

ORIGINAL ARTICLE



Validity of Danish Breast Cancer Group (DBCG) registry data used in the predictors of breast cancer recurrence (*ProBeCaRe*) premenopausal breast cancer cohort study

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ABSTRACT

Background: Validation studies of the Danish Breast Cancer Group (DBCG) registry show good agreement with medical records for adjuvant treatment data, but inconsistent recurrence information. No studies have validated changes in menopausal status or endocrine therapy during follow-up. In a longitudinal study, we validated DBCG data using medical records as the gold standard.

Material and methods: From a cohort of 5959 premenopausal women diagnosed during 2002–2010 with stage I–III breast cancer, we selected 151 patients – 77 estrogen-receptor-positive and 74 estrogen-receptor-negative – from three hospitals. We assessed the validity of DBCG registry data on patient, tumor, and treatment factors, and follow-up information on menopausal transition, changes in endocrine therapy, and recurrence. We computed positive predictive values (PPVs) with 95% confidence intervals (95%CI).

Results: Agreement was near perfect for tumor size, lymph node involvement, receptor status, surgery type, and receipt of radiotherapy, chemotherapy, or tamoxifen treatment. The PPV for a change in endocrine therapy in the DBCG was 96% (95%CI = 83, 100). The PPV for menopausal transition was 61% (95%CI = 42, 77). The PPV for DBCG-recorded recurrence was 100%. However, of 19 patients who had a recurrence documented in their medical record, 13 had the recurrence registered in DBCG.

Conclusions: DBCG data are valid for most epidemiological studies of breast cancer treatment. Data on menopausal transition may be less valid, though this interpretation depends on the suitability of medical records for making this assessment. Although recurrence is missing for some, this would not bias most ratio measures of association.

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Introduction

Prospectively collected registry data are valuable for epidemiological research, as they reduce study costs. However, since the quality of such research depends on the robustness of the source registry data, it is essential to assess their validity [1].

The Danish Breast Cancer Group (DBCG) registry was established in 1975 to standardize treatment, facilitate clinical trials, and monitor outcomes among Danish breast cancer patients [2]. Ongoing patient registration began in 1977. Between 1977 and 2005, over 90% of Danish women diagnosed with breast cancer have been reported to the DBCG registry [2,3]. Since 2006, all patients with a record of invasive breast tumors in the Danish National Pathology Registry have

been registered in the DBCG [4]. About one-third of registered patients are enrolled in clinical trials [3]. Prespecified data on tumor, treatment, and patient characteristics are collected, registered, and tracked according to standardized protocols, whether or not a patient participates in a clinical trial [3]. Thus, clinical and epidemiologic research using DBCG data benefits from being population-based and having the data quality of a clinical trial.

A study comparing DBCG registry data (1983–1989) with a complete population-based oncology department database showed high quality of clinical data and complete registration for patients aged 18–69 years, but incomplete registration of patients aged over 70 years with advanced cancer stage or lower life expectancy [5]. The validity of registry data also has been assessed using medical records and the

Danish National Patient Registry (DNPR) as gold standards [2,6]. Data were concordant on adjuvant treatment, but less accurate on first event at follow-up (local, regional, or distant recurrence; second primary cancer; contralateral cancer). A validation study comparing registry data with hospital discharge records for low-risk node-negative patients diagnosed 1989–2001, found underreporting of recurrence and second primary cancers in the registry, due largely to early discontinuation of follow-up [6].

The ongoing *Predictors of Breast Cancer Recurrence (ProBeCaRe)* longitudinal cohort study, based on DBCG registry data, is investigating molecular and other predictors of recurrence in premenopausal women. Here, we validate key variables (menopausal transition, changes in endocrine therapy, and breast cancer recurrence) in *ProBeCaRe*, using medical records as the gold standard. No previous validation study has focused on premenopausal women or validated changes in menopausal status and changes in endocrine therapy during follow-up.

