (constant, intermittent), and location (breast(s), chest area, upper or lower extremity joints). Pain due to breast cancer surgery in the breast(s) or chest area was described as a "dull ache", "discomfort", or occasionally, "sharp", "lightning", or "electric". Pain in the breast(s) or chest area was worse in certain sleeping positions (e.g., side-lying or prone) and movement of the arm(s). Pain associated with wound care (e.g., chest tube removal, surgical dressing changes) was also described. Some women reported pain in the shoulder or arm on the affected side in the immediate postoperative period. For

most women, pain interfered with sleep ("pain wakes me up at night", "I cry out in pain in sleep", "could not sleep") and restricted their ability to participate in daily activities. Participants with abdomen-based reconstruction described feeling "discomfort", "bloated", or "tightness" ("tight band") in the abdomen area that was aggravated by sudden or sharp movements (e.g., coughing, straining for bowel movements).

Pain due to chemotherapy or targeted treatments was described as "constant", "deep", "excruciating", "sore everywhere", "arthritic", with or without morning stiffness, and was frequently experienced in lower extremities joints. This type of pain was often described as "debilitating" and affected sleep, mobility (e.g., walking, going up and down stairs), bed or chair transfers, and daily activities.

Breast sensation

Most women reported a lack of feeling (numbness or no sensation) in their breast area (including axilla and in/around scar) for months following breast surgery. Many women reported their breast(s) feeling "hard", "full", "heavy", "cooler than rest of the body", feeling "electric shocks", "lightning", or "fireworks-like" sensations. These sensations were often experienced intermittently and did not seem to interfere with daily activities. A small number of women experienced phantom symptoms in their missing breast, including pain, "deep itch", or the "feeling of milk coming down".

Peripheral neuropathy

Some participants who underwent chemotherapy or targeted therapy experienced peripheral neuropathy in their hands or feet. The feeling of "numbness", "tingling", "pain", or "pins and needles" was reported. Neuropathy in the hands was reported to interfere with

fine motor tasks, such as holding a pen, buttoning a shirt, unscrewing jars, sewing, lifting a cup, or carrying or lifting grocery bags. Neuropathy in the feet caused pain or loss of balance and interfered with walking and physical activity.

Other symptoms

Additional, less frequently described symptoms included altered taste ("food tasted different", "metallic taste", or "food tasted terrible"), loss of appetite, nausea or vomiting, mouth sores, hot flashes, dry eyes, weight gain or loss, headaches, feeling lightheaded or dizzy, chest pain, dyspnea, tachycardia, vaginal dryness or itching, and frequent urination. Some women described difficulty remembering things and issues with recall, focus, or problem solving ("brain fog" or "chemo-brain") during and for months following chemotherapy.

Physical functioning

Mobility and daily activities

Women reported difficulty with mobility and daily activities due to breast cancer treatments. Some women reported difficulty with moving or lifting the arm on the surgical side, especially in the immediate postoperative period. Arm problems interfered with personal hygiene (bathing, washing hair), self-care (applying makeup, styling hair, getting dressed), household chores (meal preparation, laundry), driving, exercising, hobbies, and/or recreational activities. Reaching overhead ("I was not able to lift it all the way up", "I could not put stuff up in the high cupboard") and lifting objects ("I couldn't lift or hold things for a long period", "I was unable to carry grocery bags on the right (affected) side") were particularly challenging.

Women who were seeking or had undergone (neo)adjuvant treatments reported difficulty with mobility due to bodily pain and fatigue. Pain in the lower extremity joints made activities like getting out of bed or chair, walking, and going up and down the stairs particularly difficult: "yeah sure I can walk, but it is actually very difficult", "even just walking up and down the stairs was like a chore". Women with abdomen-based autologous reconstruction reported restrictions with bed and chair transfers in the immediate post-operative period. Participants reported using accommodations such as hired help, bath chair, gait aids (walker, cane), and specialty shoes (for neuropathy).

Sleep

Women reported concerns with the amount and quality of sleep. Women reported that they "could not sleep" and experienced "trouble falling asleep", "trouble staying asleep", and "interrupted sleep" due to the side-effects of treatments, such as nausea, hot flashes, pain, or discomfort. Suboptimal nighttime sleep often resulted in daytime fatigue, and women reported needing to nap during the day. Sleep was also affected in the post-operative period due to having to sleep in unfamiliar positions to aid in recovery (e.g., supine for post-breast and abdomen-based reconstruction surgery). A few post-operative women with limited arm mobility or abdomen weakness slept in a recliner chair or speciality bed that facilitated bed or chair transfers. Beyond the recovery period, some women with implant-based reconstruction reported discomfort or being anxious about putting pressure on their implants from their sleeping positions.

Psychological well-being

Emotional distress

All women described experiencing emotional distress during the diagnosis, treatment(s), and survivorship phase. Women described feeling anxious or worried about losing their breast(s), treatments and their side-effects, prognosis, cancer recurrence, and the impact of cancer and its treatment on their significant other and family members. Women described the off-treatment phase as particularly stressful, as they no longer felt they were proactively doing something to prevent cancer from recurring ("fear of recurrence will be there once I stop Herceptin", "not having chemotherapy makes me anxious"). Women felt distressed about new symptoms that appeared post-treatment (e.g., aches or pains) and about receiving test results speculating that they might have a recurrence.

Women described a range of emotions including feeling angry, frustrated, disappointed, or irritated that they had cancer: "my body let me down" or "what have I done to deserve this". Women experienced sadness ("depressed", "upset", "feel awful", "overwhelmed") about losing their breast(s), chemotherapy-induced alopecia, and inability to fully participate in daily activities at various times during their treatment and recovery period. Women with children were greatly concerned at thoughts of not being able to see their children grow up due to treatments not working or recurrence of cancer. Some women found themselves dwelling on their diagnosis, the effectiveness of the treatment(s), cancer recurrence, or late effects of treatments (e.g., cardiotoxicity) ("It's something you think of daily", "Cancer is always there in the back of your mind", "You don't move on for a very long time").

Positive impact

While most psychological descriptions were negative, some women described ways in which they coped and perceived the breast cancer diagnosis as an opportunity to restructure their lives, connect with friends or family members, pursue new hobbies, or travel. Women were grateful for their supportive friends and family, timely access to treatments, going into remission, and being alive ("I remember sitting thinking I've lost a breast, but I haven't lost my life"). Some women reported that the cancer diagnosis changed their outlook on life and that they lived in the present and with more gratitude.

Social well-being

This domain was used to capture social issues identified by the women in relation to the diagnosis, treatment, and survivorship phases. These codes were classified into social participation (including work), isolation, and relationships.

Social Function

Social participation

Women reported that cancer and its treatment limited their ability to participate in a variety of their usual social roles, including their ability to care for self and family (taking care of dependents), their work, and in the community. Cancer treatments had an impact on women's work lives due to side-effects of treatment (pain, fatigue, neuropathy) that persisted into the recovery and survivorship phase. Participants modified their work responsibilities by asking for accommodations ("reduced the number of hours worked",

"asked employer for help", or "took more breaks") or discontinued employment (temporarily or permanently). Participants also reported requiring assistance with childcare and help with household chores, resulting in an emotional or financial burden on the family.

Social isolation

Social isolation was described as necessary in the context of chemotherapy to avoid infection from other people at work or other social events. Symptoms such as fatigue and appearance-related changes (especially alopecia) interfered with the ability or choice to participate in social events. Treatment factors, such as the day-to-day burden associated with specific treatments like radiation therapy, also prevented women from socializing with their friends or family members. Inability to participate in meaningful activities (work or leisure) contributed to a sense of loneliness through the breast cancer experience.

Relationships

Social support (emotional, instrumental, or information) was central to women's experience of breast cancer. The social support women received in terms of drives to healthcare appointments, housekeeping, meal preparation, and childcare was invaluable. Further, women noted that talking about their illness with their significant others or family members was paramount in importance in terms of coping with the disease. Most women struggled with their new role as a dependent and worried about the impact of the caregiving responsibilities placed on their partner. Women often leaned on relatives or friends who had themselves experienced breast cancer for information about healthcare providers, treatments, side-effects, and remedies, as well as what to expect from treatments. Attending

makeup or nutrition classes organized through treatment centers or community groups was described as a positive social experience for the women.

