Acta Oncologica, 2008; 47: 239–247

informa
healthcare

ORIGINAL ARTICLE

Does the introduction of sentinel node biopsy increase the number of node positive patients with early breast cancer? A population based study form the Danish Breast Cancer Cooperative Group

ANDERS HUSTED MADSEN[1,2], ANNI RAVNSBAEK JENSEN[1], PEER CHRISTIANSEN[2], JENS PETER GARNE[5], SOEREN COLD[3], MARIANNE EWERTZ[4] & JENS OVERGAARD[1]

[1]*Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark,* [2]*Department of Surgery, Aarhus University Hospital, Aarhus, Denmark,* [3]*Department of Oncology, Odense University Hospital, Aarhus, Denmark,* [4]*Department of Oncology, Aalborg Hospital, Aarhus University Hospital, Aarhus, Denmark and* [5]*Department of Breast Surgery, Aalborg Hospital, Aarhus University Hospital, Aarhus, Denmark*

Abstract

Background. The validation series of sentinel lymph node biopsy (SLNB) in the treatment of breast cancer have shown that 10–20% more lymph node metastases are detected. However, their impact has never been studied in populations where the method has been fully implemented. In a population-based setting, the objective of the current study was to estimate the increased risk of metastases after introduction of the sentinel lymph node biopsy technique. *Methods.* We identified all new breast cancer patients in three different counties in two time periods (1996–1997 and 2002–2003). The study cohort was comprised of 2 932 patients. The main outcome was the frequency of patients with metastases. The frequencies of patients with metastases were compared as well as adjusted (using a multivariate logistic regression) and unadjusted odds-ratio for detecting lymph node metastases. *Results.* In counties where sentinel lymph node biopsy was implemented, the frequency of patients with lymph node metastases increased significantly 7.3% (95% CI: 1.0–13.7%) and 13.3% (95% CI: 7.3–19.3%), respectively. In the county without sentinel lymph node biopsy, an insignificant increase of 6.9% (-0.1–13.9%) in the frequency of patients with metastases was seen. The adjusted odds- ratio for detecting lymph node metastases was 1.41 (1.07–1.87) and 1.70 (1.30–2.23) in the counties with SLNB. *Conclusion.* The frequency of patients with metastases increased significantly in counties where sentinel lymph node biopsy was implemented.

Lymph node status is an important prognostic indicator of the outcome in patients with breast cancer. Patients with metastases to the axillary lymph nodes have a poorer prognosis than patients without them [1]. Until recently, axillary dissection of level I and II has been performed as a routine with both a diagnostic and therapeutic aim. With the introduction of sentinel lymph node biopsy (SLNB), this number has decreased because patients without metastases to sentinel lymph nodes are not treated with axillary dissection [2,3]. The SLNB has been implemented worldwide, although very few randomized studies of mortality and recurrence have been published [4]. However, small series have been published showing that the recurrence rate in sentinel node negative patients is low [5,6].

Because only a few lymph nodes are identified as sentinel lymph nodes, it is possible to perform extensive histopathological examinations using serial sectioning and staining with antibodies against cytokeratin. However, the use of specific polymerase chain reactions can detect even smaller amounts of metastatic tissue in the lymph nodes. In studies with a limited number of patients, up to 10–20% more patients with lymph node metastases are detected which will lead to up-staging of these patients [7]. In contrast, validation studies have revealed up to 8% false negative patients leading to an understaging [8].

It is believed that the use of these careful procedures leads mainly to the detection of more micrometastases [9]. With the possibility of

Correspondence: Anders Husted Madsen, Department of Surgery P, Aarhus University Hospital, Tage-Hansensgade 2, 8000 Aarhus C, Denmark. E-mail: husted@ki.au.dk

(Received 21 March 2007; accepted 3 October 2007)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860701727436

detecting small amounts of metastatic tissue in lymph nodes, the clinical impact of micrometastases has been questioned. Some studies have shown that patients with micrometastases have a survival rate between that of patients with no metastases and patients with macrometastases [10]. Others have shown that patients initially diagnosed with micrometastases can have macrometastases in sentinel as well as in non-sentinel lymph nodes if meticulous serial sectioning is performed [11,12]. The clinical impact of micrometastases is now being studied in a randomized trial [13].

Even though meticulous histopathological methods will find more lymph node metastases, the risk of lymph node metastases is a function of tumor size [14]. Further, studies have shown that the average tumor size is smaller in populations with mammography screening than in populations without [15,16]. The impact of nodal positivity of introducing SLNB in populations with mammography screening compared with populations without mammography screening is unclear.