Methods

The *ProBeCaRe* study cohort includes all premenopausal Danish women diagnosed with incident non-metastatic breast cancer in Denmark during 2002–2010, whose diagnosis was reported to the DBCG registry. Eligible patients were divided into two groups: (1) those with estrogen-receptor-positive tumors who received tamoxifen therapy (ER+/tamoxifen), and (2) those with estrogen-receptor-negative tumors who did not receive endocrine therapy (ER-/no tamoxifen). All others were excluded. Current follow-up in the cohort is through 1 July 2014.

Patients in the DBCG registry receive follow-up examinations twice yearly for the first 5 years after diagnosis and annually for the subsequent 5 years. The examinations involve clinical assessment for recurrence, and imaging studies or other diagnostic work-up if recurrence is suspected. Patients diagnosed with recurrence between follow-up examinations also are reported to the registry. We retrieved information from the registry on patient age, menopausal status at diagnosis, histologic tumor type and grade, lymph node status, tumor ER status, progesterone receptor status, human epidermal growth factor receptor-2 status, type of primary surgery (mastectomy or breast-conserving surgery), receipt of chemotherapy, radiotherapy, or endocrine treatment, change in menopausal status and endocrine therapy during follow-up, date and site of any recurrence, and date of death.

The Danish civil personal registration number, a unique personal identifier assigned to each Danish citizen at birth or upon immigration, is used in all Danish registries [7]. We used it to link data in the DBCG registry with data in other Danish registries, including the DNPR. The DNPR has recorded all non-psychiatric hospital admissions since 1977 [8] and hospital outpatient and emergency department contacts since 1995. We retrieved information from the DNPR on comorbid disease at time of breast cancer diagnosis and summarized comorbidity using the Charlson Comorbidity

Index scores, classified as 0 (no comorbidity), 1 (mild comorbidity), 2 (moderate comorbidity), and 3+ (severe comorbidity) [9].

Study population

We restricted this validation study to patients included in the *ProBeCaRe* premenopausal study cohort who were diagnosed at Aarhus, Aalborg, and Odense University Hospitals. These hospitals have contributed 356, 313, and 340 patients, respectively, to the *ProBeCaRe* study population. For each hospital, we stratified patients by diagnostic period (2002–2006, 2007–2011), ER/tamoxifen status, and stage (I, II, III), yielding 12 strata in each hospital. We assigned random numbers to each patient within each of the 36 strata, and each patient was ranked within her stratum using this number.

Medical record review

We completed a medical record review for the first five patients ranked within each stratum. If the first five reviews could not be completed in a given stratum (e.g., because of the unavailability of medical records), we selected the next ranked patient until five reviews within the stratum had been completed or available patients within the stratum were depleted.

Medical records were reviewed by one of two project nurses who were blinded to patient selection criteria. They used a standardized medical abstract form and accompanying codebook to guide the review (see Supplementary Online Content, which also shows the validated variables). We adapted the abstract form and codebook from similar research tools used in earlier studies of breast cancer patients [10–12].

In the medical record review, a new tumor in the contralateral breast was considered a second primary cancer. The DBCG registry's definition of breast cancer recurrence includes any local, regional or distant recurrence, or contralateral breast cancer, and registry records allowed us to distinguish between contralateral breast cancer and other types of recurrence.

Statistical analyses

We calculated the frequency and proportion of patients in the *ProBeCaRe* study cohort and in the validation study subset, within categories of the analytic variables. We assumed that the medical record contained perfectly classified (i.e., gold standard) information for each analytic variable. For each variable, we prepared a contingency table to compare the registry data with the medical record data. We calculated the percent agreement as the percentage of observations in the registry that were concordant with the medical record, and calculated Cohen's kappa statistic [13]. We calculated the positive predictive value (PPV) as the number of patients with a particular characteristic confirmed by the medical record divided by the total number of patients with that

Table 1. Characteristics of the *ProBeCaRe* breast cancer cohort.

