A review and meta-analysis of health state utility values in breast cancer

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A review and meta analysis of health state utility values in breast cancer (Discussion paper)

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Abstract

Background and purpose
Health-related quality of life is an important issue in the treatment of breast cancer and health-state utilities are essential for cost-utility analysis. This paper identifies and summarizes published utilities for common health-related quality of life outcomes for breast cancer, considers the impact of variation in study designs used and pools utilities for some breast cancer health states.

Data sources and study selection
13 databases were searched using key words relating to breast cancer and utility measurement. Articles were included if specified empirical methods for deriving utility values were used and details of the method, including number of respondents, were given. Articles were excluded if values were based on expert opinion or were not unique.

Data extraction and synthesis
The authors identified 49 articles which met their inclusion criteria providing 476 unique utilities for breast cancer health states. Where possible mean utility estimates were pooled using ordinary least squares with utilities clustered within study group and weighted by both number of respondents and inverse of the variance of each utility. Regressions included controls for disease state, utility assessment method and other features of study design.

Results
Utility values found in the review are summarized for six categories 1) screening related states, 2) preventative states, 3) adverse events in breast cancer and its treatment, 4) non-specific breast cancer, 5) metastatic breast cancer states and 6) early breast cancer states. Pooled utility values for the latter two categories are estimated, showing base state utility values of between 0.668 and 0.782 for early breast cancer and 0.721 and 0.806 metastatic breast cancer depending upon which model is used. Utilities were found to vary significantly by valuation method, and who conducted the valuation.

Conclusions
A large number of utility values for breast cancer are available in the literature, the states for which these refer to are often complex making pooling of values problematic.

The impact upon quality of life and length of life are both important to the assessment of treatments for breast cancer. These outcomes can be combined using the health-related quality of life measure of a QALY (quality adjusted life year). QALYs may be thought of as a 'utility' score since they represents people's preferences towards a particular health state, where 0 represents dead and 1 represents full health. Being able to locate any health state on a 0 to 1 scale allows an estimation of the number of QALYs a treatment brings, and subsequently, a comparison of the cost per QALY benefit across different treatments. The cost per QALY of competing treatments can be a useful input into medical decision making and priority setting (1).

Cost per QALY for breast cancer treatments may be derived from primary research, or from modelling interventions at different disease stages. Where modelling is conducted, modellers require a 'utility' value for each possible health state e.g. newly diagnosed breast cancer, currently undergoing chemotherapy and experiencing some toxicity from treatment. This allows them to map the profile of hypothetical patients as they pass through different scenarios and understand the QALYs gained from alternative treatments.

There are numerous studies which have investigated the utility values associated with breast cancer, unfortunately, they show considerable variation in results. For example, values for metastatic breast cancer (MBC) range from -0.52 to 0.882. What explains this variation? Firstly, there are a number of different health states which an individual with MBC may experience relating to different treatment regimes, different responses to treatment and different possible side-effects of treatment. Secondly, there are different methods for generating utility scores, which can generate different values for the exact same health state.

This study aims to systematically review health state utility values (HSUVs) for breast cancer (early and metastatic) in order to identify all breast cancer HSUVs in the current literature. It then seeks to provide a pooled estimate of HSUVs for each identifiable health state within breast cancer. It also seeks to understand the impact of different methodological techniques on the estimates of utility scores for breast cancer. This will generate a list of HSUVs that can be used in future economic evaluations, and offer greater understanding of how representative individual utility estimates are for breast cancer states.

METHODS

Methods for deriving a utility value

There are a number of methods for deriving HSUVs for economic evaluation (2), either by expert opinion (authors or expert panels) or empirically. This review is only concerned with the latter, of which there are four approaches:

Firstly, preferences may be elicited about specially constructed vignettes or scenarios which describe a particular health state. This is done in three main ways. A) Using a visual analogue scale (VAS) in which the respondent marks the health state on a line anchored from 0 (usually marked as worst imaginable health or dead) to 1 (usually

marked as full health, best health imaginable or best health imaginable for age). B) Using standard gamble (SG) questions which ask respondents to choose between a specified health state for the rest of their lives or a gamble between full health and dead (or some other better and worse outcome than the state being valued). C) Using a time trade-off (TTO) question which asks respondents to choose between a specified health state for a certain period of time representing their future life expectancy and full health (or some other better health state) for a reduced period of time. Hence respondents trade length of life for a health improvement. There are a number of possible groups who could undertake this valuation: patients, those at risk of developing the condition, members of the public (with or without a similar profile to the typical patient), or clinical staff.

Secondly, preferences of the patient population towards their own current health may be measured directly, typically also using VAS, SG or TTO.

Thirdly, a health state may be described using an existing generic multi-attribute health state descriptive system for which a set of values obtained from the preferences of a general population sample exists, such as the EQ-5D (3), SF-6D (4), or the HUI3 (5).

Lastly, condition specific or generic health related quality of life (HRQoL) instruments which either have general population preferences which place them on a 0 (dead) to 1(full health) scale or may be mapped onto existing utility scales (e.g. a value from the disease specific instrument may be mapped onto a value from the EQ-5D).

Utility values from generic instruments like the EQ-5D, HUI2 and HUI3, and those derived from direct TTO, SG and VAS are all intended to give the Q part of a QALY. These diverse methods are unlikely to generate consistent responses for the utility level of different health states, and as shall be seen later, choice of valuation method makes a considerable difference to the utility value associated with particular breast cancer related states.

Pre-scored multi-attribute health state descriptive systems found in this review include the EQ-5D (3), the HUI (5) and the HALex (6).

The EQ-5D, for example, classifies individual health states according to five dimensions: (1) mobility, (2) self care, (3) usual activity, (4) pain or discomfort, and (5) anxiety or depression. Each dimension is divided into three hierarchical levels of dysfunction, giving 245 distinct health states. The social tariff gives valuations for each health state. The social tariff, or scoring algorithm, for the UK is based on TTO preferences of a large random sample of the UK public (3). EuroQol values are anchored by '1' representing full health and '0' representing the state 'dead' with states 'worse than death' bounded by '-1'. This set of utility weights is referred to subsequently as the 'UK tariff'. The EQ-5D is often administered with a VAS (or feeling thermometer) requiring a direct valuation of the individual's health on a scale from worst health imaginable to best imaginable.

The Health Utilities Index (HUI) has two versions, the HUI2 and the HUI3 (5). The HUI3, for example, defines 960,000 health states using eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). HUI states have been valued by parents of school children from Hamilton, Canada (n=256), using SG

estimated from transformed VAS scores (7), using multi-attribute utility theory. Scores are bounded by 1 and 0.03 for the HUI2 and by 1 and -0.36 for the HUI3.

Health and Activity Limitation Index (HALex) (6) is drawn from the Healthy People 2000 survey (8), and the National Health Interview Survey which contains data on two direct measures of health: perceived health (‘*Would you say your health in general is excellent, very good, good, fair or poor?)* and activity limitation. Each person is classified into one of six categories based on age and the ability to perform a major activity giving 30 possible health states, with death assigned the 31st and worst state. A multiplicative, multi-attribute model was used to assign scores for these health states. The healthiest state is assigned a score of 1.0 and the dead state a score of 0. The value of the most dysfunctional living state, ‘limited in activities of daily living and in poor perceived health’, is assigned a value of 0.10, drawn from the HUI-1. This measure is not based on preferences of a representative sample of the public, therefore does not strictly meet the inclusion criteria, however, HSUVs using the HALex are included because they are available at the population level in the US and consequently provide an interesting comparison.

The National Institute for Health and Clinical Excellence (NICE) makes recommendations for UK public funding of treatments across different technologies and disease areas. To facilitate a consistent approach to appraisals across different areas NICE has defined a ‘reference case’ that specifies what it considers the most appropriate methods for assessing health benefits for its purposes and those which are consistent with an NHS objective of maximising health gain from limited resources. The reference case specifies that HSUVs should be derived from standardised and validated generic instruments which use a choice based method (either TTO or SG) and take preferences from the general public (1). Values derived using the third method above are therefore of additional importance in the UK context.

Literature search and data retrieval

A systematic review of HSUVs for conditions relating to breast cancer was undertaken. Published and unpublished work reporting HSUVs in male and female adults with conditions relating to breast cancer were identified. In addition to the systematic searching of electronic databases, experts were contacted, and reference lists were checked.

13 databases were searched using key terms to identify HSUVs in breast cancer[1]. These were MEDLINE, MEDLINE-in progress, MEDLINE other non-index citations, Econlit, EMBASE, Cochrane databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), Cochrane Central Register of Clinical Trials, Technology Assessment (HTA), Economic Evaluation (NHS EED)), Science Citation Index, Social Science Citation Index and the Conference Proceedings Citation Index - Science.

[1] Searched on the 18th March 2009

In addition to the databases noted above Google Scholar[2], The Center for the Evaluation of Value and Risk in Health CEA registry of preference weights[3] (1998-2007) and the Patient Reported Outcome Measurement (PROM) bibliography[4] were also searched[5].

The search terms used were adapted from the strategy adopted in Hind *et al*.(11). In addition to breast cancer terms, the main concepts used to identify HSUVs were: quality adjusted life years, healthy year equivalents, quality of well being, standard gamble, time trade-off, discrete choice experiment, health state utility, preferences and values. The detailed search terms are available from the authors (as an example, the terms used for the MEDLINE search are shown in Appendix A). This very broad strategy was designed to minimize the risk of missing relevant papers.

Inclusion criteria for the review were: concerned with an adult population with breast cancer; contained at least one original, unique utility value, used one of the four empirical methods listed above to derive HSUVs and gave details of both the elicitation technique and the respondents, and available in English or available translation. Studies were therefore excluded if they based utility values on judgement, either of a non-specified number of clinical staff, or on judgement of the author.

Study selection was conducted in a systematic sifting process over three stages: title, abstract and full text. At each stage studies were rejected that definitely did not meet the inclusion criteria. The data extracted from those studies that met the inclusion criteria (shown in Appendix B: Table 1) includes:

1) Authors, year and country from which the data is taken
2) Mean and/or median utility weight and health state or disease category to which it refers
3) Standard deviation or confidence interval if reported, or range/IQR if medians
4) The assessment method (i.e. SG, TTO, VAS, EQ-5D etc.)
5) The lower and upper bound of the scale (i.e., death or worst possible health; perfect health, or normal health etc.).
6) The respondents from whom utilities were elicited (i.e. patients, members of the community, clinicians)
7) Whether valuations are of the patients' own health or of a vignette
8) The number of respondents
9) The mean age of respondents

In order to assess whether the study results are representative of the study sample additional information was extracted on respondent selection and recruitment, inclusion and exclusion criteria, response rates and any possible problems with the study.

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[2] Searched on 1st April 2009, using the phrases "health state utilities" and "breast cancer" and at least one of HUI, TTO, SG, EQ-5D, SF-6D, SF-12, VAS, QWB, HALex or Euroqol, from 2000, searching in the subject areas of Medicine, Pharmacology and Veterinary Science and Social Science, Arts and Humanities.

[3] https://research.tufts-nemc.org/cear/default.aspx

[4] http://phi.uhce.ox.ac.uk/perl/phig/phidb_search.pl

[5] Using the key word 'cancer' and instrument type 'utilities' with the addition of 'breast' as free text. The CEA found 58 papers, all but 2 of which were identified by the initial search (Stevenson *et al*. (9) and Sonnenberg *et al*. (10)), neither of which met the inclusion criteria. The PROM bibliography found 58 papers, all of which had previously been identified. The Google Scholar search identified 306 unique papers, of which 23 had been identified by the original search, 266 were excluded at the title stage, 10 were excluded from abstracts and 7 papers were read, none of which met the inclusion criteria.

Where contact details could be attained, contact with the authors was made to attempt to get standard deviations and means if these were not reported in papers and full study details where only abstracts were available[6].

Data synthesis

HSUVs found in the review fall into six categories 1) screening related states, 2) preventative states, 3) adverse events in breast cancer and its treatment, 4) non-specific breast cancer, 5) early breast cancer states and 6) metastatic breast cancer states.

Where there are a sufficient number of values within a category meta analysis is used to provide breast cancer utilities based on combining all available evidence. Meta-regression uses the measure of utility as the dependent variable with study characteristics as independent variables, hence allows pooling of HSUVs while considering variation in study methods (e.g. respondent types, valuation method used etc.). This offers increased understanding of the impact of study design on HSUVs for breast cancer. Few meta-analysis for HSUVs have been conducted; examples include McLernon *et al.*(12) for liver disease, Bremner *et al.*(13) for prostate cancer, Tengs and Lin(14) for HIV/AIDS and Tengs and Lin(15) for stroke. No review or meta analysis has been conducted for HSUVs in breast cancer.

The method used here is simple, pooled, ordinary least squares. Values from studies where the mean estimate is given with a smaller standard deviation (hence the study is more certain about the true utility value) are given more weight than those with a larger standard deviation. Since not all studies provide a standard deviation, HSUVs are also weighted by sample size, which should correlate highly with standard deviation.

One problem with the data collected here is that most studies report more than one utility value. Often the same individual will provide a number of utility values, either using different methods to value the same state, or using the same method at different time periods, or the same method for different states. Within study and within person values are likely to be more strongly correlated with each other than would be the case if each study gave only one value.

This potential correlation between values may result in underestimates of measures of uncertainty. This may mean coefficients appearing to be significant when they are in fact not. This potential correlation is addressed in the analysis through clustering at the within study group level, which increases the standard errors. Analysis is conducted using Stata 10.

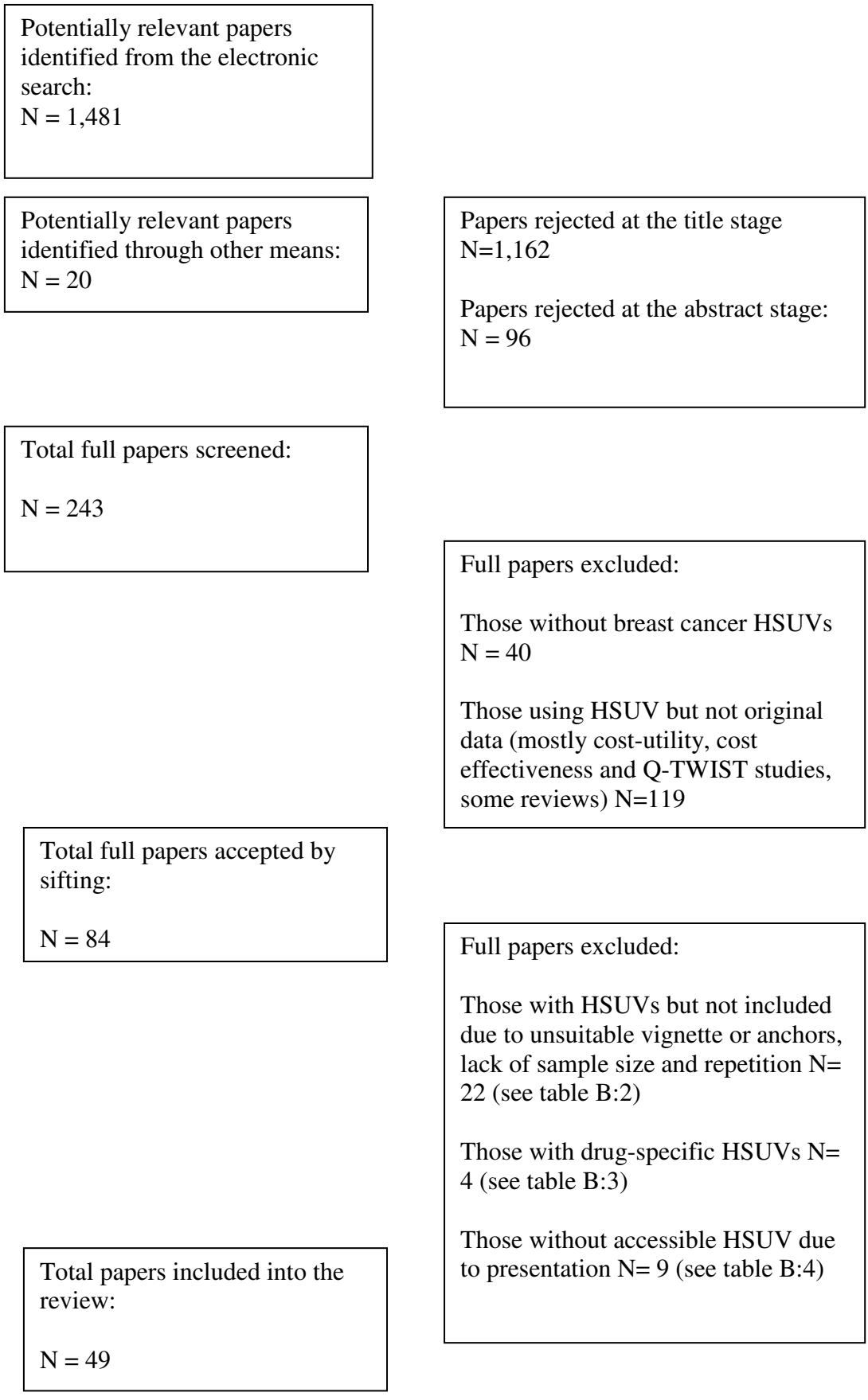
RESULTS

The electronic search identified 1,481 unique papers and 20 papers were identified through other means. 1,162 were excluded at the title stage, and 96 from abstracts.

[6] We would like to take this opportunity to thank a number of people who have kindly provided help with this study: Ruth Brown, George Dranitsaris, Diane Fairclough, Duska Franic, Jane Hall, Robert Launois, Lucio Liberato, Sue-Anne Mclachlan, Simon Pickard, Rob Simons, Sonja Sorensen, W. Warren Suh, Jung-Der Wang, Sue Ward and Eve Wittenberg

Of the 243 identified as potentially relevant 40 papers were excluded because they did not contain breast cancer HSUVs and 119 papers were excluded because they did not contain original HSUVs. A further 22 were excluded because, although containing original HSUVs, they did not meet the inclusion criteria (mostly utility values were estimated by clinicians in an *ad hoc* manner) (see Appendix B: Table B.2). A further 9 included original HSUVs but did not present these in a manner in which they could be extracted for this review (see Appendix B: Table B.3), and 4 were excluded because they contained only drug-specific valuations. A total of 49 papers were therefore included within the review (see Appendix B: Table B.1). Each of the 49 papers contributed between 1 and 36 HSUVs.

Figure 1: Flow diagram showing a summary of study selection and exclusion



The HSUVs identified for the first four categories (screening related states, preventative states, adverse events in breast cancer and its treatment, and non-specific breast cancer) are not suitable for meta-regression because an insufficient number of utility values were identified for each category. These are therefore presented and briefly discussed below.

HSUVs for breast cancer screening related states
Screening states are reported by six studies(16-21), of which Rijnsburger *et al.*(21) interviews women as they progress through a screening program and the remaining five studies derive values for hypothetical states described as vignettes.

