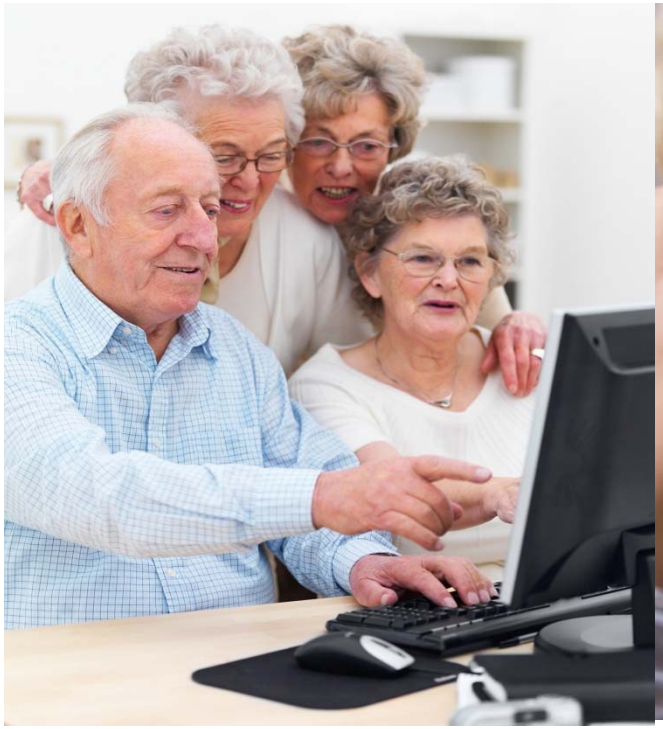
KCE REPORT 176S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BREAST CANCER SCREENING WITH MAMMOGRAPHY FOR WOMEN IN THE AGE GROUP OF 70-74 YEARS

APPENDIX



KCE REPORT 176S
GOOD CLINICAL PRACTICE

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BREAST CANCER SCREENING WITH MAMMOGRAPHY FOR WOMEN IN THE AGE GROUP OF 70-74 YEARS

APPENDIX

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COLOPHON

Title:	Breast cancer screening with mammography for women in the age group of 70-74 years - Appendix
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This document is available on the website of the Belgian Health Care Knowledge Centre.

APPENDIX REPORT

TABLE OF CONTENTS

1. REVIEW OF CLINICAL STUDIES

1.1. PICO

Benefit

- *Patient*: women between 70 and 74 years without breast cancer symptom and without high risk of breast cancer
- *Intervention*: organized screening
- *Comparison*: usual care
- *Outcomes*: mortality (all causes and specific), morbidity (mastectomy partial or complete)

Harms

- *Patient*: women between 70 and 74 years without breast cancer symptom and without high risk of breast cancer
- *Intervention*: organized screening
- *Comparison*: usual care
- *Outcomes*: diagnosis or therapeutics radiation side effects, additional diagnosis tests, true positive, true negative, over diagnosis and over treatment.

1.2. Systematic reviews (SR) and meta-analyses (MA)

A broad search of electronic databases (Medline, EMBASE, CDSR) was conducted in April 2011.

1.2.1. Search for SR and MA

Search questions	Benefit and harms of mammography screening (70-74 y)
Note	Specific search for systematic reviews and meta-analysis Update of KCE report 11 (search date 2004).
Date	18/04/2011 on OVID Ovid MEDLINE(R)
Keywords	Breast neoplasms (MESH) and mass screening (or early detection) (MESH) and mammography (MESH)

Medline (OVID): **Filter** **SR or M-A**	1. meta-analysis.pt,ti,ab,sh. 2. 1 or (meta anal$ or metaanal$).ti,ab,sh. 3. (methodol$ or systematic$ or quantitativ$).ti,ab,sh. 4. ((methodol$ or systematic$ or quantitativ$) adj (review$ or overview$ or survey$)).ti,ab,sh. 5. (medline or embase or index medicus).ti,ab. 6. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab. 7. 6 or 4 or 3 or 5 8. 7 and review.pt,sh. 9. 8 or 2 10. Case report.tw. 11. Letter.pt. 12. Historical article.pt. 13. Review of reported cases.pt. 14. Review,multicase.pt. 15. or/10-14 16. 9 not 15 17. Breast/ or Breast Diseases/ 18. Neoplasms/ 19. 17 and 18 20. exp Breast Neoplasms/ 21. (breast$ adj5 neoplas$).tw. 22. (breast$ adj5 cancer$).tw. 23. (breast$ adj5 carcin$).tw. 24. (breast$ adj5 tumo$).tw. 25. (breast$ adj5 metasta$).tw.	21

	26. (breast$ adj5 malig$).tw. 27. exp Carcinoma, Ductal, Breast/ 28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 29. mammography.mp. 30. Mammography/ 31. 29 or 30 32. mass screening.mp. or Mass Screening/ 33. early detection of cancer.mp. or "Early Detection of Cancer"/ 34. 32 or 33 35. 16 and 28 and 31 and 34 36. limit 35 to (humans and yr="2004 - Current" and "all aged (65 and over)" and (dutch or english or french or german))	
Embase 20/04/2011	'cancer screening'/exp/mj OR 'cancer screening'/exp AND ('breast cancer'/exp/mj OR 'breast cancer'/exp) AND ('mammography'/exp/mj OR 'mammography'/exp) AND ([meta analysis]/lim OR [systematic review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim) AND [female]/lim AND [aged]/lim AND [2004-2011]/py	8
CDSR 20/04/2011	Breast neoplasms) and (early detection or mass screening) and mammography, from 2004 to 2011 in Cochrane Reviews	6
DARE 20/04/2011	Breast neoplasms (MESH) and (early detection (MESH) or mass screening (MESH)) and mammography (MESH) and limit 2004-2011	18

1.3. Randomised control trials

A broad search of electronic databases (Medline, EMBASE,CCRT) was conducted in April 2011.

1.3.1. Search for RCTs

Search questions	Benefit and harms of mammography screening (69-74 y)
Note	Specific search for randomised control trials Update of Cochrane SR[1] (search date Nov 2008)
Date	20/04/2011 on Ovid MEDLINE(R) <2007 to April 2011>
Keywords	Breast neoplasms (MESH) and mass screening (or early detection) (MESH) and mammography (MESH)
Medline (OVID):	1. mass screening.mp. or Mass Screening/ 343 2. mammography.mp. or Mammography/ 3. breast neoplasm.mp. or Breast Neoplasms/ 4. limit 3 to (female and "all aged (65 and over)") 5. 1 or 2 6. 3 and 5 7. 6 and 4 8. Randomized controlled trials/ 9. Randomized controlled trial.pt. 10. Random allocation/ 11. Double blind method/ 12. Single blind method/ 13. Clinical trial.pt. 14. exp clinical trial/ 15. or/8-14 16. (clinic$ adj trial$).tw.

	17. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. 18. Placebos/ 19. Placebo$.tw. 20. Randomly allocated.tw. 21. (allocated adj2 random).tw. 22. or/16-21 23. 15 or 22 24. Case report.tw. 25. Letter.pt. 26. Historical article.pt. 27. Review of reported cases.pt. 28. Review,multicase.pt. 29. or/24-28 30. 23 not 29 31. 7 and 30 32. limit 31 to (yr="2004 -Current" and (dutch or english or french or german))	
Embase 20/04/2011	'cancer screening'/exp/mj OR 'cancer screening'/exp AND ('breast cancer'/exp/mj OR 'breast cancer'/exp) AND ('mammography'/exp/mj OR 'mammography'/exp) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [female]/lim AND [aged]/lim AND [2004-2011]/py	42
CCRCT 19/04/2011	Breast neoplasms (MESH) and (early detection (MESH) or mass screening (MESH)) and mammography (MESH), from 2004 to 2011 in Cochrane Reviews	102

1.4. Additional evidence

1.4.1. Diagnostic Errors

Search questions	Diagnostic Errors of mammography screening (69-74 y)
Note	Update of Nelson SR[2] (search date Nov-Dec 2008).
Date	30/06/2011 on Ovid MEDLINE(R) <2007 to June Week 4 2011>
Keywords	Breast neoplasms (MESH) and mass screening (or early detection or mammography) (MESH) and Diagnostic Errors (MESH)
Medline (OVID)	mass screening.mp. or Mass Screening/ (15880) 2 mammography.mp. or Mammography/ (4616) 3 breast neoplasm.mp. or Breast Neoplasms/ (38315) 4 1 or 2 (19293) 5 3 and 4 (3983) 6 exp Mammography/ae [Adverse Effects] (77) 7 exp Mass Screening/ae [Adverse Effects] (168) 8 6 or 7 (221) 9 5 and 8 (66) 10 exp Diagnostic Errors/ (15650) 11 (overtest$ or overdiagnos$ or over-test$ or over-diagnos$).mp. (590) 12 misdiagnos$.mp. (3816) 13 (false$ adj (positiv$ or negativ$)).mp. (11777) 14 ((incorrect$ or false$ or wrong$ or bias$ or mistake$ or error$ or erroneous$) adj3 (result$ or finding$ or test$ or diagnos$)).mp. (12863) 15 ((inappropriat$ or unnecess$ or unneed$) adj3 (treat$ or surg$ or therap$ or regimen$)).mp. (1934)

