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Risk of Mortality by Histologic Type of Breast Cancer in the United States

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Abstract There are several histologic types of breast cancer that beyond their histopathologic differences have distinct clinical characteristics. However, it is unclear how histology is related to risk of mortality particularly when differences in hormone receptor status, tumor size, and nodal status are incorporated. This study utilized a cohort of 319,463 breast cancer patients ≥30 years of age diagnosed from 1992 to 2007 identified from 17 population-based cancer registries that participate in the Surveillance Epidemiology and End Results Program. Multivariate adjusted risks of mortality associated with seven breast cancer histologic subtypes were estimated using Cox regression. Mucinous, tubular, and medullary carcinomas were associated with 31–79% lower risks of mortality compared to ductal carcinoma. Inflammatory breast cancer was associated with a 50–53% increased risk of mortality depending on age. While lobular carcinomas carried the same risk of mortality as ductal carcinoma among women 30–49 years of age, among women ≥50 years of age with node-negative disease lobular carcinoma was associated with an 11% reduced risk of mortality, but among those with node-positive disease it was associated with a 10% increased risk of mortality. This study confirms that mucinous, tubular, and medullary carcinomas have a more favorable prognosis compared to ductal carcinoma, and that inflammatory carcinoma has a poorer prognosis. Though many of these histologic subtypes are quite rare, consideration of the mortality risk associated with a given subtype may be clinically useful when making decisions regarding treatment and follow-up.

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Introduction

There are several established histological subtypes of invasive breast cancer. Beyond the histopathological characteristics that define and differentiate these subtypes, it is also clear that there are important clinical and molecular differences between them. The most common histologic subtype of breast cancer is invasive ductal carcinoma; and in the USA and other developed countries, it accounts for about 70–80% of all cases [1]. Tumors with an invasive lobular component, either pure invasive lobular carcinomas or mixed ductal-lobular carcinomas, are the next most common histological subtypes of breast cancer accounting for about 15–20% of all cases. There are also several rarer histological types of breast cancer that each account for less than 2% of all cases including mucinous, tubular, inflammatory, and medullary carcinomas [2]. Compared to ductal carcinomas, mucinous, comedo, tubular, and medullary carcinomas are less likely to present at an advanced stage; and mucinous, tubular, and papillary carcinomas are less likely, and comedo, medullary, and inflammatory carcinomas are more likely, to be hormone receptor negative and high grade [2].

What is less clear is the extent to which risks of mortality vary by histologic subtype. We previously published results suggesting various differences in mortality risks by histology [3], but this analysis was importantly hampered by a lack of data on hormone receptor status which is known to both vary appreciably by histologic type and to have an important influence on risk of mortality. Using data from 17 population-based cancer registries that participate in the Surveillance, Epidemiology and End Results (SEER) program this study

evaluated risks of mortality among invasive breast cancer cases diagnosed from 1992 to 2007 by histologic type. Characterizing the relative risks of mortality across histologic types of breast cancer is important because it can inform clinical decision making, choice of treatment, and plans for follow-up.

Methods

Women 30 years of age or greater without a prior history of any type of cancer who were diagnosed with invasive breast cancer between January 1992 and December 2007 were identified through 17 population-based cancer registries in the USA that participate in the National Cancer Institute's SEER Program. Women less than 30 years of age were excluded due to the rarity of breast cancer among women in this age group. The SEER registries that were included serve the states of California (through the participation of four distinct SEER registries), Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah, the areas surrounding Atlanta, Georgia; Detroit, Michigan, and Seattle, Washington, and the populations of Alaskan Natives living in Alaska and rural Georgia. The Kentucky, Louisiana, New Jersey, and Greater California registries (which includes the regions of California not covered by the Los Angeles, San Francisco/Oakland, and San Jose/Monterey registries) were added to the SEER program in 2000, so these registries only contributed data from 2000 to 2007. It is estimated that more than 95% of all incident cases in the populations under surveillance are ascertained. The primary source of data used by SEER is patient medical records, and further operational details regarding the methodology employed by the SEER Program are provided on the SEER website (seer.cancer.gov).

