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SHORT COMMUNICATION

A Comparison of Criteria to Identify Inflammatory Breast Cancer Cases from Medical Records and the Surveillance, Epidemiology and End Results Data base, 2007–2009

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■ **Abstract:** Inflammatory breast cancer (IBC) is a relatively rare and extremely aggressive form of breast cancer that is diagnosed clinically. Standardization of clinical diagnoses is challenging, both nationally and internationally; moreover, IBC coding definitions used by registries have changed over time. This study aimed to compare diagnostic factors of IBC reported in a U.S. Surveillance, Epidemiology, and End Results (SEER) registry to clinical criteria found in the medical records of all invasive breast cancer cases at a single institution. We conducted a medical record review of all female invasive breast cancers (n = 915) seen at an NCI-designated comprehensive cancer center in Detroit from 2007 to 2009. IBC cases were identified based on the presence of the main clinical characteristics of the disease (erythema, edema, peau d'orange). We compared the proportion of IBC out of all breast cancers, using these clinical criteria and the standard SEER IBC codes. In the reviewed cases, the clinical criteria identified significantly more IBC cases (n = 74, 8.1%) than the standard IBC SEER definition (n = 19, 2.1%; $p < 0.0001$). No IBC cases were identified in the cancer center records using the SEER pathologic coding, which requires the diagnosis of inflammatory carcinoma on the pathology report, a notation that is rarely made. Emphasis must be placed on the documentation of clinical and pathologic characteristics of IBC in the medical record, so that analysis of putative IBC subtypes will be possible. Our results indicate the need for a consensus on the definition of IBC to be utilized in future research. ■

Key Words: diagnostic criteria, inflammatory breast cancer, SEER

Inflammatory breast cancer (IBC) is the most aggressive and deadly form of breast cancer (1), with nearly twice the risk of death as compared to locally advanced breast cancer (2,3). Despite its name, IBC is not observed to be associated with a profuse cellular inflammatory response at the time of diagnosis. In fact, the characteristic redness and swelling of the breast in IBC that in many cases may resemble inflammation are due to lymphatic channels in the dermis being clogged by tumor cells, a process termed dermal lymphatic invasion (DLI) by tumor emboli (4,5). Currently, a clinical IBC diagnosis is made when the history and physical examination document the rapid onset (weeks to months) of the characteristic skin features and a biopsy of the breast shows carcinoma (6–8). However, the main clinical symptoms (erythema, edema, and peau d'orange) and pathologic characteristics (DLI) of IBC are not uniformly observed among patients with IBC. Therefore, in practice, by using a combination of clinical and pathologic criteria, IBC cases can be identified in different ways

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for different patients (9). The use of differing criteria for IBC diagnosis—and the relative rarity of the disease—has hampered epidemiologic research on IBC, making it difficult to obtain adequate representative samples of IBC cases and to compare results across studies.

The documentation of IBC in the Surveillance, Epidemiology, and End Results (SEER) registry data has varied over time. Historically, IBC cases were assigned according to the pathologic codes (International Classification of Diseases for Oncology [ICD-O code 8530]) (10) specifically reserved for IBC with DLI. However, a rule implemented in 2007 states that the ICD-O histology code 8530 for IBC should only be used "when the final diagnosis of the pathology report specifically states inflammatory carcinoma" (11). Beginning in 2004, the American Joint Cancer Committee (AJCC) Stage "T4d" variable has been designated by SEER to describe IBC as "a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying mass involving the majority of the breast" (12). More recently, IBC cases have been identified in the SEER registry using either the AJCC T4d variable or the extent of disease (EOD) variables, which record a combined clinical and pathologic assessment of disease abstracted from the pathology report (9). A detailed report of the EOD codes 600, 710, 715, 720, 725, 730, 750, and 780 for assigning possible IBC cases are described in a SEER report of 2009 (13). A standard IBC definition of either AJCC T4d or EOD 710-730 or pathologic ICD-O 8530 has recently been advocated to identify IBC cases from the SEER registries (14,15).