	16 (observ$ adj3 bias$).mp. (589) 17 10 or 11 or 12 or 13 or 14 or 15 or 16 (33309) 18 9 and 17 (20) 19 limit 18 to (yr="2008 -Current" and (dutch or english or french or german)) (16)
CDSR	Breast neoplasms and (early detection or mass screening or mammography) and Diagnostic Errors: no review found

1.4.2. DCIS

Search questions	DCIS in case of mammography screening (69-74 y)
Note	Update of Virnig[3] (search date Jan 2009)
Date	04/07/2011 on Ovid MEDLINE(R) <2007 to June Week 4 2011>
Keywords	Breast neoplasms (MESH) and mass screening (or early detection or mammography) (MESH) and Carcinoma,Intraductal,Noninfiltrating (MESH) and Diagnostic Errors (MESH)
Medline (OVID)	1. exp Carcinoma, Intraductal, Noninfiltrating/ (1058) 2. exp Breast Neoplasms/ (38670) 3. 1 and 2 (999) 4. exp Mass Screening/ (19596) 5. exp Mammography/ (3829) 6. 4 or 5 (22342) 7. exp Diagnostic Errors/ (15650) 8. overdiagno$.mp. (398) 9. over-diagno$.mp. (169) 10. (overtreat$ or over-treat$).mp. (758) 11. 8 or 9 or 10 (1237)
	12. 7 or 11 (16761) 13. 3 and 6 and 12 (19) 14. limit 13 to (yr="2009 -Current" and (dutch or english or french or german)) (7)
CDSR	Breast neoplasms and (early detection or mass screening or mammography) and Carcinoma,Intraductal,Noninfiltrating): no review found

1.4.3. Overtreatment

Search questions	Overtreatment in case of mammography screening (69-74 y)
Note	Update of Nelson SR[2] (search date Nov-Dec 2008).
Date	11/07/2011 on Ovid MEDLINE(R) <2007 to June week 5>
Keywords	Breast/pathology/*surgery (MESH) and Breast Neoplasms/diagnosis/*surgery(MESH) and Mass Screening (MESH) and Mastectomy/methods/*statistics & numerical data
Medline (OVID)	Breast Neoplasms/di [Diagnosis] (5088) 2 surgery.mp. (139648) 3 1 and 2 (456) 4 exp Breast/pa [Pathology] (2073) 5 surgery.mp. (139648) 6 4 and 5 (252) 7 3 or 6 (658) 8 exp Mastectomy/sn [Statistics & Numerical Data] (128) 9 7 or 8 (775) 10 exp Mass Screening/ (19691) 11 9 and 10 (51) 12 limit 11 to (female and humans and yr="2009 -Current" and (dutch or english or french or german)) (19)
CDSR	Breast neoplasms and (early detection or mass screening or mammography) and mastectomy: 7 reviews found

1.4.4. Sojourn Time

Database: Ovid MEDLINE(R) <1948 to October Week 1 2011>

Search Strategy:

1. breast neoplasms.mp. or Breast Neoplasms/ (190616)
2. Mass Screening/ (73266)
3. mammography.mp. or Mammography/ (25266)
4. 1 and 2 (8056)
5. 3 or 4 (27754)
6. sojourn.mp. (583)
7. 5 and 6 (43)

1.5. Quality Appraisal

1.5.1. Systematic reviews and meta-analyses

Items	Bisheuvel[4]	Götzsche[1]	Humphrey[5]	Jorgensen[6]	Nelson[2]	Virnig[3]
Search date	Dec 2006	Nov 2008	Dec 2001	April 2007	Dec 2008	Jan 2009
Intervention	Incidence in screened population	Breast cancer screening	Breast cancer screening	Incidence in screened population	Breast cancer screening	DCIS in screened population
Controle	Incidence in unscreened population	No breast cancer screening	No breast cancer screening	Incidence in unscreened population	No breast cancer screening	DCIS in unscreened population
1	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes
4	+/-	Yes	Yes	Yes	+/-	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes	Yes
7	-	Yes	Yes	Yes	Yes	Yes
8	-	Yes	Yes	Yes	Yes	Yes
9	Yes	Yes	Yes	Yes	Yes	Yes
Comment	Good quality	High quality	High quality	High quality	High quality	High quality

Legend of items 1 to 9 of the quality appraisal:
1. Is de vraagstelling adequaat geformuleerd?
2. Is de zoekactie adequaat uitgevoerd?
3. Is de selectieprocedure van artikelen adequaat uitgevoerd?
4. Is de kwaliteitsbeoordeling adequaat uitgevoerd?
5. Is adequaat beschreven hoe data-extractie heeft plaatsgevonden?
6. Zijn de belangrijkste kenmerken van de oorspronkelijke onderzoeken beschreven?
7. Is adequaat omgegaan met klinische en statistische heterogeniteit van de onderzoeken ?
8. Is statistische pooling op een correcte manier uitgevoerd ?
9. Zijn de resultaten van de systematische review valide en toepasbaar?

1.5.2. RCT

(Two County Trial)[7-9]

Internal validity	Yes	No	Unclear	Comments
The study addresses an appropriate and clearly focused question	X			
The assignment of subjects to treatment groups is randomized	X			
An adequate concealment method is used			X	Suboptimally randomised (public notary), Procedure was public
Subjects are kept blind about treatment allocation		X		It is not possible in case of mammography
Outcome assessors are kept blind about treatment allocation			X	Unknown
The treatment and control groups are similar at the start of the trial		X		Breast cancer mortality before study differs in Kopparberg from Ostergötland
The only difference between groups is the treatment under investigation	X			
All relevant outcomes are measured in a standard, valid and reliable way	X			Yes, after reviewing by an independent overview committee
All the subjects are analyzed in the groups to which they were randomly allocated (intention to treat)	X			
Overall assessment of the study				
Are the results of the study:				
-valid?	X			Quality is fear, but this study is the only one which assessed breast cancer screening in women aged 70-74 years
-applicable to the patient group targeted in the search question?			X	Subgroup (women aged 70-74 years) is underpowered

1.6. Data extraction table

1.6.1. Specific mortality reduction

1.6.1.1. Systematic review

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
Götzsche[1]	• SR • Funding: Danish Institute for HTA • Search date: Nov 2008 • Databases: Pubmed + search on author names in the author field • Study designs: RCT • N included studies: 9 *(New York/HIP,Malmö I and II, Two County,Canada a and b,Stockholm,Göteborg, UK Age trial)* • Intervention group: N = 298 552 • Control group: • N = 309 538	• Eligibility criteria: Women without previously diagnosed breast cancer. • Patient characteristics: • Women aged 39 to 74 years	Screening (annually or biennially) vs. Routine care	• Specific mortality reduction Follow up 13 y: Adequately randomised: RR: 0.90 (0.79, 1.02) Suboptimally randomised: RR: 0.75 (0.67, 0.83) All: RR: 0.81(0.74, 0.87)	Level of evidence: • High Distinction between adequately randomised and suboptimally randomised trials
Götzsche (subgroup patients > 50y)[1]	• SR • Funding: Danish Institute for HTA • Search date: Nov 2008 • Databases: Pubmed + search on author names in the author field • Study designs: RCT	• Eligibility criteria: Women without previously diagnosed breast cancer. • Patient characteristics: - Women aged 50 to 74 years	Screening (annually or biennially) vs. Routine care	• Specific mortality reduction Follow up 13 y: Adequately randomised: RR: 0.94 (0.77, 1.15) Suboptimally randomised: RR: 0.70 (0.62, 0.80)	Level of evidence: • High Distinction between adequately randomised and suboptimally randomised trials

	• N included studies: 8 *(New York/HIP,Malmö I and II, Two County,Canada a and b,Stockholm,Göteborg)* • Intervention group: N = 146 284 • Control group: • N = 122 590			All: RR: 0.77(0.69, 0.86)	
Humphrey[5]	- SR - Funding: USPSTF - Search date: Dec 2001 - Databases: CCTR, medline, Premedline and reference list from RCT's - Study designs: RCT • N included studies: 8 *(New York/HIP,Malmö I and II, Two County,Canada a and b,Stockholm,Göteborg)* • Intervention group: N = 233 195 • Control group: • N = 202 524.	• Eligibility criteria: Women without previously diagnosed breast cancer. • Patient characteristics: - Median age: 40-74	Screening (annually or biennially) vs. Routine care	• Specific mortality reduction Follow up 14 y: RR: 0.84 (0.77, 0.91)	Level of evidence: • High • RCT's included were rated as fair or good quality; Edinburgh trial which was rated as poor was excluded