Screening attendance is given in four studies, all of which use a VAS scale. HSUVs range from a mean of 0.790 from patients on the day of screening (anchored at worst-best health)(21), a mean of 0.804 from women in a surveillance program (anchored at dead-full health)(16), to a mean of 0.92 for the week surrounding screening from a community sample (anchored at worst-best health)(17), to a median of 0.99 from clinicians(18). Whilst it would appear that women in surveillance programmes rate the screening experience less favourably than others, the lower utility values found by Rijnsburger *et al.*(21) are not dissimilar to values for the same women 2 months prior to screening (0.819) and 1-4 weeks post screening (0.807), suggesting the need for a control group from which to derive a utility decrement of the screening procedure. One study gives a value of 0.553 (VAS dead-perfect health) for a diagnostic mammography (16), which although surprisingly low, may reflect the anxiety and absorbing nature of periods of uncertainty.

HSUVs for post screening outcomes are shown in Table 1; however, the time scale to which these refer to is not clear and results are not always in line with expectations. For example, Johnston *et al.*(20) found little difference in utility values based on community preferences from true positives and false positives.

Table 1: Mean utility values screening states

	True negative	False negative	True positive	False positive
Bonomi *et al.*(16):VAS (death-perfect) (n=137 women in screening programme)	0.891	0.485	0.457	0.810
Gerard *et al.*(19):EQ-5D (n=440 community women)	0.94	0.45	0.48	0.79
Johnston *et al.*(20) :TTO (n=440 community women)	0.91	0.66	0.66	0.66
Johnston *et al.*(20):VAS (death-best) (n=440 community women)	0.92	0.60	0.75	0.67
De Koning *et al.*(18): VAS (worst-best) (n=27 clinicians)	0.89			0.89

These HSUVs do not give a clear indication of values which could be used in modelling for breast cancer screening. Greater insight might be gained through consideration of utility loss involved in the screening process for other health conditions.

Utility values for preventative breast cancer states
Two studies report HSUVs for preventative states, such as prophylactic mastectomy and chemoprevention(22;23). Grann *et al.*(23) found HSUVs for prophylactic mastectomy ranging from 0.56 to 0.86 with higher values for TTO (using a top anchor of disease free) than VAS valuations. Cappelli *et al.*(22) found considerably lower values for double mastectomy and oophorectomy ranging from 0.13 to 0.61 with women with breast cancer giving higher valuations than either women with high risk of breast cancer or members of the general population.

Grann *et al.*(23) found values for chemotherapy prevention, estimated by TTO (using a top anchor of disease free), ranging from 0.79 to 0.90. Values from Cappelli *et al.*(22) are again lower, the SG values ranging from 0.61 for the general population group to 0.74 for the breast cancer group. However, the extent to which people are valuing the consequences of treatment or the remaining risk of developing breast cancer is unclear.

Sackett and Torrance(24) provide a value for mastectomy caused by injury of 0.63 which is considerably higher than the value they find for mastectomy due to breast cancer at 0.48. However, these values are lower than those found for mastectomy by de Haes *et al.*(17), or the post-surgery own health values reported by Jansen *et al.*(25;26). Consequently, although the TTO responses in Sackett and Torrance are for a duration of 8 years, their values may unduly reflect the initial post-operation phase.

Utility values for adverse events in breast cancer and its treatment
Three studies report HSUVs for major adverse events(27-29), including endometrial cancer, fractures (hip, spine, wrist), DVT and pulmonary embolism, stroke and hysterectomy. Values range from 0.922 for DVT(28) to 0.2 for stroke causing severe disability(27). However, these values are not necessarily representative of HSUVs found for these states when not caused by breast cancer or its treatment. Whilst these conditions may have a different impact upon HRQoL when combined with breast cancer, there is minimal evidence upon which to draw such a conclusion. The utility values for fracture states are problematic because it is not clear how long after fracture the scenarios refer yet it is accepted that utility states post fracture vary over time, the most severe states experienced in the immediate post fracture period with recovery rates varying by type of fracture (see Peasgood *et al*. (30).

Utility values for non-specific breast cancer states
Four studies give HSUVs for a general breast cancer state taken from population level surveys. Yabroff *et al.*(31) used the US Medical Expenditure Panel Survey (MEPS) to find a 0.05 utility decrement from breast cancer compared to non-cancer controls using the HALex (matched by age, gender and education). Sullivan *et al.*(32) also used the MEPS finding a utility decrement from an adjusted regression model of 0.015 for breast cancer using the EQ-5D (controlling for age, comorbidity, gender, race, ethnicity, income and education).

Ko *et al.*(33) used the US National Health Interview Survey (NHIS) and the HALex to show improving utility values over time since breast cancer diagnosis from 0.62 during the acute phase (<1 year post diagnosis) rising to 0.69 between 1 and 5 years and 0.71 5 years after diagnosis. Yabroff *et al.*(34) also used the NHIS and the HALex and found values of 0.78 for the first year after breast cancer diagnosis, 0.81 for the continuing stage and 0.64 for the last year of life, compared to controls at 0.85, 0.85 and 0.73,

respectively. These findings emphasise the important role time scale plays in the HRQoL of breast cancer patients.

Three studies took HSUVs from breast cancer patients attending hospital for treatment. Stratmann-Schoene(35) identified women who had received surgery for breast cancer (the current stage of their cancer is unclear) and reported utility values of 0.724 based on VAS (worst-best health), and 0.506 when using a model which maps the SF-12 onto VAS scores. Isogai *et al.*(36) found a value of 0.80 using the EQ-5D on 151 breast cancer patients (0.1 to 25 years since diagnosis). Shih *et al.*(37) found a utility value of 0.81 for 59 breast cancer patients in China using the SF-6D.

Utility values for early and metastatic breast cancer states
The review identified 117 useable HSUVs relevant to metastatic breast cancer (MBC) states from 20 studies: Bonomi *et al.*(16) (1 value), Cykert *et al.*(27) (1 value), De Haes *et al.*(17) (4 values) De Koning *et al.*(18) (2 values), Grann *et al.*(38) (1 value) Grann *et al.*(23) (8 values), Hauser *et al.*(39) (16 values), Hurny *et al.*(40) (5 values), Hutton *et al.*(41) (8 values), Launois *et al.*(42) (24 values), Lidgren *et al.*(43) (6 values), Lloyd *et al.*(44) (9 values), Mansel *et al.*(28) (2 values), McLachlan *et al.*(45) (1 value), Milne *et al.*(46) (12 values), Pickard *et al.*(37) (1 value), Schleinitz *et al.*(47) (2 values), Simons *et al.*(48) (9 values), Sorenson *et al.*(29) (US values: 2 values) and Walker *et al.*(49) (2 values)[7].

The review also identified 230 useable HSUVs for early breast cancer (EBC) states from 29 studies: Bernhard *et al.*(56) (3 values), Bernhard *et al.*(57) (3 values), Bonomi *et al.*(16) (7 values), Cappelli *et al.*(22) (12 values), Conner-Spady *et al.*(58) (14 values), Cykert *et al.*(27) (1 value), De Haes *et al.*(17) (8 values), De Koning *et al.*(18) (4 values), Gordon *et al.* (59) (3 values), Grann *et al.*(38) (1 value), Grann *et al.*(23) (9 values), Hayman *et al.*(60) (10 values), Hayman *et al.*(61) (16 values), Jansen *et al.*(26) (6 values), Jansen *et al.*(25) (25 values), Jansen *et al.*(62) (21 values), Jansen *et al.*(63) (8 values), Kimman *et al.*(64) (20 values), Lidgren *et al.*(43) (16 values), Lovrics *et al.*(65) (8 values), Mansel *et al.*(28) (3 values), Namjoshi *et al.*(66) (4 values), Polsky *et al.*(67) (4 values), Prescott *et al.*(68) (8 values), Sackett and Torrance(24) (1 value), Schleinitz *et al.*(47) (6 values), Sorenson *et al.*(29) (3 values), Walker *et al.*(49) (5 values), and Wolowacz *et al.*(69) (1 value)[8].

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[7] Papers with values for MBC which are excluded from the regression analysis either because of insufficient values within that category (palliative plus surgery (De Haes(17) (1 value)); advanced disease treatment (De Koning *et al.*(18) (1 value))) or because they are repeated within other studies (Brown *et al.*(50) (UK values: 10 values), Brown and Hutton(51) (US values:13 values), Kearney *et al.*(52) (8 values) (see table A:2)). Drug specific values from Dranitsaris *et al.*(53) (8 values), Dranitsaris *et al.*(54) (18 values) and Leung *et al.*(55) (18 values) are also excluded. EQ-5D New Zealand tariff values from Milne *et al.*(46) (4 values) are excluded because these same states are included using EQ-5D UK tariff values. For both MBC and EBC where VAS values are converted into SG or TTO values using a standard power transformation only the original VAS values are included. Where study utility values are given only in medians, these are transformed to an estimate of the mean based on the relationship between mean and median in the other EBC and MBC studies where both are given.

[8] Papers with values for EBC which are excluded from the regression analysis are: values from Cappelli *et al.*(22) for breast cancer without treatment (6 values); values for disease free state with no adverse events (Mansel *et al.*(28) and Sorensen *et al.*(29)); values from Grunberg *et al.*(70) for non-breast cancer specific chemotherapy with and without nausea and vomiting (2 values), those from Gerard *et al.*(71) (6 values) and Hall *et al.*(72) (6 values) because they are difficult to classify (see Table A:2). Drug specific values from Sorensen *et al.*(29) (2 values) and Mansel *et al.*(28) (2 values) are also excluded. Drug

The large number of values identified for MBC and EBC states enables data to be synthesised by meta regression and for these two categories to be modelled separately[9]. Study design features which are included as covariates for both MBC and EBC models include: mean age of respondents (imputed as deviation from the average mean age of respondents where each sample group is given equal weight), method of valuation technique (SG (which is used as the reference category), TTO with a top anchor of full health and TTO with an alternative top anchor, VAS with the anchors of worst to best health[10], VAS with the anchors of dead to full health, EQ-5D with the UK tariff, and any other methods (e.g. HUI3, HALex)), who is valuing (clinical staff (which is used as the reference category), community, patients valuing a hypothetical scenario, patients valuing their own health), and whether the valuation method allows states worse than dead (the reference category being allowing states worse than dead)[11].

The covariates for the models are drawn from the available data restricted to states where at least 3 HSUVs are available. Condition specific states within MBC which are included as covariates are: the treatment categories of starting treatment (reference category), chemotherapy, hormonal therapy, radiotherapy, and no treatment specified; the response categories of response, stable (reference category), terminal, progression and no response specified; the side-effect categories of peripheral neuropathy or severe neuropathy with or without treatment interruption, oedema with or without treatment interruption, febrile neutropenia with or without hospitalisation, sepsis, hypercalcaemia, other side-effects, and no side-effects mentioned (reference category).

Condition specific states within EBC which are included as covariates are: the surgery treatment options of mastectomy followed by reconstruction, mastectomy only, breast conserving surgery (BCS, reference category), surgery which is not specified and no surgery or no mention of surgery; the non-surgery treatment options of chemotherapy (reference category), chemotherapy with toxicity or nausea and vomiting, radiotherapy, hormonal therapy, and no mention of treatment; time scale categories of less than 1 year (reference category), over 1 year, and time scale not specified; recurrence options of recurrence, no recurrence (reference category) and no mention of recurrence; risk of recurrence categories of risk under 15%, risk over 15%, and no mention of risk (reference category).

Table 2 shows the results for regressions for EBC, (1) is weighted by the inverse of the standard deviation, (2) is weighted by sample size but uses the same observations as (1), (3) is weighted by sample size using all available utility values and (4) is weighted by sample size but drops the age control to further extend the number of included observations. Model (5) includes only the 38 EQ-5D values.

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specific values from Bernhard *et al.*(57) (18 values) are not included separately, but they are included as their combined values.

[9] This is necessary because states within EBC and MBC identified in the papers differ considerably requiring different control variables to be used.

[10] VAS values from worst to best health, where they are not recalibrated onto a dead-full health scale are not true QALY values. They are included, and controlled for, here in order to expand the sample size.

[11] VAS values from worst to best health, although could be used to value states worst than dead, since these values are not recoded to place dead as the bottom anchor they are treated as not allowing states worst than dead.

As can be seen in Table 2, the EBC models explain mean HSUVs fairly well (adjusted R^2 of between 0.575 to 0.716), however, there are few consistent significant ($p < 0.05$) findings in terms of the impact of treatment or clinical states. The base state (i.e. the constant term, which represents the mean utility value when all covariates are set at their reference category) for EBC is between 0.668 and 0.782. Differences in valuation methods generate the greatest variation in utility values. The 38 EQ-5D values give a base state value of 0.794, with clinical staff valuations giving a higher utility by 0.118 compared to community valuations. However, the explanatory power of this model is weak (adjusted R^2 of only 0.304), most likely due to the limited number of observations.

HSUVs are significantly higher for at least 1 year post diagnosis or treatment in model (1) once more emphasising the importance of the profile of HRQoL for EBC patients. Currently undergoing or having had radiotherapy is significantly positive in all models increasing HSUVs by between 0.072 and 0.127. This preference for radiotherapy (in contrast to MBC where radiotherapy lowers values) suggests value maybe given to perceived reduced risk of recurrence. Higher values for radiotherapy are present for patient and clinical staff valuations, but not community-based valuations. Compared to BCS only, mastectomy and reconstruction has lower utility, significantly so in model (2) (-0.066).

Table 2: EBC regression models, dependent variable mean utility value

Variables	(1)	(2)	(3)	(4)	(5)
Surgery (ref: BCS)					
Mastectomy & reconstruction	*-0.043*	*-0.066**	*-0.044*	*-0.042*	
	(0.209)	*(0.0742)*	*(0.176)*	*(0.360)*	
Mastectomy only	*0.049*	*0.016*	*0.018*	*0.019*	
	(0.171)	*(0.419)*	*(0.374)*	*(0.485)*	
Surgery but not specified	*0.107****	*0.109****	*0.019*	*0.027*	*0.029*
	(0.0003)	*(0.0001)*	*(0.526)*	*(0.351)*	*(0.284)*
No surgery mentioned	*0.058***	*0.017*	*0.018*	*0.028*	*0.001*
	(0.044)	*(0.552)*	*(0.394)*	*(0.408)*	*(0.989)*
Non surgical treatments (ref: chemotherapy)					
Radiotherapy	*0.111****	*0.127****	*0.084***	*0.072**	*-0.027*
	(0.009)	*(0.001)*	*(0.043)*	*(0.055)*	*(0.485)*
Chemotherapy with tox or NV			*-0.025*	*-0.060*	*0.000*
			(0.529)	*(0.102)*	*()*
Hormonal therapy	*0.017*	*-0.009*	*-0.050*	*0.019*	*-0.020*
	(0.594)	*(0.922)*	*(0.538)*	*(0.643)*	*(0.576)*
No treatment mentioned	*0.053*	*0.077*	*0.046*	*0.054*	*-0.052*
	(0.182)	*(0.104)*	*(0.271)*	*(0.140)*	*(0.187)*
Time period (ref: under 1 year)					
Over 1 year	*0.091***	*0.061*	*0.026*	*0.045*	*0.026*
	(0.013)	*(0.112)*	*(0.375)*	*(0.138)*	*(0.469)*
Time not specified	*0.033*	*0.012*	*0.014*	*0.025*	*0.028*
	(0.196)	*(0.682)*	*(0.665)*	*(0.244)*	*(0.234)*
Recurrence (ref: no recurrence)					
Recurrence	*-0.015*	*-0.072*	*-0.032*	*-0.011*	*0.015*
	(0.839)	*(0.555)*	*(0.761)*	*(0.898)*	*(0.804)*
Recurrence not mentioned	*-0.033*	*-0.038*	*0.005*	*-0.028*	*-0.015*
	(0.457)	*(0.449)*	*(0.917)*	*(0.455)*	*(0.209)*
Risk of recurrence (ref: no risk mentioned)					
Risk under 15%	*-0.003*	*-0.051*	*0.006*	*0.073*	
	(0.956)	*(0.552)*	*(0.915)*	*(0.223)*	
Risk over 15%	*0.041*	*-0.014*	*0.031*	*0.076*	
	(0.479)	*(0.893)*	*(0.708)*	*(0.323)*	
Age (deviation from mean of 53)					
Age difference	*-0.002*	*-0.004***	*-0.002*		
	(0.276)	*(0.0310)*	*(0.139)*		

Whose values (ref: community sample)					
Clinician	*0.107**	*0.093*	*0.090*	*0.168***	*0.118***
	(0.0901)	*(0.109)*	*(0.107)*	*(0.0299)*	*(0.0290)*
Patients' own health	*0.115***	*0.107***	*0.168****	*0.251****	
	(0.033)	*(0.025)*	*(0.0004)*	*(9.35e-08)*	
Patients' scenario	*0.054*	*0.073**	*0.049*	*0.103***	
	(0.304)	*(0.076)*	*(0.234)*	*(0.048)*	
States worse than dead (ref: not allowed)					
States worse than dead allowed	*-0.002*	*-0.050*	*-0.069***	*-0.024*	
	(0.943)	*(0.189)*	*(0.045)*	*(0.378)*	
Valuation method (ref: SG)					
TTO top anchor full health	*-0.025*	*-0.065*	*-0.073*	*-0.092****	
	(0.301)	*(0.224)*	*(0.104)*	*(0.009)*	
TTO top anchor not full health	*0.017*	*-0.056*	*-0.027*	*0.057*	
	(0.752)	*(0.387)*	*(0.601)*	*(0.325)*	
VAS worst-best	*-0.095***	*-0.168***	*-0.221****	*-0.205****	
	(0.0228)	*(0.0210)*	*(0.00278)*	*(7.54e-05)*	
VAS dead-full	*-0.222****	*-0.288****	*-0.282****	*-0.224****	
	(0.000202)	*(0.000454)*	*(1.23e-05)*	*(1.42e-06)*	
EQ-5D UK	*-0.095****	*-0.103**	*-0.150****	*-0.176****	
	(0.00262)	*(0.0535)*	*(0.00536)*	*(3.79e-06)*	
Other	*-0.120****	*-0.150**	*-0.179***	*-0.181****	
	(0.007)	*(0.054)*	*(0.025)*	*(0.001)*	
Constant	*0.696****	*0.782****	*0.771****	*0.668****	*0.794****
	(1.89e-09)	*(1.28e-07)*	*(1.41e-09)*	*(4.60e-10)*	*(0)*
Observations	*133*	*133*	*188*	*230*	*38*
R-squared	*0.642*	*0.716*	*0.646*	*0.575*	*0.304*

Robust p values in parentheses.
*** p<0.01, ** p<0.05, * p<0.1*
A test for normality of residuals rejects a null of normality (Shapiro-Wilk W test), suggesting potential inaccuracies with the hypothesis testing. The removal of 3 observations with the largest residuals restores normality of the residuals and does not alter the findings. Consequently, these 3 observations remain included.