The ensuing complexities of registry coding of IBC, which stems from IBC's unique and unusual presentation, makes comparing incidence of IBC between countries challenging. Furthermore, there does appear to be a heterogeneous global distribution in IBC occurrence. Based on SEER data, between 1% and 6% of all patients with breast cancer in the United States have IBC (16–18). However, in Tunisia, up to 55% of breast cancer cases have been reported as IBC (19), while more recent estimates describe IBC in Tunisia as 5–7% of breast cancer cases (20). Using a simplified clinical IBC definition of erythema, edema, and peau d'orange as its three main clinical features: most likely IBC exhibited all three features, possible IBC cases had any two of the three signs or had peau d'orange only, and non-IBC cases had edema only, erythema only, or none of these three clinical features (7,8), a population-based study demonstrated that 11% of all breast cancers in Egypt are likely IBC, which is unequivocally higher than what is currently reported in the U.S. (21). Regional variations in IBC may reflect differences in diagnostic tools, disease definition, or true differences in occurrence due to varying levels of risk factors by region. Identical criteria for the identification of IBC cases would greatly facilitate comparative studies. The specific aim of this study was to ascertain the number of IBC cases at a single institution in Detroit, Michigan for a 3-year period (2007–2009) using clinical criteria to identify IBC cases. By applying an identical case ascertainment system as was used in Egypt to medical records in the United States, we establish a means for comparisons between the burden of IBC relative to total breast cancer in Egypt and the United States. (21,22). Furthermore, we compared the IBC cases identified by the clinical criteria to what is documented in the SEER registry to determine whether IBC is being ascertained at equivalent levels using SEER case definitions at a major comprehensive cancer hospital, which provides cases to the Detroit SEER registry.

MATERIALS AND METHODS

We conducted a medical record review of all female invasive breast cancer cases over 20 years of age seen at an NCI-designated comprehensive cancer center in Detroit, Michigan from 2007 to 2009. The center is a tertiary cancer center dedicated to oncology care and research. Patients are often referred to the tertiary facility for surgery, consultations with specialists, and for short- and long-term patient care. As is true of all tertiary care centers in the United States, it is assumed that this center's patient population experiences a greater than average complexity of disease. This site was chosen due to the large patient volume, the availability of clinical resources, including electronic medical records, catchment within a SEER registry, and existing collaborations that facilitated coordination of the medical record review. Patients were eligible for the study if they had received all or part of their breast cancer diagnosis and/or treatment at the center. We excluded one patient who was seen only for part of her diagnostic tests, 34 patients who were treated for a recurrence or persistence of disease, and 12 patients where this information was missing. These patients were excluded out of concern that adequate information

would not be documented in the medical record. The final sample for our record review comprised 915 invasive breast cancer cases.

For eligible cases, information was extracted from the records regarding clinical and pathologic characteristics of the disease at diagnosis. Age, menopausal status, weight, height, tumor molecular characteristics (estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [Her2] expression), imaging, and treatment were recorded. Tumor size measurements were extracted from clinical reports based on the size of the palpable mass when information was available. We identified IBC cases according to the documentation of the main clinical characteristics of IBC in the record; erythema (redness), edema (swelling), and peau d'orange (dimpling). We then compared differences in the number of IBC cases identified by the clinical criteria (possible and most likely IBC) with the pathologic (ICD-O 8530) and the standard SEER criteria (ICD-O 8530 or EOD 710-730 or AJCC 6th edition staging T4d). Further, to be more certain that the cases being identified by the clinical criteria were truly IBC, we calculated the number of IBC cases based on a more stringent criterion of clinical IBC as well as treatment with neo-adjuvant chemotherapy, this being a hallmark of IBC (but not exclusive to IBC).