A total of 497,528 potentially eligible cases were identified. The analysis was restricted to the seven most prevalent histologic types of breast cancer that each account for at least 0.5% of all cases. The 178,065 women diagnosed with another histologic type of breast cancer, missing data on breast cancer histology, and/or missing data on any of the potential confounders of interest in this study (AJCC stage, grade, estrogen receptor status, progesterone receptor status, surgical treatment for breast cancer, and radiation therapy for breast cancer) were excluded leaving a total of 319,463 women. Histologic categories were defined by the International Classification of Diseases for Oncology (ICD-O) 3rd Edition codes assigned to cases: ductal (ICD-O code 8500, n=255,718), ductal-lobular (ICD-O code 8522, n=26,900), lobular (ICD-O code 8520 and 8524, n=21,062), mucinous (ICD-O code 8480, n=6,561), tubular (ICD-O code 8211, n=4,477), inflammatory (ICD-O code 8530, n=2,673), and medullary (ICD-O code 8510, n=2,072). Information on survival time is obtained annually by each registry through a variety of data sources including national death records, regional Health Care Financing Administration records, local voters' and Department of Motor Vehicles registration files, and local hospital records. SEER calculates survival time in months beginning with the month and year of diagnosis; and in this study, the outcome of interest was death due to breast cancer. So women were followed until whichever of the following occurred first: (1) date of death due to breast cancer, (2) date of death due to a cause other than breast cancer (censored), (3) date last known to be alive, or (4) December 31, 2007, the follow-up cutoff date used in this analysis. In order for cases that died within 1 month of diagnosis to be included in the analysis, the survival time of these cases was recategorized as being 0.5 months rather than 0 month.

Associations between histologic types of breast cancer and risks of mortality due to breast cancer were estimated using the Cox proportional hazards model [4]. Using Stata/SE 10.1 for Windows (Stata Corp, College Station, TX, USA) statistical software, Cox regression was performed to compute hazard ratios (HR), and their associated 95% confidence intervals (CI). Variables ascertained from SEER that were considered as potential confounders of the relationship between breast cancer histology and risk of mortality included: age at diagnosis, year of diagnosis, SEER registry, race/ethnicity, AJCC stage, grade, estrogen receptor (ER)/progesterone receptor (PR) status, surgical treatment for breast cancer, radiation therapy for breast cancer, and percent of the population living in the county cases were diagnosed in living below 200% of the federal poverty level in the year 2000 (according to 2000 census data). The latter variable was included as an area level measure of socioeconomic status since socioeconomic status may be associated with both histology and mortality and individual level data were not available. Each of these potential confounders was included as categorical variables according to how they are categorized in Table 1 in the multivariate-adjusted analyses presented. Given the known differences in distributions of ER/PR status, tumor size, and nodal status by histologic type, analyses stratified by these factors were also conducted.

Results

The mean follow-up time for women in this study was 5 years, though the mean follow-up was somewhat shorter for inflammatory carcinoma cases (40.2±35.7) and somewhat longer for medullary cases (76.3±50.3). Women with medullary carcinoma had the youngest mean age at diagnosis (52.8±12.8) and women with mucinous and lobular carcinomas had the oldest mean ages at diagnosis (66.5±14.2 and 63.5±13.2, respectively; Table 1). The proportions of ductal, ductal-lobular, lobular, and mucinous carcinomas increased some-

Table 1 Demographic and tumor characteristics of breast cancer cases by histologic type

