Do screen-detected breast cancers have positive margins less often than clinically detected breast cancers?

Linda de Munck[a], Sabine Siesling[a,b], Joost Bart[c], Marian B.E. Menke-Pluijmers[e], Renée Otter[a] and Pax H.B. Willemse[d]

Positive tumour margins after breast-conserving surgery (BCS) have been selected as one of the major quality criteria for the surgical treatment of localized primary breast cancer. The national guideline states that the rate of positive margins should not exceed 30% in ductal carcinoma *in situ* and 20% in invasive cancers. We aimed to determine whether BCS in women with screen-detected breast cancer (SDBC) will have positive margins less often compared with women with clinically detected breast cancer (CDBC). Furthermore, the choice of subsequent therapy is studied when margins were positive after initial BCS. Women 50–75 years of age who underwent BCS for invasive breast cancer between July 2008 and December 2009 were selected from the Netherlands Cancer Registry. Data were merged with the National Cancer Screening Program, regions North and East, to identify women with SDBC. The relation to screening history, clinical and pathological factors was evaluated for correlation with margin status using multilevel analysis. Of 1537 women with an invasive breast cancer, 873 (57%) were diagnosed through the screening programme. SDBCs were significantly smaller (87 vs. 69% T1 tumours, i.e. $\leq$ 2 cm), more often well differentiated (33 vs. 26%), preoperatively confirmed (98 vs. 96%), diagnosed in a nonteaching hospital (60 vs. 66%) and more often had negative lymph nodes (LNs) (80 vs. 68%). In 170 out of 1537 women, the resection margins were positive. Multivariable analysis showed that hospital, tumour size, multifocality, positive LNs and absent preoperative confirmation were predictors of positive margins. No difference was found between women with SDBC and CDBC. Of women with positive margins, 90% underwent additional surgery. Women diagnosed with SDBC do not have a lower risk of having positive margins after BCS than women with CDBC. Although positive margins may occur in 11% of women with invasive tumours, well below the percentage recommended by the national guideline, the presence of encouraging factors by SDBC such as a smaller tumour size, unifocality, negative LNs and the presence of preoperative confirmation should not lead to performing a more sparing excision than is considered usual for comparable CDBC. *European Journal of Cancer Prevention* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2013, **00**:000–000

Keywords: breast cancer, breast-conserving surgery, clinically detected, re-excision, resection margins, screen detected, screening, tumour size

[a]Department of Research, Comprehensive Cancer Centre the Netherlands, Utrecht, [b]Department of Health Technology & Services Research, University of Twente, Enschede, Departments of [c]Pathology, [d]Medical Oncology, University Medical Centre Groningen, University of Groningen, Groningen and [e]Department of Surgery, Albert Schweitzer Hospital, Dordrecht, The Netherlands

Correspondence to Linda de Munck, MSc, Department of Research, Comprehensive Cancer Centre the Netherlands, PO Box 19079, 3501 DB Utrecht, The Netherlands
Tel: +31 88 234 55 00; fax: +31 88 234 55 99; e-mail: l.demunck@iknl.nl

Received 1 October 2012 **Accepted** 15 January 2013

Introduction

Breast cancer is the most common type of cancer in women, with 13 257 new cases in the Netherlands in 2010, and breast-conserving surgery (BCS), followed by radiotherapy, has been accepted as the standard treatment for patients with early-stage breast cancer (Van Dongen *et al.*, 2000; Early Breast Cancer Trialists' Collaborative Group, 2005; Comprehensive Cancer Centre the Netherlands, 2011). In the Netherlands, a population-based screening programme has been implemented since 1991, inviting women 50–75 years of age for biannual mammography. Patients diagnosed with breast cancer through this programme are more often diagnosed with early-stage breast cancer, and are therefore more often suited for BCS (Fracheboud *et al.*, 2004; Samnakay *et al.*, 2005). Although successful BCS leads to better cosmetic results, less psychological burden and a better quality of life compared with mastectomy (Moyer, 1997; Curran *et al.*, 1998), the disadvantage is the risk of local recurrence (LR), which influences the prognosis. To minimize the risk of an LR, BCS requires clear histological margins. However, clear margins are not always obtained during initial surgery and 20–30% of women undergo further surgery after initial BCS (Landheer *et al.*, 2004; Dillon *et al.*, 2006; Pleijhuis *et al.*, 2009). Information on the factors associated with positive margins is likely to allow clinicians to identify subgroups of women at risk for an irradical resection. In patients with factors indicating a higher risk for positive margins, more extensive surgery can be performed at the initial operation, thus reducing the risk of positive margins and preventing further surgery.