Sexual well-being

Sexual self-image

Dysphoria due to the appearance of the breast(s) or chest area, lack of nipple(s), chest or abdomen scarring, and overall change in appearance affected women's sexual self-image and sexual interactions. Most women reported feeling less attractive in intimate scenarios and that enjoyment of their sex life was diminished by the lack of breast and/or nipple sensation and pain or discomfort in the chest area associated with surgical or radiotherapy treatments. Some women were bothered by their partners looking at and/or touching their breast area and resorted to concealing their chest area during intimate scenarios.

Sexual functioning

Women who were sexually active expressed concerns related to the side-effects of the treatments, especially fatigue, loss of libido, vaginal dryness, itching, irritation, or dyspareunia, that impacted their ability to experience sexual pleasure. Women used terms such as "lesser now", "not as often", "less frequent", "limited", "not interested", "non-existent", or "lost intimacy" to describe their experience. Many survivors reported a persistent depressed mood or sadness and/or anxiety that lasted beyond the treatment phase, secondary to fear of recurrence, impact on partner and family, and body image concerns. These factors affected some women's ability to orgasm, resulting in reduced sexual

frequency. This was particularly relevant to younger women with breast cancer and single women who had been seeking a partner.

Appearance

This domain captured women's appraisal of their physical appearance. Subdomains were categorized into appearance of the breast, abdomen (for patients with autologous reconstruction using abdominal tissue), arm (for women with lymphedema), and overall appearance.

Breasts, chest area, and nipples

The appearance of the breast(s) or chest area before and after breast cancer surgery was the most frequently mentioned concept. Women appraised their breast area by describing the contour ("caved in," "bulge", "droopy", "puckered"), symmetry ("closely matched", "looked similar", "one smaller than the other", or "one higher than the other"), shape ("concave", "flat", "hollow", or "full"), size ("same", "small", or "bigger"), and ptosis ("hang" or "droop"). Most women described the appearance of their breast in terms of how "natural" or "normal" they looked compared to before surgery and/or to other women. Women who had radiotherapy described changes to the skin of the chest area ("looks sunburnt", "I have a permanent tan").

Abdomen and belly button

For women who had autologous reconstruction using abdominal tissue, the appearance of the belly button and the abdomen scar were important concerns. Women were bothered by a shift in the position and size of the belly button ("much larger than what I used to have",

"doesn't look original", "I don't feel my belly button is my own", "sticks out a bit", or "is visible when I wear a tight top"). The position and color of the abdomen scar was not deemed an important issue as it could be concealed with clothing. Some women were bothered by dog ears that were visible when clothed.

Arms-Lymphedema

Women with lymphedema described the appearance of their affected arm(s) in terms of the size ("bigger"), contour ("rounded" or "full"), shape ("indented"), and color ("lighter" or "same as other"). Women mentioned challenges associated with concealing the arm (finding clothes that fit) and feeling self-conscious in public ("I wear long sleeves if I was going out for dinner", "I avoid wearing sleeveless tops in public").

Overall appearance

Women experienced changes in their overall appearance due to (neo)adjuvant treatments. All women who underwent chemotherapy experienced alopecia, and while some women were extremely bothered by alopecia, others perceived it as a temporary issue. Most participants coped with alopecia by cutting their hair short prior to starting chemotherapy and by wearing a wig, scarf, baseball cap, or toque in public settings. Some women reported using makeup to conceal the loss of eyebrows and eyelashes. A few women noted changes to their skin ("dry", "pale") and nails ("black", "loss of nails").

Quantitative phase

Top five HRQOL concerns: Patients

The top HRQOL concerns by the stage of breast cancer are shown in **Figure 3**. Overall, anxiety or worry, appearance of the breast(s), fatigue, impact on usual activities, and pain were the top five HRQOL concerns across all stages of breast cancer.

BREAST-Q- Item ratings: Patients

Women consistently endorsed the following items to be important to their breast cancer experience across all three BREAST-Q modules: satisfaction with appearance (closely matched, feel natural, look in mirror unclothed), psychological well-being (confident, emotionally healthy, attractive), physical well-being (pain), sexual well-being (sexually attractive, confident sexually, sexually attractive when unclothed), and adverse effects of radiation (skin feeling dry, looking different). Women who had abdomen-based radiation endorsed as most important difficulties sitting up, everyday activities, and discomfort in the abdomen area.

Selection of domains and dimensions within domains

The findings described above were used to develop the first draft of the BREAST-Q Utility module. This version measured 9 unique dimensions (i.e., 9 items) with 4-5 response options and included instructions and response options (Version 1). Based on the expert feedback, 3 new items were added, and an initial item measuring pain and unpleasant symptoms was split into two items. In addition, the instructions were modified to include

the recall period, and additional details were added to some items, resulting in Version 2, which included 12 dimensions (13 items) with 4 response levels each.

Content validation

Cognitive interviews lasted 60 ± 14 minutes and were conducted from October 2018 to April 2019. The characteristics of the study sample are shown in **Table 1**. In the first round, Version 2 was shown to five women. Based on participant feedback, several of the items and the response options were revised, resulting in Version 3. This version was further revised through four additional cognitive interviews, resulting in Version 4. This version was developed into a REDCap survey. A total of 35 multi-disciplinary experts were invited to provide feedback, out of which 27 responded (response rate, 68%). The experts included medical oncologists (n=3), radiation oncologists (n=3), breast surgeons (n=15), health economics and/or outcomes researchers (n=5), and a patient advocate. Experts were from the United States (n=10), Canada (n=7), the Netherlands (n=4), Poland (n=2) and Chile, Denmark, Italy, and United Kingdom (n=1 each). The Utility module was revised based on the expert feedback, resulting in the field-test version of the Utility module (Version 5). **Table 2** summarizes the item reduction and refinement in the different versions of the BREAST-Q Utility module.

Health state classification system

The field-test version (Version 5) of the BREAST-Q Utility module **(Appendix A)** included 10 unique dimensions: fatigue, pain, emotional distress, impact on usual activities,

how the breasts match, feeling self-conscious about how breast(s) look, breast sensation, arm mobility, treatment-related unpleasant symptoms, nausea, peripheral neuropathy, and radiated skin changes. Each dimension was measured by one or two candidate items, each with four or five response options. Response options for items asking about breast appearance, body image, and sensation were based on severity, while the response options for items asking about fatigue, pain, and emotional distress included options to measure severity and interference with daily activities to test alternate ways of measuring these concepts. The final set of field-test items totaled 21.

DISCUSSION

In this paper, we described the content development of a breast cancer-specific PBM, the BREAST-Q Utility module, using a multicenter, mixed-methods approach. The BREAST-Q Utility module was designed for women diagnosed with breast cancer of any stage and any combination of surgical or (neo)adjuvant treatments.

To the best of our knowledge, this is the first breast cancer-specific PBM developed following published guidelines for the development of PROMs(16-20) and the recommendations of Stevens and Palfreyman.(33) The patient-driven approach (also known as “bottom-up approach”) ensured that the content generated was grounded in the experiences of women with breast cancer and included the most relevant HRQOL domains based on women’s ratings of importance. A strength of this study is that the sample included women who experienced a wide range of surgical, (neo)adjuvant and targeted

treatments, pathological stages, and healthcare settings (private and public healthcare funding models). This heterogeneity ensured that the 21 items are relevant to a wide range of women undergoing breast cancer treatment.

Several approaches to developing condition-specific PBMs have been described in the literature, including item reduction of existing PROMs using traditional or modern psychometric methods. Goodwin and Green(34) conducted a systematic review of literature of published CSPBMs and found that out of the 51 published CSPBMs, 18 (35%) were developed de novo and the remaining used existing PROMs. Only two of the 18 de novo CSPBMs were developed using data from different sources (e.g., qualitative interviews with patients, expert opinion, literature review, and review of existing instruments). Hence, our study adds to literature on how to rigorously develop a condition-specific PBM that demonstrates content validity using a bottom-up approach.