Next, we tested whether there were statistically significant differences in the proportion of IBC cases identified using the standard SEER coding systems and the clinical criteria, using the McNemar's test. This nonparametric test accounts for the correlated nature of our sample by determining whether the marginal proportions differed between groups. Differences in characteristics between IBC and non-IBC cases, and in the presence of clinical symptoms of IBC within categories of clinical diagnosis, were examined using Chi-squared tests and Fisher's exact test for categorical data and *t*-tests for continuous variables. Further, we utilized Chi-squared tests, *t*-tests, and logistic regression models to assess tumor characteristics associated with pathologic evidence of disease (DLI). An alpha level of 0.05 was used to determine significance, and all test statistics were two-sided. An EpiInfo v3.5.3 database was used to record information from the medical records. Statistical analysis was conducted in both the EpiInfo and SAS (version 9; SAS Institute, Cary, NC) platforms. Institutional Review Board approval was obtained from Wayne State University and the University of Michigan.

RESULTS

Of the 915 breast cancer cases reviewed, the clinical diagnostic criteria identified significantly more IBC cases ($n = 74$, 8.1%) than the standard SEER definition ($n = 19$, 2.1%; $p < 0.001$; Table 1). Using the more stringent criteria to define likely IBC as cases treated with neo-adjuvant chemotherapy and documenting the clinical characteristics of disease, 5.5% of all breast cancers would be considered IBC (Table 1). The SEER pathologic criteria, which are dependent on the diagnosis of inflammatory carcinoma being explicitly stated on the pathology report (presumably due to findings of DLI), did not identify any cases of IBC (Table 1). Of the 19 IBC cases identified by the standard SEER criteria, 15 (79%) were also identified as IBC by the clinical criteria. However, only 15 (20.3%) of the 74 IBC cases identified by the clinical criteria were also identified as IBC by the standard SEER definition.

According to both the clinical and standard SEER IBC diagnostic criteria, IBC cases were likely to have a larger mean tumor size, and be Her2 positive as compared to non-IBC cases (Table 2). IBC cases were more likely to have DLI noted in the record as compared to non-IBC cases, though this difference was

Table 1. Comparison of different criteria and SEER coding for the identification of IBC cases out of 915 invasive breast cancer cases from 2007 to 2009

IBC criteria	IBC Count	% IBC
Main IBC criteria		
Clinical	74	8.1%
Standard	19	2.1%
IBC SEER coding		
AJCC T4d	19	2.1%
EOD-E 600	0	0.0%
EOD-E 710	10	1.1%
EOD-E 715	0	0.0%
EOD-E 720	0	0.0%
EOD-E 725	1	0.1%
EOD-E 730	7	0.8%
EOD-E 750	1	0.1%
EOD-E 780	0	0.0%
Histology 8530	0	0.0%
Other IBC criteria		
Clinical + Neo-adjuvant Chemo	50	5.5%
Standard + clinical criteria	15	1.6%
Standard only	4	0.4%
Pathologic only	0	0.0%

Clinical = Any two signs of erythema, edema, peau d'orange or peau d'orange alone.
Standard = ICD-O 8530 or EOD-E 710-730 or AJCC 6th edition T4d.
Clinical + Neo-adjuvant = Any two signs of erythema, edema, peau d'orange or peau d'orange alone AND received neo-adjuvant chemotherapy.
Pathologic = ICD-O 8530.

Table 2. Descriptive statistics of invasive female breast cancer cases (n = 915) from medical records diagnosed from 2007 to 2009 at a single institution