Characteristics	ProBeCaRe cohort		Validation subcohort	
	N = 5959	%	N = 151	%
Age at diagnosis (years)				
<35	404	6.8	18	12
35	93	1.6	3	2.0
35–49	623	11	13	8.6
40–44	1444	24	47	31
45–49	2053	35	51	33
50+	1342	23	19	13
Menopausal status at diagnosis				
Premenopausal	5959	100	151	100
Stage at diagnosis				
Stage I	1586	27	51	34
Stage II	3178	53	51	34
Stage III	1163	20	49	34
Unknown stage	32	0.5	0	0
Tumor size				
<2 cm	3323	56	83	55
2 to <5 cm	2412	42	53	35
>5 cm	200	3.4	15	9.9
Unknown	24	0.4	0	0
Lymph node count				
0	2399	40	65	43
1	1386	23	23	15
2	699	12	13	8.6
3+	1458	25	50	33
Unknown	17	0.3	0	0
Lymph node evaluation				
No	11	0.2	0	0
Yes	5948	100	151	100
Histologic grade	23	0.4	1	0.7
Unsuitable for evaluation				
I	976	16	16	11
II	2607	44	49	33
III	1834	31	68	45
Unknown	519	8.7	17	11
Type of primary surgery				
Mastectomy	2660	45	97	64
Breast-conserving surgery	3299	55	54	36
Estrogen receptor status				
ER–	1359	23	74	49
ER+	4600	77	77	51
Progesterone receptor status				
Progesterone receptor –	1504	25	52	34
Progesterone receptor+	2699	45	30	20
Unknown	1756	30	69	46
HER2 ^a status				
HER2–	3579	60	76	50
HER2+	973	16	32	21
Unknown	1407	24	43	29
Intention to treat with chemotherapy				
No	158	2.7	4	2.6
Yes	5801	97	147	97
Chemotherapy				
No	546	9.2	9	6.0
Yes	5413	91	142	94
Intention to treat with tamoxifen				
No	1421	24	74	49
Yes	4538	76	77	51
Radiation therapy				
No	922	16	38	25
Yes	5037	85	113	75
HER2 ^a targeted therapy				
No	3579	60	76	50
Yes	973	16	32	21
Unknown	1407	24	43	29
Recurrence				
No	5347	90	137	91
Yes	612	10	14	9.3
Another malignancy				
No	5885	99	149	99
Yes	74	1.2	2	1.3
Deceased at end of follow-up				

(continued)

Table 1. Continued

Characteristics	ProBeCaRe cohort		Validation subcohort	
	N = 5959	%	N = 151	%
No	5354	90	135	89
Yes	605	10	16	11
Charlson Comorbidity Score (Baseline)				
0	5459	92	123	82
1	306	5.1	8	5.3
2	91	1.5	5	3.3
3+	103	1.7	15	9.9

Premenopausal women diagnosed with stage I, II, or III breast cancer in Denmark during 2002–2011 ($n = 5959$ patients), registered in the DBCG registry, with follow-up through July 2013] and a subcohort of patients diagnosed at Aarhus, Aalborg, and Odense University Hospitals selected for medical record review ($n = 151$ patients).

^aHuman epidermal growth factor receptor-2.

characteristic in the DBCG registry. We calculated the completeness of DBCG registration of variables listed in Table 2 as the number of (for example) recurrences registered in the DBCG and listed in the medical records divided by the total number of recurrences documented in the medical records. We examined the clinical, demographic and treatment characteristics of patients with concordant and discordant recurrence data. We considered the last day of recorded follow-up in the DBCG registry as the date of recurrence, date of death, date when a patient went ‘off protocol’ (i.e., dropped out of treatment or follow-up program), or 10 years after her primary diagnosis.

To validate variables that may have changed during follow-up (changes in menopausal status and endocrine therapy), we allowed a 4-month agreement window between dates in the DBCG registry and the medical record. In sensitivity analyses, we changed this window from 1 month to up to 6 months. All analyses were conducted using SAS version 9.2, Research Triangle, NC, USA.

