Shared decision-making about treatments for early breast cancer : preferences of older patients and clinicians

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CHAPTER 2

Patients' Preferences for Surgical and Adjuvant Systemic Treatment in Early Breast Cancer: a Systematic Review

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ABSTRACT

Purpose | Treatment decisions in early breast cancer can revolve around type of surgery and whether or not to have adjuvant systemic therapy. This systematic review aims to give an overview of patient self-reported factors affecting preferences for breast-conserving surgery (BCS) versus mastectomy (MAST), the minimal benefit patients require from adjuvant chemotherapy (aCT) and/or adjuvant hormonal therapy (aHT) to consider it worthwhile, and factors influencing this minimally-required benefit.

Methods | PubMed and EMBASE were searched for relevant articles. Two reviewers independently selected articles and extracted data.

Results | We identified 15 studies on surgical and six on adjuvant systemic treatment decision-making. Factors affecting patient preference for BCS most frequently related to body image (44%), while factors influencing preference for MAST most often related to survival/recurrence (46%). To make adjuvant systemic therapy worthwhile, the median required absolute increase in survival rate was 0.1-10% and the median required additional life expectancy was 1 day to 5 years. The range of individual preferences was wide within studies. Participants in the aHT studies required larger median benefits than those in the aCT studies. Factors associated with judging smaller benefits sufficient most often (44%) related to quality of life (e.g., less treatment toxicity).

Conclusion | Decisive factors in patients' preferences for surgery type commonly relate to body image and survival/recurrence. Most participants judged small to moderate benefits sufficient to consider adjuvant systemic therapy worthwhile, but individual preferences varied widely. Clinicians should therefore consider the patient's preferences to tailor their treatment recommendations accordingly.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide and the leading cause of female cancer death. In 2008, an estimated 1.4 million women were diagnosed with breast cancer and more than 450,000 women died from the disease.[1] The European age-adjusted five-year relative survival for all stages is estimated to be 81% (95% CI: 80.2-81.7).[2] The estimated overall ten-year relative survival is 71% (95% CI: 69.9-72.1).[2] A significant proportion of the patients are diagnosed with early-stage invasive breast cancer.[3]

Different treatment options are available for early-stage invasive breast cancer. The majority of newly-diagnosed patients are eligible for two surgical options: breast-conserving surgery (BCS) with radiotherapy, or mastectomy (MAST). Randomized clinical trials with long follow-up periods have demonstrated similar survival rates for women who underwent BCS followed by radiotherapy or MAST.[4,5] Given that both treatment options are equally effective with respect to survival, patient preferences play a decisive role in determining the best treatment decision.

Another treatment decision may relate to systemic therapy following surgery. Adjuvant systemic treatments include chemotherapy and/or hormonal therapy and have been shown to significantly improve disease-free and overall survival,[6] but are associated with several adverse effects. These can negatively impact quality of life. The decision regarding adjuvant systemic therapy therefore involves a marked trade-off between the expected benefits and the potential risks. How patients value the benefits and risks will thus affect their preference for one treatment over the other.

Over the past decade, patient preferences have become an increasingly important determinant of treatment choice due to a greater emphasis on shared decision-making and patient autonomy. Breast cancer patients' involvement in treatment decisions has been shown to improve their satisfaction[7] and short and long-term well-being[8] and to increase their level of comfort with the decision made.[9] More recently, integration of data on patients' preferences into clinical treatment guidelines has been emphasized.[10,11]

Given that BCS with radiotherapy and MAST are equivalent from a strictly medical point of view, insight into the factors that play a decisive role in patients' preferences for surgery type is valuable for making treatment recommendations. Similarly, insight into patients' strength of preference for adjuvant systemic therapy is important to understand patients' willingness to accept such treatment. The aim of this systematic review is therefore twofold. First, to identify which patient self-reported factors influence their preferences for BCS versus MAST. Second, to give an overview of the benefit patients minimally require from adjuvant

chemotherapy (aCT) and/or adjuvant hormonal therapy (aHT) to consider it worthwhile, as well as of determinants of preferences and patient self-reported factors affecting minimally-required benefit.

METHODS

Search strategy

We searched PubMed and EMBASE for articles published between January 1, 1990 and October 2, 2012. Appendix 1 lists the search strings. Also, the reference lists of included articles and relevant review articles[12-16] were hand-searched for additional articles.

Selection criteria

Articles were selected if they (1) were published in English, (2) in a peer-reviewed journal, (3) included early-stage breast cancer patients, and assessed (4) patient self-reported factors affecting preferences for BCS versus MAST, or (5) patients' preferences for aCT and/or aHT. Both quantitative and qualitative studies were eligible for inclusion.

We considered the disease as early-stage if it was stage I/II(A), T_{1-2},N_{0-1},M_0 or invasive T_{1-2}. If not specified, articles were included if the words 'early', 'early stage', or 'early-stage invasive breast cancer' appeared in the sample description and/or article title. Studies also involving other patient or non-patient populations were included if results had been reported specifically for the subgroup of early breast cancer.

Articles regarding surgical treatment decision-making were selected if they (1) reported at least one patient self-reported factor (different than the surgeon's role) that distinguished preferences for BCS (with or without radiotherapy) or MAST, and (2) included participants who had been surgically treated within two years prior to the study.

Articles regarding adjuvant systemic treatment decision-making were included if a probability trade-off method[17] or a similar method was used to determine the strength of patients' preference for aCT and/or aHT. In short, the probability trade-off method requires respondents to consider potential benefits and risks of various treatment options, and the probabilities of obtaining those outcomes.[17] Minimally-required benefit is then determined by systematically increasing or reducing benefit of treatment until participants judge the benefit sufficient to outweigh the risks.

Data selection

Two reviewers (VCH, EB) independently selected articles that met the inclusion criteria based

on titles and abstracts. Next, they screened the full-texts of potentially relevant articles. When multiple articles reported on the same study, the article with the largest sample was included. Agreement about eligibility was achieved during consensus meetings.

Data extraction and analysis

The reviewers independently extracted data on study design (retrospective or prospective), participants, data collection method, time from treatment to study and response rates. If no subgroup details were reported, details regarding the total sample were extracted. Disagreements in data extraction and interpretation were resolved in consensus meetings.