Population- and register-based studies have the possibility of studying the impact of SLNB on whole populations. Only a few studies have tried this [17,18]. Such studies require registries of high quality. In Denmark, registration of cancer incidence is maintained by the Danish Cancer Registry (DCR). Since 1987 it has been mandatory to report new cancers to the DCR. The register uses multiple sources to get as high a completion as possible, and validation studies have shown that more than 99% of new breast cancers are reported. However, only very few histopathological data are reported to the DCR [19]. Breast cancer treatment is organised by the Danish Breast Cancer Cooperative Group (DBCG). It was established in 1977 as an initiator and organiser of nation-wide protocols and randomised trials. As part of these protocols, there are guidelines for the preoperative diagnostic set-up, surgical treatment, radiotherapy, and adjuvant systemic therapy. All breast cancer units participate in the protocols and trials. When a new treatment is introduced, the introduction is not necessarily at the same time in different breast cancer units. This was the case with the introduction of SLNB, which was implemented with different speeds in the Danish counties. The DBCG holds a database with high quality clinicopathological data. However, validation studies have shown that the database is missing information on approximately 10–20% of all a populations patients [20,21]. The missing patients are mainly older patients or patients with severe comorbidity. These patients are often treated outside of protocol.

The aim of this population-based study was to estimate the increased number of patients with lymph node metastases after the introduction of SLNB.

Materials and methods

We compared two time periods (1996–1997 vs. 2002–2003) in three different counties in Denmark. The three counties that were studied were Funen County (county A), Aarhus County (county B) and County of Northern Jutland (county C). On January 1, 2003 the number of inhabitants in the three counties were 473 471, 649 177 and 495 625, respectively [22]. In 1996–1997 SLNB was not implemented in any of the three counties. Since 1993, mammography screenings have been offered biannually to women 50–69 years of age in county A as part of a public health care plan. In county B and C there were no mammography screenings. In county A and B, SLNB was fully implemented in 2002–2003 as a surgical protocol with uniform guidelines from DBCG. In county C, neither sentinel lymph node biopsy nor mammography screening was implemented. A summary of the three counties and the two periods are shown in Table I.

Patients were identified using the DCR. These data were combined with the clinicopathological data from the DBCG. Missing data in the database from the DBCG were collected manually from medical records. Information of residency was obtained from the national registration number system that provides accurate information on residency.

Table I. Principal differences between 1996–1997 and 2002 and Funen, Aarhus and Northern Jutland counties.

	1996–1997	2002–2003
County A	+ mammography screening No SLNB	+ mammography screening + SLNB
County B	No mammography screening no SLNB	No mammography screening + SLNB
County C	no mammography screening no SLNB	No mammography screening No SLNB

SLNB: sentinel lymph node biopsy.

Study cohort

Overall 4302 (n = 2015 in 1996–1997 and n = 2287 in 2002–2003) patients were identified in the DCR. With the exception of patients with in situ cervical cancer of the uterus and basal cell carcinomas of the skin, patients with a prior history of invasive cancer (n = 121) were excluded. Patients diagnosed on autopsy alone (n = 29), patients without a histologically proven breast cancer (n = 112), and patients with disseminated disease at the time of diagnosis (n = 136) were also excluded. Finally, patients aged 71 years or older (n = 972) were excluded because these patients were treated outside DBCG-protocols in 1996–1997. A total of 2 932 patients with early breast cancer were then included in the analysis.

Selection of patients to sentinel lymph node biopsy

According to the guidelines from the DBCG, patients were candidates for SLNB if they had unifocal tumors smaller than 4 cm on mammograms or ultrasounds. Ultrasounds of the axillas were performed on all patients. If suspected lymph nodes were seen, fine needle aspiration was performed. If malignant cells were found, an axillary lymph node dissection was performed.

Examination of lymph nodes

Lymph nodes were examined according to guidelines from the DBCG [23]. In the first period, all lymph nodes were examined by bisectioning and staining with haematoxylin-eosin (HE). In the second period, sentinel lymph nodes were examined according to DBCG guidelines and included serial sectioning and staining with immunohistochemistry using antibodies against cytoceratin. The polymerase chain reaction method was not used. Lymph nodes from axillary dissections (level I and II) were bisected and stained with HE and these nodes were therefore not examined using serial sectioning and IHC.

Metastases were, in both periods, categorized according to the 4th version of the AJCC cancer staging manual [24]. Metastases larger than 2 mm were categorized as macrometastases, and metastases below 2 mm were categorized as micrometastases. Reporting whether metastases were found on HE- or cytokeratin-stained material did not occur.

Statistics

The Wilcoxsons rank sum test was used to compare differences between groups. The Bonferronis correction was calculated to adjust for multiple testing. Odds-ratios and absolute risk differences were calculated with corresponding 95% confidence intervals.