As with the EBC models, Table 3 shows the results for regressions for MBC, (1) is weighted by the inverse of the standard deviation, (2) is weighted by sample size but uses the same observations as (1), (3) is weighted by sample size using all available utility values and (4) is weighted by sample size but drops the age control. Model performance is fairly good with an adjusted R^2 ranging from 0.804 to 0.824.

The base state for MBC varies between 0.721 and 0.806. The reason this is higher than the base state for EBC may be explained in part by the use of the reference category of

'starting treatment' rather than 'chemotherapy' as used for EBC which according to the model reduces values by about 0.14. There are only 8 EQ-5D values for MBC, too few to run the model separately. A weighted average of these values gives a utility value of 0.416, with a large confidence interval (95% CI 0.037 to 0.795) the range in part influenced by the inclusion of a value of -0.52 for hypercalcaemia(46). The lower EQ-5D average compared to the MBC base state also arises due to the fact that the base state refers to a stable position, whereas EQ-5D values are drawn from health states where disease progression is not specified.

Compared to being at the start of treatment undergoing hormonal therapy lowers utility least (not significant), then chemotherapy (-0.127 to -0.149), then radiotherapy (-0.218 to -0.288). This is an interesting contrast to radiotherapy in EBC models, which may arise due to the more severe regime of radiotherapy for MBC. However, there are only 5 (all community-based) values for MBC with radiotherapy.

As would be expected, compared to being stable, responding to treatment raises utility (0.106 to 0.116), and progression and terminal state lowers utility (-0.143 to -0.202 and -0.296 to -0.377, respectively). The majority of utility values are of states without a specified disease progression. Those without a clear statement of disease progression have utility values lower than the stable state (-0.135 to -0.203) which suggests an implicit assumption of disease progression. There is a decline in utility values of around 0.4 to 0.5 as patients move through MBC states suggesting a dramatic loss in quality of life with disease progression. However, all values for these categories are drawn from hypothetical valuations of the respective scenarios, with no corresponding direct evidence from patients.

The impact of side-effects varies slightly between models, the most severe reduction to HSUVs is from hypercalcaemia (-0.582 to -0.679). However, these values all come from one study(46) and arise due to the low tariff value given to the worst health state (33333) on the EQ-5D UK tariff (-0.59). If the EQ-5D New Zealand tariff is used for this sample instead hypercalcaemia is valued at -0.05 rather than -0.52. Sepsis lowers utility values by -0.249 to -0.284, peripheral and severe neuropathy by up to -0.191, oedema and severe oedema by -0.096 to -0.123. The presence of other side-effects are non-significant, however, counter-intuitively, febrile neutropenia increases values by up to 0.092. As can be seen in Appendix A: Table A.1 the number of utility values for side-effects are small, hence these results should be interpreted with caution. Information on utility values for side-effects may be usefully drawn from similar treatments for different cancers (e.g. Nafees *et al*. (73)). However, a full overview of utility values for cancer treatment side-effects would require a different search strategy.

Table 3: MBC regression models, dependent variable mean utility value

VARIABLES	1	2	3	4
Treatment type (ref: starting treatment)				
Chemotherapy	-0.127***	-0.142***	-0.149***	-0.140***
	(0.00359)	(0.00632)	(0.00208)	(0.000691)
Hormonal therapy	-0.014	-0.023	-0.073	-0.033
	(0.785)	(0.683)	(0.250)	(0.573)
Radiotherapy	-0.218***	-0.231***	-0.288***	-0.238***
	(3.32e-05)	(0.000154)	(2.46e-05)	(6.76e-05)
Treatment not specified	-0.160***	-0.196***	-0.177***	-0.183***
	(0.00183)	(1.19e-06)	(0.000159)	(2.97e-06)
Response to treatment (ref: stable)				
Response	0.106***	0.107***	0.116***	0.116***
	(0.00117)	(0.000418)	(5.74e-07)	(3.75e-07)
Progression	-0.143	-0.190**	-0.202***	-0.202***
	(0.138)	(0.0404)	(0.000172)	(0.000118)
Terminal	-0.338***	-0.296***	-0.377***	-0.368***
	(0.000685)	(0.000703)	(8.74e-05)	(1.46e-05)
No response specified	-0.135*	-0.196***	-0.197***	-0.203***
	(0.0705)	(0.00278)	(0.000248)	(3.92e-05)
Side-effects (ref: no side-effects mentioned)				
Peripheral neuropathy	-0.094*	-0.140**	-0.182***	-0.191***
	(0.0665)	(0.0486)	(2.57e-05)	(5.13e-06)
Oedema	-0.097**	-0.123***	-0.089**	-0.096**
	(0.0103)	(0.000225)	(0.0366)	(0.0291)
Febrile Neutropenia			0.085**	0.092**
			(0.0481)	(0.0288)
Sepsis	-0.284***	-0.249***	-0.257***	-0.259***
	(6.36e-06)	(0.000279)	(1.43e-05)	(1.33e-06)
Hypercalcaemia	-0.582***	-0.629***	-0.679***	-0.653***
	(0)	(3.29e-10)	(0)	(0)
Side-effect	0.106	-0.016	0.092	0.095
	(0.192)	(0.898)	(0.130)	(0.112)
Age (Deviation from the mean of 46)				
Age difference	0.003	0.001	-0.000	
	(0.285)	(0.831)	(0.946)	
Whose values (ref: community)				
Clinician	0.086	0.032	0.032	0.012
	(0.304)	(0.647)	(0.627)	(0.783)
Patients valuing own health	0.213***	0.249***	0.258***	0.253***
	(0.00378)	(0.000209)	(0.000197)	(3.05e-05)
Patients valuing a scenario	0.144***	0.125**	0.139**	0.122**
	(0.00237)	(0.0200)	(0.0159)	(0.0287)

States worse than dead (ref: not allowed)				
States worst than dead allowed	0.007	-0.029	0.042	0.010
	(0.904)	(0.701)	(0.450)	(0.851)
Valuation method (ref: SG)				
TTO	0.059	0.086	0.095	0.078
	(0.386)	(0.193)	(0.168)	(0.219)
TTO top not full health	0.219***	0.254**	0.232**	0.227***
	(0.00621)	(0.0217)	(0.0120)	(0.000547)
VAS worst-best	-0.055	-0.017	-0.097	-0.015
	(0.571)	(0.875)	(0.265)	(0.807)
VAS dead-full	-0.036	-0.030	-0.026	-0.052
	(0.270)	(0.240)	(0.326)	(0.136)
EQ-5DUK	-0.086	-0.037	-0.051	-0.062
	(0.283)	(0.625)	(0.452)	(0.334)
Constant	0.721***	0.797***	0.786***	0.806***
	(1.92e-08)	(1.57e-09)	(7.32e-11)	(0)
Observations	73	73	109	117
R-squared	0.824	0.823	0.812	0.804

Robust p values in parentheses
*** p<0.01, ** p<0.05, * p<0.1
A test for normality of residuals rejects a null of normality (Shapiro-Wilk W test), suggesting potential inaccuracies with the hypothesis testing. The removal of 4 observations with the largest residuals restores normality of the residuals and does not alter the findings. Consequently, these 4 observations remain included.

Method of valuation
Choice of valuation method impacts strongly upon HSUVs in both the EBC and MBC models. The most common methods for values included in the regressions are SG and VAS (see Table A.1). The EBC regressions find VAS, EQ-5D and other methods to have significantly lower valuations than SG. In the MBC models, VAS values are insignificantly lower. In the EBC regressions TTO values, where full health is the top anchor, are generally lower than SG, significantly so for the model (4) (-0.092). However, in the MBC regressions, TTO values are not significantly different to SG. This suggests that whilst valuation method has an important impact upon the values attached to breast cancer states, there is no clear systematic relationship between the valuation methods that is relevant to all studies.

What is being valued, by whom and when?
It is often assumed that patients will give a higher value for health states than either clinicians or members of the public (14;24;74). In both the EBC and MBC models the highest values come from patients valuing their own health (0.107 to 0.251 in EBC models and 0.213 to 0.258 in MBC models compared with community valuations). MBC patients give hypothetical scenarios significantly higher values than members of the public for all models (0.125 to 0.144) but they are only significantly higher in model (4) for EBC (0.103). In addition to the distinction between patients and the public, important differences in valuation rest also on patients who are valuing their own current health versus patient valuations of a hypothetical scenario. There is some suggestion from the models that clinicians (nurses and physicians) give slightly higher valuations than members of the public but these differences are not very robust, being significant only for model 4 and 5 of EBC. As shown in Table A.1, the majority of utility values for EBC are derived from patients. In contrast, the majority of values for MBC are from non-patients, in part due to ethical concerns of conducting valuation exercises with MBC patients. This would suggest that combined utility scores which do not account of who has conducted the valuation risk undervaluing MBC states relative to EBC states.

The age of respondents may also impact upon valuations. In this data, for MBC models, the deviation in mean age of the sample from the average of the sample means is not significant. For EBC models, differences in mean age show slightly lower valuations in model (2), with each year the sample mean age is above the average sample means lowering values by 0.004.[12]

Lower and upper bounds
Within each method the top and bottom anchor states may vary. The bottom anchor may be death, worst imaginable health state which is then recalibrated to death or the worst imaginable health state. Where the bottom anchor is death without recalibration respondents are unable to value states as worse than death. Although the EQ-5D tariffs assign some states negative values that are worse than death, in some cases (e.g. Lidgren *et al.* (43)) these are reset to zero. As shown in Table A.1 about a third of the values in the regression analysis are drawn from studies that allow values that are worse than death. Franic and Pathak(75) explored the impact of allowing states worse than

[12] This negative relationship remains if we excluded patients' valuations of their own health where it might be expected that older patients report lower HSUVs due to declining health with age.

dead on utility valuations in breast cancer finding that 15% of their sample considered cancer recurrence to be worse than dead. This would suggest that not allowing states worse than dead by imposing a lower bound of zero onto valuations would raise valuations. For MBC values allowing states worse than dead does not result in significantly lower values in the regression models. For EBC, allowing states worse than dead gives significantly lower values (-0.069) in model (3).

It is assumed here that the top anchors of full health, perfect health, and excellent health are a broadly similar state but the top anchor of absence of condition is a considerably poorer health state than full or perfect health. For EBC 5 values are derived from valuation method using something other than a full health equivalent top anchor. These are from Grann *et al.*(23) who used a TTO with a top anchor of disease free and Grann *et al.*(38) who used a top anchor for TTO of normal health. For MBC 5 values are derived from TTO valuations with a top anchor of disease free, also taken from Grann *et al.*(23) and Grann *et al.*(38). Because the lower top anchor is only used in one method for each cancer type, this is included as a variant of TTO. As expected the top anchor of disease free or normal health raises utility values. The VAS values using a best-worst scale show little systematic difference to the VAS values using a dead-full health scale.

DISCUSSION

Limitations of the regression models

There may be socio-demographic or clinical factors which influence utility values which are not controlled for in the regression models since such data is not available for all samples. Individual studies show conflicting evidence for the importance of other factors (47;60). Similarly, the full diversity of the methods for generating utility values can not be modelled, due to insufficient observations. For example, the duration of the health state presented to respondents during valuation procedures varies from 3 days to the rest of life expectancy. About a third of the values used within the EBC model are derived from papers by Jansen and colleagues who use a 6 month time period followed by a return to full health (25;26;62). This is expected to raise TTO valuations due to the reduced potential for discounting of the full health years, and lower SG valuations because the use of full health as the status quo, as opposed to death, which should mean that both the health state and risk of death are valued in terms of losses. However, this would not explain the higher TTO than SG values found in the MBC models. Hall *et al.*(72) found that duration in a description of a breast cancer health state did not affect valuations, suggesting a constant proportional trade-off. However, Franic *et al.*(76) found that when the chemotherapy health state is presented as only 3 days a high percentage would not trade in SG. Consequently, values for 3 days are higher than when presented as for the rest of life.

Studies with lack of willingness to trade can not include all individual preferences. The partial cascading SG used by Hayman *et al*. (60;77) and the chained SG used by Jansen *et al.*(25;62) result in a smaller sample size for SG valuations compared to TTO and VAS. This may introduce some bias into the comparisons between methods since those for whom a value is not given are unlikely to be randomly selected. Although not included in the meta analysis (see Table B.3), a good example of non-trading in breast cancer can be seen in Perez *et al.*(78) who conducted TTO on 54 MBC patients in New Zealand. The questions involved trading days within the forthcoming month, asked monthly for 12 months. Of the 54 patients 14 did not trade on any occasion and in most

time periods over 2/3rds of respondents did not trade any days. Those facing the prospect of imminent death appear reluctant to further limit their remaining time.

For some combinations of health state and study methodology the model can predict HSUVs great than 1, yet utility scores are bounded at 1. Consequently, if such values are to be used for modelling they require capping at 1. However, where community preferences are used this only applies to very few possible combinations treatments and outcomes.

Understanding the relationship between valuation methods

The relationship between the different valuation methods has been explored in detail in the past. It is often assumed that rating scales give the lowest values followed by then TTO then SG (79). However, some studies find conflicting results with SG giving the lowest value then rating scale then TTO (Hornberger *et al*., 1992). The EBC models find SG to give the highest values, then TTO, then VAS, whereas the order in the MBC models is TTO, SG, VAS but differences are not significant.

Group level valuations of health states using different methods have been linked to each other either by linear relationships (Wolfson *et al.*(80)) or power relationships (Torrance (81)). Some breast cancer studies use a transformation from VAS to SG or TTO utilities. For example, De Haes *et al.*(17) uses a power function of TTO = 1-(1-VAS)^1.82, where VAS is anchored at worst-best imaginable health. O'Leary *et al.*(82) explored the relationship between valuation methods for cancer patients preferring a plateau model (TTO = 1.07 VAS, for VAS < 0.95, TTO = 1.00 VAS, for VAS > 0.95), as many respondents who were unwilling to trade-off any time (even in weeks) gave low rating scale values. This only had an R^2 of 0.29, hence only a relatively small proportion of the total variation in TTO utilities is explained by the rating scale. The authors note that, "These results underscore the danger of using individual or averaged rating scale values as proxies for time trade-off utilities in patients populations and suggest that among patients the constructs measured by time trade-off and the rating scale are fundamentally different" (O'Leary *et al.*(82): 136).

The models here suggest that who values the health state is more important than method of elicitation. Patients valuing their own health are between 0.107 and 0.25 higher for EBC models and 0.21 to 0.26 for MBC models than community members valuing a similar hypothetical state. Differences of this magnitude could make a considerable impact on cost-utility ratios. As would be expected, utilities from patients valuing their own health are more in-line with utility decrements identified through population level surveys.

Patient valuations may be better understood if they are placed in the dynamic context of their condition and treatment. Valuations from patients for hypothetical scenarios may be influenced by their current or past disease state and their current or past treatment regime. Hayman *et al.*(61) suggest that patient valuations may reflect a need to validate previous decisions. For example, patients who had been treated with BCS and radiotherapy preferred radiotherapy and BCS even when this led to recurrence and mastectomy (utility 0.80) compared to BCS alone which also led to recurrence and mastectomy (utility 0.75), however, the public valuations placed recurrence and mastectomy following BCS alone as higher (utility 0.84) than recurrence and mastectomy following BCS and radiotherapy (utility 0.81).

SUMMARY

This review identified 49 papers with utility values which were derived from recognised methods for the estimation of QALYs. From these, 117 values for MBC and 230 values for EBC were extracted and analysed by regression analysis. This analysis found base states values using SG valuations by members of the community to range from 0.668 and 0.782 for EBC and 0.721 and 0.806 for MBC. Utility states were found to vary according to the time profile, with quality of life improving post diagnosis for EBC without recurrence and declining dramatically with disease progression for MBC. Important differences were found according to valuation method and valuer, with breast cancer patients valuing their own health giving the highest valuations.

It is hoped that future research into quality of life in breast cancer will make greater use of multi-attribute health-related quality of life scales for which public preferences exist. Where utility values are generated there is a need to be much clearer about the time scale involved.

APPENDIX A

Acronyms

ABC: Advanced Breast Cancer
BC: Breast Cancer
BCS: Breast Conserving Surgery
BCSRT: Breast Conserving Surgery with Radiation Therapy
CMF: cyclophosphamide, methotrexate and 5-fluorouracil
DCIS: Ductal Carcinoma In Situ
EBC: Early Breast Cancer
FAC: Fluorouracil, adriamycin and cyclophosphamide
HALex: Health and Activity Limitation Index
HDC: High Dose Chemotherapy
HYE: Healthy Year Equivalents
MBC: Metastatic Breast Cancer
MRM: Modified radical mastectomy
PCNV: Post Chemotherapy Nausea and Vomiting.
PM: Prophylactic mastectomy
PN: Peripheral neuropathy
QoL: Quality of Life
RCT: Randomised Controlled Trial
SHE: Subjective Health Estimations
SG: Standard Gamble
SRE: Skeletal-Related Event
SWD: States worse than dead
TTO: Time Trade-Off
VAS: Visual Analogue Scale
WTP: Willingness to pay

Search strategy example: MEDLINE

1. exp breast neoplasms/
2. exp neoplasms/
3. exp carcinoma/
4. exp adenocarcinoma/
5. exp breast/
6. or/2-4
7. 5 and 6
8. (carcinoma adj3 breast$).tw.
9. (neoplas$ adj3 breast$).tw.
10. (adenocarcinoma adj3 breast$).tw.
11. (cancer$ adj3 breast$).tw.
12. (tumour$ adj3 breast$).tw.
13. (tumor$ adj3 breast$).tw.
14. (malignan$ adj3 breast$).tw.
15. or/8-14
16. 1 or 7 or 15
17. HALex.mp. [mp=ti, ot, ab, nm, hw, sh, ct]
18. (euroqol or euro qol or eq5d or eq 5d).tw.
19. qaly$.tw.
20. quality adjusted life year$.tw.
21. hye$.tw.
22. health$ year$ equivalent$.tw.
23. health utilit$.tw.
24. hui.tw.
25. quality of well being.tw.
26. quality of wellbeing.tw.
27. qwb.tw.
28. (qald$ or qale$ or qtimes$).tw.
29. (quality adjusted life day$ or quality adjusted life expectanc$ or quality adjusted survival$).tw.
30. standard gamble$.tw.
31. time trade off.tw.
32. time tradeoff.tw.
33. tto.tw.
34. visual analog$ scale$.tw.
35. discrete choice experiment$.tw.
36. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or short form six).tw.
37. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or short form twelve).mp. [mp=ti, ot, ab, nm, hw, sh, ct]
38. (sf6d or sf 6d or short form 6d or shortform 6d or sf 6 d).tw.
39. health state$ utilit$.tw.
40. health state$ value$.tw.
41. health state$ preference$.tw.
42. or/17-41
43. letter.pt.
44. editorial.pt.
45. comment.pt.
46. or/43-45
47. 42 not 46

48. 16 and 47

Table A.1: MBC utility values (117) & EBC utility values (230)

