Original Article

Is Survival from Infiltrating Lobular Carcinoma of the Breast Different from That of Infiltrating Ductal Carcinoma?

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abstract: Previous studies of patients with breast cancer have compared survival of invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) with contradictory results. This study examines the effect of the diagnosis of IDC or ILC in conjunction with age at diagnosis, pathologic tumor size, pathologic stage, histologic grade, and lymph node status of 307 women with IDC or ILC in 1992 in the Greater Western region of Sydney in Australia. Survival analysis was conducted using the Kaplan–Meier method. Relative risks associated with IDC or ILC and other important prognostic factors and adjusted for each other were computed using Cox proportional hazard regression. The proportion of grade I tumors was significantly higher in ILC (41%) than in IDC (16%). Conversely, the proportion of grade III tumors was only 18% in ILC as against 41% in IDC (p = 0.020). The 10-year survival of women with IDC was 69%, compared to 84% for ILC (p = 0.073). However, the 15 percentile point difference between overall survival of IDC and ILC was markedly reduced after adjustment for nodal status. The difference was eight percentile points for node-negative patients (p = 0.361) and five percentile points for node-positive patients (p = 0.464). Age at diagnosis, tumor size, pathologic stage, and lymph node status were independent prognostic indicators for 10-year survival. There was no prognostic difference between IDC and ILC. The result shows the importance of adjusting for other important clinicopathologic characteristics before comparing the overall survival of IDC and ILC.

key words: breast cancer survival, clinicopathologic characteristics, infiltrating ductal carcinoma, infiltrating lobular carcinoma

The results of studies on the effects of histologic type as an independent prognostic factor for survival of women with breast cancer have shown that infiltrating lobular carcinoma (ILC) is associated with a poorer prognosis than infiltrating ductal carcinoma (IDC) (1,2), with no difference in prognosis (3–5) or with a better prognosis (6–8). ILC is distinguished from IDC histologically by its cell type and pattern of invasion, and also by its immunohistochemical profile (9,10). ILC is more difficult to palpate and to visualize mammographically, and has a distinctive pattern of metastatic spread (8,11).

Histologic type, age at diagnosis, tumor size, lymph node status, histologic grade, and stage of disease are also important prognostic factors for survival (2,6,12–24). However, a deficiency of many studies has been the study of histologic type as a prognostic factor for survival without adjustment for these other important prognostic factors (1,3–5,7,8).

The various histologic types of breast cancer show differences in relative frequency (25). ILC is the second most common breast carcinoma after IDC of no special type (NST, not otherwise specified) (9,25). ILC represents up to 15% of all breast cancers (8,9,11,25) and has a 5-year survival of 84% (25), 7-year survival of 83% (8) and 30-year survival of 50% (6). IDC represents between 68% and 84% (11,25,26) of all breast cancers with 5-year survival of between 63% and 79% (6,25), 7-year survival of 77% (8) and 30-year survival of 37% (6). This population-based study compares the prognosis of women with ILC and IDC after adjustment for age at diagnosis, tumor size, lymph node status, histologic grade, and stage of disease.

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METHODS

Population

The population studied consisted of 526 female residents of the Greater Western region of Sydney (GWRS), defined as Western Sydney Area Health Service, South Western Sydney Area Health Service and Wentworth Area Health Service, first diagnosed with invasive breast cancer between January 1, 1992 and December 31, 1992. The women were identified through the New South Wales (NSW) Central Cancer Registry (CCR) to which notification is mandatory. The NSW CCR provided personal identification information, demographic details, notification source and unit record number, and basic tumor details for all patients. The median age at diagnosis was 54 years (range, 24–94). The information on clinical presentation, diagnosis, tumor stage, histopathology, and treatment was supplemented extensively with information from hospital records. If key details were missing, information was also sought from treating clinicians or general practitioners. This study was approved by the Human Research Ethics Committees of the three area health services in the GWRS.

