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EPIDEMIOLOGY

Sentinel and non-sentinel lymph node metastases in patients with microinvasive breast cancer: a nationwide study

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Abstract

Purpose To determine the incidence and risk factors of sentinel lymph node (SN) and non-SN metastases in patients with microinvasive breast cancer (MIBC, $T1_{mic}$). This to identify MIBC patients in whom axillary staging can be safely omitted.

Methods The Danish Breast Cancer Group database was used to identify a total of 409 women with breast cancer ≤ 1 mm who underwent sentinel lymph node biopsy (SLNB) between 2002 and 2015. After validation, 233 patients were eligible for the analysis. The incidence rates of SN and non-SN metastases were determined. The associations between clinicopathological variables and a positive SN [pN1, pN1mi, or pN0(i+)] were analyzed using univariate and multivariate designs.

Results Of 233 patients with MIBC, only 9 (3.9%) had SN macrometastases. An additional 18 (7.7%) and 23 (9.9%) had SN micrometastases and isolated tumor cells (ITCs), respectively. Of patients with SN macrometastases, two (22.2%) had non-SN macrometastases. In the adjusted analysis, a positive SN was associated with younger age ($P = 0.0001$) and a positive human epidermal growth factor 2 receptor (HER2) status ($P = 0.03$).

Conclusions The low incidence of SN macrometastases < 4% suggests omission of axillary staging in MIBC patients without staging at primary surgery, especially in older (≥ 50 years) $HER2^-$ patients. Still, the relatively high proportion of patients with non-SN macrometastases indicates that axillary treatment might be considered in SN positive patients, especially in younger $HER2^+$ MIBC patients.

Keywords Early-stage breast cancer · Microinvasive breast cancer · Sentinel lymph node · Sentinel lymph node biopsy · Sentinel lymph node metastases · Axillary lymphnode metastases · Axillary management · Axillary surgery

Introduction

Microinvasive breast carcinoma (MIBC, $T1_{mic}$) is defined as one or more areas with invasive carcinoma in the breast, none of which is larger than 1 mm in diameter [1]. Internationally, it has been estimated that MIBC accounts for 1.0–3.4% of all registered female breast carcinomas [2–5]. Microinvasion is frequently detected postoperatively in patients treated for breast carcinoma in situ. With the increasing use of mammographic screening worldwide, an increasing incidence of early-stage breast cancer has been observed, including in situ carcinomas and in situ carcinomas with microinvasion [6]. According to the international treatment guidelines, MIBC falls into the group of T1 cancer subset, and it should be treated as such. This includes axillary staging via sentinel lymph node biopsy (SLNB) [7]. However, MIBC is mainly discovered unexpectedly during postoperative histopathological examination. Consequently, axillary staging in MIBC patients is often performed subsequently during a

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reoperation. The internationally reported incidence rates of sentinel lymph node (SN) metastases in patients with MIBC range from 2 to 29% [8]. Information on metastasis rates to non-SNs is sparse. The use of subsequent axillary staging in patients with a final diagnosis of MIBC is contentious. Balancing the use of SLNB and axillary lymph node (ALN) dissection (ALND) in MIBC patients is crucial to avoiding overtreatment and side effects, such as lymphedema, chronic pain, and impaired arm movement [9, 10].

The aim of this study was to determine the incidence of SN and non-SN metastases and identify the risk factors associated with SN metastases and further metastatic spreading to non-SNs among patients with MIBC. The goal was to identify subgroups of MIBC patients who benefit from a subsequent SLNB or even ALND and subgroups in which axillary surgery can be safely omitted.

Methods

Database

This nationwide register-based cohort study was conducted using data from the Danish Breast Cancer Group (DBCG) database, which is a national, population-based breast cancer registry. Since 1977, the patient, tumor, and treatment characteristics of all Danish breast cancer patients have been prospectively registered in the DBCG database [11].

Study population

Retrospectively, data from 409 women diagnosed with MIBC (size ≤ 1 mm) between 2002 and 2015, who underwent axillary staging with SLNB, were collected from the DBCG database. The data were validated using the original pathology files. Patients with unknown tumor sizes ($n = 34$), tumor sizes of > 1 mm ($n = 86$), in situ carcinoma only or no malignancy on the final pathology report ($n = 52$), and no SLNB performed ($n = 4$) were excluded from the study. After the validation, 233 patients were eligible for the analysis (Fig. 1).