Adjusted odds-ratios were calculated using a multivariate logistic regression model. Potential confounders that were included in the model were age, menopausal status, tumor size, number of lymph nodes removed, histological type, estrogen-receptor status, and malignancy grade. Age was categorized in 10-year increments (21–30, 31–40, 41–50, 51–60 and 61–70 years). Lymph nodes were categorized as 0, 1–2, 3–4, 5–9 and 10 or histologically proven lymph nodes. The histology of the tumours was classified as ductal carcinomas, lobular carcinomas, other types and, finally, a category of carcinomas confirmed by cytology alone. Tumors were graded according to Bloom and Richardson in grades I, II and III [25]. We tested the model using Pearson's χ^2 goodness-of-fit test.

The statistical software package Stata, (intercooled version 8, Stata Corporation 4905 Lakeway Drive, College Station, Texas 77845 USA) was used.

Results

The analysis included 2 932 patients in three different counties in two periods in Denmark. Age, T-stage distribution and malignancy grade were similar across time periods and county (Table II). The histological type and estrogen receptor status remained unchanged in County A and C while a significant change was seen in county B which is probably a coincidence. In all three counties, there was a significant increase with time in the number of patients having breast conserving surgery; the highest proportion (55%) was observed in Funen as well as a similar decrease in mastectomies. Funen was also the county with the lowest average tumor size.

The number of lymph nodes *examined* (removed) differed significantly in all three counties. The proportion of patients having *fewer* than 10 lymph nodes removed increased significantly in county A (9 vs. 30%, $p < 0.01$) and county B (9 vs. 35%, $p < 0.01$). In contrast, in county C, the number of patients having *more* than 10 lymph nodes removed increased significantly (78 vs. 95%, $p < 0.01$). Analysing the number of patients who had 15 or more lymph nodes examined revealed a significant increase ($p < 0.03$) in County C from the first to the second period.

The number of micrometastases increased significantly in county A and B (4 vs. 10% in both counties, $p < 0.01$). No significant difference was seen in county C (4 vs. 6%, $p > 0.05$). Approximately half of the population of breast cancer patients in county A and B had a sentinel lymph node procedure performed.

Table II. Basic characteristics of the study population from three counties in Denmark.

	County A		County B		County C	
	1996–97	2002–2003	1996–97	2002–2003	1996–1997	2002–2003
Included patients	462	540	506	608	353	463
Age[⋆]						
Median (range)	55 (26–70)	57 (28–70)	54 (24–70)	55 (21–70)	55 (28–70)	56 (28–70)
Age						
<50 years of age	127 (27)	125 (23)	185 (37)	168 (28)	112 (32)	131 (28)
50 years of age or more	335 (73)	415 (77)	321 (63)	440 (72)	241 (68)	332 (72)
Menopausal Status[⋆]						
Premenopausal	147 (32)	164 (30)	192 (38)	211 (35)	125 (35)	167 (36)
Postmenopausal	315 (68)	376 (70)	314 (62)	395 (65)	228 (65)	295 (64)
Unknown	0	0	0	2 (0)	0	1
Tumor size						
Median (range)	16 (1–80)	15 (1–150)	19 (1–130)	20 (1–100)	20 (1–120)	20 (1–120)
T-stage[⋆]						
T1						
T1mic	1 (0)	4 (1)	1 (0.2)	2 (0.3)	1 (0.3)	4 (1)
T1a	15 (3)	15 (3)	18 (4)	19 (3)	4 (1)	7 (2)
T1b	74 (16)	103 (19)	66 (13)	54 (9)	34 (10)	33 (7)
T1c	207 (45)	237 (44)	193 (38)	220 (36)	140 (40)	202 (44)
T2	135 (29)	140 (26)	170 (34)	244 (40)	142 (40)	179 (39)
T3	6 (1)	24 (4)	21 (4)	26 (4)	9 (3)	17 (4)
T4	11 (2)	6 (1)	15 (3)	15 (2)	5 (1)	6 (1)
TX	13 (3)	11 (2)	22 (4)	28 (5)	18 (5)	15 (3)
Surgical treatment[#]						
Breast Conserving Surgery	161 (35)	298 (55)	134 (26)	209 (34)	46 (13)	118 (25)
Mastectomy	280 (60)	228 (42)	343 (68)	362 (60)	290 (82)	330 (71)
Biopsy only[†]	21 (5)	14 (3)	29 (6)	37 (6)	17 (5)	15 (3)
SN procedures	0	280 (52)	0	300 (49)	0	55 (12)
Lymph nodes examined						
Median (range)	14 (0–40)	15 (0–40)	13 (0–40)	11 (0–35)	12 (0–38)	17 (0–47)
Lymph nodes examined[#]						
20+	81 (18)	136 (25)	232 (46)	58 (10)	40 (11)	150 (32)
15–19	123 (27)	137 (30)	142 (28)	124 (20)	77 (22)	159 (34)
10–14 nodes	191 (41)	85 (16)	51 (10)	181 (30)	158 (45)	108 (23)
5–9	43 (9)	67 (12)	45 (9)	64 (11)	51 (14)	15 (3)
3–4	0 (0)	51 (9)	2 (4)	72 (12)	2 (1)	5 (1)
1–2	1 (0.2)	51 (9)	0 (0)	75 (12)	1 (0.3)	5 (1)
0	23 (5)	13 (3)	34 (7)	34 (6)	24 (7)	21 (5)
Metastatic size[ϕ]						
No metastasis	270 (62)	285 (54)	266 (56)	246 (40)	175 (53)	207 (46)
Macrometastasis	151 (34)	191 (36)	185 (39)	268 (47)	142 (43)	216 (48)
Micrometastasis	18 (4)	51 (10)	21 (4)	59 (10)	12 (4)	26 (6)
Histological type[§]						
Ductal	384 (83)	428 (79)	420 (83)	453 (75)	283 (80)	356 (77)
Lobular	46 (10)	53 (10)	37 (7)	80 (13)	35 (10)	47 (10)
Other	28 (6)	45 (8)	38 (8)	39 (6)	30 (8)	52 (11)
Cytology only	4 (1)	14 (3)	11 (2)	36 (6)	5 (2)	8 (2)
Malignancy grade [‡1]						
I	107 (28)	142 (33)	105 (25)	117 (26)	93 (32)	71 (20)
II	177 (46)	173 (40)	189 (45)	182 (40)	109 (39)	170 (48)
III	82 (21)	105 (25)	94 (19)	137 (30)	61 (22)	102 (29)
Unknown[¶]	18 (5)	8 (2)	32 (8)	17 (4)	20 (7)	13 (3)
Estrogenreceptor status§						
negative	97 (21)	97 (17)	165 (33)	125 (21)	104 (29)	95 (20)
Positive	345 (75)	426 (79)	316 (62)	443 (73)	238 (67)	359 (78)
unknown	20 (4)	17 (3)	25 (5)	40 (6)	11 (3)	9 (2)