Study Eligibility

There were 174 exclusions: 103 women were excluded because all of their treatment was given outside the GWRS; 16 women who had a previously diagnosed malignancy, except in situ carcinoma of the cervix or basal or squamous cell skin cancer were also excluded; three women were excluded because there was no pathologic evidence of a primary tumor in the breast (occult primary) with disease only in the axilla; one had bilateral breast cancer and there was one post-mortem diagnosis of breast cancer (27,28). An additional nine women were excluded due to incorrectly coded data at the CCR. Thirty-eight women could not be assigned a histologic type or were missing histologic type leaving 352 cases, of which ductal carcinoma in situ with microinvasion \((n = 19)\), tubular \((n = 7)\), medullary \((n = 11)\), mucinous \((n = 5)\), and mixed \((n = 3)\) were excluded from the analysis. After these exclusions, 277 cases of IDC (NST), which included adenocarcinoma not otherwise specified \((n = 10)\) and scirrhous \((n = 1)\), and 30 cases of ILC were available for analysis.

Deaths from Breast Cancer

The NSW CCR maintains a register of all cases of cancer diagnosed in NSW since the beginning of 1972. All patients with breast cancer not known to be dead (from breast cancer) by the NSW CCR were matched against the death records from the NSW Registry of Births, Deaths, and Marriages, enhanced by information obtained from the Australian Bureau of Statistics (29). Ten-year breast cancer survival data of the study group were provided by the NSW CCR.

Data Analysis

The outcome factor was breast cancer survival and the study factors were histologic type (IDC versus ILC), age (<40 years, 40–69 years, or ≥70 years), family history (no or yes), multifocality (no or yes), pathologic tumor diameter (<20 mm, 20–39 mm, or >39 mm), pathologic stage (T1, T2, T3, or T4), histologic grade (I, II, or III) and nodal involvement (none, 1–3, or >3). Other studies have defined young women as under 40 years of age at diagnosis and their survival was significantly lower (12,15,17,18,30–33). The age group 40–69 years was chosen because women in this age group are the main target of a coordinated breast cancer screening program which began in Australia in 1993. Information on the pathologic tumor diameter \((n = 41)\), nodal involvement \((n = 52)\), histologic grade \((n = 78)\), pathologic stage \((n = 30)\), family history \((n = 60)\), or multifocality \((n = 41)\) was not available or not applicable (if axillary nodes were not examined) for several women and these women were incorporated in the analysis as a separate category (“unknown” category).

Survival was conducted using Kaplan–Meier method, with Wilcoxon tests for statistical significance. Women were censored from the calculation of overall survival at the time of last follow-up (if not known to be dead) or death from intercurrent illness. Univariate analysis and multivariate analysis to determine independent predictors of survival were undertaken using a Cox proportional hazard regression. Two-sided p-values of less than 0.05 were considered statistically significant. Comparison of categories within a characteristic was carried out with the Pearson chi-square test and, if any of the expected frequencies was less than five, the Fisher’s exact test was used. All statistical analyses except survival plots were performed using SPSS statistical software (version 13; SPSS, Chicago, IL). Survival plots were generated using SAS statistical software (version 9; SAS Institute, Cary, NC).
RESULTS

The clinicopathologic characteristics of the women in the two histologic groups (IDC and ILC) are shown in Table 1. In this group of women, 90% were IDC. Eighty-five percent of IDC tumors were Stage I or II. A comparison of the histologic grading in the two groups indicated significant differences (Table 1). The proportion of grade I tumors was significantly higher in ILC (41%) than in IDC (16%). Conversely, the proportion of grade III tumors was only 18% in ILC as against 41% in IDC (the proportions were computed only for tumors of known grade).

There was no significant difference between the surgical treatment given to patients with IDC and that

Table 1. Clinicopathologic Characteristics of 307 Women with Infiltrating Ductal and Infiltrating Lobular Carcinoma at First Diagnosis of Breast Cancer in 1992

| Characteristic                  | Histologic type                          |
|---------------------------------|------------------------------------------|
|                                 | Infiltrating ductal (n = 277) | Infiltrating lobular (n = 30) | All (n = 307) no. (%) |
|                                 | No. (%) Survival % | No. (%) Survival % | No. (%) Survival % |
| Age, years                      | 0.154 0.789 0.231 0.068 | 0.376 0.789 0.231 0.068 | 0.942 0.942 0.942 0.942 |
| Family history                  | 0.554 (1.000) 0.231 0.169 | 0.440 0.231 0.169 | 1.000 1.000 1.000 |
| Multifocal                      | 0.686 (0.715) 0.355 0.127 | 0.355 0.127 | 0.715 0.715 |
| Tumor size, mm                  | 0.420 (0.274) 0.681 0.127 | 0.355 0.127 | 0.274 0.274 |
| Pathologic T-stage3             | 0.006 (0.020) 0.236 0.028 | 0.028 | 0.020 |
| Grade                           | 0.066 (0.020) 0.236 0.028 | 0.028 | 0.020 |
| Estrogen receptor               | 0.907 (0.681) 0.237 0.300 0.311 | 0.300 0.311 | 0.681 0.681 |
| Axillary dissection             | 0.798 0.244 0.175 0.230 | 0.244 0.175 0.230 0.244 | 0.681 0.681 |
| No. of positive nodes           | 0.507 (0.354) 0.361 0.581 0.240 | 0.361 0.581 0.240 | 0.354 0.354 |
| Surgery                         | 0.780 0.592 0.091 | 0.592 0.091 | 0.354 0.354 |