Variables

The following clinical and histopathological characteristics were retrieved from the DBCG database: age at diagnosis (≤ 49 years or ≥ 50 years), in situ carcinoma size (≤ 20 mm, 21–49 mm or ≥ 50 mm), histological type (ductal, lobular, or other), grade (I, II, III, or ungradable), estrogen receptor (ER) status [positive (1–100%), negative (0%), or unknown], human epidermal growth factor 2 receptor (HER2) status (positive, normal, or unknown), lymphovascular invasion (present or absent), focality (unifocal or multifocal), and nodal status.

Positive sentinel node

Due to a low number of patients with SN macrometastases, the SNs were considered positive when macrometastases, micrometastases, or ITCs were detected when examining the risk factors for SN metastases. The American Joint Committee on Cancer criteria for pathological regional lymph nodes (pN) were used to classify the macrometastases (≥ 2.0 mm, pN1), micrometastases (> 0.2–< 2.00 mm, pN1mi), and isolated tumor cells (ITCs) [≤ 0.2 mm, < 200 tumor cells, pN0(i+)] [1]. The SN mapping was performed according to the DBCG guidelines, and was comprised by the combination of a radioactive tracer (^{99m}Tc) and blue dye (Patent Blue) [12].

Statistical analysis

The MIBC patients with positive SNs were compared to those patients without positive SNs. The associations between the clinical and histopathological characteristics and a positive SN were analyzed using univariate and multivariate designs. The variables that were significantly associated with a positive SN in the univariate analysis were included in the multivariate analysis. Due to the high number of ungradable cases, the grade was left out of the analysis. In addition, the unknown ER and HER2 cases were included in separate categories in the analyses. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and the Wald test was used to test the overall significance of each parameter. Two-tailed P values were calculated, and the level of significance was set at 5%.

The statistical analysis was conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA). This study was approved by the Danish Data Protection Agency (J.no. RH-2015-262) and the Danish Patient Safety Authority (J.no. 3-3013-1443/1/).

Results

Of the 233 MIBC patients included in this study, 9 (3.9%) had SN macrometastases. An additional 18 (7.7%) and 23 (9.9%) had SN micrometastases and ITCs, respectively. Of the 50 (21.5%) patients with a positive SN (macrometastases, micrometastases, or ITCs), 20 (40.0%) had a completion ALND (Fig. 1). Two of these patients had non-SN macrometastases, both in the group of patients with SN macrometastases [2 out of 9 patients (22.2%)].

Nearly all the patients in this study had ductal-type MIBC (87.6%). The MIBCs were detected in a setting of DCIS