The development of the BREAST-Q Utility module is timely, as the International Society for Pharmacologic and Outcomes Research's taskforce recommends the use of a PBM that is appropriate for a specific health condition and patient population, in addition to considering the requirements of the agency to which the economic evaluation will be submitted.(35) Hence, once completed, the BREAST-Q Utility module will be highly relevant in cases where the generic PBMs fail to include treatment outcomes that are important to the women seeking or undergoing treatments for breast cancer. Further, generic measures have been shown to have problems with floor and ceiling effects and sensitivity in certain patient populations.(36, 37)

In breast cancer, for example, in a trial assessing the treatment outcome of two different breast reconstruction approaches (implant versus autologous), the use of a generic PBM would be insensitive to measuring differences in breast appearance, body image, and breast sensation. As such, the utility values derived from a generic PBM in such a trial may underestimate the benefits of an intervention. Contrarily, utility values derived from condition-specific PBMs exclusively may overestimate the treatment benefit and not allow for comparability across health conditions and interventions. Since utility values derived from condition-specific PBMs are currently not accepted in base-case cost-effectiveness analysis by most of the international agencies, we recommend using the BREAST-Q Utility module alongside a generic PBM in economic evaluations of breast cancer interventions.

Our study adds to the growing body of evidence about the impact of breast cancer diagnosis and treatments on HRQOL. Consistent with the previous qualitative and quantitative studies, we found that the diagnosis of breast cancer and its treatments have a negative impact on breast appearance (15, 38), overall appearance (39), and body image(40, 41); physical (42, 43), psychological (44-46), social (47-49), and sexual well-being (50, 51); and overall HRQOL (15, 52-55).

We found that almost all the domains and subdomains identified in this study mapped to the original BREAST-Q conceptual framework. In the BREAST-Q Version 2, however, breast sensation and lymphedema are measured by one or two items in the Physical well-being scale. More recently, novel treatments for restoring breast sensation following breast cancer surgery have been proposed.(56-58) Our study found that the lack of sensation or abnormal sensations following breast surgery can last for months or even

years, with implications for the physical, psychological, and sexual well-being of women. Additionally, the impact of arm lymphedema on the HRQOL of women has come to the forefront, with several new surgical and non-surgical treatments aimed at preventing or reducing lymphedema. There is lack of rigorously developed and validated patient-reported outcome instruments that assess breast sensation or arm lymphedema and its impact on HRQOL. To fill this gap, our team is developing new BREAST-Q modules for measuring the impact of breast sensation and arm lymphedema on the HRQOL of women diagnosed with breast cancer.

A limitation of our study is that the study sample included only English-speaking women with breast cancer living in North America. Further, most participants were diagnosed with early stage breast cancer. As a result, domains that are relevant to middle- to older-aged women with earlier stages of cancer may have been overrepresented in the Utility module. With advancements in early diagnosis and prevention, most of the women in developed countries are diagnosed at early stages(2, 59) and hence, from a health technology assessment and policy perspective, this is where the BREAST-Q Utility module has the most relevance. To address this limitation, the expertise of a multidisciplinary sample of healthcare professionals with experience in caring for patients with breast cancer was included at various stages of scale refinement. In the next phase of the study, a large sample of breast cancer patients will be surveyed to examine response patterns and data quality (e.g., floor and ceiling effects, missing data). The field test of the Utility module will help us understand any patterns in responses by specific breast cancer subgroups (e.g., cancer stage, treatment types) and patient demographics (e.g., age).

CONCLUSION

This paper describes the development of a new BREAST-Q Utility module using a mixed-methods approach. The content of the BREAST-Q Utility module is grounded in extensive feedback from women diagnosed with breast cancer and healthcare professionals with expertise in treating patients with breast cancer. The next phase of research will examine the pattern of responses and psychometric properties of the Utility module in a large sample of women with breast cancer, followed by a valuation survey to elicit utility weights for each dimension included in the module. Once developed, the BREAST-Q Utility module will be available for use in clinical research and in economic evaluations of breast cancer interventions through the Q-portfolio webpage (www.qportfolio.org).

LIST OF ABBREVIATIONS

BCT	Breast Conserving Therapy
BMI	Body Mass Index
HCP	Healthcare Professional
HRQOL	Health-Related Quality of Life
MSK	Memorial Sloan Kettering Cancer Center
PBM	Preference-Based Measure
PROM	Patient-Reported Outcome Measure
SF-6D	Short Form-6 Dimension
TGH	Toronto General Hospital
US	United States

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FIGURE LEGEND

Figure 1: An overview of the steps used in the development of the BREAST-Q Utility module

Figure 2: Item pool of the BREAST-Q Utility module

Figure 3: Conceptual framework of the BREAST-Q Utility module

Figure 4: Top 15 domains by stage of breast cancer (n=50)

Table 1: Demographic and clinical characteristics of the sample

	Qualitative interviews N=57		Cognitive interviews N=9	
Characteristic	**N**	**%**	**N**	**%**
Site of Recruitment				
Canada – JCC	22	39	6	67
Canada – TGH	21	37	3	33
United States – MSK	14	25	0	0
Stage of breast cancer				
Stage 0	9	16	1	11
Stage 1	15	26	2	22
Stage 2	20	35	5	56
Stage 3	10	18	1	11
Stage 4	3	5	0	0
Age in years				
Young adult (18 – 39)	2	4	0	0
Middle-aged adult (40 – 59)	39	68	6	67
Old adults (60 and above)	16	28	3	33
Race/Ethnicity				
Caucasian	45	79	7	78
Black or African American	2	4	1	11
Asian	5	9	1	11
Other	5	9	0	0
BMI category				
Underweight - <18.5	2	4	1	11
Normal – 18.5 to 24.9	21	37	2	22
Overweight – 25 to 29.9	24	42	4	44
Obese – 30 and higher	10	18	2	22
Marital status				
Married/Living common law	43	75	8	89
Single, never married	4	7	0	0
Divorced/separated/widowed	10	18	1	11
Employment				
Employed, full-time	24	42	3	33
Employed, part-time	12	21	3	33
Unemployed	2	4	0	0

Homemaker	3	5	0	0
Sick leave/Disabled	3	5	0	0
Retired	11	19	1	11
Other	2	4	2	22
Total annual household income (previous year)				
0 – 25,000	5	9	0	0
25,000 – 50,000	5	9	0	0
50,000 - 75,000	8	14	2	22
>75,000	31	54	7	78
Prefer not to say	8	14	0	0
Education				
High school graduate or equivalent	10	18	2	22
Some college/university (less than 4 years)	13	23	2	22
College/university (4-year bachelor's degree)	28	49	4	44
Postgraduate degree (e.g., Masters, Doctorate, etc.)	6	11	1	11
Type of (neo)adjuvant treatment				
Chemotherapy	37	65	7	78
Radiation	35	61	7	78
Hormone replacement therapy	36	63	7	78
Targeted therapy (HER2)	7	12	0	0
Type of cancer surgery				
Breast conserving therapy	9	16	2	22
Mastectomy – Unilateral	24	42	5	56
Mastectomy – Bilateral	23	40	2	22
None	1	2	0	0
Reconstruction	**N=47**		**N=7**	
Yes	36	77	4	
No	11	23	3	
Type of reconstruction	**N=36**		**N=4**	
Autologous	26	72	2	50
Implant	10	28	2	50
Laterality				
Unilateral	18	50	2	50
Bilateral	18	50	2	50
Timing of reconstruction				

Immediate	21	58	2	50
Delayed	6	17	2	50
Not available	9	25	0	0

JCC, Juravinski Cancer Center; TGH, Toronto General Hospital; MSK, Memorial Sloan Kettering Cancer Center; HER2, Human Epidermal Growth Factor Receptor

Table 2: Summary of changes made to the BREAST-Q Utility module after each round

Version 1	**Version 1 –Expert feedback**		**Version 2 – Round 1 – Cognitive interviews – patients**		**Version 3 – Round 2 Cognitive interviews - patients**		**Version 4 Expert feedback → *Version 5 (Field-test version)***	
These questions ask about how your breast cancer and/or its treatment has affected you. NOTE: If you had breast cancer surgery on both breasts, please answer thinking about the side (i.e., breast and/or arm) that causes you more difficulty or concern.	REVISE	These questions ask about how your breast cancer and/or its treatment has affected you. Please answer each question based on how you look and feel TODAY. NOTE: If you had breast cancer surgery on both breasts, please	RETAIN		RETAIN		REVISE	These questions ask about how your breast cancer and/or its treatment has affected you. Please answer each question based on the PAST WEEK.