Studies have identified factors associated with positive margins, including tumour characteristics [tumour size, multifocality and positive lymph nodes (LNs)], surgical

0959-8278 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0b013e32835f3b70

factors (presence of confirmed preoperative diagnosis) as well as differences between hospitals or pathology laboratories (Kurniawan *et al.*, 2008; Von Smitten, 2008; Lovrics *et al.*, 2009; Pleijhuis *et al.*, 2009; Persing *et al.*, 2011; Van der Heiden-van der Loo *et al.*, 2012). However, little is known about the relation between the method of detection and margin status. One could hypothesize that screen-detected breast cancers (SDBCs) are smaller and better differentiated than clinically detected breast cancers (CDBCs); therefore, they should be less prone to positive margins. Only a few studies comment on the relation of tumours diagnosed through the screening programme and clear surgical margins, compared with tumours diagnosed through other ways. One of these studies found less positive margins after referral through the screening programme and another found no relation (Dillon *et al.*, 2006; Saadai *et al.*, 2011).

The aim of this population-based study is to determine whether women with SDBC have positive margins less often after initial BCS, compared with women diagnosed with CDBC, and to identify other clinical and pathological factors associated with margin status after BCS. Furthermore, the choice of subsequent therapy is studied when margins were positive after initial BCS.

Patients and methods

Patients

Patients were selected from the population-based Netherlands Cancer Registry (NCR). The main source of notification for the NCR is PALGA, the nationwide Dutch network and registry of histological and cytological pathology, through which all newly diagnosed malignancies are reported to the cancer registry. Case ascertainment is completed using the national hospital discharge database, which receives diagnoses of admitted patients from all hospitals. After notification to the NCR, specially trained registry clerks of the Comprehensive Cancer Centre the Netherlands visit the hospitals to collect information on patient and tumour characteristics from patient files. Coding of the items is based on international coding rules (IACR); the TNM classification is used for the staging of tumours (International Union Against Cancer, 2002). For women for whom the date of pathological confirmation of the tumour and surgery was the same, diagnosis was confirmed during surgery. Therefore, a preoperative diagnosis was defined as 'no' when the date of incidence was the same as the date of surgery.

Women 50–75 years of age diagnosed in the North Eastern region of the Netherlands who underwent initial BCS for invasive breast cancer (IBC) between 1 July 2008 and 31 December 2009 were selected from the NCR ($N = 1565$). Women who received neoadjuvant treatment ($N = 9$) and women whose margin status of initial BCS was unknown ($N = 19$) were excluded. A total of 1537 women were included in the analysis.

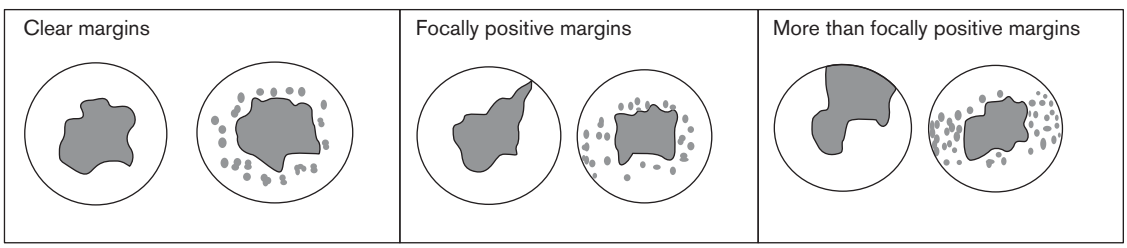
Relation to screening

Data were merged with the data of the National Cancer Screening Program, region North, and the National Cancer Screening Program, region East, together covering the North Eastern region of the Netherlands with 3.3 million inhabitants (20% of all Dutch inhabitants). Two subgroups were defined: women with breast cancer following an abnormal mammogram by screening were defined as SDBC and all other women were defined as CDBC.