		Clinical IBC			Standard IBC		
	All (n = 915)	IBC (n = 74)	Non-IBC (n = 841)	p	IBC (n = 19)	Non-IBC (n = 896)	p
Mean age (years)	57.4	57.2	57.4	0.92	59.0	57.4	0.60
Mean tumor size (cm)	3.2	6.2	2.9	< **0.001**	8.4	3.1	< **0.001**
IBC mentioned (%)	3.4	35.1	0.6	< **0.001**	84.2	1.7	< **0.001**
Derm lymph inv (%)	1.6	4.1	1.4	0.11	15.8	1.3	< **0.001**
ER							
ER positive (%)	64.8	59.5	65.3	0.19	57.9	65.0	0.60
ER negative (%)	33.1	40.5	32.5		42.1	32.9	
Unknown (%)	2.1	0.0	2.3		0.0	2.1	
PR							
PR positive (%)	55.1	56.8	54.9	0.41	63.2	54.9	0.67
PR negative (%)	42.7	43.2	42.7		36.8	42.9	
Unknown (%)	2.2	0.0	2.4		0.0	2.2	
Her2							
Her2 positive (%)	16.9	23	16.4	**0.04**	47.4	16.3	< **0.001**
Her2 negative (%)	77.6	77	77.6		47.4	78.2	
Unknown (%)	5.5	0	6.0		5.2	5.5	
Menopausal status							
Pre-menopausal (%)	24.2	31.1	23.5	0.19	21.1	24.2	0.38
Peri-menopausal (%)	6.4	4.1	6.7		0.0	6.6	
Postmenopausal (%)	63.9	63.5	64.0		78.9	63.6	
Unknown (%)	5.5	1.4	5.8		0.0	5.6	
Anthropometrics							
Mean Weight in lbs	177.6	184.1	177.0	0.21	185.7	177.4	0.55
Mean Height in ft′in″	5′5″	5′3″	5′5″	0.68	5′3″	5′5″	0.77
Race/Ethnicity							
Caucasian (%)	34.6	27.0	35.3	0.54	15.8	35.0	0.43
African-American (%)	55.0	62.2	54.3		73.7	54.7	
Hispanic (%)	1.3	1.4	1.3		0.0	1.3	
Other (%)	8.1	9.5	8.0		10.5	8.0	
Not mentioned (%)	1.0	0.0	1.1		0.0	1.0	

Standard IBC = (ICD-O 8530 or EOD-E 710-730 or AJCC T4d), Clinical IBC = any two signs of erythema, edema, peau d'orange or peau d'orange alone.
p-values for differences between IBC and non-IBC for both criteria based on Chi-squared test (or Fisher's exact test for cell counts <5) for categorical variables and t-tests for continuous variables.
Sample size: mean age (n = 915), mean tumor size (n = 814), mean weight (n = 887), mean height (n = 880).

not statistically significant for cases defined according to the clinical criteria (Table 2).

The clinical criteria specified eight cases (0.9%) that were most likely IBC as they presented all three characteristics (erythema, edema, peau d'orange). DLI was documented for 12.5% of the "Most likely IBC," 3% of the "Possible IBC," and 1.4% of the "Not IBC" according to the clinical criteria (p = 0.03; Table 3). Cases with DLI noted in the record had larger mean tumor size, were more likely to present with erythema, edema, angiolymphatic invasion, and ulcerations, and were more likely to be ER and PR negative as compared to cases without DLI (Tables 4 and 5).

DISCUSSION

Utilizing only the clinical criteria at a comprehensive cancer center in Detroit, Michigan from 2007 to 2009, we found that 8.1% of breast cancers were IBC. These results suggest for the first time, that the incidence of IBC is likely to be significantly underestimated in the United States. It is important to keep in mind that our results are based on a hospital record review at a tertiary cancer center and not a population-based sample. Women who received care at the cancer center were more likely to have aggressive disease, with more severe prognoses and therefore would have been more readily referred to a tertiary facility; for all these reasons, this hospital-based group would exhibit higher stage at diagnosis when compared to the rest of the metropolitan Detroit area (data not shown). Thus, while we found the proportion of IBC out of all breast cancers to be higher at this comprehensive cancer center, this may not be true in a US population-based sample. Furthermore, comparing population-based incidence rates would be the preferred method to compare IBC occurrence between

Table 3. Characteristics of all breast cancer cases (n = 915) by categories of IBC clinical criteria