VARIABLES	Frequency (%) MBC	Frequency (%) EBC
Surgery (some values use more than one)		
Mastectomy and reconstruction	0	12 (5.22%)
Mastectomy only	0	18 (7.83%)
BCS	0	52 (22.61%)
Non-specified surgery	0	32 (13.91%)
No surgery mentioned	0	128 (55.65%)
Non-surgical treatment		
Start of treatment	7 (5.98%)	0
Chemotherapy	57 (48.72%)	69 (30.00%)
Chemotherapy with N&V or toxicity	0	2 (0.87%)
Hormonal therapy	9 (7.69%)	10 (4.35%)
Radiotherapy	4 (3.42%)	35 (15.22%)
Treatment not specified or no treatment	41 (35.04%)	114 (49.57%)
Disease state		
Response	17 (14.53%)	0
Stable	11 (9.40%)	0
Progression	12 (10.26%)	0
Terminal	9 (7.69%)	0
Disease state not specified	68 (58.12%)	0
Side-effects		
Peripheral neuropathy	9 (7.69%)	0
Oedema	9 (7.69%)	0
Febrile Neutropenia	3 (2.56%)	0
Sepsis	3 (2.56%)	0
Hypercalcaemia	3 (2.56%)	0
Side-effect	10 (8.55%)	0
Who valued		
Community	48 (41.03%)	51 (22.17%)
Clinician	42 (35.90%)	19 (8.26%)
Patients own health	13 (11.11%)	100 (43.48%)
Patients scenario	14(11.97%)	60 (26.09%)
States worse than dead allowed	36 (30.77%)	79 (34.35%)
Method of valuation		
Standard Gamble	71 (60.68%)	67 (29.13%)
TTO top full health	8 (6.84%)	30 (13.04%)
TTO top not full health	5 (4.27%)	5 (2.17%)
VAS worst-best	6 (5.13%)	43 (18.70%)
VAS dead-full	19 (16.24%)	35 (15.22%)
EQ-5D UK	8 (6.84%)	38 (16.52%)

Other	0	12 (5.22%)
Risk of recurrence		
Under 15%	0	4 (1.74%)
Over 15%	0	12 (5.22%)
No mention of risk of recurrence risk	0	214 (93.04%)
Recurrence		
Recurrence	0	37 (16.09%)
No recurrence	0	25 (10.87%)
Recurrence not mentioned	0	168 (73.04%)
Time since diagnosis		
Under 1 year	0	50 (21.74%)
1-5 years	0	30 (13.04%)
Time not mentioned	0	150 (65.22%)

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APPENDIX B:

Table B.1: Included studies in alphabetical order

Study	Health state description	Health state value	How valued	Who valued	Comments
1. Bernhard *et al.* (2004) (56)	**Lymph node-negative BC – EBC states** CMF (cyclophosphamide, methotrexate and 5-fluorouracil) Toxicity (Median value at 3 months – peak of toxicity) (n=276) Time without symptoms and toxicity (Median scores averaged within patients over the first 24 months after randomisation, excluding the first 3 months for patients with CMF) (n=384) Relapse (Median of the SHE scores averaged within patients over the first 6 months after relapse) (n=37)	**Median** VAS: 0.76, TTO Power transformation 0.89 VAS: 0.80, TTO Power transformation 0.91 VAS: 0.62, TTO Power transformation 0.71	VAS (Subjective Health Estimations SHE: anchored at worst to best health, patients asked to imagine spending the rest of their life in their current health state, then to value it.) Converted into TTO weights using a power transformation TTO=1-(1-SHE)$^{1.6}$	Postmenopausal patients with lymph note-negative BC, within a RCT for chemotherapy. Full sample, N = 1669 Age (median) 61.	
2. Bernhard *et al*. (2008) (57) IBCSG Trial, Europe, Australia and Asia (see also Table B.3)	**EBC and high risk of relapse** **Toxicity:** Total sample (n=284) **Time without symptoms and toxicity** Total sample (n=292) **Relapse** Total sample (n=85)	**Mean** VAS: 0.60, Transformed TTO 0.77 VAS: 0.78, Transformed TTO 0.91 VAS 0.60, Transformed TTO 0.77	VAS (SHE as above) Converted into TTO as above.	344 EBC women at risk of relapse from IBCSG trial.	Data table refers to means, but text refers to medians.
3. Bonomi *et al.* (2008) (16)	**Screening states:** Screening mammography True negative	**Mean (SD), Median** 0.804 (0.14), 0.80 0.891 (0.10), 0.90	VAS anchored by death (0) and perfect health (1).	English speaking women aged 50-79 randomly	Age given in categories, taking mid-

USA	False negative Diagnostic mammography True positive False positive Treatment Lumpectomy Mastectomy Adjuvant radiation Adjuvant chemotherapy Antiestrogen therapy Disease free at 1 year Recurrence at 1 year Palliation/end of life	0.485 (0.21), 0.50 0.553 (0.20), 0.50 0.457 (0.21), 0.50 0.810 (0.15), 0.80 0.530 (0.21), 0.50 0.483 (0.22), 0.50 0.462 (0.23), 0.40 0.397 (0.21), 0.50 0.520 (0.22), 0.50 0.768 (0.13), 0.50 0.330 (0.19), 0.30 0.358 (0.27), 0.30	Each women valued 11 of 14 possible clinical scenarios. N=131	sampled from Group Health's BC Screening Program. 137 completed interviews: response rate 38%. Respondents more likely than non-responders to have undergone biopsy or treatment for BC. 6 excluded due to lack of information on BC experience.	point would give an average of 62.
4. Cappelli *et al*. (2001) (22)	**BC states** Lumpectomy and radiation therapy (n=59,60) Double mastectomy and chemotherapy (n=58, 60) Breast cancer without treatment (n=44, 60) **Positive BRCA states** No prophylaxis, monitoring only. (n=60, 60) Preventive drug therapy (n=60, 60) Prophylactic bilateral mastectomy and oophorectomy (n=38,60) **BC states** Lumpectomy and radiation therapy (n=55,55) Double mastectomy and chemotherapy (n=55,55) BC without treatment (n=44,55)	**BC group** SG 0.78 (.23), VAS 0.550 (.300) SG 0.68 (.27), VAS 0.289 (.258) SG 0.24 (.26), VAS 0.055 (.130) SG 0.84 (.19), VAS 0.433 (.288) SG 0.74 (.26), VAS 0.404 (.302) SG 0.61 (.30), VAS 0.211 (.230) **HR group** SG 0.73 (.28), VAS 0.440 (.263) SG 0.59 (.33), VAS 0.250 (.269) SG 0.17 (.22), VAS 0.063 (.099)	SG VAS anchored at 0 (least desirable) to 1 (most desírable) 13 hypothetical health states presented to participants including perfect health and death. Health status worse than dead assigned value of -0.05. If dead not assigned 0 in VAS exercise SG values transformed such that 0 = dead.	BC group (n=60) women diagnosed with BC before aged 50 within last 2 years, being treated in Ottawa Regional Cancer Centre. High risk (HR) group (n=58) women without BC with at least one female blood relative diagnosed with BC before age 50. General population (GP)	

	Positive BRCA states No prophylaxis, monitoring only. (n=55,55) Preventive drug therapy (n=55,55) Prophylactic bilateral mastectomy and oophorectomy (n=42,55) **BC states** Lumpectomy and radiation therapy (n=49,49) Double mastectomy and chemotherapy (n=49,49) BC without treatment (n=30,49) **Positive BRCA states** No prophylaxis, monitoring only. (n=49,49) Preventive drug therapy (n=49,49) Prophylactic bilateral mastectomy and oophorectomy (n=27,49)	 SG 0.81 (.19), VAS 0.500 (.289) SG 0.65 (.33), VAS 0.299 (.237) SG 0.50 (.35), VAS 0.199 (.230) **GP group** SG 0.69 (.27), VAS 0.311 (.228) SG 0.55 (.33), VAS 0.198 (.219) SG 0.17 (.24), VAS 0.067 (.119) SG 0.75 (.25), VAS 0.447 (.240) SG 0.61 (.30), VAS 0.307 (.221) SG 0.44 (.31), VAS 0.126 (.129)		group (n=51) women between 18-50 never diagnosed with BC.	
5. Conner-Spady *et al.* (2005) (58) Canada (some data also reported in Conner-Spady *et al.* (2001) (83), which reports earlier study data from T1 to T3).	**EBC states:** T1: Baseline prior to beginning treatment (n= 48) T2: Day 1 of the third cycle of FAC (n=48) T3: 3 weeks after administration of HDC (n=48) T4: 6 months after enrolment or about 8 weeks post-HDC (n=45) T5: 12 months post enrolment (n=40) T6: 18 months post enrolment (n=36)	**Mean (SD)** EQ-5D: 0.78 (0.18), QOL-VAS 0.75 (0.04) EQ-5D: 0.75 (0.18), QOL-VAS 0.77 (0.04) EQ-5D: 0.61 (0.29), QOL-VAS 0.52 (0.06) EQ-5D 0.79 (0.19), QOL-VAS 0.80 (0.04) EQ-5D 0.84 (0.19), QOL-VAS 0.84 (0.04) EQ-5D 0.84 (0.13), QOL-VAS	EQ-5D, UK tariff QOL-VAS. (*How would you rate your quality of life over the past 2 weeks: 0 very negative to 1 very positive*.) EQ-5D distribution at T3 was negatively skewed and bimodal, major mode of 0.88 and minor mode of 0.29, but more symmetrical at T1, 2 and 4. The bimodal distribution at T3 appears to arise due to the higher number of	52 patients from the Tom Baker Cancer Centre in Calgary, Alberta, 1995-1998, with stage I and II BC at high risk of relapse (although under new system all patients would be stage III). Mean age 44.7 (range 33-62).	SD for VAS scores appear low, compared to Conner-Spady *et al.* (2001). 26% of cases rated 1111 for EQ-5D at T1, but FLIC scores ranged from 110.41-142.86 suggesting ceiling effect with EQ-5D

	T7: 24 months post enrolment (n-37)	0.88 (0.03) EQ-5D 0.89 (0.13), QOL-VAS 0.89 (0.03)	level 3's in 'usual activity' at T3, and the subsequent inclusion of the N3 term.		
6. Cykert *et al.* (2004) (27) USA	**EBC, MBC & side effect states:** Curable BC Curable endometrial cancer Metastatic cancer then death within 2 years Stroke: mild debility Stroke: moderate debility Stroke: severe debility DVT: No postphlebitic syndrome DVT: Postphlebitic syndrome Pulmonary embolism Hot flushes - 85% of respondents reported no QoL decrement so this outcome is not included.	**Mean** 0.83 0.83 0.3 0.7 0.7 0.2 0.86 0.90 0.81	SG. Anchored at death-BC cure and avoiding treatment. Study notes that values were converted to utility scores where 0 =dead and 1 = excellent health, although details of this are not given.	106 women aged 50+ from urban areas of North Carolina and south Florida, 35% were African-American. Mean age 60.	
7. De Haes *et al.* (1991) (17) Netherlands	**EBC, MBC & Screening states:** 3 months – 1 year after mastectomy (one table says 2 months?) (10 months) Palliative + surgery (lasting 5 weeks) Palliative + chemotherapy (4 months) Initial surgery (2 months) Palliative + hormonal therapy (14 months) Initial radiotherapy (2 months) Initial hormonal therapy (2 years)	Mean 0.65 (SD .165) Med. 0.64 Transformed = 0.884 Mean .46 (SD .164) Med .41 Transformed = 0.617 Mean .36 (SD .170) Med .34 Transformed = 0.531 Mean .62 (SD .155) Med .67 Transformed = 0.867 Mean .47 (SD .191) Med .45 Transformed = 0.663 Mean .60 (SD .152) Med .59 Transformed = 0.803 Mean .63 (SD .168) Med .61 Transformed = 0.820	VAS. Anchored at worst imaginable to best. Transformed into a utility score, using a power function of TTO=1-(1-VAS) ^1.82	N=27 n=15 employees from the department of public health and social medicine, Netherlands. n=12 experts in BC treatment and epidemiology in the Netherlands. Age of respondents not	

	Initial chemotherapy (6 months) 3 months – 1 year after breast conserving surgery (one table says 2 months?) (10 months) Palliative + radiotherapy (1 month) Terminal illness (1 month) Screening attendance (1 week) Diagnostic phrase (5 weeks) Disease-free > 1 year after mastectomy Disease-free > 1 year after breast-conserving therapy	Mean .50 (SD .176) Med .50 Transformed 0.717 Mean 0.71 (SD 0.155) Med .74 Transformed 0.914 Mean .43 (SD .164) Med .38 Transformed 0.591 Mean .19 (SD .153) Med .17 Transformed 0.288 Mean .92 (SD .069) Med .94 Transformed 0.994 Mean .71 (SD .142) Med .71 Transformed 0.895 Mean .77 (SD .127) Med .80 Transformed 0.947 Mean .82 (SD .115) Med .83 Transformed 0.960		stated.	
8. De Koning *et al.* (1991) (18) Netherlands	**MBC, EBC and screening states** Adjuvant hormonal treatment (2 or 5 years) Advanced disease treatment (20 months) Biopsy due to false positive (5 weeks) Biopsy with benign result (5 weeks) Breast conserving therapy (10 months) Terminal, advanced (1 month) Mammographic screening (1 week) Primary radiation (2 months) Primary surgery (2 months)	**Median** 0.82 0.63 0.89 0.89 0.93 0.29 0.99 0.80 0.87	VAS. Anchored at worst possible to perfect health.	N=27 clinicians or public health experts	
9. Gerard *et al.* (1999) (19) UK Some data	**Screening states:** Short term True negative False positive Long term	**Mean (SD)** 0.94 (0.14) 0.79 (0.21)	Respondents classified screening states into EQ-5D dimensions. EQ-5D assuming dimensions 1 and 2 are	N=440 Community. Women. 209 of whom aged 40-44 and 231 aged 45-64.	

is also reported in Johnston *et al.* (1998) (20)	True positive False negative	0.48 (0.30) 0.45 (0.30)	constant. UK tariff. Also conducted TTO. 12 months and rest of life. Anchored at dead-full health. SWD not permitted		
10. Gordon *et al.* (2005) (59) Australia	**EBC states** DAART (n=36) STRETCH (n=31) Control (n=208) Regression analysis to control for age, tumour size, presence of co-morbidities, income, health insurance, living alone, perceived stress at baseline. DAART STRETCH Control	**Mean (SD)** 0.77 (SD 0.19) 0.79 (SD 0.18) 0.73 (SD 0.17) 0.84 (95% CI 0.74-0.90) 0.80 (95% CI 0.73-0.87) 0.72 (95% CI 0.70-0.75)	VAS (SHE) Anchored at worst possible to best possible.	Diagnosed primary BC, unilateral disease, aged 25-74. Allocated into: n=36 DAART (Domiciliary Allied Health and Acute Care Rehabilitation Team). Mean age 59. n=31 STRECH (Strength through recreation exercise togetherness care health). Mean age 54 n=208 Control group sourced from another sample. Mean age 55.	Women were excluded from the DAART and STRETCH groups if they were “too ill”.
11. Grann *et al.* (1998) (38)	**EBC & MBC states** BC Metastatic	**Mean (IQR)** 0.89 (IQR 0.87-1.00) 0.63 (IQR 0.50 – 0.83)	TTO. Anchored at death to health state prior to disability.	54 community-based. Mean age 38	

USA					
12. Grann *et al.* (1999) (23)	**EBC, MBC and preventative states:** BC patients without known metatstatic disease. G4, n=20 Reference group (age range 33-50) Breast cancer. Therapy includes mastectomy with reconstruction and chemotherapy. Afterwards you feel well and resume your previous activities and social and personal life. Told you have 30% risk of recurrence. Women like you live on average to 70. Metastatic disease (breast or ovarian). It has partially incapacitated you. You must spend 50% of your time at home although you are able to handle your own personal care and local shopping. You have pills that control your pain fairly effectively, but they cause moderate nausea and fatigue. Your life expectancy is 3 years beyond your current age. Prophylactic mastectomy (double). BRCA1 or BRCA2 positive. Reduce risk of BC by 90%. Chemoprevention. BRCA1 or BRCA2	**Mean (SD)** VAS: .83 (.12) VAS: .84 (.15) VAS:G1 .58 (.19), TTO:G1 0.87 (.20) VAS:G2 .57 (.23), TTO:G2 0.68 (.35) VAS:G3 .66 (.17), TTO:G3 0.83 (.22) VAS:G4 .64 (.21), TTO:G4 0.89 (.13) VAS:G1 .27 (.18), TTO:G1 0.73 (.27) VAS:G2 .34 (.29), TTO:G2 0.52 (.35) VAS:G3 .34 (.22), TTO:G3 0.59 (.27) VAS:G4 .40 (.26), TTO:G4 0.76 (.31) VAS:G1 .56 (.22), TTO:G1 0.86 (.21) VAS:G2 .63 (.23), TTO:G2 0.82 (.39) VAS:G3 .60 (.26), TTO:G3 0.76 (.26) VAS:G4 .66 (.31), TTO:G4 0.85 (.15) TTO:G1 0.90 (0.15)	VAS. Anchored at death to best possible. TTO. Anchored at death to disease free state (“eliminate the condition described in the vignette”). Living till 70.	G1: Young women community n=93. Mean age 26 G2: Older women community n=42. Mean age 40 G3: High risk women community n=22. Mean age 43 G4: Breast Cancer n= 20. Mean age 43 (range 33-50)	Test-retest on 18 response young group. 7 pairs correlation higher than 0.7, remaining 11 higher than 0.5. VAS rating for mastectomy (0.515) lowest.

	negative. 1 pill every day for 5 years. Reduce risk by 50%	TTO:G2 0.79 (0.29) TTO:G3 0.81 (0.25) TTO:G4 0.85 (0.22)			
13. Hauser *et al.* (2001) (39) USA Abstract	**MBC states:** Partial response (PR) PR with severe peripheral edema PR with severe PN Before second line treatment begins Stable disease Late progressive disease Terminal disease Sepsis	**Mean (SD)** 0.84 (.11) P, 0.71(.22) N 0.78 (.17) P, 0.63(.24) N 0.76 (.13) P, 0.56 (.24) N 0.73 (.16) P, 0.59 (.22) N 0.72 (.15) P, 0.54 (.22) N 0.63 (.18) P, 0.45 (.25) N 0.40 (.26) P, 0.19 (.21) N 0.39 (.25) P, 0.20 (.23) N	SG	45 patients (P) 57 oncology nurses (N)	Patients have higher utilities than nurses. All differences are significant.
14. Hayman *et al.* (1997) (60) USA	**EBC states:** WITH PATIENTS A. Conservative surgery and radiation therapy without local recurrence to date but with a 10% risk of local recurrence that could be salvaged with mastectomy and reconstructive surgery. (SG n=97) B. Conservative surgery and radiation therapy with a local recurrence salvaged with mastectomy and reconstructive surgery (SG n=90) C. Conservative surgery alone without a local recurrence to date but with 40% risk of local recurrence that would be salvaged with either breast-conserving surgery and radiation therapy or mastectomy and reconstructive surgery. (SG n= 96)	PATIENTS Mean 0.92 (sd 0.15) Med. 0.97 IQR 0.91-0.99 Range 0.05-1.00 Mean 0.82 (sd 0.19) Med. 0.85 IQR 0.76-0.95 Range 0-0.99 Mean 0.88 (sd 0.18) Med 0.92. IQR 0.86-0.98 Range 0-1.0	VAS. Anchored at least desirable to most desirable. Not reported but used to identify the lowest rank health state for the cascading SG method. SG. Partial cascading. Highest four health sates ranked using best outcome and lowest ranked health. Anchored death-perfect health. SWD not discussed.	Patients. N=97. Median age 56 (range 30-84) Patients with stage I or II tumours (88 had stage I), who had undergone breast-conserving surgery followed by radiotherapy (35 also had chemotherapy). They had to have completed all therapy (except tamoxifen) at least 6 months, not more than 24 months prior to the interview	Preference for stage A over C suggests the increased risk of recurrence (10% to 40%) outweighs the side effects of radiotherapy. A range of additional data were collected for patients, however, none of the factors explained more than 5%