Results

This study was approved by the DBCG, the Danish Data Protection Agency (J.nr. 2012-41-1170) and the Ethical Committee of the Central Denmark Region (J.nr. 1-10-72-22-13). A total of 151 patients were included in this validation study. From the initial list of 180 eligible patients, 28 (16%) medical records were not available in the medical journal archives. Descriptive characteristics of the parent *ProBeCaRe* study cohort and the validation study subset are presented in Table 1. Overall, the characteristics of the validation study subset were similar to those of the total cohort. However, there were some differences – patients in the validation subcohort were younger (a higher proportion aged below 35 years, and a lower proportion aged 50+ years); a higher proportion of the validation subcohort had stage III disease at diagnosis; and a higher proportion of patients in the validation subcohort received mastectomy rather than breast conserving surgery compared with the entire *ProBeCaRe* study cohort. Patients in the validation subset were more likely to have some comorbid disease at diagnosis than patients in the entire *ProBeCaRe* study (18% vs. 8%). Due to

Table 2. Comparison of DBCG registry records with medical records as a gold standard.

DBCG Registry		Medical record	
Menopausal transition (<i>n</i> = 151 patients)		Menopausal transition	
Frequency	No	Yes	Total
No	78	18	96
Yes	11	17	28
Total	89	35	124
PPV = 61% (42%, 77%)			
Kappa = 0.39 (95%CI = 0.20, 0.57)			
Completeness = 0.49 (95%CI = 0.33, 0.65)			
Registry		Medical record	
Change in endocrine therapy among ER + patients only (<i>n</i> = 77 patients)		Change in endocrine therapy	
Frequency	No	Yes	Total
No change from tamoxifen	48	3	51
Change from tamoxifen to aromatase inhibitor	1	25	26
Total	49	28	77
PPV = 96% (83%, 100%)			
Kappa = 0.89 (95%CI = -0.78, 0.99)			
Completeness = 0.89 (95%CI = 0.74, 0.97)			
Registry		Medical record	
Recurrence (<i>n</i> = 151 patients)		Recurrence	
Frequency	No recurrence	Yes recurrence	Total
No recurrence	131	6	137
Yes recurrence	0	14	14
Total	131	20	151
PPV = 100%			
Kappa = 0.80 (95%CI = 0.65, 0.95)			
Completeness = 0.70 (95%CI = 0.48, 0.86)			

PPVs of recurrence, menopausal transition, and changes in endocrine therapy during follow-up among premenopausal breast cancer patients diagnosed during 2002–2011 with stage I, II, or III breast cancer at Aarhus, Aalborg, and Odense University Hospitals (*n* = 151 patients).

the sampling criteria for the validation subset, ER status, diagnostic period, and stage characteristics were more uniformly distributed in the validation subset than in the cohort as a whole.

We observed high agreement for baseline characteristics—menopausal status at diagnosis, tumor size, lymph node status, receptor status, surgery type (mastectomy versus breast conserving surgery), and the receipt of cancer-directed treatment, including chemotherapy, radiotherapy, and tamoxifen (Supplementary Online Content Table 1). Most patients (92%) eligible for endocrine therapy began tamoxifen within 12 months of primary breast cancer surgery.

Overall, the PPV for menopausal transition in the DBCG registry was 61% [95% confidence intervals (95%CI) = 42, 77], kappa = 0.39 (95%CI = 0.20, 0.57). In total, 35 patients had menopausal transition recorded in the medical record, 17 had this registered in DBCG. Eleven patients had menopausal transition registered in DBCG without evidence of this in the medical record. The completeness of registration of menopausal transition in the DBCG was 49% (95%CI = 33%, 65%).

Among patients with ER + breast cancer (*n* = 77), 28 patients had a documented change from tamoxifen to an aromatase inhibitor in the medical record; in 25 of these patients, this information was recorded in the DBCG registry. The PPV for change in endocrine therapy in the registry was 96% (95%CI = 83, 100), kappa = 0.89, 95%CI = 0.78, 0.99). The completeness of recording of change in endocrine therapy in DBCG was 89% (95%CI = 74%, 97%).

The date of recurrence in the DBCG registry compared with the medical record showed 92% agreement when a 4-month window was used. Sensitivity analyses showed 69%

agreement for a 1-month window, 77% agreement for 2- and 3-month windows, and 92% agreement for 4-, 5-, and 6-month windows. The PPV for breast cancer recurrence in the DBCG registry was 100%, kappa = 0.80, 95%CI = 0.65, 0.95). However, we note that out of 19 patients with a recurrence documented in their medical records, 13 had this recurrence documented in the DBCG registry. The completeness of recurrence registered in the DBCG was 70% (95%CI = 48%, 86%).