1.6.1.2. Primary studies

Two County Trial

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Tabar 1985[8]	- RCT - Funding: Swedish National Board of Health and Welfare - Two County Trial: Kopparberg and Östergötland - Sample size: - N = 134 867 - Invited: 78 085 - Control: 37 396 - Duration: October 1976 – Dec 1984 - Results counted to end of 1984	• Eligibility criteria: - All women aged 39-74 - Women who had not received surgery for breast cancer • Patient characteristics: - Population based - Usual care	Invitation to screening mammography alone (1 view, 1 reader) Rounds: 40-49: 4, 50-69: 3 and 70-74: 2 vs. no invitation Screening interval: 24 months (< 50y), 33 months (> 50y) Attendance rate: 89% at the first round Follow-up time: 7 y	• Specific mortality reduction: RR: 0.69 (0.51,0.92)	Level of evidence: fair • Suboptimally randomised (public notary) • Breast cancer mortality before study differs in Kopparberg from Ostergötland • Autopsy rate low (36%) • Cause-of-death assessments not blinded • Those results were reviewed by an Independent overview committee
Nyström 2002 about the Swedish Trials[7]	- Review - Funding: Swedish National Board of Health and Welfare - Review of Swedish randomised control trial: Malmö, Ostergötland, Stockholm, Göteborg,(Kopparberg was not available at this time) - Sample size:	• Eligibility criteria: - All women aged 39-74 - Women who had not received surgery for breast cancer • Patient characteristics: - Population based - Usual care	Invitation to screening mammography alone (1 view, 1 reader) Rounds: 40-49: 4, 50-69: 3 and 70-74: 2 vs. no invitation Screening interval: 24 months (< 50y), 33 months (> 50y)	• Specific mortality reduction: RR: 0.79 (0.70,0.89)	Level of evidence: fair • Randomisation of Ostergötland study is questionable (see Tabar 1985 below)

	- N = 247 010 - Invited: 129 750 - Control: 117 260 - Duration: October 1976 – 1990 - Results counted to Dec 1996		Attendance rate: 89% at the first round Median follow-up time: 15.8 y (5.8-20.2)		
Nyström 2002[7]	• Subgroup: women aged 70-74 years in Ostergötland (part of Swedish trials, Kopparberg was not available at this time)				
	- Sample size (70-74): - Invited: 5 073 - Control: 4 859	• Eligibility criteria: • aged 70-74 years • Women who had not received surgery for breast cancer • Patient characteristics: - Population based - Usual care	Invitation to 2 rounds screening mammography alone vs. no invitation Screening interval: 33 months Median follow-up time: 17.9 y (13.6-18.9)	• Breast cancer mortality: RR: 1.12 (0.73,1.72)	Level of evidence: fair • Suboptimally randomised *(public notary)* • Breast cancer mortality before study differs in Kopparberg from Ostergötland • Autopsy rate low (36%) • Cause-of-death assessments not blinded Subgroup underpowered
Tabar 2011[9]	- Randomised control trial - Funding: Swedish National Board of Health and Welfare - Setting: Two-County Trial (Kopparberg/Dalarna and Ostergötland) - Randomized: N = 133 065 - Invited: 77 080	• Eligibility criteria: - All women aged 39-74 - Women who had not received surgery for breast cancer • Patient characteristics: - Population based - Usual care	Invitation to screening mammography alone (1 view, 1 reader) Rounds: 40-49: 4, 50-69: 3 and 70-74: 2 vs. no invitation Screening interval: 24 months (< 50y), 33	Breast cancer mortality (Consensus committee): • F.up at 10y: - RR: 0.80 (0.62,1.05) • F.up at 15y: - RR: 0.73(0.59,0.92) • F.up at 20y: - RR: 0.73(0.60,0.90) • F.up at 25y:	Level of evidence: fair • Suboptimally randomised (public notary) • Breast cancer mortality before study differs in Kopparberg from Ostergötland • Autopsy rate low

	- Control: 55 985 - Duration: October 1977/8 – 1990 - Screening phase lasted +/-7 years - Results counted to Dec 2005 in Dalarna and Dec 2006 in Ostergötland		months (> 50y) Attendance rate: 89% at the first round	- RR: 0.73(0.60,0.90) • F.up at 29y: - RR: 0.73(0.59,0.89) • F.Up = follow-up	(36%) • Cause-of-death assessments not blinded • Independent overview committee developed a consensus breast cancer case status and cause of death

1.6.2. All-cause mortality reduction

1.6.2.1. Systematic review

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
Götzsche[1]	• SR • Funding: Danish Institute for HTA • Search date: Nov 2008 • Databases: Pubmed + search on author names in the author field • Study designs: RCT • N included studies: 4 *(Malmö I Canada, Kopparberg, Stertgland)* • Intervention group: N = 94 387 • Control group: • N = 77 508	• Eligibility criteria: Women without previously diagnosed breast cancer. • Patient characteristics: - Aged 40-74	Screening (annually or biennially) vs. Routine care	• All-cause mortality reduction Follow up 13 y: Adequately randomised (N = 73 654): RR: 1.00 (0.95, 1.04) Suboptimally randomised (N=98 261): RR: 0.99 (0.97, 1.02)	Level of evidence: High • Underpowered to detect an all-cause mortality reduction

1.6.2.2. Review

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Nyström 2002[7]	• Subgroup: women aged 70-74 years in Ostergötland (part of Swedish trials, Kopparberg was not available at this time)				
	- Sample size (70-74): - Invited: 5 073 - Control: 4 859	• Eligibility criteria: • aged 70-74 years • Patient characteristics: - Population based - Usual care	Invitation to 2 rounds screening mammography alone vs. no invitation Screening interval: 33 months Median follow-up time: 17.9 y (13.6-18.9)	• All-cause mortality reduction Median follow up 15.8y: • RR: 0.99 (0.91, 1.07)	Level of evidence: fair • Suboptimally randomised *(public notary)* • Breast cancer mortality before study differs in Kopparberg from Ostergötland • Autopsy rate low (36%) • Cause-of-death assessments not blinded Subgroup underpowered

1.6.3. False positive and false negative mammography results

1.6.3.1. Systematic review

Reference	Methodology	Findings	Critical appraisal of review quality
Humphrey[5]	- SR - Funding: USPSTF - Search date: Dec 2001 - Databases: CCTR, medline, Premedline and reference list from RCT's - Study designs: RCT • N included studies: 8 *(New York/HIP,Malmö I and II, Two County,Canada a and b,Stockholm,Göteborg)* • Intervention group: N = 233 195 • Control group: • N = 202 524.	- Patient aged 70-74: sensitivity of 1st mammography: 81% (Two County trial, not applicable to individual patients because not adjusted for patient factors or technical factors positive predictive value of one view mammo: 18% to 20% - Patient aged 40-74: • Specificity of one view mammo:95.6 % (Two County trial) • Positive predictive value of one view mammo: 12% for abnormal results requiring further evaluation and from 50% to 75% for abnormal results requiring biopsy	Level of evidence: High • Underpowered to detect an all-cause mortality reduction
Nelson[2]	• Data analysis • Sources: Breast Cancer Surveillance Consortium (USA-BCSC) • Years: 2000 to 2005	- Women aged 70-79: - False positive results: 68.8 per 1000 women per screening round - False negative results: 1.5 per 1000 women per screening round - Additional imaging: 64.03 per 1000 women per screening round - Biopsy rates: 12.2 per 1000 women per screening round - Screen-detected invasive cancer:6.5 per 1000 women per screening round - Screen-detected DCIS: 1.4 per 1000 women per screening round	

1.6.4. Over-diagnosis

Reference	Study	Type of study	Findings Women aged 40-79:	Range
Nelson[2]	• *Paci, 2006* • *Olsen,2006* • *Duffy,2005*	Modelled estimations	- Rates of overdiagnosis	- Less than 1%
	• *Zahl, 2004*	Modelled estimations	- Rates of overdiagnosis	- 30%
	• *De Koning,2006*	Modelled estimations	- Rates of overdiagnosis	- Between 1 and 10%
Götzsche[1]	• *Shapiro, 1977, Shapiro, 1982, Shapiro, 1989*	Review	- Level of overdiagnosis in the trials that did not introduce early screening	- 30%
	• *Baratt 2005;Douek,2003;Fletcher,2003;Götzsche,2004;Jonsson,2005;Ries,2002;WHO,2002;Zahl,2004*	Observational studies	- Incidence increases of reported for Australia,Finland, Norway, Sweden, UK and USA	- 40% to 60%
	• *Paci,2004*	?	- Proportion of overdiagnosed cases	- 5%
	• *Olsen, 2003*	?	- No overdiagnosis	-

Biesheuvel[4]