From articles on surgical treatment decision-making, we extracted patient self-reported factors that were significantly ($p<0.05$, in univariable or multivariable analyses) associated with preferences for BCS or MAST, and information about whether these factors were measured through open or closed-ended questions. When articles did not report outcomes quantitatively, or test for statistical significance, all factors that patients reported to influence their preferences for BCS or MAST were extracted, in order to provide a complete as possible overview. The reviewers defined six categories based on the patient self-reported factors retrieved: (1) body image (e.g., wanting to keep one's breast, wanting to minimize scar size), (2) survival/recurrence (e.g., no difference in survival, concern about recurrence), (3) surgeon's opinion (e.g., surgeon's recommendation or preference for a particular type of surgery), (4) psychosocial (e.g., relevance of the breast to feelings of femininity, 'to get it over with'), (5) treatment (e.g., avoiding radiotherapy, recovery), and (6) costs (e.g., concern about costs). Two other reviewers (GJL, AMS) independently assigned the extracted factors to one of the six categories. If they disagreed, a third party (EB) resolved the disagreement. Next, for both BCS and MAST, factors within each category were counted and reported as a percentage of all retrieved factors. Percentages were also reported by study design.

From articles on adjuvant systemic treatment decision-making, details were extracted on the method for eliciting preferences, including how benefits and risks of adjuvant systemic therapy and their probabilities were presented; the minimally-required benefit; and the percentage of participants who would refuse treatment irrespective of treatment benefit. If not reported in the text, data were extracted based on figures or tables. If preferences had been examined at several time points, only the first measurement was extracted. We further extracted factors that patients reported to influence their preferences and determinants that were significantly ($p<0.05$, in univariable or multivariable analyses) related to patient preferences. VCH and EB defined four categories of determinants based on those retrieved: (1) treatment (e.g., having or not having received a particular treatment), (2) socio-demographic characteristics (e.g., age), (3) cognitive/affective factors (e.g., anxiety), and (4) quality of life (e.g., treatment toxicity). GJL and AMS independently assigned determinants to one of the four categories.

Again, EB resolved disagreements about categorization if necessary. Determinants within each category were counted and reported as a percentage of all retrieved determinants.

The quality of the studies examining patients' preferences for adjuvant systemic therapy was assessed using the PREFS checklist.[18] This checklist consists of five criteria: (1) Purpose of the study; (2) Respondent sampling; (3) Explanation of the preference assessment methods; (4) Findings reported for the total sample; and (5) Significance testing (Appendix 2). Studies were assessed against each of the five criteria. An item was scored as 'yes' if the information was present, as 'no' if the information was absent, or as 'unclear' if the information was not adequately reported. The total quality score for each study was calculated by adding the number of positive responses, resulting in a possible score from 0 to 5. In cases of discrepancy, two researchers (VCH and EB) discussed the study until consensus was achieved. As only three out of five criteria were applicable to the factors that influence patients' surgical preferences, we did not use the checklist to assess the quality of those studies.

RESULTS

Our search strategy yielded 3266 unique citations, of which 84 were selected for further review (Figure 1). Of these, 18 articles met the inclusion criteria. Another three articles were included after review of the reference lists of included articles. A total of 21 articles were included: 15 studies examined patient self-reported factors affecting preferences for surgery type and six studies examined patients' preferences for adjuvant systemic treatment.

Surgical treatment decision-making

Characteristics of the studies included

Retrospective studies

Ten studies with a retrospective design were included (Table 1).[19-28] Mean age of the participants ranged from 54 to 61 years[19,20,22,23,28] and their median age ranged from 47 to 58 years.[24-27] Timing of data collection relative to diagnosis or surgery varied widely between the studies. In studies that reported this information, mean time between diagnosis or surgery and the study ranged from one week to five months[21-23,27,28] and median time from diagnosis to study was 19 months.[24] Other studies only reported that factors were assessed after surgery,[26] during adjuvant radiotherapy or after completion of treatment[25] or within two years after surgery.[19]

Prospective studies

Five prospective studies were identified (Table 1).[29-33] Mean age of the participants ranged from 52 to 58 years[29,32] and their median age from 54 to 57 years.[30,33] Four studies[29-31,33] assessed

factors before surgery. The remaining study[32] collected their data before and after surgical treatment, but did not specify at what point in time factors were assessed.