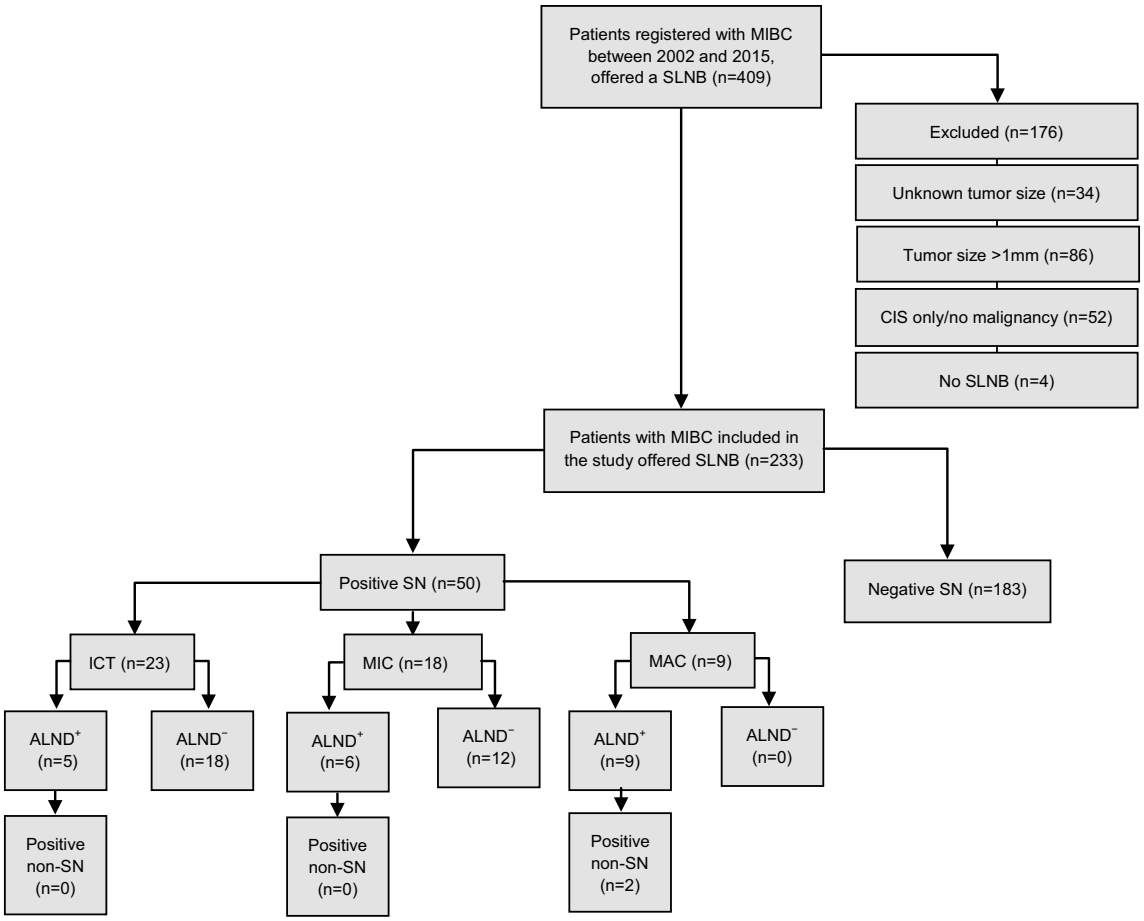

Fig. 1 Flowchart for inclusion of MIBC patients from the DBCG database. Distribution of positive SN or non-SNs (ITC, MIC, or MAC) in MIBC patients offered SLNB and ALND between 2002 and 2015. *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *MIBC* microinvasive breast cancer, *CIS* carcinoma in situ, *SN* sentinel node, *ITC* isolated tumor cells, *MIC* micrometastasis, *MAC* macrometastasis

in 225 (96.6%) of the included patients. In the remaining 8 patients, lobular carcinoma in situ (LCIS) ($n=4$, 1.7%), mixed DCIS/LCIS ($n=3$, 1.3%), and a non-invasive intracystic carcinoma ($n=1$, 0.4%) were found in the areas surrounding the microinvasive foci.

Of the patients with known ER status, 34.0% had ER negative (ER^-) MIBC, and among the women with known HER2 status, 37.6% had HER2 gene overexpression ($HER2^+$) MIBC. Table 1 summarizes the baseline clinicopathological characteristics of the 233 women with MIBC included in this study.

In the univariate analysis, a younger age (OR 4.49, 95% CI 2.17–9.25, $P<0.0001$) and an $HER2^+$ status (OR 2.81, 95% CI 1.29–6.13, $P=0.01$) were associated with an increased risk of having a positive SN. Both factors [younger age (OR 4.26, 95% CI 1.96–9.25, $P=0.0002$) and $HER2^+$ status (OR 2.62, 95% CI 1.10–6.21, $P=0.03$)] remained significantly associated with an increased risk of having a positive SN in the multivariate analysis (Table 2).

Univariate and multivariate analyses of SN macrometastasis risk factors were not possible due to a very limited number of cases. The distribution of patients with SN macrometastases versus SN negative patients (micrometastases and ITCs included) according to age and HER2 status is shown in Table 3. The proportion of SN macrometastases was higher among patients in the non-screening group (age ≤ 49) and among patients with a $HER2^+$ status.

Discussion

This study is among the largest population-based studies to date investigating the incidence and risk factors of SN and non-SN metastases in patients with MIBC. Less than 4% of the patients had SN macrometastases. More than 20% of the patients with SN macrometastases and a completion ALND had non-SN macrometastases. SN metastases were especially seen in younger patients and $HER2^+$ patients.