Type of study	Study	Estimations of overdetection as reported by primary author (CI)	Recalculated by reviewer as %	Remarks
Estimates of overdetection in included studies using the cumulative-incidence method (definition in chap 4)				
RCT	Two County (Moss)	ARD: - 0.13 (-0.29 to 0.04) per 1000 women years (women aged 40-74)	5.1	ARD: absolute risk difference
Population based programme	Paci (Italy)	RR: 109.7% (105-115) (women aged 70-74)	9.7	RR: relative risk Period: 1990-1999
Estimates of overdetection in included studies using the incidence rate method (definition in chap 4)				
Population based programme	Zahl (Sweden)	RR: 1.01 (0.96-1.05) (women aged 70-74)	1	
Population based programme	Zahl (Norway)	RR: 0.89 (0.70-1.12) (women aged 70-74)	-11	
Population based programme	Jonsson (Sweden) Initial phase	RR: 1.84 (1.50-2.24) (women aged 70-74)	84	Considered by reviewer as least biased estimation
Population based programme	Jonsson (Sweden) Stabilized phase	RR: 1.03 (0.82-1.30) (women aged 70-74)	3	

Jorgensen

Reference	Type of study	Publicly organised screening programmes	Modelled risk ratios	Remarks
Jörgensen[6]	SR of observational studies, metanalysis + modelling	England and Wales	- 1.57 (1.53 to 1.61)	• DCIS were included or estimated at 10% of diagnosis • Most common age range: 50-69 y.
		Manitoba, Canada	- 1.44 (1.25 to 1.65)	
		New South Wales, Australia	- 1.53 (1.44 to 1.63)	
		Sweden	- 1.46 (1.40 to 1.52)	
		Norway	- 1.52 (1.36 to 1.70)	
		Overall (pooled analysis)	- 1.52 (1.46 to 1.58)	

1.6.5. DCIS

Reference	Methodology	Findings	Critical appraisal of review quality
Virnig[3]	- SR - Funding: AHRQ (Agency for Healthcare Research and Quality, USA) - Search date: Jan 2009 - Databases: medline, and others - Study designs: observational • N included studies: 63	- All breast cancer patient: DCIS incidence rose there from 1.87 per 100 000 in 1973–1975 to 32.5 in 2004.	Level of evidence: High

1.6.6. Overtreatment

1.6.6.1. Systematic review

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
Götzsche[1]	• SR • Funding: Danish Institute for HTA • Search date: Nov 2008 • Databases: Pubmed + search on author names in the author field • Study designs: RCT • N included studies: 8 *(New York/HIP,Malmö I and II, Two County,Canada a and b,Stockholm,Göteborg)* • Intervention group: N = 145 536 • Control group: • N = 104 943	• Eligibility criteria: Women without previously diagnosed breast cancer. • Patient characteristics: - Median age: 39-74	Screening (annually or biennially) vs. Routine care	• Number of mastectomies and lumpectomies Adequately randomised: RR: 1.31 (1.22, 1.42) Suboptimally randomised: RR: 1.42 (1.26, 1.61) All: RR: 1.35 (1.26, 1.44)	Level of evidence: • High Distinction between adequately randomised and suboptimally randomised trials

1.6.6.2. Observational study

Reference	Methodology	Findings
Dixon[10]	• Data analysis • Sources: UK Breast Screening Programme • Years: 1998 to 2008	- Patient aged 50-69: DCIS cases: 1998: 1 500 cases, 2008: 3 500 cases Mastectomies: 1998: < 500 cases, 2008: > 900 cases

2. REVIEW OF MODELLING STUDIES

2.1. Literature search strategy

Medline, EMBASE, NHS EED and Econlit databases were consulted from January 2000 to September 2011.

Date	September 6, 2011
Database (name + access)	Ovid MEDLINE®
Date covered	1948 to Present with Daily Update
Search strategy	1 Breast/ or Breast Diseases/ (33748) 2 Neoplasms/ (237720) 3 1 and 2 (557) 4 exp Breast Neoplasms/ (188556) 5 (breast$ adj5 neoplas$).tw. (2648) 6 (breast$ adj5 cancer$).tw. (147716) 7 (breast$ adj5 carcin$).tw. (33124) 8 (breast$ adj5 tumo$).tw. (25521) 9 (breast$ adj5 metasta$).tw. (17792) 10 (breast$ adj5 malig$).tw. (7806) 11 exp Carcinoma, Ductal, Breast/ (9581) 12 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (223736) 13 mammography.mp. (25000) 14 Mammography/ (21651) 15 13 or 14 (25000) 16 Screen$.tw. (355678) 17 Mass Screening/ (72155) 18 early detection of cancer.mp. or "Early Detection of Cancer"/ (3362) 19 16 or 17 or 18 (379696) 20 12 and 15 and 19 (9236) 21 exp Models, Theoretical/ (1053977) 22 exp Models, Statistical/ (205881) 23 exp Models, Economic/ (8175) 24 exp Models, Econometric/ (3478) 25 exp Logistic Models/ (66492) 26 exp Decision Support Techniques/ (49589) 27 exp decision trees/ (7721) 28 Markov Chains/ (7491) 29 decision model$.tw. (1067) 30 decision analy$.tw. (4066) 31 mathematical model$.tw. (24610) 32 Delay time model$.tw. (1) 33 microsimulation model$.tw. (152) 34 micro-simulation model$.tw. (18) 35 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (1106524) 36 20 and 35 (929) 37 exp "Costs and Cost Analysis"/ (159357) 38 "Value of Life"/ec [Economics] (211) 39 pharmaco?economic$.tw. (2359) 40 "cost-effectiv$".tw. (56452) 41 "cost-utilit$".tw. (1722) 42 "cost-benefit$".tw. (6366) 43 "economic evaluation$".tw. (4701) 44 (value adj1 money).tw. (20) 45 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (194413) 46 20 and 45 (674)

	47 36 or 46 (1511) 48 limit 47 to yr="2000 -Current" (893) 49 letter.pt. (725169) 50 editorial.pt. (283009) 51 49 or 50 (1008116) 52 48 not 51 (854)

Date	September 5, 2011
Database (name + access)	Econlit - Ovid
Date covered	1961 to August 2011

Search Strategy	1 (breast$ adj5 neoplas$).tw. (0) 2 (breast$ adj5 cancer$).tw. (189) 3 (breast$ adj5 carcin$).tw. (3) 4 (breast$ adj5 tumo$).tw. (2) 5 (breast$ adj5 metasta$).tw. (5) 6 (breast$ adj5 malig$).tw. (0) 7 mammography.mp. (38) 8 (screening or early detection of cancer).mp. (1471) 9 1 or 2 or 3 or 4 or 5 or 6 (191) 10 7 and 8 and 9 (10) 11 limit 10 to yr="2000 -Current" (8)
Date	September 5, 2011

Database (name + access)	Embase		
Date covered	1974 to present		
Search Strategy	#19	#17 NOT #18	362
	#18	editorial:it OR letter:it	1128075
	#17	#16 AND [embase]/lim AND [2000-2012]/py	418
	#16	#13 OR #15	721
	#15	#1 AND #14	582
	#14	#9 OR #10 OR #11	184650
	#13	#1 AND #12	169
	#12	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	283351

