Background: Recent studies suggest that the use of combined estrogen and progestin hormone replacement therapy is associated with an increased risk of invasive lobular carcinoma (ILC), but that it has little association with risk of invasive ductal carcinoma (IDC). Also, the incidence rates of ILC have risen over the past 10 years while those of IDC have remained constant. Differences in survival rates by histologic types of tumor have been reported, but few of the published studies were population based or had adequate power to address this issue.

Methods: We conducted a retrospective cohort study spanning the years 1974 through 1998 using data from the 9 cancer registries that have participated in the Surveillance, Epidemiology, and End Results Program since 1974. The cohort consisted of 164938 women aged 50 to 79 years who had been diagnosed as having 1 of 7 histologic types of invasive breast cancer. Risks of mortality due to any cause were estimated using the Cox proportional hazards model.

Results: Women with ILC had a risk of mortality 11% lower than women with IDC. The magnitude of this difference has increased over the past 10 years and, from 1994 through 1998, the risk of mortality was 26% lower for women with ILC. Also, the risk of mortality was between 8% and 34% lower in women with mucinous carcinoma, comedocarcinoma, or medullary, tubular, and papillary carcinomas compared with women with IDC.

Conclusions: Differences in prognosis by histologic type of breast cancer were identified. The survival rate of women 50 to 79 years old who have ILC, the cancer whose histologic type is the most closely linked with the use of combined estrogen and progestin hormone replacement therapy, is more favorable than that of women with IDC and appears to be improving over time.

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Women 50 to 79 years old and diagnosed as having a primary invasive breast cancer between January 1974 and December 1998 were identified through 9 population-based US cancer registries participating in the National Cancer Institute’s SEER Program. We restricted our study to women 50 to 79 years old because the risk factors and outcomes of breast cancer differ by age and, particularly, menopausal status. The SEER registries that were used serve Connecticut, Hawaii, Iowa, New Mexico, Utah, and the urban areas surrounding Atlanta, Ga; Detroit, Mich; San Francisco-Oakland, Calif; and Seattle, Wash. Patients’ medical records are the principal sources of data used by SEER. It is estimated that more than 95% of all incident cancer cases in the populations under surveillance are ascertained. Further operational details and methods used by the SEER Program are provided elsewhere.

### METHODS

Table 1. Demographic, Carcinoma, and Treatment Characteristics of 164,958 Women Diagnosed as Having Breast Cancer Between 1974 and 1998

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Histologic Type, No./Row %/Column %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ductal (n = 132,284)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age, y</td>
<td>50-59</td>
</tr>
<tr>
<td></td>
<td>60-69</td>
</tr>
<tr>
<td></td>
<td>70-79</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>64.1 (8.3)</td>
</tr>
</tbody>
</table>
The 188701 women diagnosed for the first time with invasive breast cancer were eligible for this study. They were grouped according to the histologic categories of their tumors as defined by the International Classification of Diseases for Oncology (ICD-O) codes: ductal (ICD-O code 8500), lobular (8520 and 8522), mucinous (8480), comedocarcinoma (8501), medullary (8510), tubular (8211 and 8201), and papillary (8530 and 8503). The 23743 women who were assigned other ICD-O codes, and represented 12.6% of eligible subjects, were excluded from our analysis, leaving a total of 164958 women.

In addition to age at diagnosis, year of diagnosis, and histologic type, SEER data from 1974 to 1998 also include information on SEER historic stage (localized, regional, or distant) and race/ethnicity. Also, data on first courses of surgical and radiation treatments are available, but data on adjuvant chemotherapy and hormonal therapy are not. While information on marital status is provided, data regarding other sociodemographic factors, such as income and health insurance status, are not.

Information on survival is obtained annually by each registry through a variety of data sources including hospital cancer registries and discharge data sets, the Department of Motor Vehicles registration files, regional records of the Health Care Financing Administration, voters’ registration records, death records, and the Social Security death index. In addition to vital status, SEER also provides survival time for each patient. It is calculated in months using the date of diagnosis and whichever of the following occurred first: (1) date of death, (2) date last known to be alive, or (3) December 31, 1998, the follow-up cutoff date used in our analysis.