	D. Conservative surgery alone with a local recurrence salvaged with conservative and radiation therapy (SG n=94) E. Conservative surgery alone with a local recurrence salvaged with mastectomy and reconstructive surgery. (SG n = 92) WITH NURSES A. (SG n=20) B. (SG n=20) C. (SG n= 20) D. (SG n=20) E. (SG n=20)	Mean 0.87 (sd 0.18) Med. 0.94 IQR 0.84-0.97. Range 0-1.0 Mean 0.81 (sd 0.20) Med 0.88 IQR 0.75-0.95 Range 0-0.99 NURSES Mean 0.92 (sd 0.08) Med. 0.94 IQR 0.88-0.97. Range 0.7-1.0 Mean 0.78 (sd 0.18) Med. 0.81 IQR 0.75-0.87. Range 0.15 -0.99 Mean 0.88 (0.09) Med 0.89 IQR 0.84-0.96 Range 0.66-0.99 Mean 0.84 (0.14) Med 0.86 IQR 0.76-0.95. Range 0.41-0.99 Mean 0.78 (0.20) Med 0.85 IQR 0.71-0.90 Range 0.15-0.96		(although 11 did not meet this criteria). No history of recurrent or contralateral breast cancer. Female oncology nurses. N= 20. Median age 37.	of the variability in health state utilities, nor differences between states. Health states are described in detail (see paper).
15. Hayman *et al.* (2005) (61)	**EBC states:** A: BCS and RT without recurrence. Risk of 8% non-invasive and 4% invasive recurrence. B: Non-invasive recurrence salvaged with mastectomy after initial treatment with BCS and RT. C: An invasive recurrence salvaged with	**Mean (SD)** Mean: PUB 0.90 (.14) DCIS 0.93 (.13) Median: PUB 0.95 DCIS 0.97 Mean: PUB 0.88 (.16) DCIS 0.89 (.16) Median: PUB 0.94 DCIS 0.95 Mean: PUB 0.81 (.19) DCIS	SG. Partial cascading. Initially ranked using anchors of the best and worst of 8 health states from the ranking. Lowest rank assessed against death and optimal health SWD not discussed.	210 healthy women in a university-based wellness clinic. Mean age 50 (range 19-84) 120 patients with DCIS treated with lumpectomy and	Medians higher than means for both groups: skewed upwards Patients preferred having

	mastectomy after initial treatment with BCS and RT. D: BCS alone without recurrence. Risk of 13% non-invasive and 13% invasive recurrence. E: A non-invasive recurrence salvaged with BCS and RT after initial treatment with BCS alone. F: A non-invasive recurrence salvaged with mastectomy after initial treatment with BCS alone. G: An invasive recurrence salvaged with BCS and RT after initial treatment with BCS alone H: An invasive recurrence salvaged with mastectomy after initial treatment with BCS alone.	0.80 (.27) Median: PUB 0.85 DCIS 0.91 Mean: PUB 0.90 (.15) DCIS 0.91 (.15) Median: PUB 0.95 DCIS 0.96 Mean: PUB 0.90 (.15) DCIS 0.89 (.19) Median: PUB 0.95 DCIS 0.95 Mean: PUB 0.89 (.15) DCIS 0.87 (.21) Median: PUB 0.94 DCIS 0.95 Mean: PUB 0.81 (.19) DCIS 0.79 (.26) Median: PUB 0.87 DCIS 0.91 Mean: PUB 0.84 (.18) DCIS 0.75 (.29) Median: PUB 0.91 DCIS 0.86		RT. Mean age 61 (range 42-82). Mean of 39 months since completion of RT.	received RT after recurrence (C>H), whereas non patients preferred not to have received RT (H>C). Few statistically significant differences between patients and non-patients. Differences in valuations were not explained by socio-demographic or clinical factors.
16. Hurny *et al.* (1998) (40) Switzerland	**MBC or inflammatory BC states:** VAS (dead-perfect health) VAS (worst health – perfect health) VAS (worst health-perfect health)	Mean 0.659 (SD .203) Med .65 (range 0.18-1) Mean 0.613 (SD.239) Med .62 (range .03-.99)	VAS. Anchored at dead- perfect health VAS. Anchored at worst possible health - perfect health	84 ambulatory patients with metastatic or inflammatory BC seen for treatment or routine check-	Two VAS scores had correlation of 0.8. Lack of agreement was worst for

	Receiving hormonal therapy (n=36) Receiving mild chemotherapy (n=15) Receiving intensive chemotherapy (n=33)	Mean .628 (SD .234) Mean .651 (SD .221) Mean .483 (SD .285)	TTO. Anchored at excellent health for 1 year. (but given the severity of illness this is approximate life expectancy). Asked as (12, 11, 9, 6, 3, 1 or 0 months) TTO means not reported.	ups hospitals in Switzerland. Eligible patients aged 20-75, had experience of chemotherapy, had ECOG performance state of 0-3.	those at the higher end. Respondent age reported as frequencies. 19 at <= 45, 27 at 46-55, 24 at 56-65, 14 at >=65. (Estimated at 54)
17. Hutton *et al.* (1996) (41) See also Brown *et al.* (2001) (50) & Brown and Hutton (1998) (51) & Kearney *et al.* (1999) (52)	**MBC states:** Partial response Partial response and severe peripheral oedema Stable disease Before second line therapy beings Partial response and severe PN Progressive disease Sepsis Terminal disease	**Mean (Av. 5 countries)** Av: 0.81 UK: 0.84 Av: 0.75 UK: 0.78 Av: 0.62 UK: 0.62 Av: 0.59 UK: 0.56 Av: 0.53 UK: 0.62 Av: 0.41 UK: 0.33 Av: 0.20 UK: 0.16 Av: 0.16 UK: 0.13	VAS. Anchored at worst possible – best possible. Used for cascading. SG. Anchored at worst possible – best possible.	129 oncology nurses from 5 countries. Total sample, mean age 33.7, n=129	Values included are those from the combined 5 country sample.
18. Isogai *et al.* (2008) (36) Abstract only	**BC general:** N=151	**Mean** 0.80 (0.16)	EQ-5D	151 consecutive BC patients irrespective or stage or treatment attending at an outpatient clinic. Time since diagnosis 0.1 to 25	

				years. Mean age 55.2 (12.5)	
19. Jansen *et al.* (1998) (26) Netherlands	**EBC states:** Temporary states TTO: Actual health state (n=61) SG: Actual health state (n=61) TTO: Radiotherapy scenario (n=61) SG: Radiotherapy scenario (n=61) TTO: Chemotherapy scenario (n=35) SG: Chemotherapy scenario (n=35) Actual health Early state BC following mastectomy or lumpectomy, before radiotherapy Radiotherapy state: Daily radiotherapy over 6 weeks, then 4 and half months of side effects. Physical: skin reactions, fatigue, listlessness Psychological: Anxiety and worry about future Social Limitations: to daily and social activities Chemotherapy state: During 6 months 1 or 2 hospital visits per 3 weeks for chemotherapy via infusion. Physical: nausea, fatigue, hair loss Psychological: Dissatisfaction with own body Social Limitations: to daily and social activities	**Mean (SD)** 0.94 (0.12) 0.94 (0.11) 0.89 (0.13) 0.87 (0.19) 0.74 (0.26) 0.75 (0.27)	Chained TTO and SG, using an anchor state of hospitalisation following an accident. Transformed to a scale from dead to good health. In the TTO one third (34%) of patients preferred the anchor state to chemotherapy (34%). In SG 6% preferred the anchor state to chemotherapy. Utilities were not computed for these patients. SWD were not allowed.	EBC patients n= 61. After mastectomy or lumpectomy, before radiotherapy treatment. 24 patients rating the anchor state above chemotherapy therefore this state could not be estimated for these patients. Median age 57 (range 33-82).	Authors note that using the 6 month period avoids the downward bias caused by discounting in TTO.
20. Jansen *et al.* (2000) (25) Netherlands	**EBC states:** Actual T1: VAS (n=55) T1: TTO (n=54). (Value also appears in Jansen *et al.* (1998))	**Mean (SD)** 0.81 (0.12) 0.94 (0.12)	VAS. Anchored at dead to perfect health. Chained TTO Chained SG.	Patients referred to Leiden University Medical Centre for 5-7 week course of radiotherapy after	Valuation for the anchor state changes little. Own health

	T1: SG (n=51) (Value also appears in Jansen *et al.* (1998)) T2: VAS (n=55) T2: TTO (n=54) T2: SG (n=51) T3: VAS (n=55) T3: TTO (n=54) T3: SG (n=51) Radiotherapy scenario T1: VAS (n=55) T1: TTO (n=54) T1: SG (n=51) T2: VAS (n=55) T2: TTO (n=54) T2: SG (n=51) T3: VAS (n=55) T3: TTO (n=54) T3: SG (n=51) Chemotherapy scenario T1: VAS (n=53) T1: TTO (n=25) T1: SG (n=36) T2: VAS (n=53) T2: TTO (n=25) T2: SG (n=36) T3: VAS (n=53) T3: TTO (n=25)	0.94 (0.11) 0.79 (0.14) 0.92 (0.13) 0.91 (0.19) 0.81 (0.13) 0.97 (0.08) 0.91 (0.20) 0.75 (0.13) 0.89 (0.13) 0.88 (0.19) 0.73 (0.16) 0.91 (0.13) 0.86 (0.18) 0.73 (0.13) 0.90 (0.17) 0.88 (0.24) 0.53 (0.18) 0.75 (0.24) 0.68 (0.28) 0.49 (0.16) 0.75 (0.25) 0.75 (0.25) 0.51 (0.16) 0.76 (0.26)	Method similar to Jansen *et al.* (2001) T1: shortly before radiotherapy T2: final week of radiotherapy T3: two months after radiotherapy	lumpectomy or mastectomy, excluding those with prior experience of radiotherapy. (n=55). Median age 57 (33-82) 89% had lumpectomy. Chemotherapy scenario was only valued by those who did not prefer the anchor state to the chemotherapy state.	state valued higher than radiotherapy scenario at T3 (sig for VAS and SG but not TTO) Valuations of radiotherapy remained fairly stable.

	T3: SG (n=36)	0.71 (0.28)			
21. Jansen *et al.* (2001) (62) Netherlands	**EBC states:** Chemotherapy Group T1: VAS (n=42) T1: TTO (n=43) T1: SG (n=37) T2: VAS (n=42) T2: TTO (n=43) T2: SG (n=37) T3: VAS (n=42) T3: TTO (n=43) T3: SG (n=37) Control group T1: VAS (n=51) T1: TTO (n=45) T1: SG (n=45) T2: VAS (n=51) T2: TTO (n=45) T2: SG (n=45) T3: VAS (n=51) T3: TTO (n=45) T3: SG (n=45) For the chemotherapy group utility according to VAS lower in T3 than T2 or T1. Wider range of values for the control group. Lower values than from chemotherapy group. However, utilities for the anchor state were	**Median (IQR)** 0.69 (0.55-0.80) 0.88 (0.75-0.96) 0.92 (0.80-1.00) 0.69 (0.52-0.83) 0.87 (0.79-0.92) 0.96 (0.79-1.00) 0.62 (0.50-0.75) 0.87 (0.72-0.96) 0.93 (0.80-0.99) 0.50 (0.37-0.71) 0.50 (-0.11-0.84) 0.58 (-0.90-0.90) 0.49 (0.35-0.64) 0.77 (-0.02-0.88) 0.73 (-0.03-0.91) 0.50 (0.37-0.65) 0.69 (-0.02-0.88) 0.82 (0.49-0.93)	VAS. Anchored at dead to perfect health. Chained TTO Chained SG Chaining TT0 involved 6 months chemotherapy versus shorter period in the anchor health state, followed by rest of life in good health. Anchor state was hospitalization caused by serious accident. Anchor state is valued as 6 months versus shorter time in full health both followed by death. Chaining SG involved 6 months chemotherapy versus chance of full health or anchor state for 6 months, followed by good health for remainder of life. Allowed both states to be worse than dead. T1: Before chemotherapy	Patients with early BC recruited from 5 hospitals in the Netherlands. Those scheduled for adjuvant chemotherapy included if they had not undergone chemotherapy previously (n=43). Mean age 42 Control group: women with early stage BC not advised to have systemic adjuvant therapy of for whom hormonal therapy (tamoxifen) was prescribed (n=51). Mean age 56	

	slightly higher in the chemotherapy group at T2 by SG and T3 by SG and TTO (non-sig.). Might be due to age, but within each group age was not related to utilities. 'Most likely' patients may have adapted to the decision for chemotherapy – the 'anticipated adaptation' – patients wish to believe they have made the correct decision. The control group "may be more negatively inclined toward a treatment that was not offered (or was turned down". Adaptation to the decision for treatment rather than the treatment itself. Chemotherapy group. Own health state during chemotherapy VAS (n=42) TTO (n=42) SG (n=37) In all methods significantly higher than their T2 valuation. This effect is termed 'nocorresponding description', may result from differences between the description and the actual health state, or cognitive bias, or may have involved a more emotionally laden 'hot' judgement and aroused more emotional conflict.	**Median (IQR)** 0.79 (0.71-0.89) 0.93 (0.88-1.00) 0.97 (0.85-1.00)	T2: midway through chemotherapy T3: 1 month after chemotherapy Chemotherapy description designed based on the experience of 6 oncologists and 5 BC patients with early BC who had undergone chemotherapy. Chemotherapy state: One or 2 hospital visits every 3 weeks for 6 months for chemotherapy via infusion. Physical: nausea, fatigue, hair loss, difficulty in carrying out strenuous activities, frequent need to rest Psychological: dissatisfaction with one's body. Social: Limitations to work or other daily activities, restrictions on social activities.		
22. Jansen *et al.* (2004) (63)	**EBC states:** After adjuvant chemo. Choice (n= 54) After adjuvant chemo. No Choice (n = 105)	**Mean** VAS: 0.77, EQ-5D: 0.84 VAS: 0.75, EQ-5D: 0.82	VAS. Anchored at death and perfect health	448 patients with EBC.	Values found to reduce with age. But no

Netherlands	No adjuvant chemo. Choice (n=28) No adjuvant chemo. No choice (n= 174)	VAS: 0.69, EQ-5D: 0.74 VAS: 0.77, EQ-5D: 0.83	EQ-5D, UK tariff	Perceived choice n= 89. Mean age 57 Perceived no-choice n = 316. Mean age 59 Excluded: Those with metastatic disease	sig. differences with perceived choice. No chemo choice group scores lowest, authors suggest may be due to fear of recurrence and having made the incorrect decision.
23. Johnston *et al.* (1998) (20) UK	**Screening states:** TTO True negative False positive True positive False negative VAS (Rescaled 0 death 1 best imaginable) True negative False positive	 TTO Mean 0.91 (sd .21) Med. 0.98 (IQR 0.96-0.99) Mean 0.66 (sd .38) Med. 0.83 (IQR 0.22-0.96) Mean 0.66 (sd 0.29) Med. 0.75 (IQR 0.55-0.95) Mean 0.66 (sd 0.29) Med 0.75 (IQR 0.45-0.95) VAS Mean 0.92 (sd 0.18) Med. 1.0 (IQR 0.9-1.0) Mean 0.67 (sd 0.28) Med. 0.75 (IQR 0.50-0.90)	VAS. Anchored best imaginable health. Rescaled to death-good health. TTO. Valued for 12 months. SWD not allowed.	N=440 Women aged 40-44 n=209 Women aged 50-64 n= 231	

	True positive False negative	Mean 0.75 (sd 0.25 Med. 0.80 (IQR 0.60-0.98) Mean 0.60 (sd 0.27) Med. 0.63 (IQR 0.40-0.80)			
24. Kimman et al (2009) (64)	**EBC** 2 weeks post treatment (T0) A. Large deterioration (n=23) B. Small deterioration (n=14) C. No change (n=55) D. Small improvement (n=28) E. Large improvement (n=72) 12 months post treatment (T1) A. Large deterioration (n=23) B. Small deterioration (n=14) C. No change (n=55) D. Small improvement (n=28) E. Large improvement (n=72) Group determined by EORTC QLQ-C30 scores	**Mean** EQ-5D: 0.72, EQ-VAS: 0.730 EQ-5D: 0.73, EQ-VAS: 0.744 EQ-5D: 0.82, EQ-VAS: 0.790 EQ-5D: 0.78, EQ-VAS: 0.709 EQ-5D: 0.71, EQ-VAS: 0.650 EQ-5D: 0.57, EQ-VAS: 0.598 EQ-5D: 0.72, EQ-VAS: 0.694 EQ-5D: 0.82, EQ-VAS: 0.799 EQ-5D: 0.80, EQ-VAS: 0.777 EQ-5D: 0.83, EQ-VAS: 0.774	EQ-5D (UK tariff), EQ-VAS Of 220 eligible patients 29 failed to complete the study (10 dropped out and 19 did not complete instruments).	192 female patients treated for BC with curative intent, no concomitant tumours or co-morbidity requiring hospital visits. Treatment included surgery and/or radiotherapy and/or chemotherapy. Age for full sample 55.8 (10.1)	
25. Ko *et al.* (2003) (33) USA	**General BC states:** Acute < 1 year after diagnosis of BC (*n* = 64) Short term 1 to 5 (*n* =73) Long term >5 (*n* =217)	**Mean (SD)** 0.62 (0.27) 0.69 (0.24) 0.71 (0.24)	HALex scoring algorithm based on a multi-attribute utility scaling from responses to activities of daily living and perceived health status. (see paper for details) Converted to 0 near death state to 1 perfect	National Health Interview Survey (NHIS), US 337 BC. Mean age at diagnosis of BC was 56.	