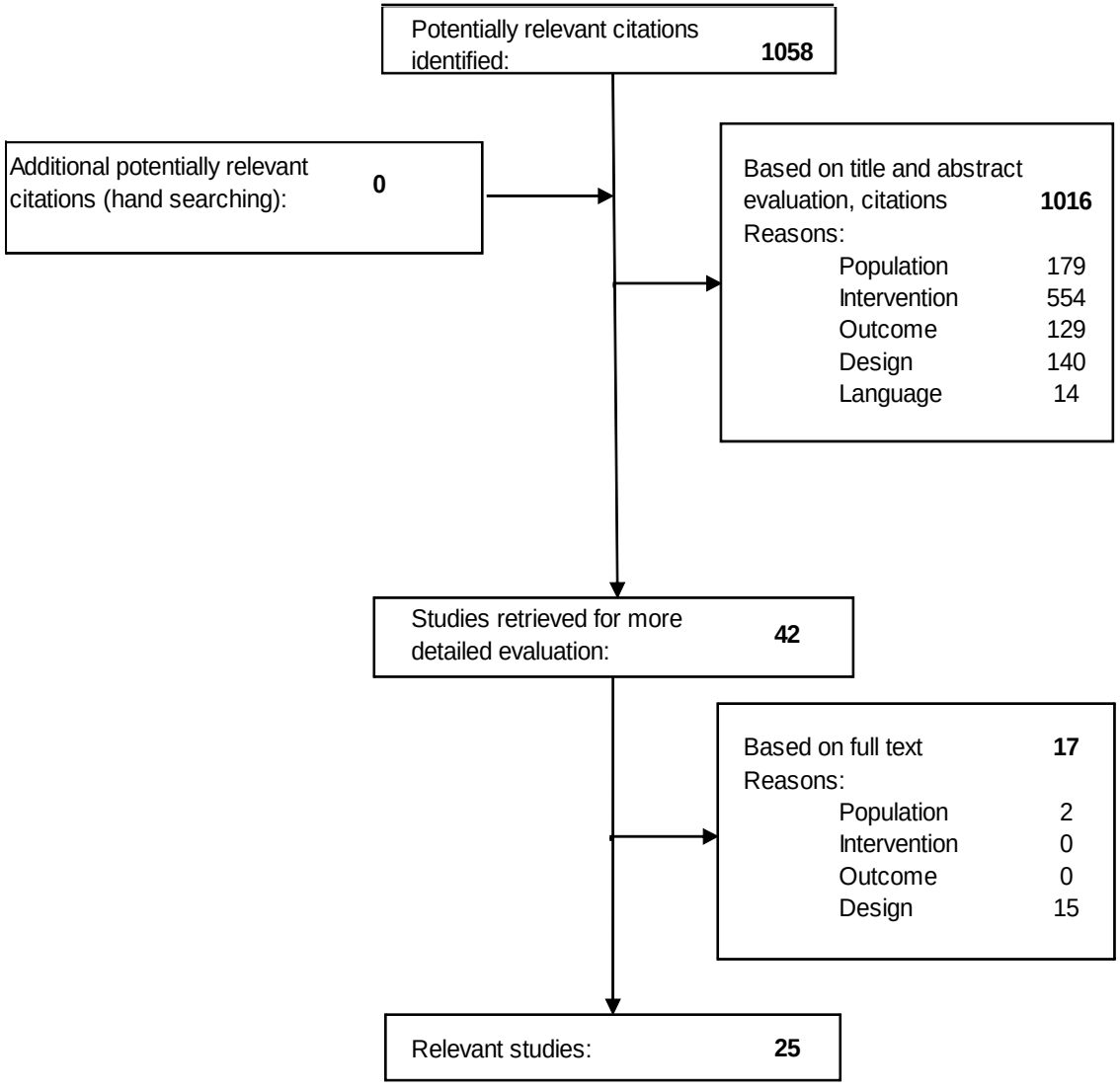
#11	'economic evaluation'/exp	171823
#10	'value' NEAR/1 'money'	20
#9	'cost-effectiveness':ab,ti OR 'cost-utility':ab,ti OR 'cost-benefit':ab,ti OR pharmacoeconomic*:ab,ti OR 'economic evaluation':ab,ti OR 'economic evaluations':ab,ti	48877
#8	'decision support system'/exp	9056
#7	'statistical model'/exp	75256
#6	'computer simulation'/exp	63626
#5	'theoretical model'/exp	50705
#4	'mathematical model'/exp	161628
#3	'computer model'/exp	19493
#2	'disease simulation'/exp	1696
#1	'cancer screening'/exp/mj OR 'cancer screening'/exp OR 'cancer screening' AND ('breast cancer'/exp/mj OR 'breast cancer'/exp OR 'breast cancer') AND ('mammography'/exp/mj OR 'mammography'/exp OR 'mammography')	7932

Note

September 5, 2011

Database (name + access)	Cochrane Database of systematic reviews – NHS EED		
Date covered			
Search Strategy	#1	MeSH descriptor Breast Neoplasms explode all trees	342
	#2	MeSH descriptor Early Detection of Cancer explode all trees	23
	#3	MeSH descriptor Mass Screening explode all trees	858
	#4	MeSH descriptor Mammography explode all trees	99
	#5	(#2 OR #3)	870
	#6	(#1 AND #4 AND #5)	51
	#7	(#6), from 2000 to 2011	29
Note			

2.2. Flow diagram



3. REVIEW OF QUALITY OF LIFE STUDIES

3.1. Search strategy

Search strategy and results for CRD HTA

Date	17/10/2011		
Database	CRD HTA		
Date covered	No restriction		
Search strategy	#	Searches	Results
	1	MeSH DESCRIPTOR mammography WITH QUALIFIER undefined IN HTA	73
	2	MeSH DESCRIPTOR breast neoplasms WITH QUALIFIER undefined IN HTA	336
	3	1 or 2	346
	4	MeSH DESCRIPTOR costs and cost analysis WITH QUALIFIER undefined IN HTA	850
	5	3 and 4	21
Note	#3 AND (“Quality-Adjusted Life Years”/ OR “Health Status Indicators”/) returned 0 hits.		

Search strategy and results for CRD NHS EED

Date	17/10/2011		
Database	CRD NHS EED		
Date covered	No restriction		
Search strategy	#	Searches	Results
	1	MeSH DESCRIPTOR breast neoplasms WITH QUALIFIER undefined IN NHSEED	344
	2	MeSH DESCRIPTOR mammography WITH QUALIFIER undefined IN NHSEED	98
	3	1 or 2	355
	4	MeSH DESCRIPTOR quality-adjusted life years WITH QUALIFIER undefined IN NHSEED	1776
	5	3 and 4	100
Note			

Search strategy and results for Medline (OVID)

Date	17/10/2011		
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)		
Date covered	1950 to Present		
Search strategy	#	Searches	Results
	1	*Breast Neoplasms/	155564
	2	*Mammography/	12588
	3	Quality-Adjusted Life Years/	5309
	4	EQ-5D.mp.	1601
	5	health utility index.mp.	79
	6	sf-6d.mp.	238
	7	time trade-off.mp.	564
	8	person$ trade-off.mp.	35
	9	standard gamble.mp.	570
	10	visual analogue scale$.mp.	10949
	11	qwb.mp.	143
	12	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	18116
	13	1 or 2	160101
	14	12 and 13	282
Note	[mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]		

Search strategy and results for Embase

Date	17/10/2011		
Database	Embase (OVID)		
Date covered	No restrictions		
Search strategy	#	Searches	Results
	#4	'breast cancer'/mj	113865
	#5	'mammography'/mj	14126
	#6	#4 OR #5	124182
	#20	'eq 5d'	2600
	#21	'health utility index'	114
	#22	'sf 6d'	357
	#23	'time trade off'	724
	#24	'standard gamble'	651
	#25	'person$ trade off'	45
	#27	'visual analog scale'/mj	343
	#28	'quality of well-being scale'	150
	#30	'quality adjusted life year'/exp/mj	620
	#31	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #27 OR #28 OR #30	4,798
	#32	#6 AND #31	60

Search strategy and results for PsycINFO (OVID)

Date	18/10/2011		
Database	PsycINFO		
Date covered	1806 to October Week 2 2011		
Search strategy	#	Searches	Results
	1	*Mammography/	647
	2	*Breast Neoplasms/	4763
	3	1 or 2	5157
	4	quality adjusted life year.mp.	206
	5	EQ-5D.mp.	559
	6	health utilit$ inde$.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	238
	7	sf-6d.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	89
	8	time trade off.mp.	128
	9	time trade-off.mp.	128
	10	person$ trade-off.mp.	11
	11	standard gamble.mp.	150
	12	visual analogue scale$.mp.	5727
	13	quality of well being scale$.mp.	115
	14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	6733
	15	3 and 14	61
Note	[mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]		