Characteristic	Ductal n=255,718		Ductal-lobular n=26,900		Lobular n=21,062		Mucinous n=6,561		Tubular n=4,477		Inflammatory n=2,673		Medullary n=2,072	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Age at diagnosis, years														
30–39	15,959	6.2	1,075	4.0	402	1.9	227	3.5	88	2.0	253	9.5	296	14.3
40–49	52,012	20.3	5,251	19.5	3,218	15.3	811	12.4	784	17.5	587	22.0	648	31.3
50–59	64,076	25.1	7,173	26.7	4,973	23.6	1,018	15.5	1,295	28.9	778	29.1	556	26.8
60–69	55,036	21.5	6,171	22.9	5,084	24.1	1,331	20.3	1,167	26.1	510	19.1	329	15.9
70–79	45,123	17.6	4,926	18.3	4,700	22.3	1,895	28.9	833	18.6	337	12.6	173	8.3
80+	23,512	9.2	2,304	8.6	2,685	12.7	1,279	19.5	310	6.9	208	7.8	70	3.4
Mean ± standard deviation	59.7±13.9		60.4±13.1		63.5±13.2		66.5±14.2		60.8±12.0		57.3±13.9		52.8±12.8	
Year of diagnosis														
1992–1995	32,125	12.6	1,954	7.3	1,593	7.6	559	8.5	433	9.7	354	13.2	410	19.8
1996–1999	44,166	17.3	3,868	14.4	3,233	15.3	1,038	15.8	861	19.2	536	20.1	422	20.4
2000–2003	84,495	33.0	10,462	38.9	7,142	33.9	2,331	35.5	1,719	38.4	1125	42.1	678	32.7
2004–2007	94,932	37.1	10,616	39.5	9,094	43.2	2,633	40.1	1,464	32.7	658	24.6	562	27.1
Mean follow-up time ± standard deviation, months	61.0±46.1		57.8±40.6		54.7±41.6		58.8±42.2		67.9±43.5		40.2±35.7		76.3±50.3	
SEER registry														
Alaska natives	329	0.1	37	0.1	21	0.1	5	0.1	1	0.0	4	0.1	5	0.2
Atlanta	12,350	4.8	772	2.9	695	3.3	211	3.2	155	3.5	126	4.7	77	3.7
Connecticut	17,624	6.9	2,060	7.7	1,683	8.0	467	7.1	334	7.5	148	5.5	206	9.9
Detroit	17,481	6.8	1,771	6.6	1,439	6.8	355	5.4	303	6.8	101	3.8	174	8.4
Greater California	45,584	16.5	5,442	20.2	4,010	19.0	1,164	17.7	714	15.9	534	20.0	257	12.4
Hawaii	7,219	2.8	265	1.0	339	1.6	211	3.2	126	2.8	24	0.9	38	1.8
Iowa	16,633	6.5	1,087	4.0	1,358	6.4	399	6.1	241	5.4	168	6.3	134	6.5
Kentucky	9,316	3.6	692	2.6	767	3.6	223	3.4	162	3.6	112	4.2	41	2.0
Los Angeles	30,517	11.9	4,988	18.5	2,419	11.5	1,005	15.3	736	16.4	591	22.1	449	21.7
Louisiana	9,609	3.8	503	1.9	620	2.9	245	3.7	127	2.8	100	3.7	78	3.8
New Jersey	21,752	8.5	2,480	9.2	1,864	8.9	492	7.5	329	7.3	150	5.6	140	6.8
New Mexico	6,739	2.6	556	2.1	594	2.8	171	2.6	110	2.5	82	3.1	56	2.7
Rural Georgia	457	0.2	31	0.1	31	0.1	10	0.2	5	0.1	6	0.2	7	0.3
San Francisco-Oakland	22,238	8.7	1,930	7.2	1,738	8.3	497	7.6	356	8.0	192	7.2	125	6.0
San Jose-Monterey	10,534	4.1	810	3.0	668	3.2	193	2.9	135	3.0	73	2.7	37	1.8
Seattle-Puget Sound	23,213	9.1	2,613	9.7	2,212	10.5	726	11.1	566	12.6	166	6.2	157	7.6
Utah	7,423	2.9	863	3.2	604	2.9	187	2.9	77	1.7	96	3.6	91	4.4

Table 1 (continued)