		answer thinking about the side (i.e., breast and/or arm) that causes you more difficulty or concern.						
How much do you experience pain and/or unpleasant sensations (e.g., pressure, tightness) in your breast area?	REVISE	How much bodily pain do you experience?	REVISE	How much pain do you experience?	RETAIN		REVISE	How much pain did you feel? Did pain interfere with your daily activities?
		Do you experience any unpleasant symptoms?	REVISE	Do you experience any unpleasant symptoms (e.g., nausea, hot flashes, tingling, or numbness in hands or feet)?	RETAIN		REVISE	Did you experience any unpleasant symptoms? Did unpleasant symptoms interfere with your

								daily activities?
How much feeling do you have in your breast area?	RETAIN		RETAIN		RETAIN		REVISE	How much feeling (sensation) do you have in your breast area?
How self-conscious are you about how your breast area looks?	RETAIN		RETAIN		RETAIN		RETAIN	
How similar (closely matched) are your breasts?	RETAIN		REVISE	How similar are your breasts? NOTE: If you had a double mastectomy without breast reconstructi on (i.e., you do not have breasts), please skip this question.	REVISE	How similar (i.e., closely matched in size and shape) are your breasts?	REVISE	How closely matched (i.e., in size and shape) are your breasts?
How much distress	RETAIN		REVISE	How much emotional	REVISE	How much emotional	REVISE	How much emotional

(e.g., anxiety, worry, sadness) do you feel because of breast cancer?				distress do you experience?		distress (e.g., anxiety, worry) do you experience?		distress (e.g., anxiety, worry) did you experience? Did emotional distress (e.g., anxiety, worry) interfere with your daily activities?
How difficult is it for you to keep up with your usual roles and responsibilities (e.g., work, caring for others, social activities)?	RETAIN		REVISE	How difficult is it for you to keep up with your usual activities?	REVISE	How difficult is it for you to keep up with your usual activities (e.g., work, housework, caring for self or others, social life)?	REVISE	How difficult was it for you to keep up with your usual activities (e.g., work, housework, caring for self or others)? Was it difficult for you to keep up with your usual

								activities (e.g., work, housework, caring for self or others)?
How difficult is it for you to lift or move your arm?	RETAIN		RETAIN		RETAIN		REVISE	How difficult is it for you to lift or move your arm? Did difficulty lifting or moving your arm interfere with your daily activities? NOTE: If both of your arms were affected by breast cancer treatment, please answer thinking of the arm that causes you

								more difficulty or concern.
How tired do you feel?	REVISE	How tired (i.e., fatigue) do you feel?	REVISE	How much fatigue do you feel?	RETAIN		REVISE	How tired did you feel? Did feeling tired interfere with your daily activities?
How difficult is it for you to do activities that use your abdomen (e.g., get out of bed, make bed)?	REVISE	Did you have breast reconstructi on using your abdomen (i.e., TRAM or DIEP flap)? If yes, please answer the following question. How difficult is it for you to do activities that use your abdomen	REVISE	Did you have breast reconstructi on using your own skin and fat (i.e., abdomen, back, thigh)? If yes, please answer the following question. Do you experience problems at the donor site where	RETAIN		DROP	

		(e.g., get out of bed, lift a heavy object)?		fat and skin were taken?				
	NEW	How much nausea do you experience?	RETAIN		RETAIN		REVISE	Did you experience any nausea? Did nausea interfere with your daily activities?
	NEW	How much neuropathy (i.e., tingling or numbness in your hands or feet) do you experience?	RETAIN		RETAIN		REVISE	Did you experience any neuropathy (i.e., tingling or numbness) in your hands or feet? Did neuropathy (i.e., tingling or numbness) in your hands or feet interfere with your

								daily activities?
	NEW	Did your breast cancer treatment include radiation therapy? If yes, please answer the following question. How does the radiated skin on your breast area look (e.g., change in colour or texture)?	REVISE	How does your radiated breast area look and feel?	REVISE	How does your radiated breast area look and feel (e.g., colour, texture, tightness)?	REVISE	How does your radiated breast area look? How does your radiated breast area feel (e.g., texture, itchy)?

Figure 1: An overview of the steps used in the development of the BREAST-Q Utility module

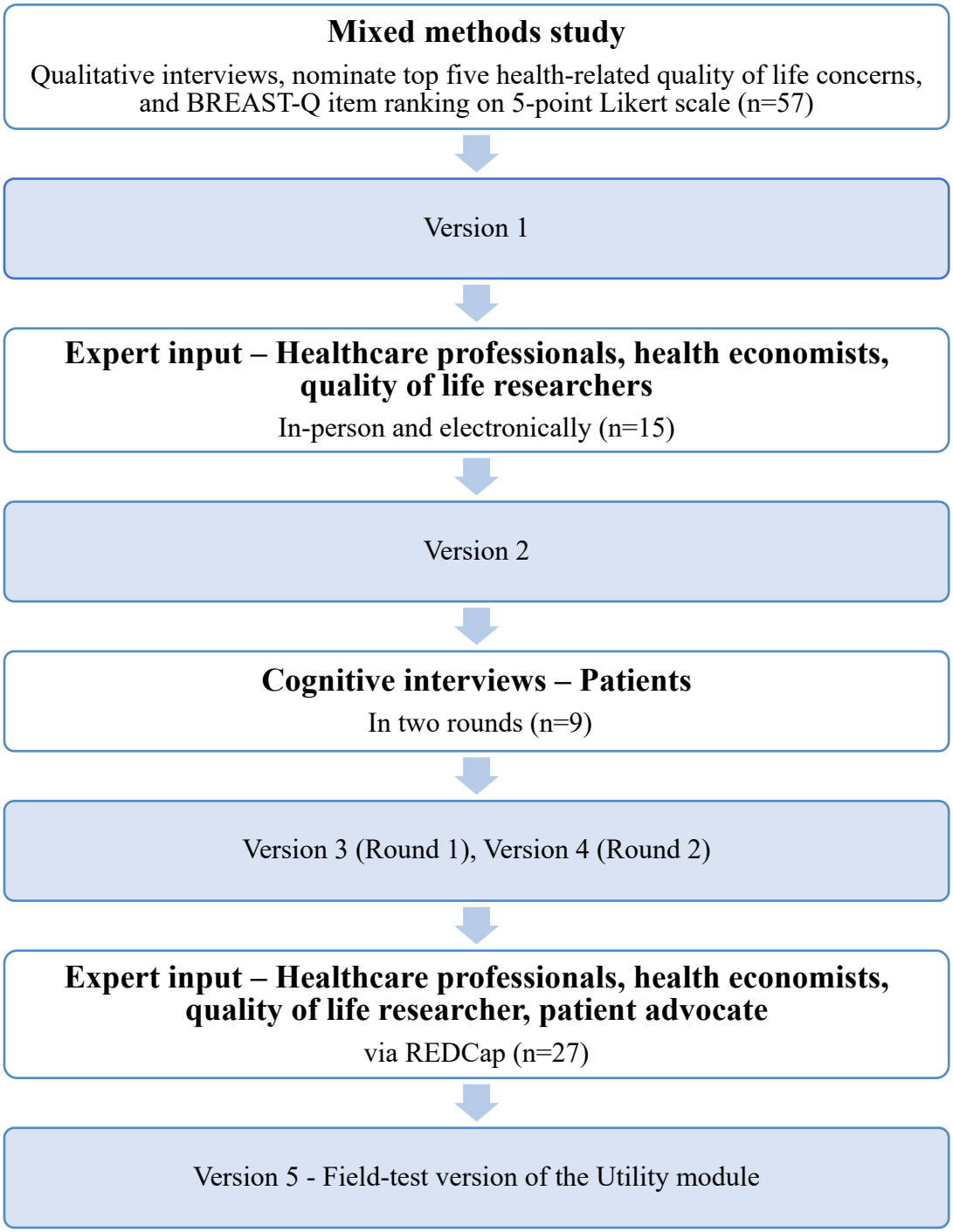


Figure 2: Item pool of the BREAST-Q Utility module (n= 57, 3948 unique codes)