Percentages in parentheses. [⋆]$p > 0.05$ in all counties. [#]$p < 0.01$ in all counties.. [ϕ]$p < 0.01$ in ounty A and B. $p > 0.05$ in county C, [‡]$p < 0.05$ in county B & C, [§]$p < 0.05$ in county B, [1]ductal carcinoma only, [†]patients with either core needle biopsy or fine needle aspiration, [¶]"cytology only" are patients who had only a fine needle aspiration from the primary tumor.

Table III shows the basic data on patients in the last period. Within each county, the patients are divided into two groups depending on whether they had a sentinel lymph node dissection performed or not. The tumor size and T-stage distributions differed significantly between patients who had a SLNB and patients who did not ($p < 0.01$), with a median tumor size of 24 mm among non-SLNB patients and 16 mm in SLNB patients in county A, and 27 mm and 19 mm, respectively, in county B. In all three counties, significantly more patients had breast conserving surgery in the SLNB group than patients who did not have a sentinel lymph node biopsy performed ($p < 0.001$). If metastases were present, one-third of the SLNB patients had micrometastases. In contrast, only 6–8% had micrometastases among non SLNB patients. Also, significantly more low grade tumors (grade I) were observed the SLNB-group compared with the non-sentinel lymph node group ($p < 0.001$). There were no significant differences between the two groups regarding age at diagnosis, histological type, and ER status.

Table IV shows the main results of the study. Of the most interest is the frequency of patients with metastases which increased significantly in both county A ($p = 0.03$) and B ($p < 0.0001$). An insignificant increase ($p = 0.06$) was found in county C. The increase in patients with metastases was 7.3% (95% CI: 1.0–13.7% in county A, 13.3%, (7.3–19.3%) in county B and 6.9% (-0.1%–13.9%) in county C. The unadjusted OR was 1.34 (1.03–1.76, $p = 0.03$), 1.72 (1.33–2.21, $p < 0.0001$) and 1.33 (0.99–1.79, $p > 0.05$), respectively. The largest increase in the frequency of patients with metastases was seen in county B. Adjusting for the influence of other prognostic factors such as age, menopausal status, tumor stage, estrogen receptor status, histological type and malignancy grade, a little change in the estimates was seen. Further, an increase in the number of patients with lymph node metastases for patients with T1b, T1c and T2 tumors was observed. The difference was pronounced in the two counties where sentinel lymph node biopsy was performed. Furthermore, the increase was most marked in patients with T2 tumors in county A and B where an 11% and 14% increase in the absolute number of patients with metastases are seen. The corresponding increase in county C was only 2%.