			health with no limitations.		
26. Launois *et al.* (1996) (42) France SD given by the author.	**MBC states: Second line-chemotherapy** Before starting chemotherapy Minor toxicities Severe skin reactions Severe arthralgia / myalgia Febrile neutropenia without hospitalisation Early progression Gastrointestinal toxicity with hospitalisation Febrile neutropenia with hospitalisation Confirmed responder Confirmed responder with oedema Confirmed responder treatment interrupted for severe oedema Confirmed responder treatment interrupted for severe neuropathy Confirmed responder with severe neuropathy Stable Stable with severe oedema Stable treatment interrupted for severe oedema Stable treatment interrupted for severe neuropathy Stable with severe neuropathy Progression Progression treatment interrupted for severe oedema Progression with severe oedema Progression with severe neuropathy Progression treatment interrupted for severe neuropathy Terminal care	**Mean (SD)** 0.86 (0.13) 0.76 (0.15) 0.72 (0.24) 0.72 (0.08) 0.66 (0.16) 0.52 (0.27) 0.48 (0.16) 0.47 (0.26) 0.81 (0.19) 0.74 (0.15) 0.64 (0.11) 0.64 (0.18) 0.57 (0.23) 0.75 (0.19) 0.73 (0.12) 0.58 (0.26) 0.58 (0.25) 0.50 (0.21) 0.65 (0.17) 0.58 (0.13) 0.53 (0.21) 0.50 (0.19) 0.45 (0.12) 0.25 (0.21)	SG. No discussion of method or anchors used.	20 nurses	

27. Lidgren *et al.* (2007) (43) Sweden	**EBC & MBC states:** **First year after primary BC (state P)** EQ-5D (n-72) TTO (n=69) State P with adjuvant chemotherapy: EQ-5D (n=23) TTO (n=22) State P with adjuvant hormone therapy: EQ-5D (n=17) TTO (n=17) **First year after recurrence (State R):** EQ-5D (n=21) TTO (n=18) State R with adjuvant chemotherapy: EQ-5D (n=7) TTO (n=5) State R with adjuvant hormone therapy; EQ-5D (n=4) TTO (n=4) **Second and following years after primary BC or recurrence (State S)** EQ-5D (n=177) TTO (n=178)	**Mean (95% CI)** 0.696 (0.634-0.747). Median 0.725. Min 0 Max 1. 0.901 (0.848-0.935). Median 1. Min 0.1. Max 1 0.620 (0.509-0.697) 0.886 (0.801-0.943) 0.744 (0.573-0.841) 0.891 (0.699-0.955) 0.779 (0.700-0.849) Median 0.725. Min 0.296. Max 1. 0.842 (0.733-0.926) Median 0.973. Min 0.5. Max 1 0.767 (0.573-0.841). 0.856 (0.656-1) 0.816 (0.729-0.963). 0.861 (0.620-0.991). 0.779 (0.745-0.811) Median 0.796. Min 0. Max 1. 0.889 (0.860-0.913) Median 1. Min 0. Max 1	EQ-5D (UK tariff) EQ-5D VAS. Anchored at worst imaginable health-best imaginable. TTO based on 10 years of live in current health state and full health. Negative EQ-5D values were set to zero, but only 3 patients and impact negligible.	361 BC patients from outpatient clinic with previous diagnosis of BC at Karolinska University Hospital, Solna, Sweden. 345 patients had data on disease state from Stockholm Oncology Centre. 335 completed EQ-5D and VAS 326 completed TT0 This study may be p up more severe non- metastatic patients s they are more likely attend outpatient cli For metastatic patients may be higher HRQOL because no inpatients are included – this excludes those with complications	EQ-5D correlates 0.65 with the VAS. Impact is mostly on dimensions 4 (pain and discomfort) & 5 (anxiety and depression). Moderate or severe pain reported by 52% in State R, 71% in State P, 74% in State M TTO sig. higher than EQ-5D for all states other than R. Correlation was 0.44. Although TTO question refers to 'in your current health state' many may

	State S with adjuvant hormone therapy: EQ-5D (n=79) TTO (n=76) **Metastatic disease (State M).** EQ-5D (n=65) TTO (n=61) State M with adjuvant chemotherapy: EQ-5D (n=38) TTO (n=35) State M with hormone therapy: EQ-5D (n=16) TTO (n=17) The lower than population values levels in state S suggest permanent negative effect of BC. Note that EQ-5D value for first year after primary is lower than that for metastatic disease.	 0.824 (0.785-0.857). 0.934 (0.890-0.960) 0.685 (0.620-0.735). Median 0.725. Min 0.093. Max 1. 0.820 (0.760-0.874). Median 0.850. Min 0.110. Max 1. 0.692 (0.611-0.746). 0.776 (0.695-0.8411) 0.648 (0.513-0.765). 0.863 (0.737-0.8940)		and end stage of disease. Mean age 57 (range 28-93)	have perceived this as temporary. Those with different TTO to EQ-5D values reported they did not want to shorten their time with their family. The greater values in state R than P may be due to a coping effect and knowing what to expect.
28. Lloyd *et al.* (2006) (44) UK	**MBC states:** Utility values for a 38.2 year old. Base state – stable metastatic disease with no toxicity Treatment response Disease progression Febrile neutropenia Diarrhoea and vomiting Hand-foot syndrome	 0.715 +0.075 -0.272 -0.150 -0.103 -0.116	15 health states identified from the literature and developed by interviews and focus groups with experts in BC none of which specified breast	Recruited from Greater London through advertisements in the local newspapers and existing UBC database of willing participants.	Males rated disease progression as a greater decrement to utility than females. Age of

	Stomatitis Fatigue Hair loss Coefficients from the log mixed model analysis are presented along with standard errors.	-0.151 -0.115 -0.114	cancer. Initially all states (including own, death, full health and worst health) rated using VAS SG, living in health state for 10 years with certainty versus probability of full health or the worst health state. Worst state is valued against dead, allowing for the possibility of being worse than dead. Utility states recalibrated to 0 (dead) 1 (full health). SG valuations analysed using a mixed model analysis to determine the change in utility score associated from moving between stages of disease and from no toxicity to one of the toxicities. Raw data were transformed using a logistic transformation. Negative scores were	Respondents complete some anchor states and half the remaining states, since 18 states considered too many. 100 completed interview. 50% female. Mean age 40.16 (sd 13.59)	participants had a positive correlation with utility values. Older participants may be more risk averse, or perceive less of a departure from their current state.

			changed to 0.02 to obtain a normal distribution for the standard regression model. Age is included in the analysis.		
29. Lovrics *et al*. (2008) (65) Canada	**EBC states:** Initial consultation (n=85) Post PET (n=74) Post Op (n=83) 3 month (n=80) 6 month (n=84) 12 month (n=73) 18 month (n=67) 24 month (n=72) Normative data from CCHS 1.1 (2000-2001) n=75,000	**Mean (SD)** 0.74 (0.26) 0.76 (0.26) 0.49 (0.33) 0.73 (0.27) 0.73 (0.28) 0.79 (0.23) 0.81 (0.22) 0.78 (0.24) 0.87 (0.21)	HUI3	Candidates for BCS at Joseph's Healthcare and Hamilton Health Sciences. Age mean 55.2	
30. Mansel *et al.* (2007) (28) UK	**EBC states:** Disease-free state, no adverse events Common adverse events (tamoxifen) Common adverse events (anastrozole) Vaginal bleeding Endometrial cancer Wrist fracture New contralateral BC Local/regional recurrence Deep vein thromboembolism Pulmonary embolism Spinal fracture Hip fracture Hormonal therapy for distant recurrence	**Mean (SD)** 0.989 (0.010) 0.970 (0.041) 0.962 (0.055) 0.933 (0.099) 0.913 (0.101) 0.916 (0.099) 0.914 (0.097) 0.911 (0.098) 0.922 (0.107) 0.890 (0.166) 0.894 (0.189) 0.858 (0.199) 0.882 (0.105)	Chained SG. Anchored at worst and perfect health, then rescaled to death and perfect health.	26 UK patients with early or advanced BC Mean age 68 years. Most patients had HR+ node-negative disease and were presently receiving tamoxifen; a minor proportion was receiving anastrozole (no patient was	Table 3 showing mean utility scores refers to n=23. (Data in Sorenson *et al.* is only based on 23 UK patients).

	Chemotherapy for distant recurrence Current health Hysterectomy	0.710 (0.254) 0.933 (0.069) 0.899 (0.101)		receiving treatment within the ATAC trial).	
31. McLachlan *et al.* (1999) (45) Canada	**MBC states:** Metastatic BC, baseline before chemotherapy	**Median (IQR)** 0.92 (0.79-1.0)	TTO using 12 months, on own health. Anchored at death-perfect health.	32 patients with MBC presenting for third line chemotherapy, in Ontario. Median age 56 (for the full n=35 sample) (range 38-77)	Scores for QLQ-c30 correlated poorly with utility scores.
32. Milne *et al.* (2006) (46) New Zealand	MBC states: State 1. Bone metastases receiving hormonal therapy. VAS (n=46) TTO (n=40) EQ-5D NZ (n=50) EQ-5D UK (n=50) State 2. Severe bone pain requiring radiotherapy VAS (n=46) TTO (n=45) EQ-5D NZ (n=50) EQ-5D UK (n=50)	 Mean 0.54 (95%CI 0.48-0.59) Med 0.53 IQR (0.4-0.68) Mean 0.65 (95%CI 0.57-0.73) Med 0.71 IQR (0.46-0.88) Mean 0.54 (95%CI 0.51-0.58) Med 0.61 IQR (0.54-0.61) Mean 0.60 (95%CI 0.54-0.65) Med 0.69 IQR (0.59-0.69) Mean 0.35 (95%CI 0.30-0.40) Med 0.32 IQR (0.25-0.48) Mean 0.45 (95%CI 0.37-0.54) Med 0.46 IQR (0.21-0.67) Mean 0.31 (95%CI 0.27-0.35) Med 0.23 IQR (0.16-0.46) Mean 0.25 (95%CI 0.18-0.33) Med 0.19 IQR (-0.02-0.52)	VAS. Anchored from worst to best imaginable, then normalised to dead-best imaginable. Allowing SWD. Positioned states on EQ-5D. Both using UK and NZ tariffs. TTO used ping pong method on living additional 12 months. Anchored at dead and full health.	50 women from Auckland. Mean age 46 (range 25-69)	Health states represented by case descriptions developed by oncology professionals. NB: Original paper has the methods mis-labelled on the data table

	State 3. Moderate to severe hypercalcemia VAS (n=46) TTO (n=50) EQ-5D NZ (n=50) EQ-5D UK (n=50) State 4. Chemotherapy rather than hormonal therapy for advanced cancer not receiving radiotherapy for bone pain. VAS (n=46) TTO (n=47) EQ-5D NZ (n=50) EQ-5D UK (n=50)	 Mean 0.13 (95%CI 0.09-0.17) Med 0.12 IQR (0.05-0.20) Mean -0.17 (95%CI -.29- -.05). Med -0.08 IQR (-0.54-0.02) Mean -0.05 (95%CI -.07- -.03). Med -0.08 IQR (-0.08-0.01) Mean -0.52 (95%CI -.56- -.48). Med -0.59 IQR (-0.59- -0.43) Mean 0.46 (95%CI 0.41-0.51) Med 0.46 IQR (0.36-0.55) Mean 0.49 (95%CI 0.40-0.57) Med 0.58 IQR (0.21-0.71) Mean 0.48 (95%CI 0.43-0.53) Med 0.54 IQR (0.31-0.61) Mean 0.51 (95%CI 0.43-0.59) Med 0.62 IQR (0.26-0.69)			
33. Namjoshi *et al.* (1998) (66) USA Abstract	**EBC states:** FACT-G dimension scores explained 26% of variation in SG, 39% of HUI, 50% of VAS, and 47% of EQ-5D FLIC dimension scores explained 42% of variation in the SG, 43% of HUI, 54% of VAS and 56% of EQ-5D	**Mean (SD)** SG 93.3 (11.5) HUI3 84.6 (16.8) VAS 86.6 (12.6) EQ-5D 87.4 (10.8)	SG HUI3 VAS EQ-5D	75 BC patients. Mean age 60. 96% had either stage I or II disease	Studies compares to FACT-G and FLIC
34. Ossa *et al*. (2007) (84)	**Chemotherapy related anaemia** No-anaemia Mild anaemia	**Mean (SD), ratio** 0.86 (0.14), 1 0.78 (0.17), 0.91	TTO. Study used TTO anchored at 0 (dead)	110 members of the public of which 4 did not	

	Moderate anaemia Severe anaemia	0.61 (0.21), 0.72 0.48 (0.21), 0.56	and 1 (ideal health for the no-anaemia state). Then assumed an EQ-5D value (21122) or 0.86 for the no-anaemia state.	trade leaving 106 with a mean age of 45.	
35. Pickard *et al*. (2007) (85) and personal comm. USA	**Advanced BC** Post chemotherapy	**Mean (SD)** 0.667 (0.25)	EQ-5D UK tariff	52 advanced breast cancer patients (stage 3/4) who had received chemotherapy (at least 2 cycles or for at least 1 month). Mean age 52 (SD=11)	
36. Polsky *et al.* (2002) (67) USA	**EBC states:** 5 months after surgery. VAS unadjusted. Choice 5 months after surgery. VAS unadjusted. No Choice 5 months after surgery. VAS adjusted for covariates. Choice 5 months after surgery. VAS adjusted for covariates. No Choice Choice of mastectomy, BCS with radiation, or BCS only. Values for 1 year and 2 years after surgery are presented graphically only.	**Mean (SD)** VAS: 78.8 (15.9), HUI: 82.5 (21.4) VAS: 74.8 (17.1), HUI: 76.8 (27.3) VAS: 78.7, HUI: 81.9 VAS: 75.3, HUI: 78.3	EQ-VAS Health Utilities Index Mark 3 (HUI3) 3-5 years after surgery	Women with breast carcinoma identified from inpatient and outpatient pathology records and surgical logs at 29 hospitals. Eligibility: patients for whom breast conservation and mastectomy were considered clinically equivalent; community dwelling, 67 years	Age given as frequencies. (estimated at Choice: 73.8, Non choice 75.5)

				of age or older, and had histologically confirmed primary T1 or T2; N0, N1, or NX; and M0 invasive breast carcinoma. Women with DCIS, bilateral carcinoma, or multicentricity were excluded. n = 683 for VAS n= 661 for HUI Choice = n=566 No choice = n=117	
37. Prescott *et al*. (2007) (68) UK PRIME trial.	**EMC states:** Radiotherapy group (n=102) Baseline 3.5 months 9 months 15 months No-radiotherapy group (n=101) Baseline 3.5 months 9 months 15 months	Mean (95%CI) 0.77 (0.73-0.80) 0.78 (0.74-0.81) 0.76 (0.71-0.81) 0.74 (0.70-0.78) 0.74 (0.70-0.77) 0.76 (0.73-0.79) 0.72 (0.68-0.76) 0.73 (0.69-0.77)	EQ-5D UK tariff.	Low risk axillary node negative breast cancer treated with BCS and endocrine therapy. Inclusion: Age 65+, low risk of local recurrence. Age radiotherapy (n=127) 72.3 (5.0) No-radiotherapy (n=128) 72.8 (5.2)	Trial also contains the EORTC and is used for a mapping study.

38. Rijnsburger *et al*. (2004) (21) Netherlands	**Screening states:** 2 months prior to screening (n=329) day of screening (n=316) 1-4 weeks post screening (n=288)	Mean EQ-5D 0.88, EQ-VAS 0.819 EQ-VAS 0.790 EQ-5D 0.88, EQ-VAS 0.807	EQ-5D (UK tariff) EQ-VAS	Women under surveillance at cancer clinic and women joining surveillance for the first time. Exclusion: evident symptoms suspicious for BC or previous BC. Mean age: 40.9	
39. Sackett and Torrance (1978) (24) Canada	**EBC states:** Mastectomy for BC, 8 years Mastectomy for injury, 8 years. Also found that for other states surveyed mean daily health state utility fell sharply as the duration (3 months, 8 years, life) of the health state increases.	 0.48 (se 0.044) 0.63 (se 0.038)	TTO. Anchored: death to perfect health	58 community sample from Ontario, 41-79 year old females.	
40. Schleinitz *et al.* (2006) (47) USA	**EBC & MBC states:** Stage I Stage II Stage III Stage IV ER+ State IV ER- Chemotherapy (TTO) Hormonal therapy (TTO) Radiation therapy (TTO) Stage I Stage II Stage III Stage IV ER-	 Med 0.91 Range (0.5-1) Med 0.75 Range (0.26-0.99) Med 0.51 Range (0.25-0.94) Med 0.36 Range (0-0.75) Med 0.40 Range (0-0.79) Med 0.50 Range (0-0.92) Med 0.58 Range (0-1) Med 0.83 Range (0.1-1) Mean 0.68 (95%CI +/-0.06) Mean 0.61 (95%CI +/-0.06) Mean 0.56 (95%CI +/-0.06) Mean 0.42 (95%CI +/-0.06)	8 health states developed via team of BC specialists, included 5 states of disease based on the TNM classification system (state I, II, III, IV receptor positive, IV receptor negative) 3 treatment modalities (chemotherapy, radiotherapy and hormonal therapy).	Convenience sample of socio-demographically diverse women, over 25 years from primary care clinics and the community. Women currently undergoing treatment for BC were excluded. N= 156	

	State IV ER+ Chemotherapy (TTO) Hormonal therapy (TTO) Radiation therapy (TTO) Those with income < $25,000 had significantly lower utilities for Stage I, II and III, and for Hormonal treatment. Single people had significantly lower utilities for all the treatment states (chemotherapy, hormonal and radiation). Those with above high school education had significantly higher utilities for states I, II and IV. Valuations varied significantly by race. Whites gave the highest valuation for Stage I, II, II and hormonal treatment (whites value stage I at 0.79, blacks valued at 0.56). Those with BC in the family gave a higher valuation for stage II, other differences non-significant. No significant differences by age.	Mean 0.41 (95%CI +/-0.06) Mean 0.48 (95%CI +/-0.06) Mean 0.54 (95%CI +/-0.07) Mean 0.61 (95%CI +/-0.07)	SG. Anchored at death and best imaginable health. Using 10 years of best imaginable health, and bisection method. Also elicited treatment utilities using TTO, based on 1 year description of treatment and recovery.	49% had family member with history of BC 61% post menopausal 46% >= 50	
41. Shih *et al*. (2006) (37) China	**BC general:**	**Mean (SD)** 0.81 (0.12)	SF-36 in Chinese, using algorithm to translate into the SF-6D	N=59 inpatient and outpatients at a cancer hospital, over 18 with a pathological diagnosis of breast cancer.	

