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EPIDEMIOLOGY

Risk of mortality of node-negative, ER/PR/HER2 breast cancer subtypes in T1, T2, and T3 tumors

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Abstract
Purpose The purpose of this study was to assess differences in breast cancer-specific mortality within tumors of the same size when breast cancer was defined using the three tumor markers estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).
Methods We identified 104,499 cases of node-negative primary female invasive breast cancer from the California Cancer Registry. Tumor size was categorized as T1a, T1b, T1c, T2, and T3. Breast cancer was defined using ER, PR, and HER2. Kaplan–Meier Survival analysis was conducted and Cox Regression was used to compute the adjusted risk of mortality for the ER+/PR+/HER2+, ER−/PR−/HER2− (TNBC), and ER−/PR−/HER2+ (HER2-overexpressing) subtypes when compared with the ER+/PR+/HER2−. Separate models were computed for each tumor size.
Results Unadjusted survival analysis showed that for all tumor sizes, the ER+/PR+ subtypes regardless of HER status have better breast cancer-specific survival than ER−/PR− subtypes. Subtype was not an important factor for risk of mortality for T1a tumors. The ER+/PR+/HER2+ subtype was only a risk for mortality in T1b tumors that were unadjusted for treatment. For all other tumor sizes, the ER+/PR+/HER2+ had the same mortality as the ER+/PR+/HER2− subtype regardless of adjustment for treatment. The HER2-overexpressing subtype had a higher risk of mortality than the ER+/PR+/HER2− subtype except for T1b tumors that were adjusted for treatment. For all tumor sizes, the TNBC had higher hazard ratios than all other subtypes.
Conclusions T1a tumors have the same risk of mortality regardless of ER/PR/HER2 subtype, and ER and PR negativity plays a stronger role in survival than HER2 positivity for tumors of all size.

Keywords Breast cancer · ER/PR/HER2 subtype · Tumor size

Introduction

The use of screening mammography has lead to increased detection of node-negative, stage 1 breast cancer [1–3]. However, the decision to treat small, node-negative breast cancer remains uncertain since women with T1a and T1b tumors have been noted to have an excellent prognosis without chemotherapy [4–8].

In addition to tumor size, tumor subtype is an important prognostic factor for breast cancer survival, but its importance is dependent in part on how subtype is defined. Many studies describe breast cancer subtypes with reference to hormone receptor status and independently, human epidermal growth factor receptor 2 (HER2) status. There are eight combinations of estrogen receptor (ER), progesterone receptor (PR), and HER2 with significant differences in the demographics, tumor characteristics, and survival but it is not common for subtype to be defined using all three markers [9, 10].

The purpose of this study was to assess differences in breast cancer-specific mortality when breast cancer is defined using all three markers and within tumors of the same size.

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Table 1 Demographic and clinicopathologic characteristics of 104,499 cases of node-negative first primary female breast cancer from the California Cancer Registry 2000–2014*