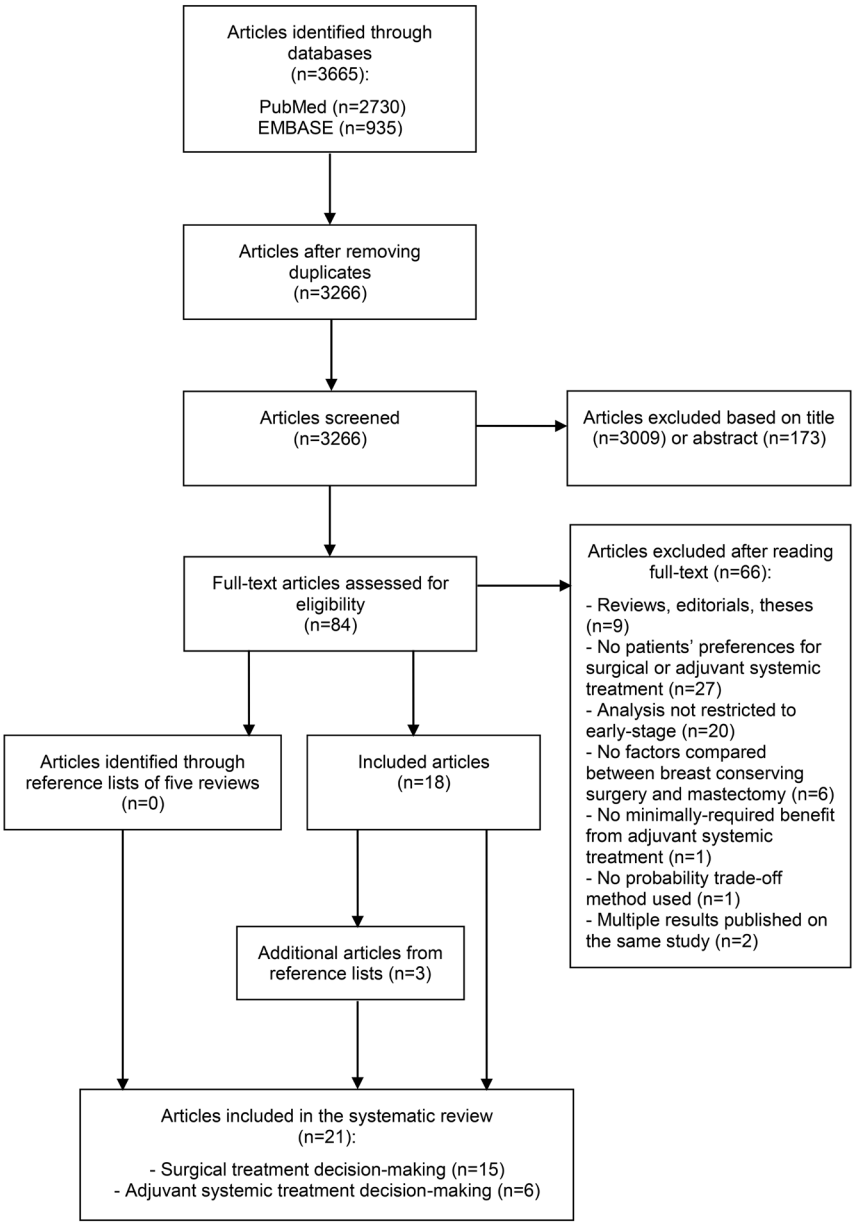

Figure 1. Flow diagram of the literature search and inclusion of articles

Table 1. Description of the studies (N=15) comparing patient self-reported factors affecting their preference for surgery type

First author (year)	Study design	Country (Setting)	Participants	N	Mean age in years (range/ sd)[a]	Data collection method	Time from diagnosis or surgery to study	Response rate
Retrospective (n=10)								
Guadagnoli (1998)[21]	Cohort	USA (Multicenter)	- Early-stage - Diagnosed between 1993-95 in Massachusetts and Minnesota - Identified from hospital pathology offices/ hospital tumor registries - Results described for women who reported that both BCS and MAST were mentioned	Unclear[b]	NR	(telephone) Interview	An average of 3 to 5 months after diagnosis	Massachusetts: 61%[c] Minnesota: 84%[c]
Benedict (2001)[20]	Cohort	USA	- Patients treated between 1995-98 - Selected from mailing lists of community-based cancer groups in two states - Results described for patients who recalled being asked to choose either BCS or MAST without surgeon making a recommendation	54	BCS: 54.2 (35-70) at diagnosis MAST: 57.4 (30-86) at diagnosis	Questionnaire	NR	58% (421/730)
Katz (2001)[22]	Cohort	USA	- All primary DCIS and a 15% random sample of non-metastatic invasive breast cancer - Diagnosed in 1998 - Identified from a SEER registry - Analyses stratified for patients who perceived a choice between BCS and MAST	122	61.4 (30-92)	Questionnaire	Average time between diagnosis and completion of survey was approximately 13 weeks	71% (183/257)[d] 85% (183/215)[e]
Mastaglia (2001)[23]	Population-based	Australia	- Early-stage - Diagnosed between 1 Oct 1996-31 March 1997 - Identified through Cancer Registry	175	57.9 (31-89) BCT: 56.1 (13.88) MAST: 59.3 (13.11)	Questionnaire	Mean time since surgery was 4.3 months (range, 0-8)	49% (175/350)
Schou (2002)[28]	Cohort	Norway (Single center)	- Primary breast cancer, clinically T_{1-2} (<5 cm) - Surgery between Sept 1999-Aug 2001 - Invited by nurse after consultation with surgeon	194	56.7 (21-83) BCS: 54.9 (8.9) MAST: 58.9 (11.7)	Questionnaire	Completed within 1 week after surgery (thus before histology report was available)	79% (194/245)

Sepucha (2007)[24]	Cohort	USA (Multicenter)	- Early-stage - A sample of newly-diagnosed patients and a sample of survivors - Identified through participating physicians of two hospital cancer centers - A pilot study to assess a decision quality measure	35	52.5[a] (32-80)	Questionnaire	Median time since diagnosis was 19 months (range, 2-100)	68% (42/62)
Ballinger (2008)[19]	Cohort	UK (Single center)	- Patients who said being offered a choice between BCS and MAST - Surgery between 2005-06 - Identified using hospital records	97	59.9 (NR) BCS: 56.2 (NR) MAST: 63.5 (NR)	Questionnaire	Within 2 years of surgery	69% (131/189)
Caldon (2011)[27]	Cohort	UK (Multicenter)	- Patients who were eligible for both BCT and MAST - Invited by members of the breast team, as soon as possible after surgery	65	58[a] (33-73)	(face to face) Interview	Mean time since surgery was 6 weeks (range, 1.9-20.6)	Unclear
Agrawal (2012)[25]	Cohort	India (Single center)	- Early-stage - Recruited at a tertiary hospital, after definitive surgical treatment	47	47[a] (NR)	(face to face) Interview	During adjuvant radiotherapy or follow up	NR
Zhang (2012)[26]	Cohort	China (Multicenter)	- Preoperative assessment showing stage I or II - Recruited at five oncology departments of tertiary hospitals - 20.5% (326/1590) did not undergo surgery	1590	48.8[a] (22-77)	Questionnaire	After surgery	88% (1590/1800)
Prospective (n=5)								
Cotton (1991)[30]	Cohort	UK (Single center)	- Primary operable breast cancer - Diagnosed in 1988 - Invited by nurse after diagnosis and outline of surgical options - Results described for patients who were eligible for both BCS and MAST	91	57.4[a] (29-69)	(face to face) Interview	The day before their surgery	Unclear

Kraus (1999)[32]	Cohort	USA (Single center)	- Early-stage - Through breast health center - Contacted by investigator by telephone and at the pre-admission screening site - The primary goal was to describe women's satisfaction with body image before and after BCS or MAST, compared to women without breast cancer	31	52 (29-82)	Questionnaire	Unclear (either 1 week before or 8 weeks after surgery[f])	100%
Molenaar (2004)[33]	Cohort; a quasi-experimental design	The Netherlands (Multicenter)	- Early-stage - Treated between 1996-99 - Were eligible for both BCT and MAST - Invited after diagnosis and treatment options was discussed - All patients received standard information, or a decision aid as a supplement, depending on the period of inclusion	180 Standard: 88 Decision aid: 92	54[a] (29-85)	Questionnaire	Completed before the treatment decision was made or before provision of the decision aid (and before treatment decision was made)	95% (180/189)
Collins (2008)[29]	Cohort	USA (Single center)	- Early-stage - Were eligible for both BCS and MAST - Who had not yet met with a surgeon to discuss surgical options - Diagnosed between Feb 2005-Aug 2007 - Standard practice includes a video decision aid before surgical consultation	125	58 (11.8) BCS: 60 (11.0) MAST: 55 (12.8)	Two questionnaires (one administered by telephone)	At two points in time: (1) after viewing a decision aid, but before surgical consultation, and (2) after surgical consultation	50% (125/249)
Gollop (2009)[31]	Cohort	New Zealand (Multicenter)	- Breast cancer patients - Diagnosed between May 2004-Dec 2006 - Invited after diagnosis and information on surgical options from their surgeon - Analyses stratified for patients who were eligible for both BCT and MAST	135	NR	Questionnaire	Completed preoperatively	Unclear