Associations between histologic types of breast cancer and risks of mortality due to any cause were estimated using the Cox proportional hazards model. Using data from the SEER registry, the Cox regression was performed to compute hazard ratios (HRs) and 95% confidence intervals (CIs) and to evaluate the effects of modifying factors. In our final multivariate models we adjusted for age at diagnosis (continuous data), year of diagnosis (continuous), SEER historic stage (categorical), SEER registry (categorical), and whether surgical and/or radiation breast cancer therapy was used as a first-course treatment, because each was hypothesized as a potential confounder. We found that year of diagnosis and SEER registry were effect modifiers, and thus we performed analyses stratified by 5-year categories of diagnosis year (1974-1978, 1979-1983, 1984-1988, 1989-1993, and 1994-1998) and by SEER registry.

**RESULTS**

The cohort of 164958 women had 132284 ductal (80.2%), 19383 lobular (11.8%), and 3923 mucinous carcinomas (2.4%); 3157 comedocarcinomas (1.9%); and 902 medullary (1.8%), 2260 tubular (1.4%), and 1049 papillary carcinomas (0.6%). Table 1 presents a comparison of various characteristics by histologic type. Women with medullary carcinomas and comedocarcinomas had the lowest mean ages at diagnosis (61.9 and 62.1 years, respectively), while women with mucinous and papillary carcinomas had the highest mean ages at diagnosis (67.4 and 66.9 years, respectively). The number of cases classified as medullary carcinoma decreased over the course of the study, while the number of cases classified as each of the other types generally increased. The mean follow-up time was longest for women with medullary and papillary carcinomas (9.5 and 8.2 years, respectively), and shortest for women with ILC (6.4 years). Numerous differences by SEER registry were also observed. For example, relatively fewer cases of ILC were diagnosed in Hawaii (7.7% of the total cases) while relatively more were diagnosed in Detroit and San Francisco-Oakland (13.1%). Multiple differences by race/ethnicity were also seen, as relatively more cases of ILC and fewer cases of comedocarcinoma were observed among non-Hispanic whites, and the opposite was true for black, Asian/Pacific Islander, and American Indian women. Localized disease was more common among women with tubular, mucinous, and papillary carcinomas (90.4%, 86.1%, and 82.5%, respectively) and less common among women with IDC and ILC (59.4% and 59.9%, respectively). More than 99.6% of women with tumors of any histologic type received surgical treatment. Finally, a first course of radiation was the most common for women with papillary carcinomas (76.4%) and the least common for women with tubular carcinomas (56.8%).

Table 2 presents risks of mortality due to any cause associated with different histologic types of breast cancer adjusted for age at diagnosis, year of diagnosis, SEER historic stage, SEER registry, surgical treatment, and radiation therapy. Compared with women with IDC, women with ILC had an 11% reduction (95% CI, 9%-14%) in their risk of mortality. Reductions in risk of mortality were also observed for women with each of the other histologic types of cancer, and women with tubular carcinomas had a 34% reduction, the largest reduction observed for any of the histologic types.

While reductions in risk of mortality were generally observed for each category of diagnosis year for each histologic type, many of these reductions were within the limits of chance (Table 3). Some variations in the magnitude of these risks were observed over time. Specifically, the risk of mortality associated with ILC decreased over the past 10 years, so that between 1994 and 1998, the risk of mortality was 26% lower for women with ILC than for women with IDC. Also, the risk of mortality associated with mucinous carcinoma was reduced by 31% compared with the risk associated with IDC between 1994 and 1998, the greatest reduction for mucinous carcinoma observed in any of the 5-year periods evaluated. Alternatively, while women with medullary and papillary carcinomas experienced decreased risks of mortality between 1974 and 1993, this reduction was no longer observed during the most recent period, 1994 to 1998.