Margin status

Margin status was defined according to the Dutch guideline for the pathology laboratories (National Breast Cancer Organization of the Netherlands, 2008). According to this guideline, surgical margins of the excised lump can be divided into three subgroups: clear margins (tumour not touching the inked surface of the specimen), focally positive margins (tumour in a limited area of the inked surface; i.e. two low-power fields, magnification $\times 100$, equalling 4–5 mm) and more than focally positive margins (Fig. 1). Margin status determines which additional treatment is provided to the patient. Patients with invasive tumours undergo re-excision in case of more than focally positive margins. Therefore, positive and focally positive margins were defined as clear margins. More than focally positive margins were defined as positive margins [invasive and/or ductal carcinoma *in situ* (DCIS) component]. Margin status was unknown in 1.2% of cases and ranged from 1 to 4% in 11 hospitals (0% in 12 hospitals). Cases with

Fig. 1



Margin status (invasive or ductal carcinoma *in situ* component).

unknown margin status were excluded from analysis ($N = 19$).

Hospitals and pathology laboratories

The type of hospital was based on the hospital where the surgery was performed. A teaching hospital was defined as a hospital that provides medical training to surgical residents. A teaching pathology laboratory was a laboratory that provides medical training to pathology residents. Surgery was performed in 23 hospitals and evaluation of surgical margins was carried out in nine pathology laboratories. Most pathology laboratories will serve more than one hospital.

Statistical analysis

χ^2-Analysis was used to compare categorical variables. Multilevel logistic regression was performed to study differences in margin status and the relation to screening. Multilevel analysis takes into account a hierarchical structure. Our data had a two-level data structure: tumours were clustered within hospitals of surgery. The magnitude of the variance of a level in combination with its standard error can be used as a rough test for judging significance of the variance. The dependency of observations within a certain level was estimated by the intraclass correlation coefficient. In a logistic multilevel analysis, the intraclass correlation coefficient can be estimated by between-group variance/between-group variance + ($\pi^2/3$) (Twisk, 2006). First, a null model without any variables was estimated. In our data, hospital was a significant factor; adding pathology laboratory as the next level did not result in a better model. Therefore, multilevel analysis was carried out taking hospital level into account. Second, tumour characteristics (tumour size, histological grade, number of breast cancer foci and nodal status), preoperative cytological/histological confirmation and type of pathology laboratory were included as covariates. Tumours coded pT1mic were included in the pT1a ($n = 5$). Variables with a significance level of less than 0.10 by univariable analysis were included in the multivariable analysis. The statistical significance level was set at a *P*-value less than 0.05. Analyses were carried out using the STATA software package, version 10.1 for Windows (Stata Corporation LP, College Station, Texas, USA).

Results

Study population and relation to the screening programme

A total of 1537 women were diagnosed with an invasive breast tumour. Of these 1537 women, 873 (57%) were diagnosed with SDBC and 664 (43%) were diagnosed with CDBC (Table 1). SDBCs were significantly smaller (87 vs. 69% T1 tumours, i.e. ≤ 2 cm; $P < 0.001$), more often well differentiated (33 vs. 26%; $P < 0.001$) and more often had negative LNs (80 vs. 68%; $P < 0.001$). Furthermore, they were more often preoperatively confirmed (98 vs. 96%; $P = 0.031$) and more often treated in a nonteaching hospital (60 vs. 66%; $P = 0.012$) or diagnosed in a nonteaching pathology laboratory (49 vs. 42%; $P = 0.012$).

Table 1 Characteristics of the study population of patients with invasive tumours (+/− ductal carcinoma *in situ* component)