NR: not reported; BCS: Breast-conserving surgery; MAST: Mastectomy; BCT: Breast-conserving therapy (breast-conserving surgery with radiotherapy); DCIS: Ductal carcinoma in situ

[a] Median

[b] A total of 1570 participants were interviewed, but the number of participants in the subgroup analysis was unclear

[c] Response rate after exclusion of women who missed the informed consent procedure, women who had language difficulties or were not located

[d] Response rate among women who were eligible for the study

[e] Response rate among women who received a questionnaire

[f] Unclear at which of the two points in time factors were assessed

Assessment of patient self-reported factors

Retrospective studies

Three studies[20,25,26] did not clearly report if they assessed patient self-reported factors through open or closed-ended questions. Two studies[21,27] used open-ended questions to assess factors and five studies[19,22-24,28] asked participants to rate the importance of predefined factors, varying from four to 17 items, on a Likert-type scale. These studies derived factors from the literature only,[22,23,28] or also from reports on focus groups and interviews with patients and providers,[24] or from consultations with a breast cancer self-help group.[19]

Prospective studies

Two studies[30,32] examined factors using open-ended questions. In the other three studies,[29,31,33] participants had to rate the importance of predefined factors on a Likert-type scale. The number of items varied from five to eight and they were based on a decision aid,[29,33] or were self-designed.[31]

Patient self-reported factors affecting their preference for BCS or MAST

Overall, 77 factors that affected patients' preferences for BCS (36 factors, Table 2) or MAST (41 factors, Table 3) were identified. The reviewers assigned 58 (75%) factors to the same category. They disagreed with the categorization of 19 factors (25%). Thus, the third party resolved the categorization of these factors.

Overall, 44% of the factors relating to preferring BCS involved body image (Table 2). The remaining factors related to survival/recurrence (17%), treatment (17%), psychosocial factors (11%) and surgeon's opinion (11%). In retrospective studies, body image-related factors were most frequently (40%) reported to affect patients' preferences. In the prospective studies, this predominance was even more pronounced (67%).

Overall, factors influencing preference for MAST most often related to survival/recurrence (46%) and treatment (39%) (Table 3). Specifically, most treatment-related factors revolved around radiotherapy. The remaining factors involved psychosocial factors (7%), surgeon's opinion (5%) and costs (2%). Body image was not reported to affect preference for MAST. Factors relating to survival/recurrence and treatment most strongly affected preferences, both in studies using a retrospective (43% versus 39%) and prospective (54% versus 38%) design.

Table 2. Number of factors reported (N=36) to affect patients' preferences for breast-conserving surgery (BCS)

First author	Body Image	Survival/ Recurrence	Surgeon's opinion	Psycho-social	Treatment	Costs
Retrospective (n=30 factors)						
Guadagnoli[21 a]			1			
Benedict[20 a]	1	1			1	
Katz[22 b,e]	1			1		
Mastaglia[23 d]		1	1			
Schou[28 d]	1			1		
Sepucha[24 d]	1					
Ballinger[19 d]	3				1	
Caldon[27 a]	3	1			1	
Agrawal[25 a]	1	1	1			
Zhang[26 a]	1	1		2	3	
Total, n (%):	12 (40)	5 (17)	3 (10)	4 (13)	6 (20)	0 (0)
Prospective (n=6 factors)						
Cotton[30 a]	1					
Kraus[32 a]	1	1				
Molenaar[33 c,d]	1					
Collins[29 e]	1					
Gollop[31 e]			1			
Total, n (%):	4 (67)	1 (17)	1 (17)	0 (0)	0 (0)	0 (0)
Overall, N (%):	**16 (44)**	**6 (17)**	**4 (11)**	**4 (11)**	**6 (17)**	**0 (0)**

[a] The study did not statistically test for significant differences
[b] No significant differences in factors between participants with ductal carcinoma in situ and invasive breast cancer
[c] No significant differences in factors between participants who received the decision aid and those who did not
[d] All factors were tested in univariable analysis only
[e] All factors were tested in multivariable analysis only

Table 3. Number of factors reported (N=41) to affect patients' preferences for mastectomy (MAST)

First author	Body Image	Survival/ Recurrence	Surgeon's opinion	Psycho-social	Treatment	Costs
Retrospective (n=28 factors)						
Guadagnoli et al.[21 a]		1	1			
Benedict et al.[20 a]		2			2	
Katz et al.[22 b,e]		2			2	
Schou et al.[28 d]		1				
Sepucha et al.[24 d]					1	
Ballinger et al[19 d]		1			2	
Caldon et al.[27 a]		2			2	
Agrawal et al.[25 a]		1	1			
Zhang et al.[26 a]		2		2	2	1
Total, n (%):	0 (0)	12 (43)	2 (7)	2 (7)	11 (39)	1 (4)
Prospective (n=13 factors)						
Cotton et al.[30 a]		2		1	1	
Kraus et al.[32 a]		2			1	
Molenaar et al.[33 c,d]		1			1	
Collins et al.[29 e]		1			1	
Gollop et al.[31 e]		1			1	
Total, n (%):	0 (0)	7 (54)	0 (0)	1 (8)	5 (38)	0 (0)
Overall, N (%):	**0 (0)**	**19 (46)**	**2 (5)**	**3 (7)**	**16 (39)**	**1 (2)**

[a] The study did not statistically test for significant differences
[b] No significant differences in factors between participants with ductal carcinoma in situ and invasive breast cancer
[c] No significant differences in factors between participants who received the decision aid and those who did not
[d] All factors were tested in univariable analysis only
[e] All factors were tested in multivariable analysis only

Adjuvant systemic treatment decision-making

Characteristics of the studies investigating patient preferences for adjuvant chemotherapy

Three retrospective studies[34-36] and one prospective study[37] were included (Table 4). Mean age of the patients ranged from 42 to 54 years[35,37] and the median age from 49 to 55 years.[34,36] Two studies[34,36] reported they included patients who had been treated with aCT, but in one[36] it was unclear whether a proportion (<1%) of the participants did receive aCT. The remaining retrospective study included patients with and without aCT experience.[35] The prospective study specifically aimed to compare preferences between patients who were about to start aCT (50%) versus those who would not undergo aCT (50%).[37] The quality assessment of the studies is presented in Table 4. Three studies were considered to be of high quality[34,35,37] (scoring four out of five criteria) and one study[36] was judged to be of low quality (two out of five).