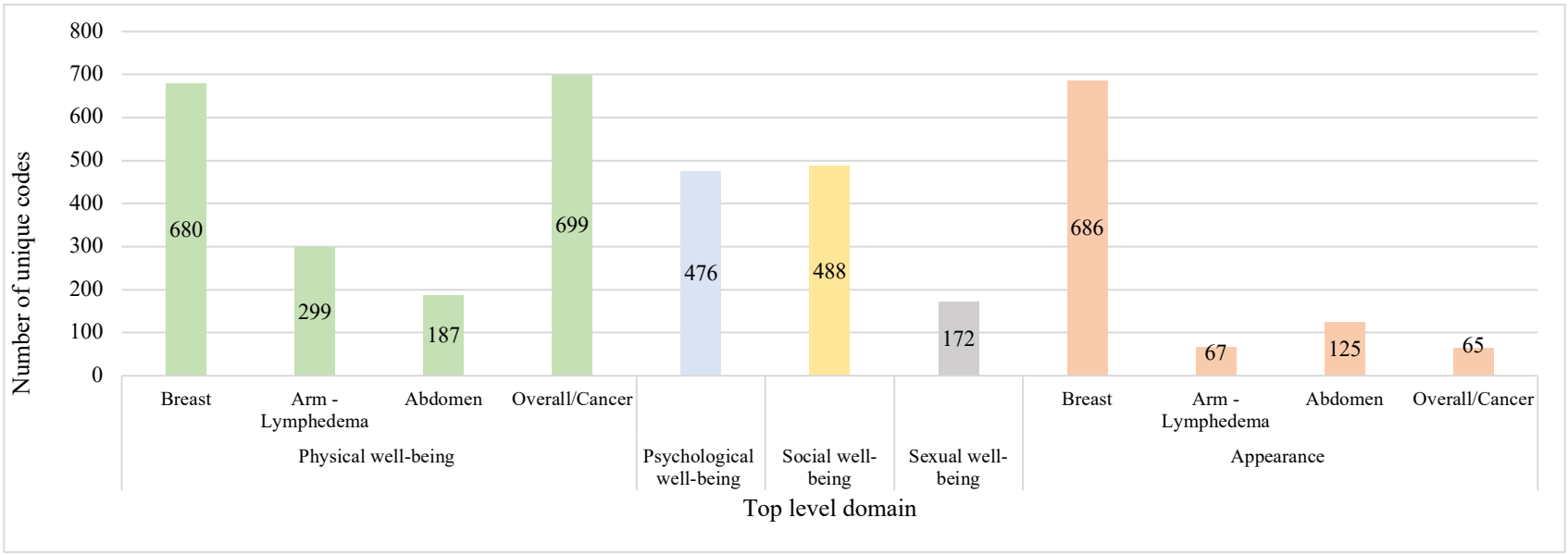


Figure 3: Conceptual framework of the BREAST-Q Utility module (n= 57, 3948 unique codes)

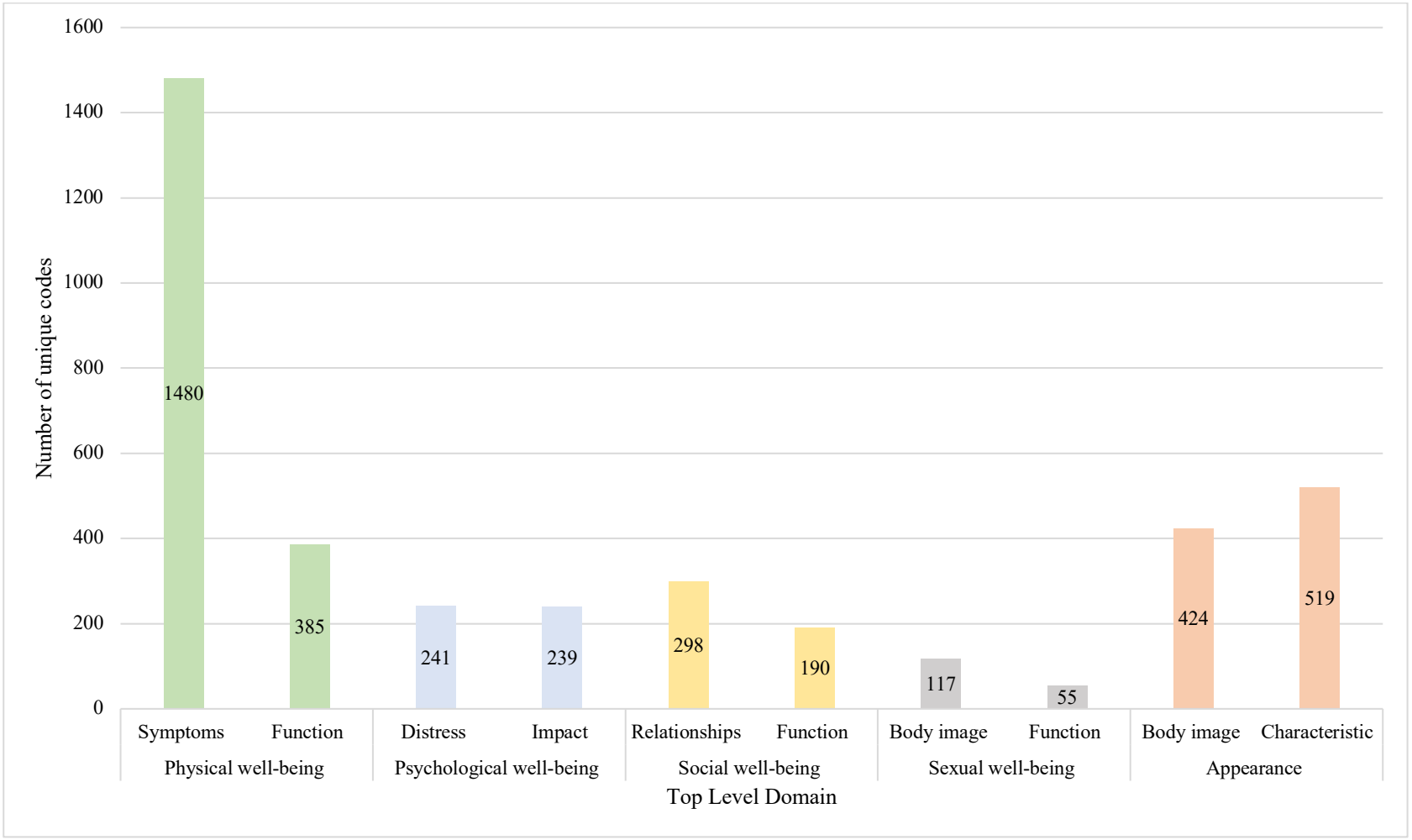
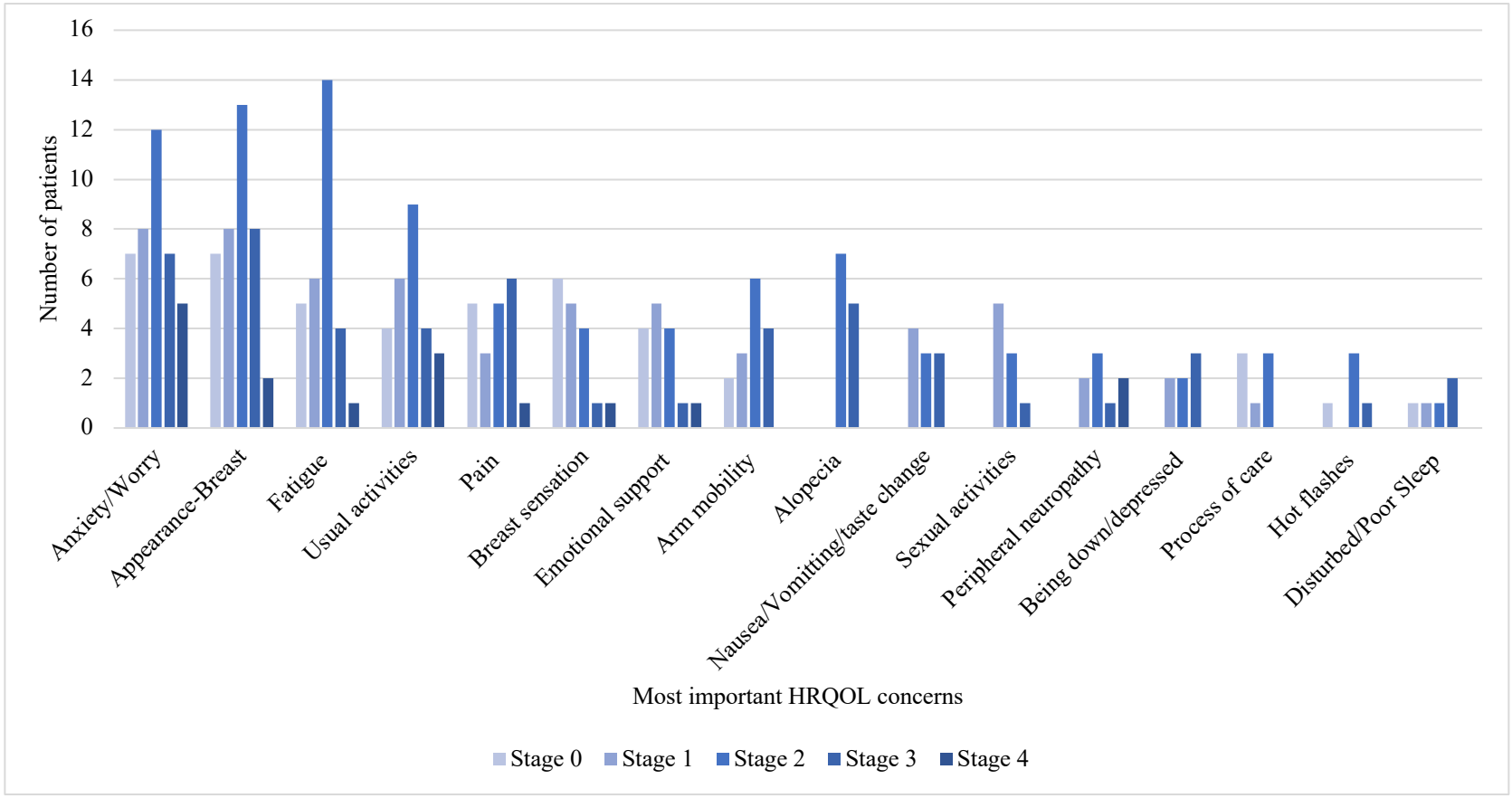