Characteristic	Ductal n=255,718		Ductal-lobular n=26,900		Lobular n=21,062		Mucinous n=6,561		Tubular n=4,477		Inflammatory n=2,673		Medullary n=2,072	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Race/ethnicity														
Non-Hispanic white	200,233	78.3	22,420	83.3	18,186	86.3	5,152	78.5	4,028	90.0	1960	73.3	1325	63.9
African American	21,790	8.5	1,561	5.8	1,126	5.3	469	7.1	159	3.6	321	12.0	400	19.3
Asian/Pacific Islander	18,164	7.1	1,437	5.3	819	3.9	599	9.1	156	3.5	115	4.3	128	6.2
Hispanic white	12,445	4.9	1,282	4.8	780	3.7	271	4.1	103	2.3	252	9.4	195	9.4
American Indian/Alaska Native	1,826	0.7	86	0.3	70	0.3	43	0.7	24	0.5	9	0.3	7	0.3
Other	1,260	0.5	114	0.4	81	0.4	27	0.4	7	0.2	16	0.6	17	0.8
AJCC stage														
I	124,108	48.5	11,894	44.2	8,398	39.9	4,311	65.7	4,080	90.5	0	0.0	745	36.0
II	102,332	40.0	11,621	43.2	9,016	42.8	1,962	29.9	398	8.9	0	0.0	1211	58.4
III	20,678	8.1	2,680	10.0	2,835	13.5	205	3.1	18	0.4	2129	79.6	99	4.8
IV	8,600	3.4	705	2.6	813	3.9	83	1.3	11	0.2	544	20.4	17	0.8
Grade														
1	43,704	17.1	5,235	19.5	5,658	26.9	3,850	58.7	3,971	88.7	43	1.6	22	1.1
2	105,856	41.4	14,624	54.4	11,610	55.1	2,294	35.0	456	10.2	579	21.7	152	7.3
3	101,309	39.6	6,649	24.7	3,443	16.7	385	5.9	49	1.1	1894	70.9	1721	83.1
4	4,849	1.9	392	1.5	351	16.3	32	0.5	1	0.0	157	5.9	177	8.5
Tumor size, cm														
<2.0	144,431	56.5	14,523	54.0	9,430	44.8	4,127	62.9	4,232	94.5	50	1.9	783	37.8
2.0–4.9	90,069	35.2	9,676	36.0	8,018	38.1	2,012	30.7	211	4.7	203	7.6	1158	55.9
5.0+	18,116	7.1	2,397	8.9	3,282	15.6	390	5.9	27	0.6	2248	84.1	120	5.8
Missing	3,102	1.2	304	1.1	332	1.6	32	0.5	7	0.2	172	6.4	11	0.5
Nodal status														
Negative	163,976	64.1	16,003	59.5	12,737	60.5	5,785	88.2	4,184	93.5	310	11.6	1459	70.4
Positive	87,936	34.4	10,613	39.5	7,996	38.0	706	10.8	283	6.3	2002	74.9	604	29.2
Missing	3,806	1.5	284	1.1	329	1.6	70	1.1	10	0.2	361	13.5	9	0.4
ER/PR status														
ER+/PR+	160,943	62.9	21,258	79.0	16,206	76.9	5,509	84.0	3,656	81.7	969	36.3	226	10.9
ER+/PR−	31,070	12.2	3,616	13.4	3,605	17.1	833	12.7	669	14.9	357	13.4	134	6.5
ER−/PR+	5,374	2.1	316	1.2	279	1.3	33	0.5	58	1.3	126	4.7	75	3.6
ER−/PR−	58,331	22.8	1,710	6.4	972	4.6	186	2.8	94	2.1	1221	45.7	1637	79.0

Surgical treatment														
None	6,156	2.4	411	1.5	523	2.5	97	1.5	25	0.6	420	15.7	10	0.5
Breast conserving surgery	145,949	57.1	13,723	51.0	9,636	48.5	4,270	65.1	3,690	82.4	190	7.1	1331	64.2
Total mastectomy	103,613	40.5	12,766	47.5	10,903	51.8	2,194	33.4	762	17.0	2063	77.2	731	35.3
Radiation treatment														
None	118,659	46.4	13,065	48.6	10,524	50.0	3,082	47.0	1,600	35.7	1177	44.0	894	43.1
Treated with radiation	137,059	53.6	13,835	51.4	10,538	50.0	3,479	53.0	2,877	64.3	1496	56.0	1178	56.9
% of population in county living below 200% of the federal poverty level in the year 2,000 quartiles														
≥36.31%	57,646	22.5	7,139	26.5	4,384	20.8	1,673	25.5	1,100	24.6	964	36.1	640	30.9
26.96–36.30%	61,122	23.9	6,068	22.6	5,059	24.0	1,535	23.4	996	22.2	572	21.4	505	24.4
19.61–26.95%	67,108	26.2	6,454	24.0	5,570	26.4	1,776	27.1	1,064	23.8	619	23.2	454	21.9
≤19.60%	69,842	27.3	7,239	26.9	6,049	28.7	1,577	24.0	1,317	29.4	518	19.4	473	22.8