Table 4. Description of the studies (N=6) examining patients' preferences for adjuvant systemic treatment

First author (year)	Study design	Country (Setting)	Participants	N	Mean age in years (range/sd)[a]	Data collection method	Time from aT to study	Response rate	Quality score (0-5)[b]	P	R	E	F	S
aCT (n=4)														
Lindley (1998)[35]	Retrospective, cohort study	USA	- Early-stage - Completed aT between 1988-91 and were disease-free - Review of records of a breast cancer program - 36% (31/86) did not undergo aCT	86	54 (29-86)	Questionnaire and (telephone) Interview	>2 years from completion of aT	72% (86/120)	4	√		√	√	√
Simes (2001)[36]	Retrospective, cohort study	Australia (Single center)	- Early-stage - Recruited in participating clinic between Nov 1986-Dec 1987 - Unclear whether <1% had received aCT	104	49[a] (25-67) at time of interview	(face to face) Interview	≥3 months after completion of aCT	81% (104/129)	2			√		√
Duric (2005)[34]	Retrospective, cohort study	Australia (Multicenter)	- Early-stage - Recruited in participating clinics	97	55[a] (25-69) at time of interview	(face to face) Interview	Average time between finishing aCT and interview was 17 months (range, 3-34)	86% (131/152)	4	√		√	√	√
Jansen (2001)[37]	Prospective, cohort study	The Netherlands (Multicenter)	- Early-stage - Recruited in hospitals between June 1996-Nov 1999 - Two patient groups: patients scheduled for aCT and patients not scheduled for aCT	76 aCT: 38 no-aCT: 38	aCT: 42 (29-50) no-aCT: 55 (38-77)	(face to face) Interview	Before start of aCT and at a similar point in time in the no-aCT group	54% (38/71)	4	√		√	√	√

aHT (n=2)													
Duric (2005)[38]	Retrospective, cohort study	UK (Multicenter)	- Early-stage - Premenopausal - Had been treated with tamoxifen, goserelin, or both, in a randomized trial (goal was to evaluate 2 years of aHTs in women ≤50 years) - 8% (7/85) did not undergo aHT	85	45[a] (31-54) at time of interview	(face to face) Interview	6-30 months after finishing aHT	71% (85/120)	4	√	√	√	√
Thewes (2005)[39]	Retrospective, cohort study	Australia	- Early-stage - Premenopausal - Had been treated with tamoxifen, goserelin, or both (with or without oophorectomy) for ≥3 months - Majority still treated at the time of the study - Review of databases of clinics	102	36 (sd, 3) at time of diagnosis	(face to face) Interview	Mean time since diagnosis was 27 months (sd, 5)	75% (102/137)	3	√	√		√

aT: Adjuvant systemic therapy; aCT: Adjuvant chemotherapy; aHT: Adjuvant hormonal therapy; [a] Median; [b] Quality assessment according to the PREFS checklist; P: Purpose; R: Respondents; E: Explanation; F: Findings; S: Significance; √: the criterion was met

Assessment of patient preferences for adjuvant chemotherapy

All four studies presented participants with two treatment strategies: treatment with aCT versus treatment without aCT. Descriptions of potential risks of aCT varied between the studies. In two studies,[34,36] patients were asked to state their preference based on their own experiences with aCT. The other studies[35,37] gave patients information about the risks of aCT regardless of the patient's experience or treatment plan. The studies differed in how much detail they gave about aCT schedules, e.g., describing aCT as a six-month therapy,[34,36] or as an outpatient administration of one cycle of therapy per month for six months.[35,37] In the studies, the benefit of aCT was expressed as an increased probability of cure[35] or (disease-free[37]) survival,[34,36] or in terms of additional life expectancy.[34-36] In all studies, the survival probabilities or life expectancies for both treatment options was made explicit. Three studies used probability of survival without aCT as starting point, and then asked participants what additional benefit of aCT they would require to make it worthwhile.[34,36,37] In contrast, in Lindley et al.[35] the starting point was probability of survival with aCT and likelihood of survival without aCT was systematically decreased.

Median required increase in survival rate from adjuvant chemotherapy

Table 5 summarizes the minimum absolute increase in survival rate that participants considered sufficient to make aCT worthwhile. The median required benefit ranged from 0.1% to 7%. Required benefit seemed to be independent of baseline survival probabilities.[34-36] Although most participants judged small benefits sufficient to make aCT worthwhile, individual preferences varied widely within each study. Additionally, 2-19% of the participants would refuse aCT irrespective of benefit. Jansen et al.[37] observed that most patients who were scheduled for aCT would accept it for significantly less benefit than patients who were not scheduled for aCT (median required benefits: 1% versus 12%). Moreover, a higher proportion of patients would accept aCT for no (0%) benefit in those who were scheduled for aCT than in those who would not undergo aCT (39% versus 8%). Similarly, Lindley et al.[35] showed that for each scenario, patients who had been treated with aCT were significantly more willing to accept aCT than patients who had not been treated with aCT.

Median required additional life expectancy from adjuvant chemotherapy

Three studies assessed patients' preferences in terms of additional life expectancy (Table 5).[34-36] Most participants considered small increases, ranging from 1 additional day to 0.8 additional years, sufficient to make aCT worthwhile. Simes et al.[36] reported that participants required larger benefits on the longer (15 years) versus shorter (5 years) term. Variation in individual preferences was large within the studies and 1-10% would refuse aCT irrespective of benefit. Again, Lindley et al.[35] observed that the proportion of patients who would accept aCT was higher in those treated with aCT than those without such treatment experience.