Discussion

Up to 13% of the patients included in our study are shifted to more advanced stages. These patients previously staged as N0 will instead be staged as N1 or even N2 or N3 [9,26,27]. This will result in improved survival in all groups without any real change in overall outcome as described by Feinstein [28]. He gave this phenomenon the generic title *stage migration* or the eponym the "Will Rogers Phenomenon".

Few studies have examined the impact on whole populations after implementing SLNB [17,18]. Vanderveen et al. [18] reported an overall non-significant increase in the number of patients with lymph node metastases. This increase was found among patients with T1a and T1b tumors. In contrast to our findings, no increase among patients with T1c or T2 tumours was observed. If any of their patients were detected by mammography screening is unclear. Van der Heiden-van der Loo [17] compared with a period during implementation of SLNB and found an overall 10% increase in the number of patients with metastases during the implementation which was caused mainly by the detection of micrometastases. Our results are in accordance with this finding.

Interestingly, we found that the frequency of patients with macro metastases increased to 2 and 8% in county A and B, respectively. It is believed that SLNB will only reveal micrometastases. However, in a study by Viale et al. [12], the use of serial sectioning revealed macro metastases in a substantial number of patients whose non-sentinel lymph nodes were initially bisected and stained. Further, Weaver has discussed the consequences and dilemmas about using serial sectioning in the evaluation of sentinel lymph nodes [29]. In accordance with these papers, our results indicate that meticulous histopathological methods used to evaluate sentinel lymph nodes also reveal macro metastases.

We found that patients in the SLNB groups represented a highly selected group of patients. Ultrasonography and fine needle aspiration of suspected lymph nodes are used in the diagnostic work-up and are a possible explanation of this selection [30]. In fact, the highest frequency of patients with metastases was in the groups that did not have a sentinel lymph node procedure performed. This could explain the selection of patients to SLNB. Further, the pathological setup is now much more focused upon finding lymph node metastases. This change in diagnostic scenario and paradigm could also explain why more metastases are found in whole populations after SLNB is implemented

Studies that examined the extent of stage migration are basically cross-sectional studies. The results in these types of studies are difficult to interpret because the role of exposure and outcome are not controlled as in a prospective, clinical trial. We noticed, based on the national cancer incidence reports from the Danish Board of Health [31], that

Table III. Basic characteristics of patients from the last period.