what from 1992 to 2007, while the proportions of tubular, inflammatory, and medullary tumors declined somewhat. While relatively high proportions of tubular and lobular tumors were non-Hispanic whites (90.0% and 86.3%, respectively), comparatively few medullary cases were non-Hispanic whites (only 63.9%). Tubular cases rarely presented as stage III or IV disease (0.6%), but by definition all inflammatory cases were stage III or IV. Marked differences by grade were also observed with 88.7% of tubular cases presenting as grade 1 compared to only 1.1% of medullary cases and 1.6% of inflammatory cases. With respect to ER/PR status, 84.0% of mucinous cases and 81.7% of tubular cases were ER+/PR+, while 79.0% of medullary cases and 45.7% of inflammatory cases were ER−/PR−.

In multivariate-adjusted analyses adjusted for ER/PR status, among women 30–49 years of age, women diagnosed with inflammatory carcinoma had an increased risk of mortality compared to ductal carcinoma patients (HR=1.53, 95% CI: 1.38–1.70), while mucinous (HR=0.52, 95% CI: 0.36–0.76), tubular (HR=0.21, 95% CI: 0.07–0.67), and medullary (HR=0.38, 95% CI: 0.30–0.48) cases had reduced risks of mortality (Table 2). Among breast cancer patients ≥50 years of age, in analyses not adjusted for ER/PR status both ductal-lobular and lobular carcinoma patients appeared to have a reduced risk of mortality compared to ductal carcinoma patients, but these reductions were attenuated when ER/PR status was adjusted for. In multivariate analyses adjusted for ER/PR status, lobular (HR=0.93, 95% CI: 0.88–0.98), mucinous (HR=0.69, 95% CI: 0.59–0.80), tubular (HR=0.47, 95% CI: 0.33–0.66), and medullary (HR=0.50, 95% CI: 0.41–0.60) carcinoma cases had reduced risks of mortality, while inflammatory cases had an increased risk (HR=1.50, 95% CI: 1.41–1.61). None of these risk estimates changed substantially when the analysis was restricted to women diagnosed from 1992 to 2002, wherein all patients included had the opportunity to be followed for at least a full 5 years.

In analyses focusing on women 30–49 years of age at diagnosis stratified by ER/PR status, among ER+/PR+ cases inflammatory carcinoma (HR=1.54, 95% CI: 1.27–1.87) patients had an elevated risk of mortality compared to ER+/PR+ ductal cases (Table 3). Among ER−/PR− cases, ductal-lobular (HR=1.20, 95% CI: 1.01–1.44), lobular (HR=1.30, 95% CI: 1.01–1.68), and inflammatory (HR=1.79, 95% CI: 1.48–2.16) carcinoma patients had elevated risks of mortality compared to ductal carcinoma cases, while medullary carcinoma patients had a reduced risk (HR=0.42, 95% CI: 0.33–0.54). Among women ≥50 years of age when diagnosed with an ER+/PR+ breast cancer, mucinous (HR=0.68, 95% CI: 0.56–0.82) and tubular (HR=0.58, 95% CI: 0.40–0.84) carcinoma patients had a reduced risk of mortality compared to ductal carcinoma patients, while inflammatory carcinoma patients had an increased risk (HR=1.44, 95% CI:

Table 2 Risk of breast cancer specific mortality by histologic type according to age at diagnosis, 1992–2007