*p-Values are for comparison of categories of each variable by histologic type using the Pearson’s chi-square test or the Fisher’s exact test. For characteristics with an unknown category, the p-values without unknown category are shown within parentheses.

1 p-values are for comparison of survival difference of each category of Clinicopathologic variable using Wilcoxon test.

2 Clinical if T4.

3 The patient died from intercurrent illness within the first year of follow-up.
given to patients with ILC (p = 0.780). Furthermore, there was no difference in the age distribution (p = 0.154) of the two histologic types. Similarly, there was no significant difference in the frequency for the known presence of cancer in first-degree female relatives (13% versus 9%, p = 1.00), for the presence of multifocality (9% versus 12%, p = 0.715), positive nodes (48% versus 35%, p = 0.194), and estrogen receptor (ER)-positive tumors (54% versus 59%, p = 0.681). The above proportions were computed only for tumors of known family history, multifocality, positive nodes, and ER status.

The 5- and 10-year overall survival of the study population was 78% and 71%. Ten-year survival of women with IDC was 69%, compared to 84% for ILC (p = 0.073) (Table 2; Fig. 1). However, the 15 percentile difference between overall survival of IDC and ILC was markedly reduced after adjustment for nodal status. For example, this difference was eight percentile points for node-negative patients (Fig. 2; p = 0.361) and five percentile points for node-positive patients (Fig. 3; p = 0.464). The result shows the importance of adjustment for a range of possible confounding clinicopathologic characteristics.

Ten-year survival of younger women (aged <40 years) was 49%, compared to 74% for older women aged 40–69 years (p = 0.004; Table 2) and to 69% for women over 69 years (p = 0.031). Women with tumors <20 mm in pathologic diameter had a 10-year survival rate of 87%, compared to 63% for