	County A		County B		County C	
	Non-SN pts	SN pts	Non-SN pts	SN pts	Non-SN pts	SN pts
Sentinel Lymph Node procedures performed	260	280	308	300	408	55
Nodal status						
N ÷	117 (45)	168 (60)	77 (25)	170 (35)	186 (46)	21 (35)
N+	130 (50)	112 (40)	197 (64)	130 (65)	208 (51)	34 (65)
N ×	13 (5)		34 (11)		14 (3)	
Age						
Median (range)	54 (28–70)	57 (35–70)	54 (21–70)	55 (30–70)	55 (28-70)	55 (36–70)
Age						
<50 years of age	74 (28)	51 (18)	87 (28)	81 (27)	113 (28)	18 (33)
50 years of age or more	186 (72)	229 (82)	221 (72)	219 (73)	295 (72)	37 (67)
Menopausal Status						
Premenopausal	96 (37)	68 (24)	107 (35)	105 (35)	149 (37)	19 (35)
Postmenopausal	164 (63)	212 (76)	201 (65)	195 (65)	260 (63)	36 (65)
Tumor size*						
Median (range)	24 (1-150)	16 (3-45)	27 (1-100)	19 (1–75)	23 (1–120)	21 (9–40)
T-stage§						
T1						
T1mic	4 (2)	0	1 (0.3)	1 (0)	4 (1)	0
T1a	11 (4)	4 (1)	8 (3)	11 (3)	7 (2)	0
T1b	36 (14)	67 (24)	22 (7)	32 (11)	32 (8)	1 (2)
T1c	86 (33)	151 (54)	68 (22)	152 (51)	173 (42)	29 (53)
T2	82 (32)	58 (21)	146 (47)	98 (33)	154 (38)	25 (45)
T3	24 (9)	0	23 (7)	3 (1)	17 (4)	0
T4	6 (2)	0	15 (5)	0	6 (1)	0
TX	11 (4)	0	25 (8)	3 (1)	15 (4)	0
Surgical treatment#						
Breast Conserving Surgery	84 (33)	214 (76)	45 (15)	164 (55)	88 (22)	30 (55)
Mastectomy	162 (62)	66 (24)	226 (73)	136 (45)	305 (75)	25 (45)
Biopsy only	14 (5)	0	37 (12)	0	15 (3)	0
Lymph nodes examined						
20+	94 (36)	42 (13)	40 (13)	18 (6)	140 (34)	10 (18)
15–19	87 (33)	50 (20)	87 (28)	37 (12)	135 (33)	24 (44)
10–14	50 (19)	35 (13)	112 (36)	69 (23)	100 (25)	8 (15)
5–9	12 (5)	55 (20)	25 (8)	39 (13)	10 (2)	5 (9)
3–4	1 (0.4)	50 (18)	4 (1)	68 (23)	1 (0.4)	4 (7)
1–2	1 (0.4)	48 (17)	1 (0.3)	69 (23)	1 0.4)	4 (7)
0	15 (6)	0	39 (12)	0	21 (5)	0
Metastatic size if metastases^						
Macrometastases	120 (92)	71 (63)	185 (94)	83 (64)	190 (92)	25 (73)
Only micrometastases	10 (8)	41 (37)	12 (6)	47 (36)	17 (8)	9 (29)
Histological typeϕ						
Ductal	206 (79)	222 (79)	214 (69)	239 (80)	309 (76)	47 (86)
Lobular	16 (6)	37 (13)	40 (13)	37 (12)	43 (11)	4 (7)
Other[1]	38 (15)	21 (8)	54 (18)	24 (8)	48 (12	4 (7)
Malignancy grade‡[2]						
I	50 (24)	92 (41)	35 (16)	82 (34)	58 (19)	13 (28)
II	87 (42)	86 (38)	88 (41)	94 (39)	145 (47)	25 (53)
III	63 (31)	40 (18)	81 (34)	56 (23)	94 (30)	8 (17)
Unknown	6 (3)	3 (1)	10 (4)	7 (3)	12 (4)	1 (2)
ER status†						
negative	61 (23)	35 (13)	69 (22)	55 (18)	84 (21)	12 (22)
positive	178 (68)	242 (86)	193 (63)	242 (81)	302 (74)	43 (78)
unknown	21 (8)	3 (1)	46 (15)	3 (1)	21 (5)	0

* p =0,04 in county A p <0.001 in county B, p =0.21 in county C, §p =0.03 in county A, p <0.001 in county B, p =0.22 # p <0.001 in all three counties, ^p <0.001 in all three counties, ϕp =0.43 in county A, p =0.49 in county B, p =0.11 in county C, [1]includes patients with cytology only, [2] ductal carcinomas only, ‡p <0.001 in county A, p =0.02 in county B, p =0.15 in county C, † p =0.01 in county A, p =0.17 in county B, p =0.81 in county C.

Table IV. Primary result of the study: Included patients, risk estimates and T-stages with and without metastases stratified by county and time period.

	County A						County B						County C					
	1996–1997			2002–2003			1996–1997			2002–2003			1996–1997			2002–2003		
Included patients	462			540			506			608			353			463		
Number of SLNB	0			280			0			300			0			55		
	Node ÷ 270 (58)	Node + 169 (37)	Unknown 23 (5)	Node ÷ 285 (53)	Node+ 240 (45)	Unknown 13 (2)	Node ÷ 266 (53)	Node+ 206 (41)	Unknown 34 (7)	Node ÷ 246 (41)	Node+ 327 (54)	Unknown 34 (6)	Node ÷ 175 (50)	Node+ 154 (44)	Unknown 24 (7)	Node ÷ 207 (46)	Node+ 242 (53)	Unknown 5 (1)
Absolut Risk difference	7.3% (1–13.7%)						13.3% (7.3–19.3) p <0.0001						6.9% (−0.1–13.9%) P =0.06					
Unadjusted OR (95% CI)	1.34 (1.03–1.76)						1.72 (1.33–2.21)						1.33 (0.99–1.79)					
Adjusted OR[1] (95% CI)	1.41 (1.07–1.87)						1.70 (1.30–2.23)						1.23 (0.90–1.68)					
T-stage	Node ÷	Node +	Unknown	Node ÷	Node+	Unknown	Node ÷	Node+	Unknown	Node ÷	Node+	Unknown	Node ÷	Node+	Unknown	Node ÷	Node+	Unknown
T1mic	1 (100)	0	0	4 (100)	0	0	1 (100)	0	0	2 (100)	0	0	1 (100)	0	0	2 (50)	2 (50)	0
T1a	12 (80)	2 (13)	1	13 (87)	2 (13)	0	18 (100)	0	0	16 (84)	3 (16)	0	3 (75)	0	1	6 (86)	1 (14)	0
T1b	62 (84)	9 (12)	3	83 (81)	20 (19)	0	47 (71)	18 (27)	1	39 (72)	15 (28)	0	26 (76)	7 (21)	1 (3)	26 (79)	7 (27)	0
T1c	129(62)	77 (37)	1	132 (56)	104 (44)	0	115 (60)	74 (38)	4	111 (50)	109 (50)	0	84 (60)	53 (38)	3 (2)	99 (49)	103 (51)	0
T2	60(44)	72 (53)	3	49 (35)	91 (65)	0	72 (42)	96 (56)	2	72 (30)	172 (70)	0	56 (39)	84 (59)	2 (2)	69 (39)	110 (61)	0