Histology	Number of cases	Number of deaths	Not adjusted for ER/PR status		Adjusted for ER/PR status		Adjusted for ER/PR status only 1992–2002	
			HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Women 30–49 years of age at diagnosis								
Ductal	67,971	7,719	1.00	Ref	1.00	Ref	1.00	Ref
Ductal-lobular	6,326	551	0.92	0.84–1.00	1.04	0.95–1.13	1.05	0.96–1.16
Lobular	3,620	288	0.89	0.79–1.01	1.00	0.88–1.12	1.04	0.92–1.19
Mucinous	1,038	28	0.47	0.330.69*	0.52	0.36–0.76*	0.58	0.39–0.87*
Tubular	872	3	0.19	0.06–0.60*	0.21	0.07–0.67*	0.23	0.07–0.70*
Inflammatory	840	446	1.60	1.45–1.77*	1.53	1.38–1.70*	1.58	1.41–1.77*
Medullary	944	78	0.46	0.37–0.58*	0.38	0.30–0.48*	0.39	0.30–0.49*
Women 50+ years of age at diagnosis								
Ductal	187,747	18,434	1.00	Ref	1.00	Ref	1.00	Ref
Ductal-lobular	20,574	1,502	0.84	0.79–0.88*	0.95	0.90–1.00	0.96	0.90–1.02
Lobular	17,442	1,391	0.85	0.80–0.89*	0.93	0.88–0.98*	0.90	0.85–0.97*
Mucinous	5,523	168	0.63	0.54–0.74*	0.69	0.59–0.80*	0.67	0.56–0.80*
Tubular	3,605	33	0.45	0.32–0.64*	0.47	0.33–0.66*	0.45	0.31–0.66*
Inflammatory	1,833	1,003	1.56	1.46–1.67*	1.50	1.41–1.61*	1.52	1.41–1.64*
Medullary	1,128	102	0.63	0.52–0.77*	0.50	0.41–0.60*	0.53	0.43–0.66*

[a] All hazard ratios (HR) are adjusted for age, diagnosis year, registry, race/ethnicity, stage, grade, surgery, radiation, and quartile of % incounty living below 200% of the federal poverty level

*$p<0.05$

1.28–1.62). Among ER−/PR− cases, inflammatory carcinoma (HR=1.53, 95% CI: 1.39–1.69) patients had an increased risks of mortality, and medullary cases had a decreased risk of mortality (HR=0.48, 95% CI: 0.38–0.60) compared to ductal carcinoma patients.

While risks of mortality by histologic type did not vary appreciably among ER+/PR+ breast cancer patients ≥50 years of age when stratified by stage (data not shown), they did vary by both tumor size and nodal status. Among ER+/PR+ breast cancer patients ≥50 years of age with tumors ≥ 5.0 cm, ductal-lobular (HR=0.85, 95% CI: 0.73–0.99), lobular (HR=0.78, 95% CI: 0.68–0.89), and mucinous (HR=0.52, 95% CI: 0.34–0.78) carcinoma patients each had lower risks of mortality compared to ductal carcinoma patients (Table 4). Among ER+/PR+ breast cancer patients ≥50 years of age with node-negative disease, lobular carcinoma patients had a lower risk of mortality compared to ductal carcinoma patients (HR=0.79, 95% CI: 0.69–0.91), but among women with node-positive disease they had a higher risk of mortality (HR=1.10, 95% CI: 1.01–1.21). Lastly, when analyses were restricted to ER+/PR+ breast cancer patients ≥ 50 years of age with tumors <2.0 cm, among those with node-negative disease lobular patients had a non-statistically significant lower risk of mortality compared to ductal patients (HR=0.83, 95% CI: 0.66–1.04), but among those with node-positive disease lobular patients had a higher risk of mortality (HR=1.51, 95% CI: 1.18–1.95). Nodal status did not substantially modify risks of mortality for either ductal-lobular or mucinous carcinomas.

Discussion

This study is consistent with previous reports in observing that mucinous, tubular, and medullary carcinomas are associated with a more favorable prognosis compared to ductal carcinoma, while inflammatory carcinoma is associated with a higher risk of mortality [3, 5–7]. Here, we observe that these associations do not vary appreciably by either age at diagnosis or ER/PR status. Tubular cases had particularly low risks of cause specific mortality as only nine of the 2,888 tubular cases included in this study died of their disease. It is well known that the majority of inflammatory and medullary cases are hormone receptor negative [2], but interestingly their prognoses are markedly different. When analyses were restricted to ER−/PR− cases, inflammatory carcinoma was associated with an increased risk of mortality while medullary carcinoma was associated with a lower risk of mortality compared to ductal carcinoma. Current clinical guidelines regarding the use of adjuvant hormonal therapy for breast cancer are based on hormone receptor expression and do not incorporate

Table 3 Risk of breast cancer specific mortality by histologic type according to ER/PR status