Signs	Most likely IBC	Possible IBC	Not IBC	p
Total number of cases (%)	8 (0.9)	66 (7.2)	841 (91.9)	–
Erythema (%)	**8 (100)**	**27 (40.9)**	**26 (3.1)**	< **0.001**
Edema (%)	**8 (100)**	**30 (45.5)**	**20 (2.4)**	< **0.001**
Peau d'orange (%)	**8 (100)**	**46 (69.7)**	**0 (0.0)**	< **0.001**
Angiolymphatic invasion (%)	**2 (25.0)**	**17 (12.5)**	**105 (25.8)**	**0.01**
Ulcerations (%)	**1 (12.5)**	**10 (15.2)**	**24 (2.9)**	< **0.001**
Palpable mass (%)	**6 (75.0)**	**64 (97.0)**	**758 (90.2)**	**0.06**
Diffuse enlargement (%)	**5 (62.5)**	**20 (30.3)**	**23 (2.7)**	< **0.001**
Bruising (%)	0 (00.0)	2 (3.0)	12 (1.4)	0.56
Warmth (%)	**0 (00.0)**	**2 (3.0)**	**0 (0.0)**	< **0.001**
Nipple retraction (%)	**2 (25.0)**	**13 (19.7)**	**46 (5.5)**	< **0.001**
Dermal lymphatic invasion (%)	**1 (12.5)**	**2 (3.0)**	**12 (1.4)**	**0.03**

p-value for difference (Chi-squared or Fisher's exact test with cell counts<5).
Most likely IBC= all three main clinical characteristics noted as present (erythema, edema, peau d'orange).
Possible IBC = any two main clinical characteristics or peau d'orange only noted as present.
Not IBC = erythema only, edema only, or no clinical characteristics noted as present.

countries; however, incidence rates could not be calculated based on our study design. Finally, our ability to apply the clinical criteria for IBC case identification is predicated on the quality of the medical records. If the quality of the medical records varies significantly between countries, we will still be limited in our ability to draw conclusions on global differences in IBC occurrence. However, hospital medical records are typically considered accurate and adequate for use in epidemiologic research of this kind, and the clinical diagnostic criteria used in this study have been successfully applied to medical records in a previous study (21). To our knowledge, this is the first study to utilize the precise IBC clinical criteria used in our previous work in Egypt to calculate the proportion of IBC out of all breast cancers at a cancer center in the United States. The study was not designed to validate the clinical criteria or advocate for the clinical definition of IBC; rather, it allowed us to use an identical system to ascertain IBC cases in global comparative analyses. There is a wide variation in the symptom presentation of IBC, and most of the clinical characteristics associated with IBC are nonspecific (23). In our study, due to this nonspecificity of the clinical characteristics of IBC, cases appearing to be locally advanced breast cancers may have been identified as IBC. Therefore, relying on a clinical diagnosis of IBC can lead to a wide variability in reporting and presents serious challenges for researchers (17).

Table 4. Characteristics of breast tumors with and without dermal lymphatic invasion (DLI)

	DLI (n = 15)	No DLI (n = 900)	p-value
Mean age (years)	58.1	57.4	0.8
Mean tumor size (cm)	3.9	1.4	**0.003**
Erythema (%)	26.7	6.3	**0.014**
Edema (%)	26.7	6.0	**0.011**
Peau d'orange (%)	6.7	6.1	0.6
Angiolymphatic invasion (%)	60.0	12.8	**<0.001**
Ulcerations (%)	33.3	3.3	**<0.001**
Palpable mass (%)	86.7	90.7	0.42
Diffuse enlargement (%)	6.7	5.2	0.56
Bruising (%)	0.0	1.6	0.80
Warmth (%)	0.0	0.2	0.97
Nipple retraction (%)	6.7	6.7	0.65
IBC mentioned (%)	26.7	3.0	**0.001**
ER			
ER positive (%)	26.7	65.4	**0.004**
ER negative (%)	73.3	32.4	
ER missing (%)	0.0	2.1	
PR			
PR positive (%)	20	55.7	**0.013**
PR negative (%)	80	42.1	
PR missing (%)	0	2.2	
Her2			
Her2 positive (%)	33.3	16.7	0.17
Her2 negative (%)	66.7	77.8	
Unknown (%)	0.0	5.6	
Menopausal status			
Premenopausal (%)	21.4	24.2	0.66
Perimenopausal (%)	14.3	6.3	
Postmenopausal (%)	57.1	64.2	
Unknown (%)	7.1	5.2	
Race/ethnicity			
Caucasian (%)	50	34.6	0.66
African-American (%)	50	55.4	
Hispanic (%)	0	1.3	
Other (%)	0	8.3	
Not mentioned (%)	0	0.3	
Anthropometrics			
Mean weight in lbs	174.0	178.6	0.74
Mean height in ft'in″	5′4″	5′5″	0.92