Discussion

Our study shows strong agreement between DBCG registry data and medical records for patient, tumor, and treatment variables recorded at diagnosis, findings that are consistent with previous validation studies [3,5,14]. In addition, the longitudinal design of the parent ProBeCaRe study allowed evaluation of changes in menopausal status and endocrine therapy during follow-up [15]. Our findings suggest that changes in endocrine therapy as documented in the DBCG registry are valid.

However, DBCG registry data on menopausal transition appears to be less valid and medical records, seem to be a poor gold standard for this variable. In the absence of a confirmatory blood test or oophorectomy, it may be difficult to distinguish menopausal transition from the transient side effects of chemotherapy or tamoxifen [16]. Tamoxifen- or chemotherapy-induced transient amenorrhea can preclude the assessment of ovarian function [17], leading to difficulty in determining the optimal time to switch from tamoxifen to aromatase inhibitors. Several medical records that we

reviewed mentioned irregular menses during chemotherapy, with menstruation resuming after treatment, or amenorrhea during tamoxifen treatment, but a premenopausal status on blood tests. Given the potentially poor validity of menopausal transition in the DBCG registry, we recommend that future studies using DBCG registry data should model menopausal status as a baseline covariate. Modeling the type of endocrine therapy recorded in the DBCG registry as a time-varying variable is more defensible.

Breast cancer recurrence is the outcome in our longitudinal *ProBeCaRe* study. Our findings suggest that a record of breast cancer recurrence may be missing in the DBCG registry for up to 30% of patients, despite these patients being within 10 years of their primary breast cancer diagnosis. We also note that these patients did not have any evidence of a withdrawal from follow-up. Previous studies validating registry data for patients diagnosed 1989–2001 with follow-up through March 2007 indicate some underreporting [5,6], due to withdrawal from follow-up of patients who developed a new primary malignancy [5] and, early termination of follow-up in patients perceived to have low recurrence risk – contrary to DBCG guidelines [6]. Underreporting of recurrence has also been observed among patients aged over 70 years at diagnosis [6]; although such patients are not included in our premenopausal cohort. The missing registration of recurrence for 30% of patients will impact estimates of the absolute risk of recurrence, so the risk difference of recurrence in *ProBeCaRe* will be downwardly biased by 30% [15,18]. However, this 30% is expected to be non-differential as we found no examples of false positive recurrences recorded in the registry. Therefore, ratio measures of association using recurrence as the outcome are likely to be unbiased [19]. This expectation of no bias arises because the non-differential sensitivity reduces the numerator and the denominator of ratio estimates of association in equal proportion, and therefore cancels, so long as there are also no false-positive recurrences. We have included the mathematical equations to illustrate this bias, and an example to illustrate the various bias scenarios in the online Supplementary Appendix 1.

Several factors should be considered when interpreting our study. We restricted this validation study to patients diagnosed at three major hospitals. The characteristics of patients diagnosed at these hospitals are representative of the entire *ProBeCaRe* study cohort, supporting the generalizability of our findings to the parent study population. Nonetheless, aside from the expected differences due to the sampling criteria for the validation subcohort, we did observe some differences in baseline characteristics of the entire *ProBeCaRe* study cohort and the validation subcohort, including the distribution of comorbid disease and age. We believe that these differences are secondary to the stratified sampling. Although our validation study included fewer patients than in previous validation studies, we performed detailed medical record review to assess data quality for patient, tumor, treatment, and follow-up characteristics, some of which have not been validated previously. Many patients included in our study may still be undergoing active treatment and follow-up, so not all medical records were available from the hospital archives. Although misclassification of

breast cancer recurrence affects the recurrence rate, it is unlikely to bias associations measured on the relative scale. The high PPVs for all variables except menopausal transition support the validity of the DBCG data.

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No potential conflict of interest was reported by the authors.

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