Histology	ER+/PR+ cases				ER+/PR− cases				ER−/PR− cases			
	Number of cases	Number of deaths	HR[a]	95% CI	Number of cases	Number of deaths	HR[a]	95% CI	Number of cases	Number of deaths	HR[a]	95% CI
Women 30–49 years of age at diagnosis												
Ductal	40,411	2,994	1.00	Ref	5,770	756	1.00	Ref	19,547	3,580	1.00	Ref
Ductal-lobular	4,853	353	1.08	0.96–1.20	529	52	0.80	0.60–1.06	516	129	1.20	1.01–1.44*
Lobular	3,081	181	0.96	0.83–1.12	269	34	1.15	0.81–1.64	184	62	1.30	1.01–1.68*
Mucinous	877	25	0.75	0.50–1.11	114	–	n/a		39	3	0.44	0.14–1.38
Inflammatory	282	118	1.54	1.27–1.87*	84	39	1.74	1.23–2.47*	419	253	1.79	1.48–2.16*
Medullary	88	6	0.44	0.20–0.98*	42	4	0.46	0.17–1.24	772	64	0.42	0.33–0.54*
Women 50+ years of age at diagnosis												
Ductal	120,532	8,175	1.00	Ref	25,300	2,761	1.00	Ref	38,784	6,978	1.00	Ref
Ductal-lobular	16,105	955	0.95	0.88–1.01	3,087	278	0.90	0.80–1.02	1,194	244	1.10	0.97–1.26
Lobular	13,225	969	0.95	0.89–1.02	3,336	332	0.95	0.85–1.07	788	173	0.93	0.80–1.08
Mucinous	4,632	116	0.68	0.56–0.82*	719	37	0.87	0.63–1.21	147	14	0.66	0.39–1.12
Tubular	2,885	28	0.58	0.40–0.84*	606	1	0.07	0.01–0.50*	72	1	0.21	0.03–1.52
Inflammatory	687	312	1.44	1.28–1.62*	273	143	1.48	1.24–1.77*	802	506	1.53	1.39–1.69*
Medullary	138	16	0.93	0.57–1.51	92	10	0.73	0.39–1.35	865	75	0.48	0.38–0.60*

[a] All hazard ratios (HR) are adjusted for age, diagnosis year, registry, race/ethnicity, stage, grade, surgery, radiation, and quartile of % in county living below 200% of the federal povery level.

*$p<0.05$

Table 4 Risk of breast cancer specific mortality by histologic type among ER+/PR+ breast cancer patients 50+ years of age according to tumor size and nodal status

Histology	Tumor <2.0cm				Tumor 2.0–4.9cm				Tumor ≥5.0cm			
	Number of cases	Number of deaths	HR[a]	95% CI	Number of cases	Number of deaths	HR[a]	95% CI	Number of cases	Number of deaths	HR[a]	95% CI
Ductal	78,227	2,213	1.00	Ref	35,687	3,900	1.00	Ref	5,504	1,577	1.00	ref
Ductal-lobular	9,238	231	1.00	0.88–1.15	5,560	468	0.94	0.85–1.03	1,158	206	0.85	0.73–0.99*
Lobular	6,151	152	1.06	0.86–1.20	4,969	374	0.87	0.78–0.97*	1,836	274	0.78	0.68–0.89*
Mucinous	3,006	39	0.81	0.59–1.12	1,371	46	0.52	0.39–0.70*	239	24	0.52	0.34–0.78*

Histology	Node negative				Node positive			
	Number of cases	Number of deaths	HR[a]	95% CI	Number of cases	Number of deaths	HR[a]	95% CI
All ER+/PR+ cases 50+ years of age								
Ductal	83,812	2,811	1.00	Ref	34,927	4,542	1.00	Ref
Ductal-lobular	10,173	282	0.90	0.80–1.02	5,745	591	1.00	0.92–1.09
Lobular	8,293	223	0.79	0.69–0.91*	4,642	568	1.10	1.01–1.21*
Mucinous	4,197	78	0.70	0.55–0.88*	384	25	0.61	0.41–0.91*
ER+/PR+ cases 50+ years of age with a tumor size <2.0cm								
Ductal	64,137	1,360	1.00	Ref	13,959	784	1.00	Ref
Ductal-lobular	7,151	129	1.00	0.83–1.20	2,076	100	1.03	0.83–1.27
Lobular	5,051	80	0.83	0.66–1.04	1,090	68	1.51	1.18–1.95*
Mucinous	2,884	36	0.77	0.55–1.08	120	2	0.58	0.15–2.35