	N (%)		
	SDBC	CDBC	Total
Tumour size‡			
1A	62 (7)	27 (4)	89 (6)
1B	257 (29)	108 (16)	365 (24)
1C	439 (50)	323 (49)	762 (50)
2+	111 (13)	205 (31)	316 (21)
Unknown	4 (1)	1 (0)	5 (0)
Histological grade‡			
Well differentiated	289 (33)	170 (26)	459 (30)
Moderately differentiated	398 (46)	263 (40)	661 (43)
Poorly differentiated	147 (17)	195 (29)	342 (22)
Unknown	39 (5)	36 (5)	75 (5)
Number of breast cancer foci			
Unifocal	826 (95)	622 (94)	1448 (94)
Multifocal	47 (5)	42 (6)	89 (6)
Nodal status‡			
Negative	702 (80)	454 (68)	1156 (75)
Positive	171 (20)	210 (32)	381 (25)
Preoperative cytol/histol confirmation*			
Yes	855 (98)	638 (96)	1493 (97)
No	18 (2)	26 (4)	44 (3)
Type of hospital*			
Teaching	525 (60)	441 (66)	966 (63)
Nonteaching	348 (40)	223 (34)	571 (37)
PA laboratory*			
Teaching	450 (52)	385 (58)	835 (54)
Nonteaching	423 (49)	279 (42)	702 (46)
Total	873 (100)	664 (100)	1537 (100)

CDBC, clinically detected breast cancer; cytol, cytological; histol, histological; PA, pathology; SDBC, screen-detected breast cancer.
*$P < 0.05$.
‡$P < 0.001$.

Predictors of positive margins

In 170 of the 1537 (11%) women, the resection margin was positive (Table 2). There was no difference between the women with SDBC compared with the women with CDBC. Table 2 shows the percentages of positive margins for invasive tumours. The percentage of positive margins is divided into positive margins for the invasive tumour or just the DCIS component. A large range of percentages in positive margins was found between hospitals (range 2–29%). In a multilevel analysis taking into account hospital, there was no difference between women with SDBC compared with women with CDBC (Table 3). Nevertheless, margin status was affected by other factors. Larger tumour size, multifocality, positive LNs and the absence of preoperative confirmation were all predictors of positive margins. In univariable analysis, the localization of the tumour and histological grade were related to positive margins as well.

Subsequent treatment for positive margins after breast-conserving surgery

A total of 170 women (11%) with an invasive tumour had positive margins after BCS, of whom 111 women (65%) had a positive invasive component. Most women (90%)

Table 2 Percentage of invasive tumours with positive margins, by detection method

	SDBC			CDBC		
	Total (*N*)	INV positive (%)	DCIS positive (%)	Total (*N*)	INV positive (%)	DCIS positive (%)
Tumour size						
1A	62	5	23	27	4	19
1B	257	3	2	108	10	4
1C	439	8	3	323	5	2
2+	111	14	4	205	12	3
Unknown	4	0	50	1	0	0
Histological grade						
Well differentiated	289	5	2	170	8	2
Moderately differentiated	398	9	4	263	7	4
Poorly differentiated	147	6	6	195	9	4
Unknown	39	5	13	36	8	3
Number of breast cancer foci						
Unifocal	826	6	4	622	7	3
Multifocal	47	17	11	42	26	5
Nodal status						
Negative	702	6	5	454	5	3
Positive	171	12	4	210	13	3
Preoperative cytol/histol confirmation						
Yes	855	7	4	638	7	3
No	18	11	11	26	27	12
Type of hospital						
Teaching	525	7	4	441	7	3
Nonteaching	348	7	5	223	10	4
PA laboratory						
Teaching	450	5	4	385	6	4
Nonteaching	423	9	4	279	10	3
Total	873	7 ($n=59$)	4 ($n=38$)	664	8 ($n=52$)	3 ($n=21$)

The number of patients is followed by the percentage with positive margins of the invasive component (INV positive) and the percentage with positive margins of the DCIS component in an invasive tumour (DCIS positive).
CDBC, clinically detected breast cancer; cytol, cytological; DCIS, ductal carcinoma *in situ;* histol, histological; PA, pathology; SDBC, screen-detected breast cancer.

were treated with a subsequent re-excision or mastectomy, 5% received radiotherapy and 5% received no additional treatment specific for positive margins (Table 4). Of women with an invasive tumour in whom the invasive component had free margins, but the DCIS component was more than focally positive ($n = 59$, 35%), additional re-excision or mastectomy was performed in 83%, 12% received radiotherapy and 5% received no treatment specific for positive margins. No differences in subsequent treatment were found between women with SDBC and CDBCs. The differences in subsequent treatment between positive invasive components and positive DCIS components were not significant ($P = 0.053$ and 0.619 for the SDBCs and CDBCs, respectively).