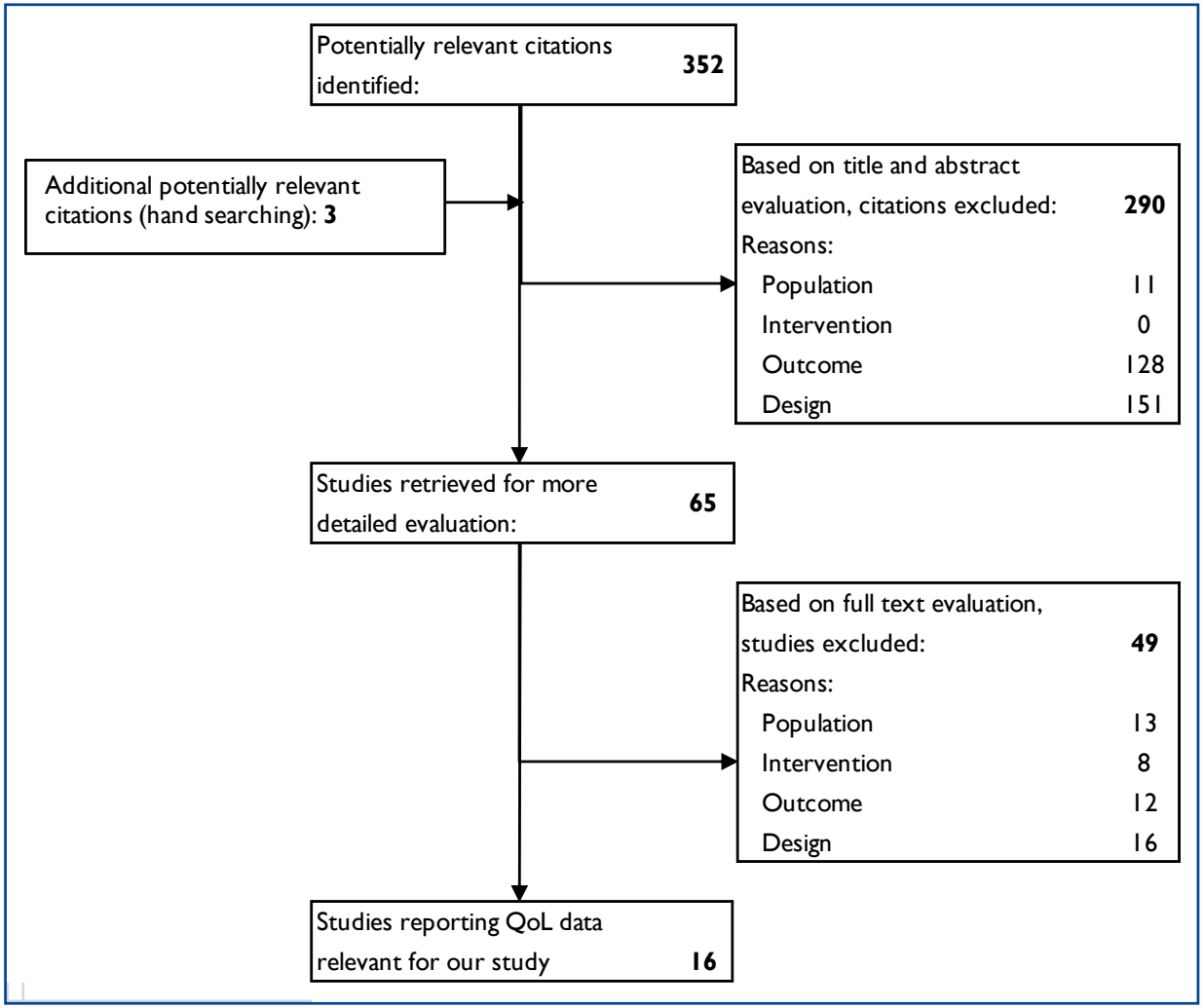
3.2. Results of the search strategy

A total of 524 papers were identified from the databases consulted: 282 with Medline, 60 with Embase, 61 with PsycINFO, 100 with CRD NHS EED and 21 with CRD HTA. After removing 172 duplicates, 352 citations were left.

Search results for quality of life studies

Databases	References identified
CDR HTA	21
CRD NHS EED	100
Medline (OVID)	282
EMBASE (OVID)	60
PsycINFO (OVID)	61
Total references identified	524
Duplicates	172
Total	352

Flowchart of the literature selection process



3.3. Summary of selected studies

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Burström 2001 (Sweden)	EQ-5d	Swedish population	UK tariffs (general population; TTO)	Male	20-29	NA	413	0.909 (S.E. 0.011)
				Female				0.873 (S.E. 0.011)
				Male	30-39		509	0.904 (S.E. 0.010)
				Female				0.859 (S.E. 0.011)
				Male	40-49		460	0.868 (S.E. 0.015)
				Female				0.858 (S.E. 0.012)
				Male	50-59		520	0.845 (S.E. 0.014)
				Female				0.833 (S.E. 0.014)
				Male	60-69		312	0.829 (S.E. 0.014)
				Female				0.784 (S.E. 0.017)
				Male	70-79		256	0.797 (S.E. 0.024)
				Female				0.792 (S.E. 0.019)
				Male	80-88		79	0.720 (S.E. 0.051)
				Female				0.740 (S.E. 0.033)
	TTO		NA	Male	20-29	Based on 10 years of life in the state	413	0.940 (S.E. 0.011)
				Female				0.945 (S.E. 0.009)
				Male	30-39		509	0.931 (S.E. 0.011)
				Female				0.944 (S.E. 0.009)
				Male	40-49		460	0.937 (S.E. 0.010)
				Female				0.944 (S.E. 0.009)
				Male	50-59		520	0.937 (S.E. 0.009)
				Female				0.925 (S.E. 0.010)
				Male	60-69		312	0.910 (S.E. 0.013)
				Female				0.894 (S.E. 0.015)
				Male	70-79		256	0.834 (S.E. 0.021)
				Female				0.888 (S.E. 0.017)
				Male	80-88		79	0.743 (S.E. 0.051)
				Female				0.673 (S.E. 0.040)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Gerard 1999 (UK)	EQ-5d (mobility and ability to self-care are	Women in the general population eligible for	UK tariffs (general population; TTO)	True negative (effect on 1 year)	40-64 years (50-64 = 52.5%)	NA	440	Mean 0.94 (SD: 0.14)
				False positive (effect on 1 year)				Mean: 0.79 (SD: 0.21)
				True positive (effect lifelong)				Mean 0.48 (SD 0.30)
				False negative (effect lifelong)				Mean 0.45 (SD 0.30)
	TTO (in two stages for temporary heath descriptions)	Women in the general population eligible for breast cancer	NA	True negative	40-64 years (50-64 = 52.5%)	Based on 1 year of life in the state	440	Mean 0.91 (SD: 0.21)
				False positive		Based on 1 year of life in the state		Mean: 0.65 (in the text) and 0.66 (in the table) (SD: 0.38)
				True positive		Lifelong		Mean 0.66 (SD 0.29)
				False negative		Lifelong		Mean 0.66 (SD 0.29)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Lidgren 2007 (Sweden)	EQ-5d (negative values were set to 0, but only three patients (negligible impact)	Sweden women with a previous diagnosis of breast cancer aged 28-93 years (>65 years = 22%)	UK tariffs (general population; TTO)	Primary breast cancer within one year or less, no recurrence and no metastatic diseases (P); assume to include adverse effect of the surgery, radiotherapy, chemotherapy and psychological effect of receiving the diagnosis)	mean age: 56	NA	72	Mean 0.696 (95%CI: 0.634-0.747) Median 0.725 (range: 0.00-1.00)
				At least one recurrence (loco-regional and/or contra-lateral) within one year or less and no metastatic disease (R)	mean age: 59		21	Mean 0.779 (95%CI: 0.700-0.849) Median 0.725 (range: 0.296-1.00)
				Diagnosis of primary breast cancer or latest recurrence of more than one year, and no metastatic disease (S)	mean age: 58		177	Mean 0.779 (95%CI: 0.745-0.811) Median 0.796 (range: 0.00-1.00)
				Metastatic disease (M)	mean age: 56		65	Mean 0.685 (95%CI: 0.620-0.735) Median 0.725 (range: 0.093-1.00)
				(P) and receiving ajuvant chemotherapy			23	Mean 0.62 (95%CI: 0.509-0.697)
				(P) and receiving ajuvant hormone therapy			17	Mean 0.744 (95%CI: 0.573-0.841)
				(R) and receiving ajuvant chemotherapy			7	Mean 0.767 (95%CI: 0.573-0.841)
				(R) and receiving ajuvant hormone therapy			4	Mean 0.816 (95%CI: 0.729-0.963)
				(S) and receiving ajuvant hormone therapy			79	Mean 0.824 (95%CI: 0.785-0.857)
				(M) and receiving ajuvant chemotherapy			38	Mean 0.692 (95%CI: 0.611-0.746)
				(M) and receiving ajuvant hormone therapy			16	Mean 0.648 (95%CI: 0.513-0.765)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Lidgren 2007 (Sweden)	TTO	Women with a previous diagnosis of breast cancer aged 28-93 years (>65 years = 22%)	NA	First year after primary breast cancer (P)		Based on 10 years of life in the state	69	Mean 0.901 (95%CI: 0.848-0.935) Median 1.00 (range: 0.10-1.00)
				First year after recurrence (R)			18	Mean 0.842 (95%CI: 0.733-0.926) Median 0.973 (range: 0.50-1.00)
				Second and following years after primary breast cancer or recurrence (S)			178	Mean 0.889 (95%CI: 0.860-0.913) Median 1.00 (range: 0.00-1.00)
				Metastatic disease (M)			61	Mean 0.820 (95%CI: 0.760-0.874) Median 0.850 (range: 0.110-1.00)
				(P) and receiving ajuvant chemotherapy			22	Mean 0.886 (95%CI: 0.801-0.943)
				(P) and receiving ajuvant hormone therapy			17	Mean 0.891 (95%CI: 0.699-0.955)
				(R) and receiving ajuvant chemotherapy			5	Mean 0.856 (95%CI: 0.656-1.00)
				(R) and receiving ajuvant hormone therapy			4	Mean 0.861 (95%CI: 0.620-0.991)
				(S) and receiving ajuvant hormone therapy			76	Mean 0.934 (95%CI: 0.890-0.960)
				(M) and receiving ajuvant chemotherapy			35	Mean 0.776 (95%CI: 0.695-0.841)
				(M) and receiving ajuvant hormone therapy			17	Mean 0.863 (95%CI: 0.737-0.894)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Johnston 1998 (UK)	TTO (in two stages for temporary heath descriptions)	Women in the general population eligible for breast cancer	NA	True negative	40-64 years (50-64 = 52.5%)	Based on 1 year in the state	440	Mean (sd): 0.91 (0.21) Median (IQR): 0.98 (0.96-0.99)
				False positive		Based on 1 year in the state		Mean (sd): 0.66 (0.38) Median (IQR): 0.83 (0.22-0.96)
				True positive		Lifelong		Mean (sd): 0.66 (0.29) Median (IQR): 0.75 (0.55-0.95)
				False negative		Lifelong		Mean (sd): 0.66 (0.29) Median (IQR): 0.75 (0.45-0.95)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Domeyer 2010 (Greece)	EQ-5D	Patient (see health state)	Spanish tariffs (general population; TTO)	Women with benign lesions and without severe co-morbidities (excluded if previous breast cancer)		Morning before biopsy	102	0.729 +/- 0.224
						4 days after VABB	102	0.787 +/- 0.208 (p 0.005)
						18 months after VABB	78	0.769 +/- 0.225 (p 0.251)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Freedman 2010 (US)	EQ-5D	Patient (see health state)	US tarrifs (general population)	Woman with early stage breast cancer (American Joint Committee on Cancer Stages 0: 18%, 1: 68%, or 2: 13%) after treatment with breast-conserving surgery and radiation (Conventional : 64%; IMRT: 36%) with our without systemic therapy. Nodal stage 0 = 61%	18-44: 13% 45-64: 57%	1 year	482	0.87
						5 years	171	0.89 (95% CI 0.87-0.91)
						10 years	64	0.9 (95% 0.86-0.94)
						15 years	21	0.9 (95% 0.83-1.0)
					18-44	5 years	12	0.95
						10 years	10	0.96
					45-64	5 years	87	0.90
						10 years	35	0.93
					>64	5 years	56	0.88
						10 years	10	0.76