[1]Adjusted for age, tumor stage, ER-status, menopausal status, histological subtypes, malignancy grade.
OR = odds-ratio ci = confidence interval.

the overall increase in early breast cancer increased by 16% during the period where SLNB was implemented. There has been a similar increase in other western European countries as well [32]. This increase might, of course, seriously influence the results.

By including a control county where SLNB was not implemented, we were able to get an impression of whether unknown factors other than implementation of SLNB could influence the results. In county C, we found an insignificant increase of 6.9% (but closely significant, 95% confidence interval: −0.1–13.9%, p = 0.06) in the number of patients with lymph node metastases. Ten percent of the patients in county C (55 patients) had a SLNB in our control county. Half of these patients were part of a validation series; the other half was treated at neighbouring hospitals in other counties, where the method was implemented. Excluding the 55 patients who had a SLNB from our analyses did not change the estimates. A very plausible explanation for the finding in county C is that the quality of axillary surgery or the pathological examinations of the lymph nodes improved from the first to the last period since the number of patients with more than 15 nodes examined increased from 33 to 66%. Increasing the number of examined lymph nodes from axillary dissections have been found to increase the degree of nodal involvement and this is a likely explanation for the finding in county C [33,34].

Patients in Denmark are treated according to programs that include different medical, adjuvant regimens. Between the two periods in this study the program for adjuvant therapy was shifted as well as the algorithm for allocating patients to adjuvant therapy [23]. We were therefore not able to examine if the increased number of patients with lymph node metastases influenced the number of patients receiving adjuvant therapy. Theoretically, some patients received adjuvant therapy only because of lymph node metastases. However, others would receive adjuvant therapy because of primary tumor characteristics. An increased survival seen after implementing SLNB will not purely be ascribed to the "Will Rogers" phenomenon.

The weakness of the study is the cross-sectional design which is a weak design when cause and effect should be established. Possibly, the observed increase in the number of breast cancer patients might influence the results. In the study done by Vanderveen, there was an average increase per year in the prevalence of patients with early breast cancer on 40% in the last period where SLNB was implemented. The studies by Van der Heiden-van der Loo and Vanderveen [17,18] did not include a control in their studies. Even though they found a steady increase in the number of patients with lymph node metastases, it can be hypothesized that a similar increase might as well have been seen in an area without implementation of SLNB.

Conclusion

We conclude from this study that SLNB probably results in up-staging of 7–15%. Other studies with a different design need to confirm the findings.

Acknowledgements

This work was supported by a grant from the Danish Cancer Society

References

[1] Jatoi I, Hilsenbeck SG, Clark GM, Osborne CK. Significance of axillary lymph node metastasis in primary breast cancer. J Clin Oncol 1999;17:2334–40.

[2] Lauridsen MC, Garne JP, Sorensen FB, Melsen F, Lernevall A, Christiansen P, et al. Sentinel lymph node biopsy in breast cancer–experience with the combined use of dye and radioactive tracer at Aarhus University Hospital. Acta Oncol 2004;43:20–26.

[3] Miltenburg DM, Miller C, Karamlou TB, Brunicardi FC. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res 1999;84:138–42.

[4] Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A Randomized Comparison of Sentinel-Node Biopsy with Routine Axillary Dissection in Breast Cancer. N Engl J Med 2003;349:546–53.

[5] Swenson KK, Mahipal A, Nissen MJ, Tuttle TM, Heaton K, Lally RM, et al. Axillary disease recurrence after sentinel lymph node dissection for breast carcinoma. Cancer 2005; 104:1834–9.

[6] Palesty JA, Foster JM, Hurd TC, Watroba N, Rezaishiraz H, Edge SB. Axillary recurrence in women with a negative sentinel lymph node and no axillary dissection in breast cancer. J Surg Oncol 2006;93:129–32.

[7] Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 1995;222:394–9.