Figure 4: Most important HRQOL concerns



Additional file 1: Field-test version of the BREAST-Q Utility module

(NOTE: Once the field test of the BREAST-Q Utility module is complete, the items will be reduced and refined as appropriate. This is <u>NOT THE FINAL VERSION</u> of the BREAST-Q Utility module)

These questions ask about how your breast cancer and/or its treatment has affected you. Please answer each question based on the PAST WEEK.

1) **How tired did you feel?**
   - ☐ I did NOT feel tired.
   - ☐ I felt a LITTLE tired.
   - ☐ I felt QUITE tired.
   - ☐ I felt VERY tired.
   - ☐ I felt EXTREMELY tired.

2) **Did feeling tired interfere with your daily activities?**
   - ☐ I did NOT feel tired.
   - ☐ I felt tired, but it interfered with NONE of my daily activities.
   - ☐ I felt tired, and it interfered with SOME of my daily activities.
   - ☐ I felt tired, and it interfered with MOST of my daily activities.
   - ☐ I felt tired, and it interfered with ALL of my daily activities.

3) **How much pain did you feel?**
   - ☐ I had NO pain.
   - ☐ I had MILD pain.
   - ☐ I had MODERATE pain.
   - ☐ I had SEVERE pain.

4) **Did pain interfere with your daily activities?**
   - ☐ I had NO pain.
   - ☐ I had pain, but it interfered with NONE of my daily activities.
   - ☐ I had pain, and it interfered with SOME of my daily activities.
   - ☐ I had pain, and it interfered with MOST of my daily activities.
   - ☐ I had pain, and it interfered with ALL of my daily activities.

5) **How much emotional distress (e.g., anxiety, worry) did you experience?**
   - ☐ I experienced NO distress.
   - ☐ I experienced MILD distress.
   - ☐ I experienced MODERATE distress.
   - ☐ I experienced SEVERE distress.

6) **Did emotional distress (e.g., anxiety, worry) interfere with your daily activities?**
   - ☐ I experienced NO distress.

- ☐ I experienced distress, but it interfered with NONE of my daily activities.
- ☐ I experienced distress, and it interfered with SOME of my daily activities.
- ☐ I experienced distress, and it interfered with MOST of my daily activities.
- ☐ I experienced distress, and it interfered with ALL of my daily activities.

7) How difficult was it for you to keep up with your usual activities (e.g., work, housework, caring for self or others)?

- ☐ It was NOT difficult.
- ☐ It was a LITTLE difficult.
- ☐ It was QUITE difficult.
- ☐ It was VERY difficult.
- ☐ It was EXTREMELY difficult.

8) Was it difficult for you to keep up with your usual activities (e.g., work, housework, caring for self or others)?

- ☐ It was NOT difficult for me to keep up with my usual activities.
- ☐ It was difficult for me to keep up with SOME of my usual activities.
- ☐ It was difficult for me to keep up with MOST of my usual activities.
- ☐ It was difficult for me to keep up with ALL of my usual activities.

9) How self-conscious were you about how your breast area looks?

- ☐ I was NOT self-conscious about my breast area.
- ☐ I was a LITTLE self-conscious about my breast area.
- ☐ I was QUITE self-conscious about my breast area.
- ☐ I was VERY self-conscious about my breast area.
- ☐ I was EXTREMELY self-conscious about my breast area.

10) How much feeling (sensation) do you have in your breast area?
<u>NOTE</u>: If you had breast cancer surgery on both breasts, please answer thinking about the breast that causes you more difficulty or concern.

- ☐ I have COMPLETE feeling in my breast area.
- ☐ I have a LOT of feeling in my breast area.
- ☐ I have SOME feeling in my breast area.
- ☐ I have a LITTLE feeling in my breast area.
- ☐ I have NO feeling in my breast area.

11) How closely matched (i.e., in size and shape) are your breasts?

- ☐ My breasts are closely matched (NOT different).
- ☐ My breasts are a LITTLE different
- ☐ My breasts are QUITE different.
- ☐ My breasts are VERY different.
- ☐ My breasts are EXTREMELY different.

12) How difficult is it for you to lift or move your arm?

NOTE: If both of your arms were affected by breast cancer treatment, please answer thinking of the arm that causes you more difficulty or concern.

- ☐ It is NOT difficult for me to lift or move my arm.
- ☐ It is a LITTLE difficult for me to life to move my arm.
- ☐ It is QUITE difficult for me to lift or move my arm.
- ☐ It is VERY difficult for me to lift or move my arm.
- ☐ It is EXTREMELY difficult for me to lift or move my arm.

13) Did difficulty lifting or moving your arm interfere with your daily activities?

- ☐ It was NOT difficult to lift or move my arm.
- ☐ My arm was difficult to lift or move, but it interfered with NONE of my daily activities.
- ☐ My arm was difficult to lift or move, and it interfered with SOME of my daily activities.
- ☐ My arm was difficult to lift or move, and it interfered with MOST of my daily activities.
- ☐ My arm was difficult to lift or move, and it interfered with ALL of my daily activities.

14) Did you experience any unpleasant symptoms?

- ☐ I had NO unpleasant symptoms.
- ☐ I had MILD unpleasant symptoms.
- ☐ I had MODERATE unpleasant symptoms.
- ☐ I had SEVERE unpleasant symptoms.

15) Did unpleasant symptoms interfere with your daily activities?

- ☐ I had NO unpleasant symptoms.
- ☐ I had unpleasant symptoms, but they interfered with NONE of my daily activities.
- ☐ I had unpleasant symptoms, and they interfered with SOME of my daily activities.
- ☐ I had unpleasant symptoms, and they interfered with MOST of my daily activities.
- ☐ I had unpleasant symptoms, and they interfered with ALL of my daily activities.

16) Did you experience any nausea?