p-values for differences between DLI and non-DLI based on Chi-squared test (or Fisher's exact test for cell counts <5) for categorical variables and t-tests for continuous variables. Sample size: mean age (n = 915), mean tumor size (n = 814), mean weight (n = 888), mean height (n = 880).

While our review did identify 1.6% of cases with mention of DLI, no cases were coded as pathologic ICD-O 8530, probably because they did not specifically mention IBC on the pathology report. The importance of DLI in IBC diagnosis remains controversial. Some experts prefer a pathologic definition of IBC inferring that DLI is required for IBC diagnosis (24,25). There is also a suggestion that pathologic confirmation of DLI could represent EOD, with cases diagnosed earlier having less DLI (26). However, when utilizing cancer registry data, reliance on DLI for diagnosis may lead to profound underestimation of IBC incidence (27).

In our study sample, tumor characteristics differed between cases with and without DLI, suggesting

Table 5. Odds ratios for tumor characteristics associated with dermal lymphatic invasion (DLI)

	Crude odds ratio (95% CI)
Angiolymphatic invasion	10.2 (3.6, 29.3)
Ulcerations	14.5 (4.7, 45.0)
ER (negative versus positive)	5.5 (1.8, 17.6)
PR (negative versus positive)	5.3 (1.5, 18.9)
Erythema	5.4 (1.7, 17.4)
Edema	5.7 (1.8, 18.5)
Mean tumor size	1.2 (1.1, 1.3)

Sample size for angiolymphatic invasion, ulcerations, ER, PR, erythema, and edema: DLI ($n = 15$), no DLI ($n = 900$), sample size for mean tumor size: DLI ($n = 13$), no DLI ($n = 801$).

potential etiologic subtypes of IBC based on the presence of DLI. A study of prognostic factors in IBC found no prognostic value for the diagnostic selection group (clinical or pathologic definition), suggesting that either definition is justified to diagnose IBC (28). However, in a systematic review, Kim *et al.* found that the main cause of differences in treatment outcomes was the criteria used across studies to identify IBC (29). Furthermore, SEER data suggest that patients with clinical but no pathologic features of IBC have a better prognosis than those with pathologic evidence of IBC (16); in other words, the manner in which IBC is classified at the time of diagnosis has implications for treatment and prognosis. Therefore, it is imperative that pathologic evidence of disease continue to be documented explicitly in the pathology reports at diagnosis along with reference to IBC if suspected, so that potential subtypes of IBC based on the presence or absence of DLI can be further investigated.

We conclude that relying on varying systems of IBC identification to compare incidence across regions should be avoided. Inclusion of the clinical criteria in identifying IBC from medical records will increase the detection of IBC cases, which may lead to improved patient care. Given the current SEER codification rules, this study demonstrates that our ability to identify IBC through the explicit diagnosis being written on the pathology report is very close to zero. Emphasis must be placed on the documentation of clinical and pathologic characteristics of IBC in the medical record, so that analysis of putative IBC subtypes will be possible and we can further evaluate and come to a consensus on the definition of IBC to be utilized in future research. The findings of this study add to our understanding of the global variation in IBC incidence and have important implications for diagnosis, treatment, prognosis, and future research on IBC.

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CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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