	T1a and micro (<1–4.99) $n = 9077$	T1b (5.00–9.33) $n = 23,770$	T1c (10.00–19.33) $n = 43,688$	T2 (20.00–49.99) $n = 24,655$	T3 (50.00+) $n = 3307$	Total $n = 104,499$
Mean age (years) ± SD	60.14 ± 11.80	61.90 ± 11.74	60.59 ± 12.69	58.98 ± 13.71	57.83 ± 14.86	59.92 ± 13.618
Age						
<46	1001 (11.0%)	2080 (8.8%)	5443 (12.5%)	4225 (17.1%)	723 (21.8%)	13,472 (12.9%)
46–69	5993 (66.0%)	15,055 (63.3%)	26,962 (61.7%)	14,566 (59.1%)	1837 (55.5%)	64,413 (61.6%)
70+	2083 (22.9%)	6635 (27.9%)	11,283 (25.8%)	5864 (23.8%)	749 (22.6%)	26,614 (25.5%)
ER/PR/HER2 subtype						
ER+/PR+/HER2−	5734 (63.2%)	17,126 (72.0%)	28,859 (66.1%)	12,704 (51.5%)	1460 (44.1%)	65,883 (63.0%)
ER+/PR+/HER2+	693 (7.6%)	1382 (5.8%)	3334 (7.6%)	2091 (8.5%)	271 (8.2%)	7771 (7.4%)
ER+/PR−/HER2−	954 (10.5%)	2301 (9.7%	3750 (8.6%)	220 (8.9%)	333 (10.1%)	9541 (9.1%)
ER+/PR−/HER2+	315 (3.5%)	458 (1.9%	1001 (2.3%)	79 (3.2%)	99 (3.0%)	2670 (2.6%)
ER−/PR+/HER2−	56 (0.6%)	122 (0.5%)	301 (0.7%)	238 (1.0%)	35 (1.1%)	752 (0.7%)
ER−/PR+/HER2+	24 (0.3%)	37 (0.2%)	112 (0.3%)	87 (0.4%)	14 (0.4%)	274 (0.3%)
ER−/PR−/HER2−	634 (7.0%)	1697 (7.1%)	4710 (10.8%)	4943 (20.0%)	793 (24.0%)	12,777 (12.2%)
ER−/PR−/HER2+	667 (7.3%)	647 (2.7%)	1621 (3.7%)	1592 (6.5%)	304 (9.2%)	4831 (4.6%)
Tumor grade						
Well differentiated; grade 1	3886 (42.8%)	10,307 (43.4%)	11,838 (27.1%)	3476 (14.1%)	487 (14.7%)	29,994 (28.7%)
Moderately differentiated; grade 2	3745 (41.3%)	10,091 (42.5%)	20,167 (46.2%)	9520 (38.6%)	1223 (37.0%)	44,746 (42.8%)
Poorly differentiated; grade 3	1338 (14.7%)	3251 (13.7%)	11,362 (26.0%)	11,310 (45.9%)	1524 (46.1%)	28,785 (27.5%)
Undifferentiated; grade 4	108 (1.2%)	121 (0.5%)	321 (0.7%)	349 (1.4%)	75 (2.3%)	974 (0.9%)
Race/ethnicity						
White	6099 (67.2%)	16,986 (71.5%)	29,405 (67.3%)	14,778 (59.9%)	1912 (57.8%)	69,180 (66.2%)
Black	408 (4.5%)	1027 (4.3%)	2240 (5.1%)	1700 (6.9%)	299 (9.0%)	5674 (5.4%)
Hispanic	1278 (14.1%)	3132 (13.2%)	6708 (15.4%)	4667 (18.9%)	680 (20.6%)	16,465 (15.8%)
Asian/Pacific Islander	1292 (14.2%)	2625 (11.0%)	5335 (12.2%)	3510 (14.2%)	418 (12.6%)	13,180 (12.6%)
Socioeconomic status (SES)						
SES 1—lowest	815 (9.0%)	2004 (8.4%)	4413 (10.1%)	3089 (12.5%)	505 (15.3%)	10,826 (10.4%)
SES 2	1271 (14.0%)	3461 (14.6%)	6817 (15.6%)	4286 (17.4%)	596 (18.0%)	16,431 (15.7%)
SES 3	1782 (19.6%)	4746 (20.0%)	8721 (20.0%)	4972 (20.2%)	649 (19.6%)	20,870 (20.0%)
SES 4	2281 (25.1%)	5906 (24.8%)	10,692 (24.5%)	5855 (23.7%)	722 (21.8%)	25,456 (24.4%)
SES 5—highest	2928 (32.3%)	7653 (32.2%)	13,045 (29.9%)	6453 (26.2%)	837 (25.3%)	30,916 (29.6%)
Chemotherapy	703 (7.7%)	2918 (12.3%)	12,624 (28.9%)	12,426 (50.4%)	2042 (61.7%)	30,713 (29.4%)
Radiation therapy	4930 (54.3%)	14,743 (62.0%)	24,856 (56.9%)	10,904 (44.2%)	1606 (48.5%)	57,039 (54.6%)
Endocrine therapy	4048 (44.6%)	12,259 (51.6%)	22,549 (51.6%)	10,216 (41.4%)	1229 (37.1%)	50,301 (48.1%)
Surgery						
None	4 (0.04%)	17 (0.1%)	64 (0.1%)	139 (0.6%)	65 (2.0%)	289 (0.3%)