- ☐ I had NO nausea.
- ☐ I had MILD nausea.
- ☐ I had MODERATE nausea.
- ☐ I had SEVERE nausea.

17) Did nausea interfere with your daily activities?

- ☐ I had NO nausea.
- ☐ I had nausea, but it interfered with NONE of my daily activities.
- ☐ I had nausea, and it interfered with SOME of my daily activities.
- ☐ I had nausea, and it interfered with MOST of my daily activities.
- ☐ I had nausea, and it interfered with ALL of my daily activities.

18) Did you experience any neuropathy (i.e., tingling or numbness) in your hands or feet?

- ☐ I have NO neuropathy.
- ☐ I have MILD neuropathy.
- ☐ I have MODERATE neuropathy.
- ☐ I have SEVERE neuropathy.

19) Did neuropathy (i.e., tingling or numbness) in your hands or feet interfere with your daily activities?

- ☐ I have NO neuropathy.
- ☐ I have neuropathy, but it interfered with NONE of my daily activities.
- ☐ I have neuropathy, and it interfered with SOME of my daily activities.
- ☐ I have neuropathy, and it interfered with MOST of my daily activities.
- ☐ I have neuropathy, and it interfered with ALL of my daily activities.

Did your breast cancer treatment include radiation therapy? If yes, please answer the following question.

20) How does your radiated breast area look?
<u>NOTE</u>: If you had radiation on both breasts, please answer thinking about the breast that bothers you the most.

- ☐ My breast area looks the SAME as before radiation.
- ☐ My breast area looks a LITTLE different than before radiation.
- ☐ My breast area looks QUITE different than before radiation.
- ☐ My breast area looks VERY different than before radiation.
- ☐ My breast area looks EXTREMELY different than before radiation.

21) How does your radiated breast area feel (e.g., texture, itchy)?
<u>NOTE</u>: If you had radiation on both breasts, please answer thinking about the breast that bothers you the most.

- ☐ My breast area feels the SAME as before radiation.
- ☐ My breast area feels a LITTLE different than before radiation.
- ☐ My breast area feels QUITE different than before radiation.
- ☐ My breast area feels VERY different than before radiation.
- ☐ My breast area feels EXTREMELY different than before radiation.

DECLARATIONS

Ethics approval and consent to participate: This study is approved by the Hamilton Integrated Research Ethics Board, Hamilton, Canada. Ethics approval for the study (Project no. 2078) and data sharing agreement is also obtained from the ethics review boards and legal department of TGH (Project no. 16–5934) and MSK (Project no. 17-147A(1)), respectively. The ethical aspects of this research will comply with the guidelines of the national granting councils (The Canadian Institutes of Health Research) as outlined in the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. All participants provided signed consent to participation and confirmed verbal consent before the interviews.

Consent for publication: This manuscript does not contain any identifiable data. Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The BREAST-Q Utility module is owned by Memorial Sloan-Kettering Cancer Center and McMaster University. Pusic, Klassen, and Kaur are co-developers of the BREAST-Q Utility module. The other authors have no competing interests to report in relation to the content of this article.

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Authors' contribution: AP, AK, SC, and MK were responsible for conceptualizing the project, designing the study, and drafting the manuscript. MK and ET conducted the interviews, and all listed authors participated in the data analysis or interpretation. All listed authors provided intellectual feedback on the manuscript and helped with revisions. All listed authors approved the manuscript for submission.

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CHAPTER 5

Summary and Conclusion

Summary

The objectives of this dissertation were to systematically review the existing health utility estimates available in the published breast cancer literature, develop a conceptual framework to identify dimensions that are important to measure HRQOL of women diagnosed with breast cancer, and use the conceptual framework to develop the BREAST-Q Utility module. All of these objectives were successfully met.

In Chapter 2, comprehensive lists of published health utilities organized by stage of breast cancer and type of intervention that could be used for future model-based economic evaluations for breast cancer were described. An important highlight of the review was the considerable heterogeneity in health utilities. Subsequently, the published health utilities for breast cancer economic models need to be carefully chosen according to health state description and patient and treatment characteristics, and sensitivity analyses should consider a wide range of values matched for the target patient and treatment characteristics. This review also identified some gaps in the literature. More specifically, it called attention to the need for health utility data for hormone replacement therapy and targeted therapy-relevant health states. Most patients receive these treatments over a prolonged period of time (e.g., tamoxifen is recommended for five years or more after primary diagnosis) and experience a range of side-effects.(1) Furthermore, the review identified the lack of a breast cancer-specific preference-based measure, and the development of such a tool became the focus of subsequent chapters in this dissertation.

In Chapter 3, the protocol for an international, multi-phased, mixed-methods study to develop the breast cancer-specific preference-based measure, the BREAST-Q Utility module, was described. A limited number of de novo preference-based measures exist in the literature, and only a handful of those measures are developed using extensive patient input as recommended by the US FDA(2), Medical Outcomes Trust(3), and COSMIN(4).(5) Hence, this chapter will be of value to future clinicians and researchers who are interested in developing a patient-driven, condition-specific preference-based measure.

Chapter 4 reports the results of the mixed-methods study to develop the conceptual framework and the descriptive system of the BREAST-Q Utility module. The results of this study contribute to the breast cancer literature by furthering our understanding of the HRQOL concerns of women diagnosed with breast cancer.

BREAST-Q Utility module

The BREAST-Q Utility module was developed to measure the frequency and severity of common breast cancer-related symptoms and their impact on HRQOL. Some of the dimensions included in the BREAST-Q Utility module overlap with the areas of the HRQOL included in other generic preference-based measures. For instance, the EQ-5D contains the dimensions of pain and anxiety or depression. While not described using the same terms, the dimension of pain and emotional distress are similar in concept. Likewise, the SF-6D contains the dimensions of pain, mental health, vitality, and social functioning,

which are analogous to the pain, emotional distress, being tired, and usual activities dimension respectively in the BREAST-Q Utility module. As such, the BREAST-Q Utility module includes the generic domains of health as per the definition of World Health Organization.(6) Moreover, the new module also measures HRQOL domains that are specific to women diagnosed with breast cancer. The qualitative approach used in the development of the Utility module led to the development of statement-based items and response options to measure the dimensions identified as important and relevant in breast cancer. This approach makes the descriptive system more amenable to valuation, as health states can be formed from these statements(7). This feature will be relevant in the future valuation study used to generate the scoring algorithm of the BREAST-Q Utility module. Once the scoring algorithm is developed, the BREAST-Q Utility module could be used to estimate health utilities and consequently calculate quality adjusted life years (QALYs) in cost-effectiveness analyses of breast cancer-specific interventions.

Making the case for the BREAST-Q Utility module

Recent ISPOR Taskforce guidelines provide a framework for researchers considering the collection of utility data for use by health technology assessment (HTA), pricing, and reimbursement authorities to establish the cost-effectiveness of new interventions.(8) An important consideration in these guidelines is the selection of the appropriate health utility estimates for conditions and populations. Many HTA authorities require that utilities be estimated from a preference-based measure and a value set developed using data from a

general population sample from the authority's country. The guidelines recommend that the type of preference-based measure (i.e., generic or condition-specific) should be driven by the HTA authority's requirements and the appropriateness to the health condition and acceptability of the patient population in which the preference-based measure is going to be administered.(8)

The BREAST-Q Utility module, as a breast cancer-specific measure, has face and content validity for women with breast cancer. This module will be useful in HTA when generic PBMs are not appropriate or have poor psychometric performance in breast cancer or a specific patient group with breast cancer.(8, 9) The Utility module will also be useful when the generic PBMs are not sensitive or responsive to the unique concerns of women with breast cancer. In situations where generic measures have demonstrated acceptable psychometric performance, the BREAST-Q Utility module can be used in sensitivity analyses of an economic model to understand how the use of generic PBMs may have impacted the incremental cost-effectiveness ratios.(9) The Utility module can also be used to enhance an understanding of the variability in patient outcomes across different types of breast cancer treatments, patient groups, or healthcare systems.