42. Simons (2007) (48) USA Abstract Some data kindly given by Rob Simons at Global Health Economics and Outcomes Research, NJ, USA	**ABC states:** VAS Baseline ABC Treatment response No treatment response but no progression Disease progression SG Baseline ABC Treatment response No treatment response but no progression Disease progression Health state of toxicity	**Mean (SD) (range)** 52.65 (18.06) (9.0–85.0) 72.64 (14.38) (16.0-95.0) 59.22 (16.51) (12.0-97.0) 34.32 (15.91) (5.0-70.0) 0.64 (0.18) (0.15-0.95) 0.75 (0.16) (0.25-0.95) 0.67 (0.18) (0.25-0.95) 0.51 (0.20) (-0.05-0.95) 0.34 (0.26) (0.05-0.95)	FACT-B QOL data used to compare health narratives. Toxicities described separately. VAS SG. Anchored at dead and perfect health.	N=100 peri-post menopausal women. Mean age 55.76, range 40-85 63% post menopausal, 11% had BC previously 16% another type of cancer	Those who had experienced BC before gave sig. higher valuations.
43. Sorenson *et al.* (2004) (29) Abstract Also taken from Locker *et al.* (2007) (86) Also taken from presentation (same title) kindly	**EBC, MBC and side effects** POOLED SAMPLE (n=67) Disease free, no adverse events Adverse events No. 1 (weight gain, hot flushes, vaginal discharge) Adverse events No. 2 (weight gain, joint pain, hot flushes, vaginal discharge) Endometrial cancer Local/Regional Recurrence DVT Hip fracture Hormonal Tx/Distant cancer Chemotherapy / Distant cancer Current health USA sample (n=44): Disease-free state, no adverse events Common adverse events (tamoxifen)	**Mean (SD)** 0.974 (0.033) 0.963 (0.042) 0.959 (0.50) 0.865 (0.198) 0.816 (0.244) 0.796 (0.250) 0.730 (0.290) 0.724 (0.289) 0.432 (0.392) 0.907 (0.129) 0.965 0.959	Chained SG. Anchored at worst to perfect health. Rescaled to dead-perfect health. 14 states assessed including own health	Women aged 55–70 years in the UK and the USA with a history of stage one or two operable EBC and experience with adjuvant hormonal therapy. UK = 23 USA = 44 Pooled sample, mean age 67.8 years. 51% with arthritis USA sample mean age 67.5	The worst health state very different valuation between US and UK samples. More chemotherapy in the US within the sample. Pooled data not included since included separately via

given by Sonja Sorensen, at MEDTAP Int. USA and UK UK values also reported in Mansel *et al.* (2007) (28)	Common adverse events (anastrozole) Vaginal bleeding Wrist fracture Local/regional recurrence Hormonal therapy for distant recurrence Endometrial cancer Spine fracture New contralateral BC Deep vein thrombosis Pulmonary embolism Hip fracture Chemotherapy for distant recurrence Current health	0.958 0.926 0.852 0.766 0.642 0.839 0.751 0.702 0.729 0.741 0.664 0.288 0.893 (0.15)			UK (Mansel *et al.* (2007) (28) and the US data reported in the abstract.
44. Stratmann-Schoene *et al.* (2006) (35) Germany	**General BC state:** Own health state: VAS Predicted by SF-12 model	**Mean (SD)** 0.724 (.176) (95%CI .697-.744) 0.506 (.237) (95%CI .475-.537)	VAS, anchored at worst imaginable health state – best imaginable health state. SF-12 Each respondent valued the best and worst health state which can be described by the SF-12. All valuations were then standardized on this worst health state scale by linear transformation. Standardization on the 'dead' health state scale was not carried out.	N=199 Women who had received surgical treatment for BC. Postal survey. Mean age 56.4. Interviews. Mean age 60.6.	

45. Sullivan *et al.* (2005) (32) USA	**General BC state:** Marginal decrement in EQ-5D score after controlling for age, co-morbidity, gender, race, ethnicity, income and education. Cancer of the breast (n=236; mean age 64)	Unadjusted Mean EQ-5D 0.810 25% 0.768 50% 0.827 75% 1.000 Disutility of condition from the regression model (adjusted) -0.0150 (se 0.0010)	EQ-5D algorithm based on US community preferences. OLS, Tobit (since 46% of MEPS sample rated themselves as 11111), and censored least absolute deviations estimated (CLAD) robust alternative to the maximum likelihood estimation for the Tobit model, which does not require normally distributed errors. Evidence of heteroscedasticity and nonnormality of the residuals, hence Tobit model not reported.	Medical Expenditure Panel Survey (MEPS), diagnoses based on ICD-9 codes. Contains the EQ-5D. Research uses pooled 2000, 2001 and 2002 data giving 38,678 unique individuals (>= 18) with valid EQ-5D scores.	
46. Walker *et al.* (2006) (49) UK Abstract	**EBC & MBC states:** Early disease free survival (< 5 years) Metastatic disease Later disease free survival (> 5 years) Contra-lateral primary disease Loco-regional recurrence	**Mean** VAS: 0.697, SG: 0.75 VAS: 0.225, SG: 0.48 SG: 0.85 SG: 0.58 SG: 0.57	VAS. SG.	N=100 of general UK public	
47. Wolowacz *et al.* (2008) (69) 20	**EBC node positive:** Remission (n=929)	**Mean (variance)** 0.79 (0.016)	Data collected in trial BCIRG001. EORTC QLQ-C30 mapped onto the EQ-5D using algorithm from Kind (2005). UK tariff.	Patients who had completed chemotherapy and had not experienced a relapse.	

countries.				Inclusion: Age 18-70, had a score on the Karnofsky performance scale of 80% or more, and had undergone primary surgery with axillary-node dissection. Median age for the original sample for BCIRG001 was 49.	
48. Yabroff *et al.* (2004) (31) USA	**General BC state:** BC Non cancer control	**Mean (95% CI)** 0.75 (0.73-0.78) 0.80 (0.80-0.81)	Applies HALex utility weights to their self-reported health (excellent, very good, good, fair, or poor) and reported limitations in usual activities. HALex utility weights were obtained from the 2000 Medical Expenditure Panel Survey by mapping responses to self-rated health and limitations in usual activities questions to independently obtained utility measures from the EQ-5D. USA TTO tariff.	2000 Medical Expenditure Panel Survey BC n= 339 Non cancer controls n= 5468	

49. Yabroff et al (2007) (34) USA	**General BC state** Initial (within 1 year of diagnosis) (n=389) Continuing (n=381) Last year of life (n=150) Non-cancer control (matched by age, education and gender) Initial (within 1 year of diagnosis) (n=1945) Continuing (n=1905) Last year of life (n=150)	**Mean (95% CI)** 0.78 (0.76-0.80) 0.81 (0.79-0.82) 0.64 (0.61-0.68) 0.85 (0.84-0.86) 0.85 (0.84-0.85) 0.73 (0.69-0.76)	As above.	1986-1994 National Health Interview Survey.	

Table B.2: Studies which are not included but have accessible utility values

Study	Health state description	Health state value	How valued	Who valued	Comments & reason for exclusion.
1. Ashby *et al.* (1994) (87) UK	5 states. All involve diagnosis 1 year previously and no evidence of cancer returning. No longer experiencing any side effects of drugs. States vary on mastectomy/lumpectomy, supportive partner, sexual relationships, concern for recurrence, confidence, concern about appearance, friends and family, and interests. W: Lumpectomy, occasional concern of recurrence, confident in control, enjoys friends, interests as before, partner supportive, sexual relations good.	Study shows values disaggregated by age, gender and respondent group (e.g. patient, GP etc.) Mean 0.784 Med. 0.850 (IQR 0.650-0.950)	TTO using 20, 30, 40 or 50 years depending upon age. Anchors: Death - healthy Assumed all states better than dead.	49 nurses, 20 hospital doctors, 24 GPs, 28 university staff from Brunel university, 17 breast cancer patients 1 year previous, non recurring. Total sample N=138.	Not included because social conditions are included within the vignettes. *BC patients rated mastectomy higher than non-patients.* *Worst 3 states are rated higher by the eldest group.*

	L: Mastectomy, with plastic surgery to make a new breast, occasional concern of recurrence, confident in control, enjoys friends, interests as before, partner supportive, sexual relations good. P: Mastectomy, occasional concern of recurrence, confident in control, occasional concern for appearance, enjoys friends, interests as before, partner supportive, sexual relations good. K: Lumpectomy, some swelling and stiffness in arm restricting movement, engulfed by fear of recurrence and death, not able to go out, tearful, not sleeping well, partner not supportive, sexual relations declined. T: Mastectomy, some swelling and stiffness in the arm restricting movement, engulfed by fears of recurrence and death, not able to go out, tearful, not sleeping well, very sensitive about appearance, partner not supportive, sexual relations declined.	Mean 0.714 Med. 0.850 (IQR 0.550-0.950) Mean 0.703 Med. 0.850 (IQR 0.550-0.950) Mean 0.284 Med. 0.125 (IQR 0.000-0.550) Mean 0.257 Med. 0.050 (IQR 0.000-0.450).		Age of respondents given as frequency data.	*Mean values suggest preference order of lumpectomy, mastectomy with reconstruction, then mastectomy, although median values are the same for each of these states.* *A large drop in values arises when mental health states and social support deteriorates.*
2. Brown *et al.* (2001) (88) UK	**MBC states:** Start of second-line therapy Partial/complete response Stable disease Progressive disease Terminal disease PN with partial/complete response Severe oedema with partial/complete response Severe skin condition with partial/complete	**Mean (SD)** 0.64 (0.15) 0.84 (0.12) 0.62 (0.22) 0.33 (0.24) 0.13 (0.12) 0.62 (0.16) 0.78 (0.15) 0.56	SG Respondents valued a core of 8 states plus an additional random 5 states from the full 23 states. Marker states worst possible and best	30 oncology nurses in the UK. Sample age not stated.	Not included because values are reported combined with other country values in Hutton *et al.* (1996) (41) (except those which are estimated from other toxicities).

	response (estimated from other toxicities) Febrile neutropenia and hospitalised Infection without hospitalisation Severe skin condition, and infection not included since these were estimated from other toxicities.	 0.24 (0.12) 0.48	possible were also included.		
3. Brown and Hutton (1998) (51) USA	**MBC states:** At start of second-line chemotherapy Partial / full response (PR) Stable disease (SD) Progressive disease (PD) Terminal disease PN + PR PN + SD Severe edema + PR Sever edema + SD Severe skin condition Cardiac toxicity Febrile neutropenia with hospitalisation Infection no hospitalisation	**Mean. US: n=29, Av of 6 countries** US: 0.69 Av: 0.64 US: 0.84 Av: 0.81 US: 0.70 Av: 0.65 US: 0.49 Av: 0.39 US: 0.23 Av: 0.16 US: 0.58 Av: 0.56 US: 0.41 Av: 0.44 US: 0.82 Av: 0.76 US: 0.68 Av: 0.62 US: 0.65 Av: 0.56 US: 0.54 Av: 0.59 US: 0.42 Av: 0.30 US: 0.56 Av: 0.60	SG. Anchored dead - perfect health.	US oncology nurses (n=29). Mean age 39. 25-30 nurses each from Germany, Italy, Netherlands, Spain and UK also used.	
4. Brown *et al.* (2005) (89) & Brown *et al.* (2004) (90) UK Abstract	Reported in Mansel *et al.* (2007) (28) & Sorensen *et al.* (2004) (91)		SG. Anchored dead - perfect health.		Not included because values reported in Mansel *et al.* (2007) (28)
5. Buxton *et al.* (1987)	W: Lumpectomy, good physical, good mental	**Mean (95% CI)** 0.722 (0.699-0.775)	TTO using 20, 30, 40 or 50 years depending	N=121 Nurses, hospital	Not included because social conditions are

(92) UK	L: Mastectomy, good physical, good mental P: Mastectomy, no new breast, as L but occasional concern for appearance K: Lumpectomy, poor physical, poor mental T: Mastectomy, poor physical, poor mental	0.695 (0.640-0.750) 0.680 (0.623-0.737) 0.271 (0.212-0.330) 0.237 (0.182-0.292)	upon age. Anchors: Death - healthy Using ping pong method. Assumed all states better than dead.	doctors and GPs and university staff.	included within the vignettes. Data also reported in Ashby *et al.* (2004). This data does not include the 17 breast cancer patients included in Ashby *et al.* (2004). However, this study does show confidence intervals. *The values are lower for all states compared to the sample that includes 17 BC patients.*
6. Carter *et al.* (1998) (93)	Local recurrence Mastectomy Metastatic disease Radiation* Reversible complication* Tamoxifen* Endometrial CA *Utilities become 1.0 upon completion of treatment or recovery from complication.	0.8 0.99 0.50 0.99 0.99 0.999 0.95 *Not stated whether these are means or medians of values from individual professionals or a group consensus.*	'Basic Reference Gamble' (SG) Anchors: dead – absence of disease. Patients under observation with no evidence of disease were assigned an initial utility of 1, and 0 at the time of death.	Panel of health care professionals familiar with Basic Reference Gamble (SG) and BC. Sample size & age not stated.	Not included because no sample size or SD included.
7. Franic *et al.* (2003)	Post-chemotherapy nausea and vomiting, PCNV	**Mean (SD)** **3 days v Rest of Life**	VAS. Anchored initially at least to	Convenience sample of 18 women aged 22-	Not included because the PCNV states are

(76) USA	VAS 3 days vs rest of life. Own health Complete alleviation Partial alleviation No alleviation SG 3 days v rest of life. Own health Complete alleviation Partial alleviation No alleviation	0.944 (.069) v 0.939 (.073) 0.741 (.115) v 0.676 (.225) 0.490 (.165) v 0.307 (.215) 0.276 (.164) v 0.136 (.135) 0.994 (.019) v 0.985 (.032) 0.968 (.058) v 0.927 (.066) 0.942 (.074) v 0.810 (.141) 0.866 (.138) v 0.644 (.243)	most desirable. Rescaled to death and perfect health. SG top-down titration method. Anchored death - perfect health. Both methods allowed SWD.	50 with no history of breast cancer or chemotherapy. Mean age 28.	general cancer states rather than specifically related to breast cancer. High percentage of respondents would not trade for the 3 day condition in SG.
8. Franic *et al.* (2005) (94) USA	P1: Complete alleviation of PCNV (no nausea and vomiting episodes, varied diet, not depressed or anxious, able to work and socialize) for 3 days versus partial alleviation P2: Partially alleviation of PCNV (ongoing nausea and one vomiting episode per day, somewhat depressed and anxious, unable to work, and limited social activity) for 3 days, versus no alleviation P3: Complete alleviation of PCNV (ongoing nausea and two vomiting episodes per day, somewhat depressed and anxious, unable to work and declined social activity) for 3 days versus no alleviation C1: Cure (small scar on one breast, arthritis, not depressed or anxious, able to work and socialize) for indefinite period versus treatment (small scar on both breasts, not depressed or anxious, able to work, declined social activity)	QALY gain 0.00035 (SG) QALY gain 0.00192 (VAS) QALY gain 0.0007 (SG) QALY gain 0.0015 (VAS) QALY gain 0.0034 (SG) QALY gain 0.0107 (VAS) QALY gain 31.18 (SG) QALY gain 26.7 (VAS)	VAS. Anchored initially at least desirable to most desirable. Rescaled to death and perfect health. Valuation included own health, perfect health and death SG. Top down titration method. The time horizon of 3 days was given. Both VAS and SG were compared to rankings, participants were allowed to change them.	119 women, >= 22 yrs, no prior diagnosis of BC or cancer requiring treatment. Mean age 29, 82% graduate students.	Not included because comparisons are to other conditions not perfect health. In the PCNV study at least 20% of respondents refused to gamble. Respondents felt they could tolerate anything for 3 days, so not worth risking death for. Study also compares values to WTP

	resulting in 12 additional life years C1: Treatment resulting in additional 12 years of life versus recurrence (small scar, depressed and anxious, unable to work, social activities have ceased) for 2 additional years of life C3: Cure for an indefinite period versus recurrence for 2 additional life years.	 QALY gain 9.33 (SG) QALY gain 5.73 (VAS) QALY gain 40.5 (SG) QALY gain 32.4 (VAS)	Both methods allowed SWD.		
9. Gerard *et al.* (1993) (71) Australia	**Early BC states** Lumpectomy, good physical health otherwise, good mental health Lumpectomy, poor physical health otherwise, poor mental health Lumpectomy, recurrence leads to mastectomy, good physical health otherwise, poor mental health Mastectomy, unilateral, good physical health otherwise, good mental health Mastectomy, unilateral, good physical health otherwise, poor mental health Mastectomy, unilateral, poor physical health, poor mental health	 0.75 (n=44 without BC) 0.77 (104 women) 0.25 (n= 44 without BC) 0.31 (104 women) 0.21 (n=44 without BC), 0.27 (104 women) 0.76 (n=44 without BC), 0.80 (104 women) 0.28 (n=44 without BC), 0.33 (104 women) 0.23 (n=44 without BC), 0.31 (104 women)	TTO. Anchored at dead to good health.	104 community women (aged 45-69) with and without BC, of which 44 without breast cancer, living in Sydney metropolitan area	Not included because health states are difficult to classify
10. Grimison *et al*. (2009) (95) Australia & New Zealand.	**EBC and MBC states** Advanced Cancer before treatment (n=295) EBC trial, before treatment (n=91) EBC trial, during treatment (n=51) EBC trial, after treatment (n=111)	**Mean (SD)** 0.88 (0.13) 0.94 (0.07) 0.87 (0.15) 0.96 (0.06)	Utility-Based Questionnaire-Cancer (29 items plus single global health status) Algorithm to translate to utilities, derived in work on cancer patients via TTO	Advanced cancer trial n=325, 18 or above. Early cancer trial n=126. High risk early state breast cancer, 16-65 years.	Not included because the method for deriving the utilities is not standard practice.

			questions. Algorithm gives extra weight to responses about aspects of HRQOL that are more highly correlated with response on the global health question.		
11. Grunberg *et al.* (1996) (70) USA	Chemotherapy with no nausea or vomiting Chemotherapy (3 days) with nausea or vomiting	**Mean** 0.79 0.27	VAS. Anchored from terrible to wonderful. Rating scenario of no PCVN and 3 vomiting episodes and 3 days of nausea.	30 chemo patients (second or later course) mean age 56, 22 women, 8 breast cancer. 15 with history of vomiting.	Not included because states are not specific to breast cancer. *Study suggests that PCNV has a severe impact upon HRQoL – it is unclear if this result is driven by those with experience of PCNV, those without experience or both.*
12. Hall *et al.* (1992) (72) Australia	**EBC states:** Lumpectomy, good physical, good mental Mastectomy, good physical, good mental Lumpectomy, good physical, poor mental Mastectomy, good physical, poor mental Lumpectomy, poor physical, poor mental Mastectomy, poor physical, poor mental	**Mean (95% CI)** 0.80 (0.75-0.85) 0.77 (0.71-0.83) 0.31 0.31	HYE, TTO Time used in TTO based on respondents life expectancy, choice of 30, 20 or 10 years. Anchored: death-full health.	N=104 44 women in the community, and 60 BC patients, diagnosed 1-10 years previously, non recurring. Community sample, mean age 54.9 (41-70). BC patients mean age 58.1 (40-70). Total sample, mean	Not included because states are difficult to classify. Interpretation in Earle *et al.* (2000) is different. Appears to be the same sample as Gerard *et al.*

				56.3 years range (40-70).	
13. Hillner and Smith (1991) (96) USA	Apply to the year chemotherapy is given: Minor toxicity with chemotherapy Major toxicity with chemotherapy First recurrence After first recurrence Second recurrence After second recurrence Third recurrence Minor toxicity defined as severe nausea and vomiting or weakness sufficient to require a reduction in activities of daily living, but not hospitalisation. Major toxicity requires hospitalisation.	**Value (range)** 0.90 (0.7-1.0) 0.80 (0.5-0.95) 0.70 (0.6-0.8) 0.85 (0.7-0.9) 0.50 (0.4-0.9) 0.70 (0.6-0.8) 0.30 (0.2-0.4) *Not stated whether these are means or medians of values from individual professionals or a group consensus.*	Not stated, assumed to be based on judgement from dead (0) to well (1).	Survey of oncologists and oncology nurses. Sample size not stated.	Not included because sample size not given.
14. Hillner, Smith and Desch (1992) (97) USA	**MBC states** Chemotherapy, high dose, with complicated autologous bone marrow transplantation Chemotherapy, induction high dose Chemotherapy, uncomplicated high dose, with autologous bone marrow transplantation Complete remission, chemotherapy continued Partial remission Progressive disease Stable disease Standard chemotherapy	**Value (range)** 0.10 (0.05-1.0) 0.50 (0.3-1.0) 0.30 (0.1-1.0) 0.85 (0.8-1.0) 0.60 (0.5–1.0) 0.40 (0.2-1.0) 0.50 (0.3-1.0) 0.70 (0.5-1.0) *Not stated whether these are means or medians of values from individual professionals or a group consensus.*	VAS Anchored: dead - well	Focus group of oncology physicians and nurses	Not included because sample size not given, but since this is a focus group sample size not likely to help.