**Table 2. Multivariate-Adjusted Risks of Mortality by Histologic Type of Carcinoma**

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Patients Alive, No. (%)</th>
<th>Yes</th>
<th>No</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal</td>
<td>77 637</td>
<td>54 647</td>
<td>41.3</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Lobular</td>
<td>12 988</td>
<td>63 953</td>
<td>33.0</td>
<td>0.89 (0.86-0.91)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>2563</td>
<td>13 603</td>
<td>34.7</td>
<td>0.80 (0.76-0.85)</td>
</tr>
<tr>
<td>Comedocarcinoma</td>
<td>2219</td>
<td>93 830</td>
<td>29.7</td>
<td>0.92 (0.86-0.98)</td>
</tr>
<tr>
<td>Medullary</td>
<td>1602</td>
<td>130 000</td>
<td>44.8</td>
<td>0.82 (0.78-0.87)</td>
</tr>
<tr>
<td>Tubular</td>
<td>1841</td>
<td>41 850</td>
<td>18.5</td>
<td>0.66 (0.60-0.73)</td>
</tr>
<tr>
<td>Papillary</td>
<td>659</td>
<td>39 370</td>
<td>37.2</td>
<td>0.81 (0.73-0.90)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results Program.

*All HRs are adjusted for diagnosis age, year of diagnosis, SEER historic stage, SEER registry, surgical treatment, and radiation therapy.
Some variations by SEER registry were also observed (Table 4). Compared with women having IDC, women with ILC had a 7% to 29% decrease in risk of mortality in all registries except Utah’s. Additionally, reduced risks of death that were not within the limits of chance were observed for mucinous, medullary, tubular, and papillary tumors in 6, 4, 7, and 3 of the 9 registries, respectively.

A limitation of this study is that the classification of tumors by histologic type was not conducted in a centralized location, and that histopathologic definitions of tumors have changed over time. What is somewhat reassuring, however, is that our results are concordant with other published results; and when we stratified by year of diagnosis, the directions of the risks we observed were fairly consistent over time. Furthermore, statistically significant reductions in risks of mortality associated with lobular, mucinous, and tubular carcinomas were observed in 6 or more of the 9 cancer registries evaluated, which supported our study’s generalizability.

Another concern is that we lacked information regarding certain potential confounders, including hormonal, reproductive, anthropometric, and lifestyle factors, that may be associated with histologic type of cancer and survival time. In addition, we lacked data on other treatments, such as hormonal therapy and chemotherapy, that study subjects may have received. These treatments are known to improve survival time, and it is likely that their administration also differs by histologic type of cancer, making them important potential confounders. For example, it has been reported that lobular tumors are more likely than ductal tumors to be hormone receptor–positive,32 and thus are more likely to be candidates for hormonal treatment, ie, treatment with tamoxifen. Thus, the risk of mortality associated with ILC may be decreasing as tamoxifen use, which reduces mortality due to hormone receptor–positive breast cancer,33 is increasing.

Although patterns of use of tamoxifen and chemotherapy for breast cancer changed over the study period, our data suggest that, in particular, lobular, mucinous, and
tubular carcinomas were and continue to be associated with lower risks of mortality than IDC, and that the magnitude of this lower risk has increased over time as ILC was associated with an 8% lower risk of mortality compared with IDC between 1974 and 1983, and a 24% lower risk between 1994 and 1998. Given that since 1987 ILC incidence rates have increased steadily in the United States among women older than 50 years, while IDC incidence rates have held constant since 1987, this finding is particularly important.7 Furthermore, there is a growing body of evidence linking the use of CHRT to an elevated risk of ILC.13 Recent data from the Women’s Health Initiative randomized trial comparing CHRT to placebo indicates that CHRT use is associated with an increased risk of breast cancer.31 While the Women’s Health Initiative investigators have not reported on whether this risk differs by histologic type, 5 case-control studies have shown that the risk of breast cancer associated with CHRT use varies by histologic type. All 5 studies found that current or recent use of CHRT increased the risk of ILC 2.0- to 3.9-fold, while only 1 found that it also increased the risk of IDC.7 Considered along with results from this study, it appears that the types of breast carcinomas CHRT users have a greater risk of developing, such as ILC, have a relatively favorable prognosis. However, further studies are needed and we encourage investigators assessing the relationship between CHRT use and breast cancer incidence to stratify their analyses by histologic type.

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REFERENCES