Strengths and limitations

The main strength of this dissertation is that it represents new knowledge, as it is the first breast cancer-specific preference-based measure designed to measure issues relevant to women with breast cancer across different stages and treatments. In contrast to previously

published de novo measures, which have used a combination of qualitative work with patients, expert opinion, or review of existing measures(5), our study used all three approaches to identify the dimensions and design the items for the BREAST-Q Utility module. Strengthening our work, a multi-phase, mixed-methods study design was used, and the sample included a heterogeneous sample of women from three tertiary care centers located in two countries. The clinical co-investigators were engaged in the project throughout the course of the study, and an international team of breast cancer clinicians provided feedback during the development and refining of the Utility module. This approach enhanced the content validity of the Utility module.

We succeeded in our goal of collecting rich qualitative data that allowed us to go beyond the planned objectives of this dissertation. The qualitative data from the work presented in Chapter 4 was mapped to the original conceptual framework of the BREAST-Q. This evidence was used to demonstrate content validity of the original BREAST-Q framework, developed in 2010, in a new sample of women with breast cancer. We found that most of the interview data from the new sample of women with breast cancer surgery mapped to the original BREAST-Q scales.(10) This exercise demonstrated that when patient-reported outcome (PRO) instruments are developed using extensive patient input, they remain relevant and comprehensive over time. Such evidence of content validity of a PRO instrument in the long term has rarely been demonstrated in the literature.

A few gaps in the conceptual framework of the BREAST-Q were also identified through the mapping exercise. The current version of BREAST-Q (version 2) measures concepts such as arm lymphedema and breast sensation post-breast cancer surgery with a

limited number of items. Since 2010, when the BREAST-Q was published, new treatment options have become available for managing arm lymphedema, resulting in increased awareness and ongoing evaluation of the condition. Additionally, while the focus of breast reconstruction post-mastectomy has been restoring the appearance of the breast, new surgical techniques aim to restore the "feeling" in the breast.(11) Restoring sensation of the reconstructed breasts is considered the new frontier of breast reconstruction surgery.(12) Lastly, breast animation deformity or breast distortion has been reported in the last decade or so in women who undergo submuscular implant placement following immediate breast reconstruction.(13) This complication has been shown to have substantial impact on the HRQOL of women, but has only recently become a topic of general concern.(14, 15) The prevalence and etiology of animation deformity are yet to be established. As such, to ensure that the measurement of patient outcomes with the BREAST-Q "keeps up" with the evolving clinical practice and research in breast cancer, three new breast cancer modules were developed: (1) Arm Lymphedema, (2) Breast Sensation (women with breast reconstruction), and (3) Breast Animation deformity (women with implant-based reconstruction). Further, additional breast cancer scales (work, fatigue, cancer worry) were developed from the qualitative data. These new scales have now been field-tested to establish their psychometric properties, and the results will be published in peer-reviewed journals.

There are some limitations to the work presented in this dissertation that warrant attention and future study. While the women who participated in the development of the BREAST-Q Utility module were diverse in terms of their educational background, marital

status, and employment status, the group was homogeneous in terms of other demographic characteristics. Most of the women in the study were middle-aged to older women, Caucasian, with total household income of over USD/CAD 75,000 and diagnosed with early stage breast cancer – a sample not necessarily representative of the women diagnosed with breast cancer at a population level. The experiences of women who identify as indigenous, racial or ethnic minorities, belonging to lower socio-economic status, or residing in rural and remote areas were not reflected in this work. Future research could explore how these subgroups of women with breast cancer may uniquely experience HRQOL impact of breast cancer diagnosis and treatment. Further, for feasibility reasons, the development of the Utility module only included women who could speak and understand English, thus limiting the experiences of non-English speakers and warranting future studies.

Our sample was also limited in terms of women with advanced stages of breast cancer, as a few women with metastatic cancer were recruited. This limitation may be due to the advances in diagnostic and screening interventions, which result in breast cancer being diagnosed at earlier stages. Another explanation could be that women at the end stage or experiencing substantial HRQOL issues pertaining to aggressive treatments may be more reluctant to participate in an interview-based study. We accounted for the limited number of women with metastatic breast cancer in our qualitative study by seeking input from clinicians who routinely care for women with advanced stages of the disease and provide palliative and end-of-life care. Future research to determine if the Utility module is responsive to the HRQOL concerns of the above under-represented patient population

could be conducted. This work was completed within the context of tertiary health centers located in metropolitan cities in North America, the evidence is generalizable to particularly well-resourced healthcare systems, such as those in Australia and Europe. Further evidence of the content validity of the Utility module in low- and middle-income countries will be required. Lastly, we recruited participants from Canada and the US. Even though these two countries differ substantially in terms of their healthcare systems and access to healthcare, participants were broadly comparable with respect to the treatments received and HRQOL experiences. Future studies should explore the impact of access to healthcare on the HRQOL and subsequently on the utility values of women with breast cancer.

Use of findings from this research

This dissertation conforms to the Canadian Institute of Health Research's framework for knowledge translation.(16) The use of the integrated knowledge translation approach facilitated the engagement of women with breast cancer, healthcare professionals, and researchers throughout the development of the Breast-Q Utility module. The need for a breast cancer-specific preference-based measure emerged as a result of discussions between healthcare professionals with expertise in treating and managing women with breast cancer, quality of life researchers, and health economists. As such, these three groups were engaged from the stage of protocol development and mutually agreed on the processes and methodology to co-develop the knowledge and assemble empirical evidence to develop

the Utility module. This engagement of the stakeholders was prioritized throughout the development of the Utility module to improve the likelihood that the Utility module would be perceived as useful and applicable in clinical research. Women diagnosed with breast cancer were involved in the development and content validation of the Utility module by means of in-depth, semi-structured, and cognitive debriefing interviews, respectively. Our team created frequent and varied opportunities for ongoing participation of clinicians and researchers in the development of Utility module through scheduled face-to-face meetings and/or telephone calls and maintained regular email study updates. We used end-of-grant KT strategies(16) to disseminate the results of the work to the target audiences, including women diagnosed with breast cancer, clinicians who care for them, and researchers creating evidence to guide that care. The first phase of the end-of-grant KT activities for the research in this dissertation was the presentation of results at academic conferences and publications in high impact clinical journals. To that end, several KT activities to-date have been completed. The results of Chapter 2 (systematic review) were presented at the 39th Annual North American Meeting of the Society of Medical Decision-Making(17), and the manuscript is under consideration for publication. Chapter 3 was published in the open-access, peer-reviewed British Medical Journal Open.(18) Lastly, the preliminary results described in Chapter 4 were presented as an oral abstract at the 25th Annual meeting of the International Society of Quality of Life Research(19) and as a poster at the 2019 Annual CanPROS congress(20), and the manuscript has been submitted to the BioMed Central Women's Health Journal.

The subsequent end-of-grant KT efforts will involve making the Utility module available through the Q-Portfolio website (http://qportfolio.org) at no charge to academic users. We will also liaise with our team's international network of patient partners and clinicians to encourage the uptake of BREAST-Q Utility in research.

Planned future research

The development and validation of a novel instrument is an iterative process and involves an ongoing cycle of testing in various patient populations and settings. Consequently, we are currently analyzing data from over 1700 women with breast cancer recruited through the Army of Women in the United States. As outlined in Chapter 3, we will assess the measurement properties of the BREAST-Q Utility module, and the data will be examined to determine the distribution of responses by age, stage of breast cancer, and treatment phase (i.e., currently receiving treatment vs. survivorship). The refined post-field-test version of the Utility module will be shown to a new sample of women with breast cancer to ensure its content validity. Following these tasks, a valuation study will be conducted to generate preference weights so that the BREAST-Q Utility module can be used as a preference-based measure in the cost-effectiveness analyses of breast cancer interventions. The exact nature of the valuation study will be finalized in due course.

Conclusion

This dissertation described a patient-driven approach for the development of a breast cancer-specific preference-based measure called the BREAST-Q Utility module. In-depth qualitative interviews with women diagnosed with breast cancer provided rich descriptions of the impact of breast cancer and its treatments, which included impact on HRQOL (physical, psychological, social, and sexual well-being) and appearance (breasts and overall). We leveraged data from the interviews with the BREAST-Q ranking data, clinician input, systematic review of literature, and review of existing measures to develop and refine the content of the BREAST-Q Utility module. Future studies will be conducted to assess the psychometric properties of the Utility module and to generate utility weights so that it can be used to calculate QALYs for cost-effectiveness analyses.

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