Table 1 The clinical and pathological characteristics of 233 Danish women with microinvasive breast cancer who underwent SLNB between 2002 and 2015

	Total	SN negative	SN positive	SN positive, subdivided in: ITC, MIC, and MAC		
	N (%)	*N* (%)	*N* (%)	ITC *N* (%)	MIC *N* (%)	MAC *N* (%)
	233	183 (78.5%)	50 (21.5%)	23 (9.9%)	18 (7.7%)	9 (3.9%)
Age (years)						
≤49	41 (17.6)	22 (53.7)	19 (46.3)	8 (19.5)	6 (14.6)	5 (12.2)
≥50	192 (82.4)	161 (83.9)	31 (16.1)	15 (7.8)	12 (6.3)	4 (2.1)
In situ size (mm)						
≤20	124 (53.2)	103 (83.1)	21 (16.9)	12 (9.7)	6 (4.8)	3 (2.4)
21–49	62 (26.6)	48 (77.4)	14 (22.6)	4 (6.5)	7 (11.3)	3 (4.8)
≥50	47 (20.2)	32 (68.1)	15 (31.9)	7 (14.9)	5 (10.6)	3 (6.4)
Type						
Ductal	204 (87.6)	160 (78.4)	44 (21.6)	19 (9.3)	16 (7.8)	9 (4.4)
Lobular	7 (3.0)	6 (85.7)	1 (14.3)	0 (0)	1 (14.3)	0 (0)
Other	22 (9.4)	17 (77.3)	5 (22.7)	4 (18.2)	1 (4.6)	0 (0)
Grade						
I	39 (41.9)	35 (89.7)	4 (10.3)	2 (5.1)	2 (5.1)	0 (0)
II	40 (43.0)	34 (85.0)	6 (15.0)	3 (7.5)	2 (5.0)	1 (2.5)
III	14 (15.1)	13 (92.9)	1 (7.1)	0 (0)	0 (0)	1 (7.1)
Ungradable	140	101 (72.1)	39 (27.9)	18 (12.9)	14 (10.0)	7 (5.0)
Estrogen receptor status						
Positive	132 (66.0)	111 (84.1)	21 (15.9)	11 (8.3)	7 (5.3)	3 (2.3)
Negative	68 (34.0)	52 (76.5)	16 (23.5)	6 (8.8)	5 (7.4)	5 (7.4)
Too small to estimate	33	20 (60.6)	13 (39.4)	6 (18.2)	6 (18.2)	1 (3.0)
HER2 status						
Positive	62 (37.6)	43 (69.4)	19 (30.7)	6 (9.7)	6 (9.7)	7 (11.3)
Normal	103 (62.4)	89 (86.4)	14 (13.6)	8 (7.8)	4 (3.9)	2 (1.9)
Unknown*	68	51 (75.0)	17 (25.0)	9 (13.2)	8 (11.8)	0 (0)
Lymphovascular invasion						
Present	7 (3.0)	4 (57.1)	3 (42.9)	2 (28.6)	0 (0)	1 (14.3)
Absent	226 (97.0)	179 (79.2)	47 (20.8)	21 (9.3)	18 (8.0)	8 (3.5)
Focality						
Unifocal	227 (97.4)	178 (78.4)	49 (21.6)	22 (9.7)	18 (7.9)	9 (4.0)
Multifocal	6 (2.6)	5 (83.3)	1 (16.7)	1 (16.7)	0 (0)	0 (0)

SLNB sentinel lymph node biopsy, *SN* sentinel lymph node, *OR* odds ratio, *ITCs* isolated tumor cells, *MIC* micrometastasis, *MAC* macrometastasis, *HER2* human epidermal growth factor receptor 2

*Not routinely assessed before 2010/too small to estimate

The risk of SN metastases in MIBC patients has been investigated in other studies. Most of them were small, including less than 200 patients [13, 14]. The clinical impact of micrometastases and ITCs in the SN has become progressively smaller and axillary staging is not routinely recommended in these patients. The previously reported SN positive rates range from 2 to 29% [8], but the incidence of SN macrometastases alone is low, ranging from 1.4 to 3.2% [8, 13, 15, 16]. This is in accordance with our study.