Table 5. Minimum increase in survival rate and life expectancy that participants considered worthwhile

First author	Minimum increase in survival rate				Minimum increase in life time				Significant determinants of preferences[f]
	5-year survival rate without aT (%)	Median desired increase (%)	Range (%)	Participants unwilling to accept aT(%)	Life expectancy without aT (yrs)	Median desired increase	Range	Participants unwilling to accept aT(%)	
aCT (n=4)									
Retrospective studies									
Lindley[35 g]	95[a] 75[a] 50[a]	5 5 5	5-25[b] 5-25[b] 5-25[b]	11 12 13	5[c]	6 m	1-24 m[d]	10	- Less life disruption during aCT (Q) - Having had previous aCT (T)
Simes[36 h]	65 85	2 2	>0-25 >0-15	2 3	5 15	0.6 yrs 0.8 yrs	>0-15 yrs >0-5 yrs	1 9	- Less treatment toxicity (Q) - Received a full dose of aCT(T) - Not received radiotherapy (T) - Had better social support (S) - Had others at home dependent on their support (S)
Duric[34 h]	65 85	0.1 0.1	0.1-35 0.1-15	0 3	5 15	1 d 1 d	1 d-20 yrs 1 d-20 yrs	2 4	- Recalled being less troubled by nausea[i] (Q), fatigue[i] (Q), altered sense of taste[i] (Q), or hair loss[i] (Q), - Recalled a better appetite[i] (Q), emotional[i] (Q), physical (Q) and overall well-being (Q) during aCT - Recalled being less troubled by problems with needles or injections[i] (T) - Recalled being less troubled by anxiety[i] (C), problems concentrating[i] (C), thought of actually having aCT[i] (C), or problems coping with aCT[i] (C) - Had a friend or relative who died from cancer (C) - Had dependents (S) - Had support available at all times during aCT[i] (S)
Prospective studies									
Jansen[37 g]	80[e]	7	0-20	19	NS	NS	NS	NS	- Scheduled for aCT (T)
aCT		1	0-20	3					
no-aCT		12	0-20	34					

aHT (n=2)									
Retrospective studies									
Duric[38 h]	60	10	1-40	0	5	3 yrs	1 d-20 yrs	0	- Less treatment toxicity (Q)
	80	10	1-20	0	15	5 yrs	1 d-30 yrs	0	- Had tamoxifen (with or without goserelin) (T)
Thewes[39 h]	65	2	0-35	2	5	3 m	0-15 yrs	0	- Less treatment toxicity (Q)
	85	2	0-15	7	15	6 m	0-15 yrs	1	

aT: Adjuvant systemic therapy; aCT: Adjuvant chemotherapy; aHT: Adjuvant hormonal therapy; NS: not studied; d: days; m: months; yrs: years; Q): factor related to quality of life; (T) treatment-related factor; (C) cognitive/ affective-related factor; (S) factor related to socio-demographic characteristics

As an example, in Simes and Coates[36] approximately half of the participants considered aCT to be worthwhile for an absolute increase in survival of 2%, in addition to a 5-year survival rate of 65% without aCT. Thus, most participants would accept aCT if the 5-year survival rate with aCT was 67% (65+2%). In this scenario, the required benefit ranged from more than 0 to 25%. Two per cent of the respondents indicated that they would refuse aCT irrespective of benefit. In the other scenario, a 5-year survival rate of 85% without aCT, the median required benefit was also 2% and the required benefits ranged from >0-15%. Three per cent of the respondents would refuse aCT. In the same study, most participants required an absolute gain of 0.6 years, if the life expectancy was 5 years without aCT. The required benefit ranged from >0-15 years. One per cent of the respondents indicated that they would refuse aCT, irrespective of a maximum benefit of 15 years in that scenario. In another scenario, if the life expectancy was 15 years without aCT, the median required benefit was 0.8 years in this study. In that scenario, the minimally-required benefit ranged from >0-5 years. Nine per cent would refuse aCT irrespective of benefit.

[a] Starting point was a survival rate with aCT, survival time was not reported
[b] The minimum benefit was set at a gain of 5% and the maximum benefit at 25%
[c] Starting point was a 5-year life expectancy with aCT
[d] The minimum benefit was set at a gain of three months and the maximum benefit at a gain of 24 months
[e] 5-year disease-free survival rate without aCT
[f] Factors significantly associated with judging smaller benefits sufficient to consider adjuvant systemic therapy worthwhile
[g] All factors were tested in univariable analysis only
[h] All factors were tested in univariable and multivariable analyses
[i] The factor was significant in univariable analysis only

Characteristics of studies investigating patient preferences for adjuvant hormonal therapy

Table 4 describes the characteristics of two retrospective aHT studies.[38,39] Both studies included only premenopausal patients. In Thewes et al.[39], most participants were undergoing aHT during the study. In Duric et al.[38] 7% of the participants had not been treated with aHT, but were included in the analyses. The studies were considered to be of medium[39] (scoring three out of five criteria) and high[38] (four out of five) quality, respectively (Table 4).

Assessment of patient preferences for adjuvant hormonal therapy

The aHT studies used similar methods as those used in two aCT studies.[34,36] In short, participants were asked to choose between treatment with aHT versus treatment without aHT based on their personal experience. In Duric et al.[38], those participants without aHT experience received information about the potential side effects of aHT. The studies explored patients' preferences for both survival rate and life expectancies scenarios (5 versus 15 years).

Median required increase in survival rate from adjuvant hormonal therapy

In Thewes et al.[39], most participants judged small (2%) benefits sufficient to make aHT worthwhile, while in Duric et al.[38], the majority required moderate (10%) benefits (Table 5). In both studies, the range in individual preferences was wide. In Thewes et al.[39], 5% of the participants would consider the treatment worthwhile for a benefit of 0%, while 2-7% would refuse aHT irrespective of benefit.

Median required additional life expectancy from adjuvant hormonal therapy

Table 5 also shows the minimum absolute increase in life expectancy judged sufficient to consider aHT worthwhile. While Thewes et al.[39] reported that most participants required an additional 3-6 months to consider aHT worthwhile, Duric et al.[38] observed larger (an additional 3-5 years) median required benefits. Both studies reported larger median required benefits in the 15-year versus the 5-year life expectancy scenario. Individual preferences varied greatly within the studies. Thewes et al.[39] reported that few participants (4-5%) would accept aHT at no benefit, while 1% would refuse aHT irrespective of benefit.