Table 1 continued

	T1a and micro (<1–4.99) $n = 9077$	T1b (5.00–9.33) $n = 23{,}770$	T1c (10.00–19.33) $n = 43{,}688$	T2 (20.00–49.99) $n = 24{,}655$	T3 (50.00+) $n = 3307$	Total $n = 104{,}499$
Lumpectomy	6242 (68.8%)	18,519 (77.9%)	31,670 (72.5%)	13,830 (56.1%)	936 (28.3%)	71,197 (68.1%)
Mastectomy	2831 (31.2%)	5234 (22.0%)	11,954 (27.4%)	10,686 (43.3%)	2308 (69.7%)	33,013 (31.6%)

* Percentages are of total cases within a tumor size

Methods

The study utilized the California Cancer Registry (CCR) to identify 104,499 cases of node-negative primary female invasive breast cancer first diagnosed between January 1, 2000 and December 31, 2014 and reported to the CCR as of December 31, 2015 (ICDO-3 sites C50.0–C50.9) [11]. Cases had complete data for tumor size, grade, American Joint Commission on Cancer (AJCC) stage of diagnosis, cause of death, age, socioeconomic status (SES), and race/ethnicity.

Cases were reported to the Cancer Surveillance Section of the California Department of Public Health from hospitals and other facilities providing care or therapy to cancer patients residing in California [12]. Breast cancer-specific mortality was defined as a death due to breast cancer as documented by the codes ranging from C50.01 to C50.91 of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [13].

Tumor size was categorized as T1a and micro (<1.00–4.99 mm), T1b (5.00–9.99 mm), T1c (10.00–19.99 mm), T2 (20.00–49.99 mm), and T3 (50.00+ mm).

ER and PR status were recorded according to pathologists' interpretation of the assays. ER and PR were considered negative if immunoperoxidase staining of tumor cell nuclei was less than 5%. ER and PR status may also have been determined by examining cytosol protein. ER was considered negative if there were fewer than 3 fmol/mg of cytosol protein, and PR was considered negative if there were fewer than 5 fmol/mg of cytosol protein [11].

HER2 was assessed through immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). IHC is scored on a qualitative scale from 0 to 3+, based on interpretation of staining intensity, with 0 through 1+ classified as negative, 2+ as borderline, and 3+ as positive [14] FISH was scored on a quantitative scale with less than 2 copies of the HER2 gene classified as negative and two or more copies as positive [15].

Using ER, PR, and HER2, eight breast cancer subtypes were defined: ER+/PR+/HER2−, ER+/PR+/HER2, ER+/PR−/HER2−, ER+/PR−/HER2, ER−/PR+/HER2−, ER−/PR+/HER2+, ER−/PR−/HER2− (triple-negative or TNBC), and ER−/PR−/HER2+ (HER2-overexpressing).

SES was derived using data from the 2000 US census for cases diagnosed from 2000–2005 and the American Community Survey was used for cases diagnosed from 2006–2014 [16]. This SES variable is an index that utilizes education, employment characteristics, median household income, proportion of the population living 200% below the Federal Poverty Level, median rent and median housing

Table 2 Kaplan–Meier unadjusted 5 year and 10 year breast cancer-specific survival and 95% confidence intervals for the ER+/PR+/HER2−, ER+/PR+/HER2+, ER−/PR−/HER2+, and ER−/PR−/HER2− breast cancer subtypes