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Lovrics 2008 (Canada)	HUI-III	Patient (see health state)	Canadian tariffs (general population of Hamilton)	Women with early-stage breast cancer with modified radical mastectomy or breast-conservation surgery and tumor size: T1 (0.1-2 cm) : 77%; T2 (2.1-5 cm): 22%; T3 (>5 cm): 1% / Nodal stage: N0: 66%; N1/N2: 34%.	Mean 55.2 (>50: 66%)	Initial consultation	85	Mean 0.74; sd 0.26 (95% CI: 0.68-0.79)
						24h following Pet scanning	74	Mean 0.76; sd 0.26 (95% CI: 0.70-0.91)
						1 week pos-op	83	Mean 0.49; sd 0.33 (95% CI: 0.42-0.56)
						3 months after surgery	80	Mean 0.73; sd 0.27 (95% CI: 0.68-0.79)
						1 year after surgery	73	Mean 0.79; sd 0.23 (95% CI: 0.74-0.83)
						2 years after surgery	72	Mean 0.78; sd 0.24 (95% CI: 0.74-0.84)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Mansel 2007 (UK)	Chained standard gamble method	UK patients with early or advanced breast cancer	NA	Most patients had HR+, node-negative disease and were presently receiving tamoxifen	Mean 68 years	NA	23	0.933 (sd 0.069)
				Disease-free state (no adverse event)				0.989 (sd 0.010)
				Common adverse events (tamoxifen)				0.970 (sd 0.041)
				Common adverse events (anastrozole)				0.962 (sd 0.055)
				New contralateral breast cancer				0.914 (sd 0.097)
				Local/regional recurrence				0.911 (sd 0.098)
				Hormonal therapy for distant recurrence				0.882 (sd 0.105)
				Chemotherapy for distant recurrence				0.710 (sd 0.254)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Prescott 2007 (UK)	EQ-5d	Patient aged 65 years or more, receiving adjuvant endocrine therapy, medically suitable to attend for all treatments and follow-up, with histologically confirmed unilateral breast cancer of tumour, node, metastasis	UK tariffs (general population; TTO)	Patients with breast-conserving surgery and radiotherapy (Tumor grade 1: 37.8%; grade 2 : 56.7%; grade 3: 7%)	Mean 72.3 (sd 5.0)	Baseline (after breast-conserving surgery and before radiotherapy)	102	0.77 (95%CI: 0.73-0.80)
						3.5 months after surgery		0.78 (95%CI: 0.74-0.81)
						9 months after surgery		0.76 (95%CI: 0.71-0.81)
						15 months after surgery		0.74 (95%CI: 0.70-0.78)
				Patients with breast-conserving surgery and no-radiotherapy (Tumor grade 1: 37.8%; grade 2 : 56.7%; grade 3: 7%)	Mean 72.8 (sd 5.2)	Baseline	101	0.74 (95%CI: 0.70-0.77)
						3.5 months after surgery		0.76 (95%CI: 0.73-0.79)
						9 months after surgery		0.72 (95%CI: 0.68-0.76)
						15 months after surgery		0.73 (95%CI: 0.69-0.77)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Turnbull 2010 (UK)	EQ-5d	Patients aged 18 years or over, having undergone X-ray mammography and ultrasound scanning during the current treatment episode, with pathologically	UK tariffs (general population; TTO)	Patients with primary breast cancer and receiving magnetic resonance imaging (WLE or mastectomy according to results)	>=50 years: 77%; median age: 57 (range: 27-86)	Baseline (wide local excision is planned)	727	Mean: 0.86 (sd 0.007; 95%CI 0.84-0.87)
						6 months after surgery		Mean: 0.80 (sd 0.009; 95%CI 0.78-0.82)
						12 months after surgery		Mean: 0.81 (sd 0.007; 95%CI 0.80-0.82)
				Patients with primary breast cancer and without receiving magnetic resonance imaging (after WLE, patient management and treatment followed local practice)		Baseline	719	Mean: 0.86 (sd 0.006; 95%CI 0.85-0.87)
						6 months after surgery		Mean: 0.80 (sd 0.008; 95%CI 0.78-0.81)
						12 months after surgery		Mean: 0.81 (sd 0.007; 95%CI 0.80-0.83)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Vacek 2003 (US)	QWB	Women recently diagnosed with breast cancer (Mean age: 65.9 +/- 10.9)	US tariffs (general population; TTO)	Patient with breast cancer (stage at diagnosis: In situ: 18.1%; Local: 60.6%; Regional: 18.6%; distant: 2.7%); 60.6% had mastectomy; 43.6% received radiation; 24.6% received chemotherapy; 57.4% took tamoxifen.	39-93	Mean of 45 weeks after diagnosis	195	Mean 0.716 (sd: 0.097; range: 0.467-1.00)
						Mean of 105 weeks after diagnosis	178	Mean 0.706 (sd: 0.100; range: 0.423-1.00)
						Mean of 162 weeks after diagnosis	168	Mean 0.685 (sd: 0.106; range: 0.469-0.899)
						Mean of 267 weeks after diagnosis	145	Mean 0.680 (sd: 0.103; range: 0.432-0.899)
					40-49	Mean of 45 weeks after diagnosis	15	Mean: 0.700 (sd: 0.086)
					50-64	Mean of 45 weeks after diagnosis	55	Mean: 0.731 (sd: 0.088)
					65-85	Mean of 45 weeks after diagnosis	116	Mean: 0.710 (sd: 0.101)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Lloyd 2006 (UK)	SG (Negative scores were changed to 0.02)	UK population (50% women)	NA	Stable disease (metastatic breast cancer) with no side effects	38.2	Based on 10 years of life in the state	100	0.715
				If treatment respond	38.2		100	0.79 (own calculation)
				Disease progression + febrile neutropenia + diarrhoea and vomiting + hand-foot syndrome + stomatitis + fatique + hair loss	38.2		100	0.03 (own calculation)
				Stable disease with no side effects	70		100	0.84 (own calculation)
				If treatment respond	70		100	0.89 (own calculation)
				Disease progression + febrile neutropenia + diarrhoea and vomiting + hand-foot syndrome + stomatitis + fatique + hair loss	70		100	0.06 (own calculation)
				Stable disease with no side effects	74		100	0.86 (own calculation)
				If treatment respond	74		100	0.90 (own calculation)
				Disease progression + febrile neutropenia + diarrhoea and vomiting + hand-foot syndrome + stomatitis + fatique + hair loss	74		100	0.06 (own calculation)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Dranitsaris 2000 (Canada)	TTO	Canadian women livin in Ontario	NA	At baseline: postmenopausal women with advanced breast cancer who are Estrogen receptor positive, anthracycline naïve and have failed first-line hormonal therapy with tamoxifen.	Mean age: 50.5 (20-81)	Based on x months of life in the state (x not clearly specified)	25	
				no response to letrozole and progression during FAC				Mean: 0.45 (95%CI 0.37-0.55)
				no response to letrozole but response to FAC				Mean: 0.67 (95%CI 0.55-0.79)
				response to letrozole				Mean: 0.80 (95%CI 0.49-0.73)
				no response to anastrozole and progression during FAC				Mean: 0.45 (95%CI 0.37-0.55)
				no response to anastrozole but response to FAC				Mean: 0.67 (95%CI 0.55-0.79)
				response to anastrozole				Mean: 0.80 (95%CI 0.70-0.92)
				no response to megestrol acetate and progression during FAC				Mean: 0.45 (95%CI 0.35-0.55)
				no response to megestrol acetate but response to FAC				Mean: 0.64 (95%CI 0.52-0.76)
				response to megestrol acetate				Mean: 0.80 (95%CI 0.69-0.91)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Dranitsaris 2000 (Canada)	TTO	Female health care professionals (e.g. oncology pharmacists and nurses)	NA	no response to letrozole and progression during FAC	Mean age: 37 (22-61)	Based on x months of life in the state (x not clearly specified)	25	Mean: 0.53 (95%CI 0.45-0.92)
				no response to letrozole but response to FAC				Mean: 0.57 (95%CI 0.49-0.65)
				response to letrozole				Mean: 0.78 (95%CI 0.71-0.84)
				no response to anastrozole and progression during FAC				Mean: 0.53 (95%CI 0.45-0.92)
				no response to anastrozole but response to FAC				Mean: 0.57 (95%CI 0.49-0.65)
				response to anastrozole				Mean: 0.72 (95%CI 0.66-0.78)
				no response to megestrol acetate and progression during FAC				Mean: 0.40 (95%CI 0.30-0.48)
				no response to megestrol acetate but response to FAC				Mean: 0.53 (95%CI 0.44-0.61)
				response to megestrol acetate				Mean: 0.67 (95%CI 0.58-0.76)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Brown 1998 (USA)	SG	Oncology nurses (US, Italy, Spain, the Netherland, Germany, UK)	NA	Patients with advanced breast cancer and receiving docetaxel or paclitaxel after failing previous chemotherapy	/	NA	>129	
				At start of second line chemotherapy				0.64
				Partial/full response (PR)				0.81
				Stable disease (SD)				0.65
				Progressive disease (PD)				0.39
				Terminal disease				0.16
				Peripheral neuropathy+PR				0.56
				Peripheral neuropathy+SD				0.44
				Severe edema+PR				0.76
				Severe edema+SD				0.62
				Severe skin condition				0.56
				Cardiac toxicity				0.59
				Febrile neutropenia with hospitalization				0.30
				Infection no hospitalization				0.60
				Death				0.00