Discussion

In 170 out of 1537 (11%) women with IBC, the resection margins were positive. No difference in the risk of positive margins was found between women with SDBC compared with women with CDBC. The Dutch guideline states that the upper limit of positive margins is 20% for invasive cancer (National Breast Cancer Organization of the Netherlands, 2008). Our results show that the percentage of positive margins for invasive tumours is well within the upper limit according to the guidelines. Van der Heiden-van der Loo *et al.* (2012) presented results on positive margins after BCS on a national level, and found a percentage of 9% positive margins for IBC.

The clinical relevance of positive margins still remains controversial. Most evidence supports the view that positive margins herald LR. The most plausible explanation is that for a high volume of residual tumour, radiotherapy alone is not sufficient to eliminate all tumour cells. However, the question of whether and how close margins affect LR is still unresolved. This lack of consistency in the definition of free margins contributes towards the lack of consensus on end results. In the literature, various definitions are used (Taghian *et al.*, 2005; Law and Kwong, 2009). In our study, positive margins were defined specifically for invasive tumours. Patients with invasive tumours with more than focally positive margins should undergo a re-excision as LR rates are high even after radiotherapy with a booster dose. Patients with an invasive tumour with focally positive margins always receive a radiotherapy booster dose. Looking at the three subgroups (clear, focally positive, more than focally positive) of margin status separately resulted in similar results and no difference was found between SDBC and invasive CDBC ($P = 0.389$, results not shown). Furthermore, we excluded women with an unknown margin status, which might be a reason for bias. We do not have any information on why margin status is unknown, but it ranged from 1 to 4% in 11 hospitals (0% in 12 hospitals) and it is unlikely that it is unknown for a specific subgroup of patients or hospitals.

We have found just a few papers evaluating data from a breast screening programme. Dillon *et al.* (2006) found less involved margins in screen-detected invasive cancers.

Table 3 Multilevel analysis on positive margin status in all invasive tumours taking hospital level into account (*N*=1537)

	Univariable analysis			Multivariable analysis		
	OR	95% CI		OR	95% CI	
Relation to screening programme						
SDBC	Reference			Reference		
CDBC	1.04	0.74	1.46	0.80	0.55	1.16
Tumour size						
1A	3.53	2.02	6.18‡	4.72	2.56	8.72‡
1B	0.86	0.54	1.37	1.02	0.63	1.66
1C	Reference			Reference		
2+	2.08	1.39	3.12‡	1.68	1.08	2.60*
Unknown	7.30	1.11	48.22*	6.18	0.79	48.48
Histological grade						
Well differentiated	Reference			Reference		
Moderately differentiated	1.70	1.12	2.59*	1.68	1.08	2.62*
Poorly differentiated	1.89	1.17	3.07*	1.76	1.03	3.01*
Unknown	2.29	1.08	4.82*	1.32	0.59	2.94
Number of breast cancer foci						
Unifocal	Reference			Reference		
Multifocal	4.04	2.43	6.72‡	4.00	2.36	6.79‡
Nodal status						
Negative	Reference			Reference		
Positive	1.87	1.32	2.65‡	1.94	1.32	2.87†
Preoperative cytol/histol confirmation						
Yes	Reference			Reference		
No	3.17	1.60	6.29†	3.43	1.64	7.19†
Type of hospital						
Teaching	Reference			–		
Nonteaching	1.28	0.77	2.13	–	–	–
PA laboratory						
Teaching	Reference			–		
Nonteaching	1.48	0.86	2.53	–	–	–

CDBC, clinically detected breast cancer; CI, confidence interval; cytol, cytological; histol, histological; OR, odds ratio; PA; pathology; SDBC, screen-detected breast cancer.
*$P<0.05$.
†$P<0.01$.
‡$P<0.001$.