[8] Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: A metaanalysis. Cancer 2006;106:4–16.

[9] Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20:3628–36.

[10] Kuijt GP, Voogd AC, van de Poll-Franse LV, Scheijmans LJ, van Beek MW, Roumen RM. The prognostic significance of axillary lymph-node micrometastases in breast cancer patients. Eur J Surg Oncol 2005;31:500–5.

[11] Viale G, Maiorano E, Mazzarol G, Zurrida S, Galimberti V, Luini, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. Cancer 2001;92:1378–84.

[12] Viale G, Maiorano E, Pruneri G, Mastropasqua MG, Valentini S, Galimberti V, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. Ann Surg 2005;241:319–25.

[13] Galimberti V. International Breast Cancer Study Group Trial of Sentinel Node Biopsy. J Clin Oncol 2006;24:210–1.
[14] Koscielny S, Tubiana M, Le MG, Valleron AJ, Mouriesse H, Contesso G, et al. Breast cancer: relationship between the size of the primary tumour and the probability of metastatic dissemination. Br J Cancer 1984;49:709–15.
[15] Jensen AR. A comparative population based study on breast cancer patients in Denmark and Sweden–Aspects of early diagnosis, axillary surgery and registration. 2002. Faculty of Health Sciences, University of Aarhus.
[16] Jensen AR, Garne JP, Storm HH, Engholm G, Moller T, Overgaard J. Does stage at diagnosis explain the difference in survival after breast cancer in Denmark and Sweden? Acta Oncol 2004;43:719–26.
[17] van der Heiden-van der Loo, Bezemer PD, Hennipman A, Siesling S, van Diest PJ, Bongers V, et al. Introduction of sentinel node biopsy and stage migration of breast cancer. Eur J Surg Oncol 2006;32:710–14.
[18] Vanderveen KA, Schneider PD, Khatri VP, Goodnight JE, Bold RJ. Upstaging and Improved Survival of Early Breast Cancer Patients after Implementation of Sentinel Node Biopsy for Axillary Staging. Ann Surg Oncol 2006.
[19] Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. Eur J Cancer Prev 2002;11:359–64.
[20] Jensen AR, Storm HH, Moller S, Overgaard J. Validity and representativity in the Danish Breast Cancer Cooperative Group–a study on protocol allocation and data validity from one county to a multi-centre database. Acta Oncol 2003;42: 179–85.
[21] Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 2000;11:669–74.
[22] Key Indicators. Statistics Denmark www.dst.dk. 2006.
[23] DBCG. Guidelines from the Danish Breast Cancer Cooperative Group. www.dbcg.dk. 2006.
[24] Flemming ID, Cooper JS, Henson DE, Hutter RV, Kennedy BJ, Murphy GP, et al. "AJJC Cancer Staging Manual." Lippincott - Raven, 1997.
[25] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19:403–10.
[26] Galimberti V, Veronesi P, Arnone P, De CC, Renne G, Intrntra M, et al. Stage migration after biopsy of internal mammary chain lymph nodes in breast cancer patients. Ann Surg Oncol 2002;9:924–8.
[27] Tjan-Heijnen VC, Buit P, de Widt-Evert LM, Ruers TJ, Beex LV. Micro-metastases in axillary lymph nodes: an increasing classification and treatment dilemma in breast cancer due to the introduction of the sentinel lymph node procedure. Breast Cancer Res Treat 2001;70:81–8.
[28] Feinstein AR, Sosin DA, Wells CK. The Will Rogers Phenomenon: Improved technologic diagnosis and stage migration as a source of nontherapeutic improvement in cancer prognosis. Transactions of the Association of American Physicians 1984;97:19–24.
[29] Weaver DL. Pathological evaluation of sentinel lymph nodes in breast cancer: a practical academic perspective from America. Histopathology 2005;46:702–6.
[30] van Rijk MC, Deurloo EE, Nieweg OE, Gilhuijs KG, Petersen JL, Rutgers EJ, et al. Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. Ann Surg Oncol 2006;13:31–5.
[31] Cancer incidence in Denmark 2001. National Board of Health 2006; Copenhagen.
[32] Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Time trends of breast cancer survival in Europe in relation to incidence and mortality. Int J Cancer 2006;119:2417–22.
[33] Saha S, Farrar WB, Young DC, Ferrara JJ, Burak WE. Variation in axillary node dissection influences the degree of nodal involvement in breast cancer patients. J Surg Oncol 2000;73:134–7.
[34] Grabau DA, Jensen MB, Blichert-Toft M, Andersen JA, Dyreborg U, Carstensen B, et al. The importance of surgery and accurate axillary staging for survival in breast cancer. European Journal of Surgical Oncology 1998;24:499–507.