[a] All hazard ratios (HR) are adjusted for age, diagnosis year, registry, race/ethnicity, stage, grade, surgery, radiation, and quartile of % in county living below 200% of the federal poverty level

*$p<0.05$

histology. Though we lacked data on receipt of adjuvant hormonal therapy, if one assumes that there should not be marked differences in the utilization of hormonal therapy by histologic type, then other factors must be contributing to the favorable prognoses of mucinous and tubular patients compared to ductal patients in our analysis restricted to ER+/PR+ patients. What characteristics beyond the greater frequency of hormone receptor positivity among mucinous and tubular cases contribute to their substantially lower risks of mortality is unclear and further investigation is warranted.

More controversial is whether lobular carcinoma is a "favorable" breast cancer subtype. Most [6, 8–10], but not all [11, 12] recent studies suggest that lobular carcinoma does have a better prognosis when directly compared to ductal carcinoma. However, limitations of these studies include sample size and ability to conduct multivariate-adjusted analyses, particularly analyses that incorporate factors such as hormone receptor status and tumor stage, size, and nodal status. One recent study utilizing data from 15 trials conducted by the International Breast Cancer Study Group did calculate multivariate-adjusted risk estimates and found that lobular patients had a better overall survival within 10 years of diagnosis (HR=0.84, 95% CI: 0.73–0.96), but a poorer overall survival over 10 years after diagnosis (HR=1.50, 95% CI: 1.22–1.96) [13]. However, when the analysis was restricted to ER+ cases, the survival advantage for lobular carcinoma within 10 years of diagnosis was attenuated (HR=0.92, 95% CI: 0.79–1.07) and quite consistent with the results presented here. Not accounting for hormone receptor status likely explains why several studies have found that lobular carcinoma is associated with a lower risk of mortality. As evidence by the data shown here, the reduction in risk of mortality observed for both ductal-lobular and lobular breast carcinomas among women ≥50 years of age disappeared once analyses were adjusted for ER/PR status. This is consistent with the observations that both lobular carcinomas are more likely to be hormone receptor positive and that hormone receptor positive tumors have a better prognosis than hormone receptor negative disease. One subset of women in which lobular carcinoma was associated with a lower risk of mortality compared to ductal carcinoma was among women ≥50 with ER+/PR+ disease and tumors ≥2.0 cm in size. A potential explanation of this finding is that the growth pattern of lobular and ductal tumors are quite distinct as lobular tumors are often characterized by discrete linear strands of cancer cells [14, 15]. Thus, the tumor burden and number of cancer cells in a ≥2.0 cm lobular tumor is likely on average to be less than that of a typical ductal carcinoma with the same clinical characteristics. In contrast, we observed a 10% elevated risk of mortality among lobular patients with node-positive tumors compared to ductal patients with node-positive disease, and a further 51% elevated risk when the analysis was additionally restricted to women with tumors <2.0 cm in size. This suggests that lobular tumors that have spread to lymph nodes may be more clinically aggressive than ductal tumors with lymph node involvement.

The primary limitation of this study was a lack of information on other potential confounders that could influence the associations of interest. Specifically, we lacked data on use of chemotherapy, use of hormonal therapy, HER2 status, and patient characteristics such as body mass index, lifestyle factors, and co-morbid conditions. Misclassification of histology is also an issue since histologic diagnoses were made by a large number of pathologists in individual institutions across the 17 SEER registries. What is reassuring though is that many of risk estimates are quite similar to other published results indicating that the bias resulting from this misclassification may be minimal.

In summary, several differences in risk of mortality persist by histologic type of breast cancer. This study is consistent with numerous prior studies in finding that mucinous, tubular, and medullary carcinomas have a favorable prognosis compared to ductal carcinoma, while inflammatory carcinoma carries a higher risk of mortality. These results also suggest that the relative mortality of lobular carcinoma compared to ductal carcinoma appears to depend on both tumor size and lymph node involvement. Though many of the histologic subtypes studied here are quite rare, consideration of the risk of mortality associated with a given subtype may be useful when making clinical decisions regarding treatment and follow-up as the differences can be quite extreme with tubular carcinoma being the most favorable subtype and inflammatory carcinoma being the least favorable.

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