Factors affecting patient preferences for adjuvant systemic treatment

Determinants of patient preferences

All six studies examined associations between patient characteristics and treatment preference. The number of determinants examined varied from nine to 37. Altogether, the studies reported 27 significant determinants of patient preferences (24 for aCT and three for aHT, Table 5). The reviewers assigned 78% (21/27) of the determinants to the same category. The third party resolved the categorization of the other six determinants (22%).

Most significant determinants related to quality of life (12/27, 44%). The remaining determinants related to treatment (6/27, 22%), cognitive/affective factors (5/27, 19%) and socio-demographic characteristics (4/27, 15%). As shown in Table 5, significant determinants of preference varied between the studies. Additionally, some determinants were not consistently associated with treatment preference. For example, two[34,36] out of five studies[34,36-39] found that having dependents was significantly associated with judging smaller benefits worthwhile. Another socio-demographic factor with no consistent significant association included having (better[36]) social support.[34] As described earlier, the prospective study[37] ascertained a significant association between being versus not being scheduled for aCT and preferences for the therapy. This study found no other significant associations.

Patient self-reported factors influencing their preferences

Thewes et al.[39] qualitatively explored factors that patients reported had influenced their treatment preferences and found three main factors: (1) altruism (e.g., the belief that accepting treatment would increase knowledge and therefore benefit future patients), (2) a sense of control, or the idea of doing something to deal with the disease, and (3) the belief that accepting treatment could offer benefits that are not yet fully known.

DISCUSSION

Our systematic review of patient preferences for breast-conserving surgery (BCS) versus mastectomy (MAST) and the benefit patients minimally require from adjuvant chemotherapy (aCT) and/or adjuvant hormonal therapy (aHT) to consider it worthwhile, show that patients who prefer one or the other type of surgery are driven by different motives and that patients' preferences for adjuvant systemic therapy widely vary.

Surgical treatment decision-making

Patients who prefer BCS are predominantly driven by body image, while for patients who prefer MAST survival and/or recurrence is the most prominent factor. It is disturbing that survival was a driving factor in preferring MAST over BCS, because survival probabilities are the same, regardless of surgery type, in early breast cancer. Possible explanations are that women were not informed about the equivalent survival rates or that the information was unconvincing.

As one may expect, factors determining preferences varied according to whether they were assessed prospectively or retrospectively. Prospective assessment of factors revealed that body image and survival/recurrence determined patient preferences for, respectively, BCS or MAST. Retrospectively, other factors, and mainly those related to treatment, were influential

as well. In those who have undergone treatment, this experience may well outrank factors that determined preferences when the decision was made.

Adjuvant systemic treatment decision-making

Most patients judged small to moderate benefits sufficient to consider adjuvant systemic therapy worthwhile. However, studies reported that some patients would accept treatment for little or no benefit, while others would refuse treatment no matter the benefit. Determinants most consistently associated with patient preferences, once patients had experienced the treatment, related to quality of life. Patients were more willing to accept therapy if they had experienced better well-being during the particular adjuvant systemic therapy.

Our review revealed that clinical characteristics (e.g., nodal status) did not predict patients' preferences, nor did socio-demographic factors. These findings imply that it is difficult to predict individual preferences based on disease or socio-demographic characteristics. One retrospective study[39] qualitatively explored patients' motives and found other factors (e.g., doing something to deal with their disease). It is possible that such motives better explain patients' treatment preferences. Hence, future research should examine potential determinants beyond socio-demographic or disease characteristics, and preferably in a prospective manner in order to be able to generalize findings to new patients.

Interestingly, one aHT study found higher median required benefits than those reported by the aCT studies. At first sight this is surprising, as it is commonly assumed that patients perceive the side effects of aHT to be milder compared to aCT. Yet, the results cannot be easily compared because the aHT studies involved premenopausal patients who were significantly younger than patients in the aCT studies. At the same time, the results are in line with recent studies showing that some breast cancer patients who had received aHT did not consider its efficacy to outweigh its side effects.[40,41] Clearly, clinicians should not underestimate how impactful patients can perceive side effects of aHT. To examine how differently patients value the risks and benefits of these therapies, further research could examine preferences for aCT and aHT within the same patient population.

Limitations and future research

Some limitations of the included studies should be noted. Most studies were retrospective or carried out after a treatment decision had been made. As a result, findings most probably were influenced by patients' need for so-called 'cognitive dissonance reduction'. According to this theory, individuals have a tendency to reduce inconsistencies between previous decisions, in this case the treatment decision, and current beliefs or treatment preferences.[42] Thus, patients are expected to have adjusted their current beliefs about treatments in favor

of the treatment they received or would undergo. Therefore, generalization of the findings to patients who are facing a treatment decision should be done with caution. We recommend that future studies are carried out before the treatment decision is made to exclude this cognitive dissonance reduction and to be better able to generalize the findings to new patients.

Regarding surgical treatment decision-making, it is important to note that in most studies, patients were asked to rate the importance of a predetermined list of items. A possible drawback of this method is that it does not invite participants to identify other factors. Nevertheless, studies that used open-ended questions to elicit factors reported factors that were very much comparable to those from the predetermined lists.

Remarkably, none of the aHT studies included postmenopausal patients. Future research should focus on this patient group, as a majority have hormone receptor-positive disease and are eligible for aHT. Furthermore, it has been shown that aHTs in older patients have increased over time.[43]

Furthermore, only one study[28] addressed preferences of patients aged 65 years and older; it found that fear of recurrence and the need for additional treatment (e.g., radiotherapy) most frequently affected older (≥70 years) patients' preference for MAST. We identified a few studies[44-49] that examined treatment decision-making in older breast cancer patients, but they did not meet our inclusion criteria. These studies showed that fear of recurrence,[45] the surgeon's recommendation,[45] and wanting no additional therapy beyond surgery[47] influenced older patients' preference for MAST. Body image[45,47] and equivalence of survival rates[45] affected preference for BCS. Others examined whether factors affecting surgical decision-making differed by age[44,48] and showed that older patients were less concerned about body image,[44,48] recurrence,[44,48] or work-related issues[48] than younger patients. Interestingly, one study[48] found that older versus younger patients were more concerned about transportation, while others[44] reported that frequent trips for radiotherapy were of greater concern to younger patients. Considering the increasing number of older breast cancer patients,[50] preferences in this population should be further explored, especially since current disease management in older patients can involve aCT. To date, the evidence is inconclusive as to whether older patients would require greater survival gains from aCT than younger patients, to consider it worthwhile.[46,49,51-53]

Clinical implications

The large variation in patients' preferences and factors influencing their preferences suggests that individual patient views and preferences should be sought and incorporated in treatment decisions. Clinicians should inform patients about all available treatment options

and discuss the benefits and risks with each patient. Body image and survival/recurrence are important issues that should be addressed during consultations between patients and their surgeon. Additionally, clinicians should explicitly ask the patient which potential benefits and risks she considers important, and correct possible misconceptions about breast cancer and treatment. By identifying patient preferences, clinicians will be better able to tailor treatment recommendations to the needs, values and priorities of individual patients.