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Brown 1998 (USA)	SG	Oncology nurses (US)	NA	Patients with advanced breast cancer and receiving docetaxel or paclitaxel after failing previous chemotherapy	Mean 39 (25-30 years)	NA	29	
				At start of second line chemotherapy				0.69
				Partial/full response (PR)				0.84
				Stable disease (SD)				0.70
				Progressive disease (PD)				0.49
				Terminal disease				0.23
				Peripheral neuropathy+PR				0.58
				Peripheral neuropathy+SD				0.41
				Severe edema+PR				0.82
				Severe edema+SD				0.68
				Severe skin condition				0.65
				Cardiac toxicity				0.54
				Febrile neutropenia with hospitalization				0.42
				Infection no hospitalization				0.56
				Death				0.00

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Hutton 1996 (UK)	SG	Oncology nurses (US, Canada, Italy, Spain, Germany, UK)	NA	Patients with recurrent metastatic breast cancer and receiving second line therapy after failing previous chemotherapy	Mean age : 33.7	NA	129	
				Partial response (PR)				0.81
				PR and severe peripheral oedema				0.75
				Stable disease				0.62
				Before second-line therapy begins				0.59
				PR and severe neuropathy				0.53
				Progressive disease				0.41
				Sepsis				0.20
				Terminal disease				0.16
		Oncology nurses (UK)	NA	Patients with recurrent metastatic breast cancer and receiving docetaxel or paclitaxel after failing previous chemotherapy	/	NA	30	
				Partial response (PR)				0.84
				PR and severe peripheral oedema				0.78
				Stable disease				0.62
				Before second-line therapy begins				0.56
				PR and severe neuropathy				0.62
				Progressive disease				0.33
				Sepsis				0.16
				Terminal disease				0.13

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Milne 2006 (New Zealand)	EQ-5d	New Zealand general population (women)	UK tariffs (general population; TTO)	Patient with bone metastases who is receiving hormonal therapy	Range: 25-69 (mean: 46 years)	NA	50	Mean: 0.54 (95% CI: 0.51-0.58) Median: 0.61 (IQR: 0.54-0.61)
				Patient with severe bone pain requiring radiotherapy				Mean: 0.31 (95% CI: 0.27-0.35) Median: 0.23 (IQR: 0.16-0.46)
				Patient with moderate to severe hypercalcaemia				Mean: -0.05 (95% CI: -0.07--0.03) Median: -0.08 (IQR: -0.08-0.01)
				Patient receiving chemotherapy rather than hormonal therapy for her advanced cancer and who is not receiving radiotherapy for bone pain				Mean: 0.48 (95% CI: 0.43-0.53) Median: 0.54 (IQR: 0.31-0.61)
	EQ-5d	New Zealand general population (women)	NZ tariffs (general population; EQ-5d VAS)	Patient with bone metastases who is receiving hormonal therapy	Range: 25-69 (mean: 46 years)	NA	40	Mean: 0.65 (95% CI: 0.57-0.73) Median: 0.71 (IQR: 0.46-0.88)
				Patient with severe bone pain requiring radiotherapy			45	Mean: 0.45 (95% CI: 0.37-0.54) Median: 0.46 (IQR: 0.21-0.67)
				Patient with moderate to severe hypercalcaemia			50	Mean: -0.17 (95% CI: -0.29--0.05) Median: -0.08 (IQR: -0.54-0.02)
				Patient receiving chemotherapy rather than hormonal therapy for her advanced cancer and who is not receiving radiotherapy for bone pain			47	Mean: / Median: 0.58 (IQR: 0.21-0.71)

Authors, years, country	Instrument	Respondant	Tariffs (for generic instruments)	Health state	Age (years)	Time	Sample size	Weight
Milne 2006 (New Zealand)	TTO	New Zealand general population (women)	NA	Patient with bone metastases who is receiving hormonal therapy	Range: 25-69 (mean: 46 years)	Based on 1 year of life in the state	46	Mean: 0.54 (95% CI: 0.48-0.59) Median: 0.53 (IQR: 0.40-0.68)
				Patient with severe bone pain requiring radiotherapy				Mean: 0.35 (95% CI: 0.30-0.40) Median: 0.32 (IQR: 0.25-0.48)
				Patient with moderate to severe hypercalcaemia				Mean: 0.13 (95% CI: 0.09-0.17) Median: 0.12 (IQR: 0.05-0.20)
				Patient receiving chemotherapy rather than hormonal therapy for her advanced cancer and who is not receiving radiotherapy for bone pain				Mean: 0.46 (95% CI: 0.41-0.51) Median: 0.46 (IQR: 0.36-0.55)

4. DECISION ANALYSIS

4.1. Breast cancer stage specific relative survival

Breast cancer stage specific relative survival per year from Belgium (2001-2006) (all ages)

Stage	0	1	2	3	4	5
I	100%	100%	100%	99%	99%	98%
II	100%	97%	93%	91%	89%	87%
III	100%	90%	84%	78%	72%	68%
IV	100%	70%	61%	48%	39%	32%

Breast cancer stage specific relative survival per year from the Netherlands (1989-2008) (all ages)

Stage	0	1	2	3	4	5	6	7
I	100%	100%	99%	99%	99%	98%	97%	96%
IIa	100%	99%	98%	96%	95%	93%	91%	90%
IIb	100%	99%	96%	93%	90%	87%	84%	83%
IIIa	100%	99%	94%	90%	85%	81%	76%	73%
IIIb	100%	91%	78%	68%	61%	57%	53%	49%
IIIc	100%	95%	86%	78%	69%	62%	56%	52%
IV	100%	68%	51%	38%	29%	22%	18%	16%
onbekend	100%	86%	81%	77%	73%	72%	73%	75%

Breast cancer stage specific relative survival per year from the Netherlands (1989-2008) (>70)

Stage	0	1	2	3	4	5	6	7	8
I	100%	99%	99%	99%	98%	98%	96%	95%	93%
II	100%	98%	95%	92%	89%	85%	83%	81%	79%
III	100%	92%	81%	72%	63%	59%	53%	48%	42%
IV	100%	58%	42%	31%	22%	16%	13%	12%	10%

Breast cancer stage specific relative survival per year from the United Kingdom (1990-1994) (>70)

Stage	0	1	2	3	4	5	6	7	8	9	10
I	100%	100%	98%	96%	94%	92%	90%	90%	89%	88%	87%
II	100%	96%	88%	82%	77%	73%	70%	68%	65%	64%	63%
III	100%	83%	70%	62%	56%	50%	47%	44%	42%	41%	40%
IV	100%	44%	29%	20%	15%	13%	11%	10%	9%	8%	7%

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