| Table 2. Results of Univariate and Multivariate Survival Analysis by Histologic Type and Other Clinicopathologic Characteristics at 10-Year Follow-Up |
|-----------------------------------------------|
| **Factor**                                | **Survival** | **Univariate analysis** | **Multivariate analysis** |
|                                            | Rate %       | 95% CI | p  | RR | 95% CI | p  | RR | 95% CI | p  |
| Histologic type                           |              |        |    |    |        |    |    |        |    |
| Infiltrating ductal                       | 69.1         | 63.4–74.8 | 0.073 | 2.28 | 0.83–6.21 | 0.109 | 1.73 | 0.61–4.87 | 0.301 |
| Infiltrating lobular                      | 84.2         | 69.9–98.5 | 1.00 |      |        |    |    |        |    |
| Age at diagnosis                          |              |        |    |    |        |    |    |        |    |
| <40                                       | 49.4         | 31.8–67.0 | 0.004 | 2.29 | 1.32–3.97 | 0.003 | 1.83 | 1.03–3.25 | 0.038 |
| 40–69                                     | 74.4         | 68.1–80.7 | 1.00 |      |        |    |    |        |    |
| >69                                       | 69.0         | 56.5–81.5 | 0.743 | 1.16 | 0.67–2.00 | 0.609 | 1.06 | 0.56–1.94 | 0.852 |
| Family history                           |              |        |    |    |        |    |    |        |    |
| No                                        | 68.8         | 62.3–75.3 | 1.00 |      |        |    |    |        |    |
| Yes                                       | 73.6         | 55.8–91.4 | 0.250 | 0.70 | 0.32–1.53 | 0.373 | 0.63 | 0.28–1.43 | 0.271 |
| Unknown                                   | 75.5         | 63.9–87.1 | 0.358 | 0.76 | 0.42–1.38 | 0.364 | 0.91 | 0.49–1.73 | 0.790 |
| Multifocality                            |              |        |    |    |        |    |    |        |    |
| No                                        | 72.1         | 66.0–78.2 | 1.00 |      |        |    |    |        |    |
| Yes                                       | 71.2         | 53.2–89.2 | 0.563 | 1.15 | 0.53–2.52 | 0.724 | 1.00 | 0.44–2.31 | 0.995 |
| Unknown                                   | 60.3         | 44.6–76.0 | 0.124 | 1.85 | 1.05–3.26 | 0.032 | NC  | NC      | NC  |
| Tumor size, mm                           |              |        |    |    |        |    |    |        |    |
| <20                                       | 86.7         | 80.2–93.2 | 1.00 |      |        |    |    |        |    |
| 20–39                                     | 63.4         | 54.6–72.2 | <.001 | 3.08 | 1.69–5.64 | <.001 | 2.13 | 0.98–4.66 | 0.058 |
| >39                                       | 54.8         | 34.4–75.2 | 0.001 | 3.83 | 1.77–8.29 | 0.001 | 3.06 | 1.01–9.22 | 0.047 |
| Unknown                                   | 60.3         | 44.6–78.0 | <.001 | 4.06 | 1.96–8.41 | <.001 | 1.87 | 0.76–4.61 | 0.172 |
| Pathologic T-stage                       |              |        |    |    |        |    |    |        |    |
| T1                                        | 81.6         | 75.3–87.9 | 1.00 |      |        |    |    |        |    |
| T2                                        | 60.0         | 50.0–70.0 | 0.001 | 2.35 | 1.44–3.84 | 0.001 | 1.02 | 0.52–2.00 | 0.96  |
| T3                                        | 47.6         | 3.5–91.7 | 0.238 | 2.79 | 0.85–9.19 | 0.092 | 0.76 | 0.17–3.50 | 0.726 |
| T4                                        | 26.2         | 0.0–56.0 | <.001 | 12.96 | 5.59–30.04 | <.001 | 6.27 | 1.77–22.16 | 0.004 |
| Unknown                                   | 71.7         | 55.0–88.4 | 0.187 | 1.68 | 0.76–3.70 | 0.198 | NC  | NC      | NC  |
| Histologic grade                         |              |        |    |    |        |    |    |        |    |
| I                                         | 83.3         | 71.3–95.5 | 1.00 |      |        |    |    |        |    |
| II                                        | 71.9         | 62.3–81.5 | 0.339 | 1.64 | 0.67–3.99 | 0.278 | 1.24 | 0.49–3.13 | 0.646 |
| III                                       | 60.7         | 50.1–71.1 | 0.012 | 2.79 | 1.17–6.64 | 0.021 | 1.79 | 0.73–4.36 | 0.205 |
| Unknown                                   | 74.0         | 63.8–84.2 | 0.271 | 1.64 | 0.65–4.10 | 0.293 | 1.22 | 0.47–3.18 | 0.681 |
| No. of positive lymph nodes               |              |        |    |    |        |    |    |        |    |
| 0                                         | 85.7         | 79.8–91.6 | 1.00 |      |        |    |    |        |    |
| 1–3                                       | 64.8         | 53.2–76.4 | 0.001 | 2.73 | 1.48–5.01 | 0.001 | 2.15 | 1.14–4.06 | 0.018 |
| >3                                        | 45.9         | 31.2–60.6 | <.001 | 4.79 | 2.65–8.66 | <.001 | 3.40 | 1.81–6.36 | <.001 |
| Unknown                                   | 62.6         | 47.5–77.7 | 0.001 | 3.19 | 1.64–6.20 | 0.001 | 2.07 | 0.90–4.77 | 0.086 |

195% CI, 95% confidence interval of survival or relative risk; RR, relative risk of dying; NC, not computed because they were linearly dependent covariates (e.g., when tumor size was unknown so was the focality status and vice versa).

Clinical if T4. p-Value is for comparison of each category with the reference category. Number in each category is shown in Table 1.
The ten-year survival rate (82%) of women with T1 tumors was significantly higher than that of women with T2 tumors (60%; p = 0.001) and with T4 (26%, p < 0.001) (Table 2). No significant difference was found between women with T1 and T3 or tumors with unknown stage (Table 2).