	5-year (95% CI)	10-year (95% CI)
T1a		
ER+/PR+/HER2−	99.3% (99.3%, 99.4%)	98.5% (98.0%, 99.0%)
ER+/PR+/HER2+	99.6% (99.6%, 99.6%)	98.4% (97.0%, 99.7%)
ER−/PR−/HER2+	97.7% (97.2%, 98.1%)	96.0% (93.9%, 98.1%)
ER−/PR−/HER2−	97.2% (96.9%, 97.9%)	95.6% (93.3%, 97.8%)
T1b		
ER+/PR+/HER2−	99.4% (99.3%, 99.4%)	98.4% (98.0%, 98.7%)
ER+/PR+/HER2+	99.0% (98.8%, 99.3%)	97.1% (95.9%, 98.3%)
ER−/PR−/HER2+	97.3% (97.0%, 97.6%)	94.3% (91.5%, 97.0%)
ER−/PR−/HER2	95.5% (95.1%, 95.9%)	92.6% (90.9%, 94.3%)
T1c		
ER+/PR+/HER2−	98.7% (98.6%, 98.7%)	96.1% (95.7%, 96.5%)
ER+/PR+/HER2+	98.2% (98.0%, 98.4%)	95.3% (94.3%, 96.3%)
ER−/PR−/HER2+	95.1% (94.6%, 95.5%)	92.2% (90.5%, 93.8%)
ER−/PR−/HER2−	92.6% (92.2%, 92.9%)	89.4% (88.3%, 90.6%)
T2		
ER+/PR+/HER2−	96.5% (96.3%, 96.6%)	91.0% (90.1%, 91.8%)
ER+/PR+/HER2+	95.6% (95.2%, 95.9%)	89.9% (88.0%, 91.8%)
ER−/PR−/HER2+	92.0% (91.3%, 92.7%)	87.6% (85.5%, 89.9%)
ER−/PR−/HER2−	86.5% (86.1%, 87.0%)	82.2% (80.8%, 83.6%)
T3		
ER+/PR+/HER2−	94.1% (93.6%, 94.7%)	88.1% (85.3%, 91.0%)
ER+/PR+/HER2+	93.1% (91.1%, 95.2%)	78.0% (69.8%, 86.2%)
ER−/PR−/HER2+	83.1% (80.9%, 85.2%)	78.0% (72.4%, 83.7%)
ER−/PR−/HER2−	77.3% (75.3%, 79.3%)	72.4% (68.3%, 76.5%)

value of census tract of residence for case and denominator population. A principal component analysis was used to identify quintiles of SES ranging from 1 (the lowest) to 5 (the highest) [17]. This area based SES measure has been used in many studies utilizing cancer registry data [18–26].

Race/ethnicity was classified based on information obtained from the medical record which was derived from patient self-identification, assumptions based on personal appearance, or inferences based on the race of the parents, birthplace, surname, or maiden name. The four mutually exclusive categories of race/ethnicity used in this study were white, African American or black, Hispanic, and Asian/Pacific Islander (API).

Statistical analysis

Contingency tables were used to evaluate the distribution of age, subtype, tumor grade, race/ethnicity, treatment, and SES for each tumor size. Differences in mean age between the tumor sizes were compared using analysis of variance and post hoc tests.

Kaplan–Meier survival analysis and the Log-Rank test were used to compare unadjusted survival rates among the subtypes for each tumor size. Five-year and 10-year survival and 95% confidence intervals were reported. Cox Proportional Hazards modeling was used to compute the risk of mortality for the ER+/PR+/HER2+, TNBC, and HER2-overexpressing subtypes when compared with the ER+/PR+/HER2−. These four subtypes were chosen to facilitate comparison of ER+/PR+ tumors with ER−/PR− tumors and to evaluate the effect of HER2-positivity.

Separate models were computed for each tumor size so that all hazard ratios (HR) and 95% confidence intervals (CI) assessed differences between tumor subtypes of the same size. One set of models was adjusted for age, tumor grade, race/ethnicity, and SES. The second set of models included all of these variables and in addition, surgery (lumpectomy, mastectomy), chemotherapy, hormone therapy, and radiation therapy. Stage was excluded from analyses because of its strong correlation with tumor size. Variables were considered statistically significant and HRs were interpreted only when the Wald χ^2 was $p < 0.05$.

All analyses were performed using IBM SPSS 21.0 [27]. This research study involved analysis of existing data from the CCR without subject identifiers or intervention. Therefore, the study was categorized as exempt from institutional review board oversight.