Table 4 Subsequent treatment for positive margins after breast-conserving surgery

	N (%)			
	SDBC	CDBC	Total	*P*-value
Invasive component				
Re-excision + RT[a]	27 (46)	19 (37)	46 (41)	0.248
Mastectomy	29 (49)	25 (48)	54 (49)	
RT only	1 (2)	5 (10)	6 (5)	
No further treatment	2 (3)	3 (6)	5 (5)	
Total	59 (100)	52 (100)	111 (100)	
DCIS component				
Re-excision + RT[b]	11 (29)	11 (52)	22 (37)	0.239
Mastectomy	19 (50)	8 (38)	27 (46)	
RT only	5 (13)	2 (10)	7 (12)	
No further treatment	3 (8)	0 (0)	3 (5)	
Total	38 (100)	21 (100)	59 (100)	

CDBC, clinically detected breast cancer; DCIS, ductal carcinoma *in situ*; RT, radiotherapy; SDBC, screen-detected breast cancer.
[a]Two patients had re-excision without RT.
[b]Four patients had re-excision without RT.

In their study, they defined involved margins as foci of DCIS or invasive carcinoma within 5 mm from the resection margin. In our study, we did not collect data on the precise margin distance, but we used the presence of a tumour within the resection surface as the definition for positive margins. Furthermore, in contrast to Dillon *et al.* (2006), we did carry out a multivariable analysis to take other patient-related and tumour-related factors into account, which might be the reason for a different outcome. Kurniawan *et al.* (2008) included only patients diagnosed through a breast screening programme. Therefore, they could not compare the relation of positive margins between women with screen-detected and other tumours, but they did find that tumour size and multifocality are risk factors for positive margins, as well as the presence of calcifications on mammography. These results are in agreement with those of our study. Lovrics *et al.* (2009) found that tumour size, positive LNs and multifocality were risk factors for positive margins, next to other tumour characteristics. Dillon *et al.* (2006) found that tumour size, multifocality and absence of preoperative confirmation were risk factors. The absence of preoperative confirmation can serve as a proxy for the use of a needle plus ultrasound localization technique. Failure of this method is associated with compromised margins, and our result supports this association. All three studies mentioned above found a significant risk of tumour size: larger tumours have an increased risk of positive margins. In our study, however, we found that T1A tumours were also at high risk. Most of the T1A cases had an extensive DCIS component (microinvasive cancers). Because a characteristic of DCIS is its extensive and discontinuous spread throughout a single duct system, this may explain the fact that even these small SDBCs carry the same risk of positive margins as the CDBCs.

Chiarelli *et al.* (2012) found that clinically detected tumours are more often undifferentiated and have a high mitotic index. This might be another reason for a more wispy growth type, with its inherent higher chance of irradical resection. It has also been argued that tumours detected by the initial or prevalent screening round would have more favourable characteristics than subsequent SDBCs. Therefore, inclusion of all SDBCs in our study may not provide the right comparison. We have focused on margin status and we found positive margins in 7% for invasive components and 4% for DCIS components in all (prevalent and subsequent) SDBCs. Analysis of subsequent SDBCs only yielded the same results, with 7 and 4%, respectively (results not shown), and so the screening round did not have an influence on margin status.

Of the women with positive margins after initial BCS, 90% underwent a re-excision. This is in accordance with the breast cancer guideline and in agreement with other studies reporting re-excision rates from 70 to 93% (Mullenix *et al.*, 2004; Kurniawan *et al.*, 2008).

Conclusion

Women diagnosed with SDBC do not have a lower risk of having positive margins after BCS than women with CDBC.

Although positive margins may occur in 11% of women with invasive tumours, well below the percentage recommended by the national guideline, the presence of encouraging factors by SDBC such as a smaller tumour size, unifocality, negative LNs and the presence of preoperative confirmation should not lead to performing a more sparing excision than is considered usual for comparable CDBC.

Acknowledgements

The authors thank the National Cancer Screening Program, region North (Bevolkingsonderzoek Noord) in Groningen, and Hilko Schippers and the National Cancer Screening Program, region East (Bevolkingsonderzoek Oost) in Enschede for providing data on mammography screening. Furthermore, all registry clerks of the Comprehensive Cancer Centre the Netherlands and Comprehensive Centre South are thanked for their effort in gathering the data.

Conflicts of interest

There are no conflicts of interest.

References

Chiarelli AM, Edwards SA, Sheppard AJ, Mirea L, Chong N, Paszat L, *et al*. Breast Screening Study Group (2012). Favourable prognostic factors of subsequent screen-detected breast cancers among women aged 50–69. *Eur J Cancer Prev* **21**:499–506.