The ten-year survival rate (83%) of women with grade I tumors was significantly higher than that of women with grade III tumors (61%; p = 0.012). No significant difference was found between women with grades I or II tumors (p = 0.339).

When compared with women with negative nodes, both cohorts of node-positive cases (1–3 and >3 nodes positive; p = 0.001) and women with unknown (p < 0.001) nodal status had a significantly higher risk of breast cancer mortality (Table 2). No significant difference was found between women with positive nodes and unknown nodal status. No significant differences were found between women with or without family history (p = 0.250) or multifocality (p = 0.563).

Table 2 also presents the relative risks (RRs) of dying associated with histologic type, age at diagnosis, pathologic tumor size, pathologic stage, histologic grade, and number of positive lymph nodes based on Cox regression analysis. The univariate analysis showed a statistically significant trend for higher RR with greater pathologic tumor size (p < 0.001), younger age at diagnosis (p = 0.003), higher tumor stage (p < 0.001), grade III tumors (p = 0.021), and number of positive lymph nodes (p = 0.001). A multivariate analysis showed age at diagnosis, the pathologic tumor size, pathologic stage, and involvement of axillary lymph nodes were independent predictors of survival in this group of women. This means that, after eliminating the effects of each other, younger age at diagnosis, increasing pathologic tumor size, increasing tumor stage, and positive lymph node status all showed a higher risk of dying. Both univariate and multivariate analysis showed that there was no significant difference in RR of breast cancer-related death between women with IDC and ILC tumors (Table 2). Furthermore, there was no survival difference between...
IDC and ILC for any subcategory of clinicopathologic characteristic (Table 1).

DISCUSSION

Carcinoma of the breast includes a number of histologic types of which the two most common are IDC and ILC representing up to 88% of all breast carcinomas (5). In our study IDC and ILC represented 87% of all breast cancers. The results of the present investigation showed that there was no significant difference between survival of women with IDC or ILC tumors. Although not significant, the RR of breast cancer-related death for IDC in comparison to ILC decreased from 2.28 to 1.73 after adjustment for other important clinicopathologic characteristics. This shows the importance of eliminating the effects of other prognostic factors before comparing the RR of IDC and ILC. A deficiency of many studies has been comparing survival of IDC and ILC without adjustment for other important prognostic factors (1,3–5,7,8).

In the present series, ILCs were significantly more often of low histologic grade and IDC were of high histologic grade. ILCs have also been found to be associated with a low histologic grade by others (6,34). The distribution of stage of disease and lymph node metastasis at the time of diagnosis was not significantly different between the two groups. The results are similar to those of other studies (3,8). Fifty-four percent of IDC patients had ER-positive tumors compared to 59% for ILC (p = 0.681). Some series reported a higher number of ER-positive patients in the ILC group compared to IDC (4,11), but one study found no difference between the groups with regard to receptor status (7). There was no difference in the age distributions (p = 0.154) nor in the frequency of tumor size between the groups (p = 0.274). The results are consistent with other series (5,6,11).

There are several advantages to this study: First, it is a population-based study with over 10 years of follow-up; Second, reliable data were used in the study—for example, information provided by the CCR was supplemented extensively with, and supported by, information from hospital records, treating clinicians, or general practitioners. One potential weakness of the study is the relatively small sample of ILC (n = 30). Furthermore, pathologic information for lymphovascular invasion (LVI; 66% missing) and ER (45% missing) were excluded from the analyses. These variables could account for differences in survival and further studies need to be conducted that include more complete pathologic details including LVI and ER status, which are now reported more reliably.

Previous studies reported a higher RR with young age at diagnosis, greater tumor size, number of positive lymph nodes, and higher pathologic stage (12,17,19,20). The current study found that age at diagnosis, tumor size, lymph node status, and pathologic stage were independent prognostic indicators. Survival declined with increasing nodal status after adjustment for the effects of histologic type, age, tumor size, grade, and path stage and survival declined with increasing tumor size after adjustment for histologic type, age, nodal status, grade, and path stage. This was also true for age and pathologic stage.

This study found that there was no prognostic difference between IDC and ILC after adjustment for age at diagnosis, tumor size, stage of disease, nodal status, histologic grade, multifocally, and family history in a population-based study with over 10 years of follow-up.

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