To our knowledge, few previous studies have investigated risk factors of SN metastases in MIBC patients. In one study, microinvasive lobular carcinomas were more likely to involve the SN when compared to microinvasive ductal carcinomas [17]. In another study, lymphovascular invasion was the only parameter found to be associated with a positive SN. In that study, SN was regarded as positive when macrometastases and micrometastases were detected [15]. Risk factors of metastases to ALNs have been examined to a greater extent. Most of these studies were small, and the results should be considered with caution. The clinicopathological characteristics, such as lymphatic invasion, the presence of comedonecrosis, multifocal DCIS, DCIS size, high-grade DCIS, palpable DCIS, and a younger age have been suggested as risk factors for ALN metastases in MIBC patients [3]. Among these

Table 2 The patient and tumor characteristics and their associations with positive SN in 233 Danish women with microinvasive breast cancer who underwent SLNB between 2002 and 2015

	Total	SN negative	SN positive*	Univariate analysis	*P* value	Multivariate analysis	*P* value[a]
	N	*N* (%)	*N* (%)	OR (95% CI)		OR (95% CI)	
	233	183 (78.5%)	50 (21.5%)				
Age (years)							
≤ 49	41	22 (53.7)	19 (46.3)	4.49 (2.17–9.25)	< 0.0001	4.26 (1.96–9.25)	0.0002
≥ 50	192	161 (83.9)	31 (16.2)	1.00		1.00	
In situ size (mm)							
≤ 20	124	103 (83.1)	21 (16.9)	1.00	0.11		
21–49	62	48 (77.4)	14 (22.6)	1.43 (0.67–3.05)			
≥ 50	47	32 (68.1)	15 (31.9)	2.30 (1.06–4.98)			
Type							
Ductal	204	160 (78.4)	44 (21.6)	1.00	0.90		
Lobular	7	6 (85.7)	1 (14.3)	0.61 (0.07–5.17)			
Other	22	17 (77.3)	5 (22.7)	1.07 (0.37–3.06)			
ER status							
Positive	132	111 (84.1)	21 (15.9)	1.00		1.00	
Negative	68	52 (76.5)	16 (23.5)	1.63 (0.79–3.37)	0.19	0.95 (0.42–2.16)	0.90
Too small to estimate	33	20 (60.6)	13 (39.4)	3.44 (1.48–7.96)	0.004	2.63 (0.89–7.79)	0.08
HER2 status							
Positive	62	43 (69.4)	19 (30.6)	2.81 (1.29–6.13)	0.01	2.62 (1.10–6.21)	0.03
Normal	103	89 (86.4)	14 (13.6)	1.00		1.00	
Unknown**	68	51 (75.0)	17 (25.0)	2.12 (0.97–4.65)	0.06	1.52 (0.56–4.14)	0.41

SN sentinel lymph node, *SLNB* sentinel lymph node biopsy, *OR* odds ratio, *CI* confidence interval, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2

[a]Adjusted for age, estrogen receptor, and HER2 status

*Positive SN: isolated tumor cells, micrometastasis, and macrometastasis

**Not routinely assessed before 2010/too small to estimate

Table 3 Distribution of SN negative MIBC patients versus MIBC patients with SN macrometastases according to age and HER2 status

	Total	SN negative[a]	SN macrometastases
	N (%)	*N* (%)	*N* (%)
	233	224 (96.1)	9 (3.9)
Age (years)			
≤ 49	41 (17.6)	36 (87.8)	5 (12.5)
≥ 50	192 (82.4)	188 (97.9)	4 (2.1)
HER2 status			
Positive	62 (37.6)	55 (88.7)	7 (11.3)
Normal	103 (62.4)	101 (98.1)	2 (1.9)
Unknown*	68	68 (100)	0 (0)

SN sentinel lymph node, *MIBC* microinvasive breast cancer, *HER2* human epidermal growth factor receptor 2

[a]Micrometastases and isolated tumor cells included

*Not routinely assessed before 2010/too small to estimate

characteristics, we were only able to confirm a younger age as a significant risk factor for SN metastases.

The association between ALN metastases and the ER and HER2 status has been sparsely investigated, and the results are conflicting [15, 18]. One study found that an ER^- status was predictive for ALN metastases in MIBC patients, while another study found the opposite association [3, 19]. None of these studies found a significant association between the HER2 status and ALN metastases. We did not find a significant association between the ER status and SN metastases in our study, but we demonstrated an increased risk of a positive SN in $HER2^+$ patients.