15. Jeruss *et al.* (2006) (98)	8 clinical scenarios (see paper)	Values from 0.56 to 0.89	EQ-5D	Based on the judgement of 4 oncologists	Not included because EQ-5D scores are based on clinical judgement.
16. Kearney *et al.* (1999) (52)	**ABC states:** Start of second-line chemotherapy Sepsis Partial response (PR) Stable disease (SR) PR and severe PN PR and severe peripheral oedema Terminal disease Late progressive disease Start of second-line chemotherapy Sepsis Partial response (PR) Stable disease (SR) PR and severe PN PR and severe peripheral oedema Terminal disease Late progressive disease Start of second-line chemotherapy Sepsis Partial response (PR) Stable disease (SR) PR and severe PN PR and severe peripheral oedema Terminal disease Late progressive disease	(n=29) US: 0.63 (differs from B&H) US: 0.26 (not included in B&H) US: 0.84 (as B&H) US: 0.70 (as B&H) US: 0.58 (as B&H) US: 0.82 (as B&H) US: 0.23 (as B&H) US: 0.49 (as B&H) (n=30) UK: 0.56 (differs from Brown 2001) UK: 0.16 (not inc. in Brown 2001) UK: 0.84 (as Brown 2001) UK: 0.70 (as Brown 2001) UK: 0.58 (as Brown 2001) UK: 0.82 (as Brown 2001) UK: 0.23 (as Brown 2001) UK: 0.49 (as Brown 2001) (n=25-30) IT: 0.54 GER: 0.66 SP:0.65 IT: 0.23 GER: 0.23 SP:0.18 IT: 0.75 GER: 0.78 SP:0.86 IT: 0.59 GER: 0.70 SP:0.64 IT: 0.51 GER: 0.52 SP:0.43	SG. Anchored dead - perfect health.	129 oncology nurses from 5 countries. Total sample, mean age 33.7, n=129	Not included because values are reported in Hutton *et al.* (1996)

	Start of second-line chemotherapy Sepsis Partial response (PR) Stable disease (SR) PR and severe PN PR and severe peripheral oedema Terminal disease Late progressive disease	IT: 0.69 GER: 0.73 SP:0.75 IT: 0.19 GER: 0.14 SP:0.11 IT: 0.50 GER: 0.39 SP:0.39 AV: 0.59 AV: 0.20 AV: 0.81 AV: 0.62 AV: 0.53 AV: 0.75 AV: 0.16 AV: 0.41			
17. Launois *et al*. (1997) (99)	States relating to second line chemotherapy e.g. terminal care before staring chemotherapy	 0.25 0.86	Simplified version of the HUI	6 independent doctors and nurses	Not included because of limited size and details of sample, taken from CRD review, original article in French.
18. Norum *et al.* (1997) (100)	Modified radical mastectomy (MRM) Breast-conserving surgery (BCS) Anxiety and depression was reported to be a severe problem in 8.6–10.2% in the mastectomy group and 5.4–10.8% in the BCS group. The same figures in the slight to moderate problem category were 33.6–41.4% and 29.7–37.8%, respectively. This is assumed to be the only affected dimension.	Mean 0.84 Mean 0.87	Assumed EQ-5D values from health states taken from QOL study by Holmberg *et al.*. (1989).		Not included because data is not original.
19. Jansen *et al*. (2000) (101)	EBC During chemotherapy	VAS 0.77 (0.15) n=41 TTO 0.90 (0.12) n=41 SG 0.93 (0.10) n=38	TTO, VAS (anchored at 0 dead to 1 perfect health) and chained	41 EBC patients having adjuvant chemotherapy	Not included because data is used elsewhere (Jansen *et al*. 2000

			SG		(25))
20. Richardson *et al.* (1996) (102)	EBC M: Mastectomy, good physical, good mental J: Mastectomy, fair physical, fair mental B: Mastectomy, poor physical, poor mental, relapse. W: M (5 years) & J (10 years) & B (1 year)	**Mean** SG 0.86, TTO 0.80, VAS 0.75 SG 0.44, TTO 0.41, VAS 0.48 SG 0.19, TTO 0.16, VAS 0.24 SG 0.43, TTO 0.41, VAS 0.46	SG (n=45), TTO (n=47), VAS (n=47)	63 female volunteers recruited from local self-help and activity groups and hospital volunteer workers. Average age 56.	Not included because states are hard to classify, e.g. they contain how supportive patient's husband is.
21. Unic *et al.* (1998) (103) Netherlands	VAS Prophylactic mastectomy (PM) compared to BC screening as preferred state. (n=47) TTO 4 (all proven carriers) preferred PM to BCS 47 preferred BCS of those TTO values for PM were (n=46) Respondents found TT0 harder than VAS. Authors argue this reflects the difficult of the decision which is obscured in VAS (page 274)	**Mean (SD)** First session: 0.5 (0.27) Second session: 0.45 (0.28) First session: 0.77 (0.25) Second session: 0.69 (0.29)	VAS. Anchored: death - most preferred state. TTO. Anchored: death - most preferred state. Durations used changed according to age	Healthy women with a family history of BC referred for screening. n=47 for VAS, n=46 for TTO	Not included because the anchors are not comparable to dead/full health *Constant proportional trade-off explored and found significantly lower utilities for shorter durations.* *Test-retest for first 2 sessions for TTO = 0.76 and 0.96 for last two.*
22. Wittenberg *et al.* (2005) (104) USA	Advanced cancer states, for patients with advanced BC or prostate cancer. Very good: Able to work full time and manage household, able to eat wash etc. and drive car	**Median (SD)** ALL: 0.99 (0.11) PC: 0.99 (0.11)	Chained SG. Anchored: worst health - perfect health. Using bisection	49 patients with HR prostate cancer. Mean age 69.8 (range 45-85)	Not included because vignettes are difficult to classify. *Utility values were*

	without assistance, feel well most of the time, have good relationships and receive strong support, basically a calm person and look forward to things. Good: Need a lot of help to work full-time or manage household or only work part time. Able to eat, wash, etc. and drive care without assistance, lack energy some of the time, have good relationships and receive strong support, sometimes troubled, anxious and depressed. Moderate: Not able to work in any capacity, able to eat, wash etc. and drive car without assistance, lack energy some of the time, have good relationships and receive strong support, sometimes troubled, anxious and depressed. Poor: Not able to work in any capacity, need assistance to eat, wash, drive, feel ill most of the time, have good relationships and receive strong support, sometimes troubled, anxious and depressed.	BC: 1.0 (0.11) ALL: 0.85 (0.19) PC: 0.83 (0.16) BC: 0.92 (0.21) ALL: 0.80 (0.22) PC: 0.75 (0.20) BC: 0.91 (0.23) ALL: 0.30 (0.27) PC: 0.25 (0.25) BC: 0.30 (0.30)	pattern. Rescaled to dead-perfect health	51 patients with MBC. Mean age 53.5 (range 33-77) Total: N=100 Mean age 61.5 (33-85).	*found to be independent to patient's current health state.* *Prostate cancer patients tend to give a lower value than breast cancer patients c.f. Lloyd et al. (2006).*

Table B.3: Studies with drug specific utility values

Study	**Health state description**	**Health state value**	**How valued**	**Who valued**	**Comments**
1. Bernhard *et al*. (2008)	**EBC and high risk of relapse** Baseline Standard Dose-CT Dose Intensive-EC	**Mean** 0.75 (+/-0.2) 0.73 (+/-0.3)	VAS (Subjective Health Estimations SHE: anchored at worst to best health,	243 EBC women at risk of relapse from IBCSG trial.	Data table refers to means, but text refers to medians.

(57) IBCSG Trial, Europe, Australia and Asia (also see values from Table B.1)	3 months from randomisation Standard Dose-CT Dose Intensive-EC 6 months from randomisation Standard Dose-CT Dose Intensive-EC 9 months from randomisation Standard Dose-CT Dose Intensive-EC 12 months from randomisation Standard Dose-CT Dose Intensive-EC 18 months from randomisation Standard Dose-CT Dose Intensive-EC **Toxicity:** SD-CT: 4 courses of standard-dose anthracycline-based chemotherapy followed by 3 courses of classical CMF (n=135) (months 1-6) DI-EC: 3 cycles of adjuvant dose-intensive epirubicin and cyclophosphamide chemotherapy administered with filgrastim and progenitor cell support (n=149) (months 2-3) **Time without symptoms and toxicity** SD-CT (n=140) DI-EC (n=152) **Relapse** SD-CT (n=51) DI-EC (n=34)	 0.65 (+/-0.3) 0.61 (+/-0.4) 0.67 (+/-0.3) 0.79 (+/-0.3) 0.75 (+/-0.3) 0.83 (+/-0.2) 0.79 (+/-0.3) 0.84 (+/-0.2) 0.80 (+/-0.2) 0.86 (+/-0.2) **Toxicity:** VAS: 0.60, TTO 0.77 VAS: 0.57, TTO 0.74 **Time without symptoms** VAS: 0.80, TTO 0.92 VAS: 0.77, TTO 0.90 **Relapse** VAS: 0.80, TTO 0.92 VAS: 0.77, TTO 0.90	patients asked to imagine spending the rest of their life in their current health state, then to value it). SHE converted to TTO in study described above.		
2.	**Metatstatic bone disease: ABC**	**Mean (95% CI) healthy**	TTO. Healthy months	25 Canadian women	

Dranitsaris *et al.* (1999) (53) Canada	SRE with pamidronate No SRE with pamidronate SRE with placebo No SRE with placebo	**months equivalent** Public 5.46 (4.39-6.53) Staff 4.80 (3.39–5.63) Public 7.73 (6.30-9.16) Staff 9.92 (9.24-10.60) Public 3.68 (2.75-4.61) Staff 4.13 (3.36–4.90) Public 6.76 (5.39-8.13) Staff 7.89 (6.87–8.92)	equivalent. 12 months in health state. Anchored at dead to perfect health. No option of state worse than dead.	living in Ontario (>=18yrs). Median age 45 (range 22-66) And 25 female health care professionals with experience in oncology. Median age 40, range 26–56).	
3. Dranitsaris *et al.* (2000) (54) Canada	**Second-line hormonal therapy in ABC:** **Letrozole:** No response and progression during chemotherapy: FAC (5-FU, doxorubicin and cyclophosphamide) No response to letrozole but response to FAC Response to letrozole **Anastrozole:** No response and progression during FAC No response to anatrozole but response to FAC Response to anatrozole **MA (Megestrol acetate)** No response and progression during FAC No response to MA but response to FAC Response to MA	**Mean (95% CI)** Pub: 0.45 (0.37-0.55) Staff: 0.53 (0.45-0.92) Pub: 0.67 (0.55-0.79) Staff: 0.57 (0.49-0.65) Pub: 0.80 (0.49-0.73) [error in original] Staff: 0.78 (0.71-0.84) Pub: 0.45 (0.37-0.55) Staff: 0.53 (0.45-0.92) Pub: 0.67 (0.55-0.79) Staff: 0.57 (0.49-0.65) Pub: 0.80 (0.70-0.92) Staff: 0.72 (0.66-0.78) Pub: 0.45 (0.35-0.55) Staff: 0.40 (0.30-0.48) Pub: 0.64 (0.52-0.76) Staff: 0.53 (0.44-0.61) Pub: 0.80 (0.69-0.91)	TTO. Quality adjusted progression free periods were measures as 'Healthy month equivalent' for time in each outcome. Rescaled to be anchored at death and perfect health.	25 Canadian women living in Ontario (>=18years). Median age was 50.5 (range 20-81), 36% received post secondary education, 8% had received some form of cancer therapy in the past. Also 25 health care workers, median age 37 (range 22-61), 96% received post secondary education, 0% had received cancer therapy.	The paper notes that due to an absence of data from head-to-head comparison between letrozole and anastrozole and identical side effect profile was assumed. Differences in valuations in responses to letrozole and anastrozole must derive from future expectations.

		Staff: 0.67 (0.58-0.76)			
4. Fountzilas *et al*. (2009) (105) Greece	**MBC:** Paclitaxel and carboplatin every 3 wks (PCb) Pre (n=100) Post (n=78) 6 month follow-up (n=74) Pre (n=100) Post (n=79) 6 month follow-up (n=74) Docetaxel & gemcitabine every 3 wks (GDoc) Pre (n=100) Post (n=73) 6 month follow-up (n=62) Pre (n=97) Post (n=73) 6 month follow-up (n=61) Paclitaxel weekly (Pw) Pre (n=100) Post (n=73) 6 month follow-up (n=62) Pre (n=97) Post (n=73) 6 month follow-up (n=61)	**Mean (SD), Median** EQ-5D: 0.62 (0.26), 0.69 EQ-5D: 0.68 (0.22), 0.70 EQ-5D: 0.70 (0.27), 0.78 VAS: 0.66 (0.21), 0.70 VAS: 0.70 (0.16), 0.70 VAS: 0.73 (0.19), 0.75 EQ-5D: 0.59 (0.25), 0.66 EQ-5D: 0.65 (0.21), 0.69 EQ-5D: 0.69 (0.23), 0.76 VAS: 0.67 (0.20), 0.70 VAS: 0.70 (0.16), 0.70 VAS: 0.61 (0.17), 0.80 EQ-5D: 0.63 (0.24), 0.69 EQ-5D: 0.66 (0.25), 0.69 EQ-5D: 0.74 (0.22), 0.78 VAS: 0.72 (0.19), 0.70 VAS: 0.73 (0.18), 0.75 VAS: 0.81 (0.14), 0.80	EQ-5D, European tariff.	Inclusion: Patients with histologically proven MBC, life expectancy >= 12 weeks, age >=18. Age: PCb (n=136) median 60; GDoc (n=144) median 60; Pw (n=136) median 60.5	
5. Leung *et al.* (1999) (55) Canada	**MBC states:** Paclitaxel: Toxicity from treatment Response to treatment No response to treatment Docetaxel: Toxicity from treatment	**Mean (Healthy volunteers, Patients)** 0.12 HV, 0.11 PAT 0.62 HV, 0.61 PAT 0.24 HV, 0.26 PAT	TTO. 4 months treatment v months in perfect health.	25 healthy, oncology care providers. Median age 34 (range 23-55)	No significant differences between patients and healthy volunteers

	Response to treatment No response to treatment Vinorelbine: Toxicity from treatment Response to treatment No response to treatment	0.10 HV, 0.09 PAT 0.51 HV, 0.49 PAT 0.17 HV, 0.17 PAT 0.23 HV, 0.16 PAT 0.80 HV, 0.77 PAT 0.41 HV, 0.33 PAT		25 patients (11 metastatic, others stage I/II). Median age 55 (range 31-73)	

Table B.4: Studies for which utility values could not be presented

Study	Comment
1. Chie *et al*. (2000) (106) Taiwan	Utility values from 21 experts in Taiwan using VAS, TTO and SG for 17 BC states. Most data is presented graphically. Three rounds of interviews were used, and experts were presented with median values, scores converged to median values for most phases in the second and third rounds. SG and TTO values were higher than VAS, except for terminal/hospice stage. Utility values which are reported are VAS (anchored at dead-perfect health) values reported for screening phase (100 or 90), finding of a tumour (75), diagnosis (70), adjuvant chemotherapy (50), BCS (65), MRM (60), recurrence or metastasis (30), terminal stage in general ward (10), terminal at home or hospice (12.5). TTO and SG values are reported for diagnosis phase (90).
2. Franic and Pathak (2003) (75)	Study considers the impact of excluding values worse than dead. A sample of women (n=119, without experience of BC) valued 3 states: cure, treatment and recurrence. Utility values are only presented as differences between states.
3. Hayman *et al.* (2001) Abstract only.	SG utility values for combinations of treatment (BCS and radiotherapy) from a group of 120 women with a history of DCIS and 97 women with a history of stage I/II BC. Utility values are presented only as differences.
4. Hwang and Wang (2004) (107) Thailand	Cross-sectional survey on 223 BC patients using SG and the questionnaire WHOQOL-100 rescaled to 0-1. 64, 72, 69 and 28 patients in stages I–IV, respectively. Only quality-adjusted survival time (QAST) shown.
5. Kestle *et al.* (1989) (108) Canada Abstract only	Data from an RCT comparing 12 and 36 weeks of adjuvant chemotherapy. Uses TTO anchored at death and good health. Utility values are only presented as changes.
6. Perez *et al.* (2001) (77) New Zealand	Study includes 54 patients presenting at Dunedin Hospital, New Zealand, with metastatic cancer. 5 refused to complete the TTO task due to moral, philosophical or other reasons. 21 died during the study, 9 withdraw due to poor health. Mean age 58.7, 50% had been diagnosed for more than 1 year. Respondents asked to trade off days in the forthcoming month to change current health status (assumed

	the same as last month). TTO exercise completed monthly for 12 months (13 datasets). Also completed Spitzer QoL uniscale (5 VAS from 0-2, added together). In most time periods over 2/3rds of women did not trade any days (14 did not trade on any occasion.). Data not reported in an appropriate format.
7. Polsky *et al.* (2003) (77) USA	Considers the impact of patient choice on health state preferences following mastectomy and BCSRT. Assessed 3-5 years after surgery on 1,320 of the surviving subjects, using EQ-VAS. Values only shown graphically.
8. Stalmeier *et al*. (1996) (109)	Studies investigating preference reversal in TTO valuations using values for MBC state. Valuations are from students without BC. Data is not presented in a usable format.
9. Suh *et al.* (2003) (110) Abstract only.	Abstract refers to data from a study collecting utility values for 8 non-metastatic health states from n=210 healthy women and n=112 women with DCIS. No other details available.