Conclusion

Breast cancer patients' preferences for surgery type most frequently relate to body image and survival/recurrence. Most patients considered small to moderate benefits sufficient to make adjuvant systemic therapy worthwhile, however patient's preferences varied widely and some patients would accept adjuvant systemic therapy for no benefit. Additional studies are needed that focus on older and postmenopausal patients and that assess determinants and preferences before the treatment decision is made.

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APPENDIX 1. Search strategy per database	
Database	**Search strategy**
PubMed	("Patient Preference"[MeSH] OR "patient preference"[ti] OR (Patients'[ti] AND preferences[ti]) OR "patient preferences"[ti] OR (Patients'[ti] AND preference[ti]) OR "prefer"[ti] OR "preferred"[ti] OR "preference"[ti] OR "preferences"[ti] OR "Choice"[ti] OR "choices"[ti] OR "choose"[ti] OR "decision"[ti] OR "decide"[ti] OR "Choice Behavior"[MeSH:NoExp] OR "Patient Education as Topic"[Majr] OR "Decision Making"[Mesh] OR "Patient Satisfaction"[Majr]) AND ("Breast Neoplasms"[Mesh] OR ((breast*[tiab] OR mammary[tiab]) AND (neoplasm*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR cancer*[tiab] OR carcinoma*[tiab]))) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapeutic"[All Fields] OR "treatment"[All Fields] OR "mastectomy, simple"[MeSH Terms] OR "mastectomy"[All Fields] OR "mastectomy"[MeSH Terms] OR "surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR "surgical"[All Fields] OR "general surgery"[MeSH Terms] OR "breast conserving"[All Fields] OR "lumpectomy"[All Fields] OR "drug therapy"[Subheading] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR "radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms] OR "adjuvants, pharmaceutic"[MeSH Terms] OR "adjuvants"[All Fields] OR "adjuvant"[All Fields] OR "adjuvants, immunologic"[Pharmacological Action] OR "hormonal"[All Fields] OR "hormones"[MeSH Terms] OR "hormones"[All Fields] OR "hormone"[All Fields] OR "hormones"[Pharmacological Action] OR "reconstructive surgical procedures"[MeSH Terms] OR "reconstructive surgical procedures"[All Fields] OR "reconstruction"[All Fields])
EMBASE	(patient* preference*.mp. OR exp patient preference/ OR ((patient*.ti.) AND ("prefer".ti. OR "preferred".ti. OR preference*.ti. OR Choice*.ti. OR "choose".ti. OR "decision*".ti. OR "decide".ti.)) OR exp *Decision Making/ OR exp *Patient Satisfaction/) AND (exp breast tumor/ OR ((breast*.ti,ab. OR mammary.ti,ab.) AND (neoplasm*.ti,ab. OR tumor*.ti,ab. OR tumour*.ti,ab. OR cancer*.ti,ab. OR carcinoma*.ti,ab.))) AND (exp "therapy"/ or therapy.mp. OR "therapeutic*".mp. or "treatment".mp. or exp mastectomy/ or "mastectomy".mp. or exp surgery/ or "surgery".mp. or exp surgical technique/ or "surgical".mp. or "breast conserving".mp. or "lumpectomy".mp. or exp chemotherapy/ or "chemotherapy".mp. or exp drug therapy/ or "drug therapy".mp. or exp radiotherapy/ or "radiotherapy".mp. OR adjuvant*.mp. or exp cancer adjuvant therapy/ or exp adjuvant therapy/ or exp adjuvant chemotherapy/ OR hormon*.mp. or exp hormone/ OR exp breast reconstruction/ or reconstructi*.mp.)

APPENDIX 2. PREFS checklist for assessing quality[18]		
Question	**No/not clear**	**Yes**
(1) Purpose: Is the purpose of the study in relation to preferences clearly stated?	The purpose/research question/ objectives/aim doesnot mention preference, but may mention satisfaction, quality of life, ratings, acceptance	Any reference in the research question/ objectives/aim to preference, utility/disutility, willingness to pay, importance, priorities, goals, revealed preference (e.g., choice to continue)
(2) Respondents: Are the responders similar to the non-responders?	Evidence of significant differences OR No assessment of the difference between responders and non-responders OR Responders are compared only to a target population rather than non-responders	Any evidence that the responders do not differ significantly from the non-responders
(3) Explanation: Are methods of assessing preferences clearly explained?	The question(s) or response options are not clear	The actual preference question is reported in the text or an appendix, or if it is referenced and available elsewhere, and if it is clear what response options were available to respondents, even if the mode of the question (e.g., written, oral, online) is not clear OR For studies with multiple questions relating to preferences such as conjoint/discrete choice studies, it is clear what was presented to respondents and what responses were available
(4) Findings: Were all respondents included in the reported findings and analysis of preference results?	Some responses are excluded from the analysis and the possibility of this introducing systematic bias has not been ruled out OR It is not clear whether all respondents were included in the analysis	All respondents who completed the preference question were included in the analysis OR For studies with multiple questions relating to preferences such as conjoint/discrete choice studies, all respondents who at least partially completed the preference questions were included in the analysis OR If some respondents who at least partially completed the preference questions were excluded from the analysis (e.g., non-traders, lexicographic preferences, failed test question, irrational preferences, did not complete) AND there is any evidence that those excluded do not differ significantly from those included
(5) Significance: Were significance tests used to assess the preference results?	The study reports only proportions, counts, graphs, etc.	The study reports p values, p value ranges (e.g., $p<0.05$), confidence intervals, means with standard deviations or standard errors in relation to the preference results (e.g., testing the preference hypotheses or study objectives)