Comprehensive Cancer Centre the Netherlands (2011). Available at: *http://www.cancerregistry.nl* [Accessed 16 March 2012].

Curran D, van Dongen JP, Aaronson NK, Kiebert G, Fentiman IS, Mignolet F, *et al.* (1998). Quality of life of early-stage breast cancer patients treated with radical mastectomy or breast-conserving procedures: results of EORTC trial 10801. *Eur J Cancer* **34**:307–314.

Dillon MF, Hill ADK, Quinn CM, McDermott EW, O'Higgins N (2006). A pathologic assessment of adequate margin status in breast-conserving therapy. *Ann Surg Oncol* **13**:333–339.

Early Breast Cancer Trialists' Collaborative Group (2005). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* **366**:2087–2106.

Fracheboud J, Otto SJ, van Dijck JAAM, Broeders MJM, Verbeek ALM, de Koning HJ (2004). Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer* **91**:861–867.

International Union Against Cancer (2002). *TNM classification of malignant tumours*. 6th ed. Geneva: Wiley-Liss.

Kurniawan ED, Wong MH, Windle I, Rose A, Mou A, Buchanan M, *et al.* (2008). Predictors of surgical margin status in breast-conserving surgery within a breast screening program. *Ann Surg Oncol* **15**:2542–2549.

Landheer MLEA, Klinkenbijl JHG, Pasker-de Jong PCM, Wobbes T (2004). Residual disease after excision of non-palpable breast tumours: analysis of tumour characteristics. *Eur J Surg Oncol* **30**:824–828.

Law TT, Kwong A (2009). Surgical margins in breast conservation therapy: how much should we excise? *South Med J* **102**:1234–1237.

Lovrics PJ, Cornacchi SD, Farrokhyar F, Garnett A, Chen V, Franic S, *et al.* (2009). The relationship between surgical factors and margin status after breast-conserving surgery for early stage breast cancer. *Am J Surg* **197**:740–746.

Moyer A (1997). Psychosocial outcomes of breast-conserving surgery versus mastectomy: a meta-analytic review. *Health Psychol* **16**:284–298.

Mullenix PS, Cuadrado DG, Steele SR, Martin MJ, See CS, Beitler AL, *et al.* (2004). Secondary operations are frequently required to complete the surgical phase of therapy in the era of breast conservation and sentinel lymph node biopsy. *Am J Surg* **187**:643–646.

National Breast Cancer Organization of the Netherlands (2008). Guideline breast cancer. Available at: *http://www.oncoline.nl*. [Accessed 16 June 2011].

Persing S, James T, Mace J, Goodwin A, Geller B (2011). Variability in the quality of pathology reporting of margin status following breast cancer surgery. *Ann Surg Oncol* **18**:3061–3065.

Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM (2009). Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. *Ann Surg Oncol* **16**:2717–2730.

Saadai P, Moezzi M, Menes T (2011). Preoperative and intraoperative predictors of positive margins after breast-conserving surgery: a retrospective review. *Breast Cancer* **18**:221–225.

Samnakay N, Tinning J, Ives A, Willsher P, Archer S, Wylie E, *et al.* (2005). Rates for mastectomy are lower in women attending a breast-screening programme. *ANZ J Surg* **75**:936–939.

Taghian A, Mohiuddin M, Jagsi R, Goldberg S, Ceilley E, Powell S (2005). Current perceptions regarding surgical margin status after breast-conserving therapy. *Ann Surg* **241**:629–639.

Twisk JWR (2006). *Applied multilevel analysis*. Cambridge: Cambridge University Press.

Van der Heiden-van der Loo M, de Munck L, Visser O, Westenend PJ, van Dalen T, Menke MB, *et al.* (2012). Variation between hospitals in surgical margins after first breast-conserving surgery in the Netherlands. *Breast Cancer Res Treat* **131**:691–698.

Van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, *et al.* (2000). Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. *J Natl Cancer Inst* **92**:1143–1150.

Von Smitten K (2008). Margin status after breast-conserving treatment of breast cancer: how much free margin is enough? *J Surg Oncol* **98**:585–587.