Only 40% of patients with SN metastases had a completion ALND in our study. According to the Danish guidelines, only SN macrometastases should lead to completion ALND [12]. Until 2012, ALND was still recommended in patients with micrometastases or ITCs in the SN. From 2012 until recently, ALND has been recommended in patients with ITCs or / micrometastases in ≥ 3 SNs. Despite these recommendations, completion ALND was

only performed in 11 out of the 41 patients with ITCs/micrometastases during the study period.

In the group of patients with SN macrometastases who underwent ALND, we identified non-SN macrometastases in more than 20% of patients. Reported rates of non-SN macrometastases in MIBC patients with SN macrometastases are scarce and differ in literature. In patients with SN macrometastases, Orzalesi et al. [4] demonstrated non-SN macrometastases in one out of five (20%), Pimiento et al. [18] in two out of four (50%), and Zavagno et al. [20] in three out of four (75%) patients. This indicates that MIBC patients with SN macrometastases may need axillary treatment, either ALND or axillary radiotherapy [21]. Still, the numbers are small, and conclusions should be taken with caution.

In our study, 34% of the patients with known ER status were ER^-, and 38% of the patients with known HER2 status were $HER2^+$. Similar or higher rates [ER^- (33–57%), $HER2^+$ (41–57%)] have been described earlier [3, 5, 17, 22]. Paradoxically, nationally reported rates of ER^- and $HER2^+$ status in the patients with primary invasive breast cancer are considerably lower [ER^- (13%), $HER2^+$ (14%)] [23]. The paradox is well known and has been described before [24]. MIBC is considered to represent an interim stage in the progression from in situ carcinoma to invasive carcinoma [25]. For HER2, it has been suggested that the expression might decrease during the progression [26]. Another study suggests that invasive carcinoma might develop from DCIS with a low HER2 expression [24]. The underlying mechanisms for this paradox are yet to be explored.

The ductal MIBC rate found in our study was close to 88%, while the lobular MIBC rate was 3%. These findings are similar to the earlier reported rates of ductal (87–95%) and lobular (4–6%) MIBC [5, 14, 27], but they vary from the nationally reported rates of invasive ductal (80%) and invasive lobular (12%) carcinomas [23]. Further examinations are needed to verify and explain this observation.

This study has some potential limitations. Although it is among the largest studies on the subject to date [14, 28], the relatively low number of MIBC patients is a potential bias to the identification of the clinicopathological characteristics associated with the risk of a positive SN risk.

The retrospective design of our study holds a risk of misclassification and missing data. A large proportion of the patients had missing ER and HER2 status, because assessment was not always technically possible due to the paucity of invasive tissue. Furthermore, the HER2 assessment was first introduced partially in 2005 and nationally for all Danish breast cancer patients in 2010 [11]. More than 50% of the study population had missing HER2 status between 2002 and 2008, while only 19% had missing HER2 values between 2009 and 2015. The proportion of missing HER2 status was higher among older patients (31%) compared to younger patients (22%). However, the proportion of missing HER2 status was also higher among patients with high-grade MIBC, lymphovascular invasion, and ER^- status. This refutes the potential bias associated with selective HER2 testing in patients with more aggressive disease.

Conclusion

This study demonstrates a low incidence of SN macrometastases (< 4%) in patients with MIBC. The odds of SN metastases were almost a threefold higher in patients with a $HER2^+$ status and nearly a fivefold higher in patients under the age of 50. If SN macrometastases are detected, a considerable proportion (22%) has further metastatic spread to non-SN and might need axillary treatment. However, to avoid overtreatment, we advise against the routine use of axillary staging in MIBC patients above 50 years of age with a $HER2^-$ status. Thus, axillary staging should be confined to younger $HER2^+$ MIBC patients without staging at primary surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The register-based study was approved by the Data Protection Agency (J. No. RH-2015-262) and the Danish Patient Safety Authority (J. No. 3-3013-1443/1/). Approvals from Ethical Committees are not needed for registry-based research in Denmark.

Informed consent The Danish Breast Cancer Group administering the Danish Breast Cancer Database is approved by the National Health Data Authorities (J. No. 14/915974.). The Central Denmark Region holds permission to collect, store, and process data in the Danish Breast Cancer Database on all persons diagnosed with cancer in Denmark without obtaining individual consent (J. No. KPU-2001-04-2001-54-0277). In Denmark, informed consent is not required for register-based research that does not involve contact with study participants or biological samples.

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