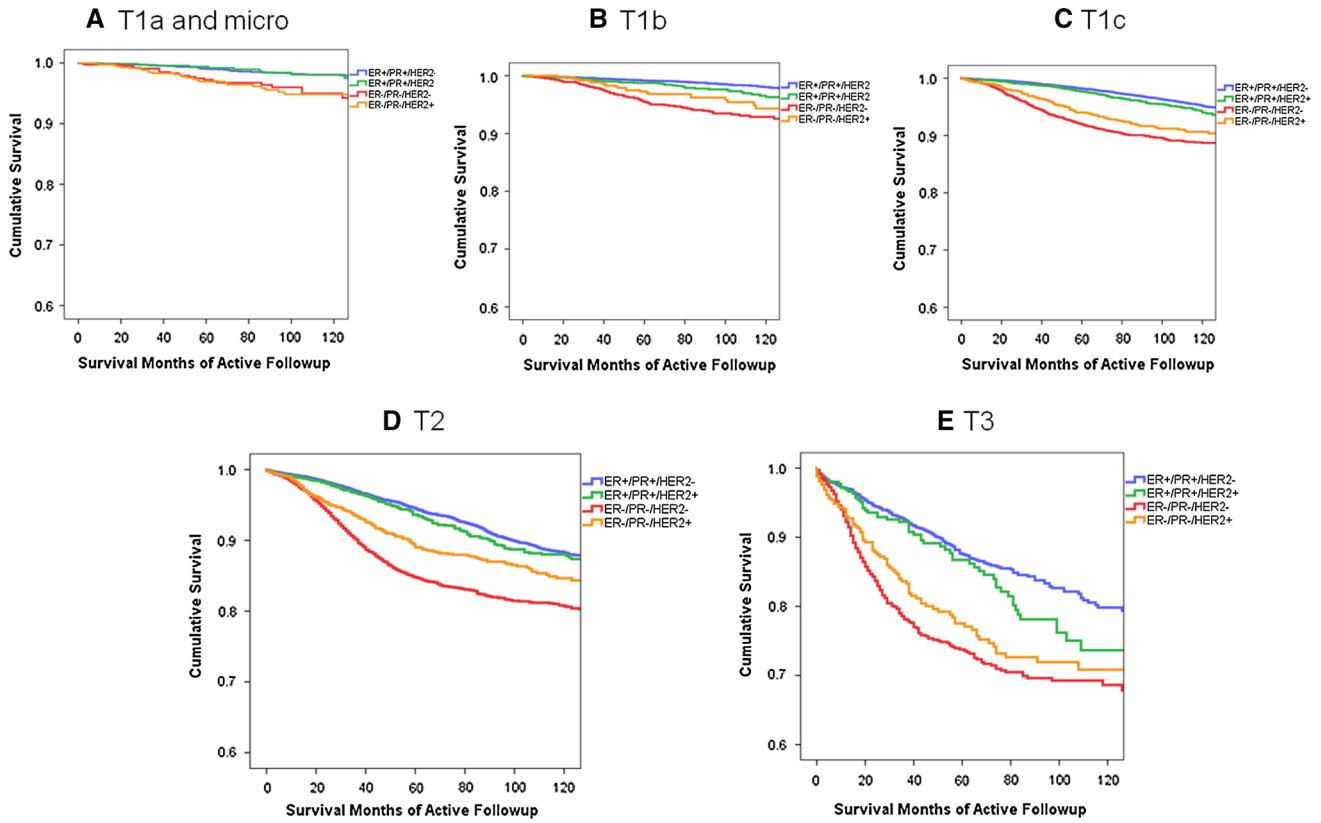

Fig. 1 Unadjusted Kaplan–Meier breast cancer-specific survival for T1a (**a**), T1b (**b**), T1c (**c**), T2 (**d**) and T3 (**e**). The ER+/PR+/HER2− had better survival than the ER+/PR+/HER2+ subtype for T1b ($\chi^2 = 9.24$, $p = 0.002$) (**b**) and T1c tumors ($\chi^2 = 6.15$, $p = 0.013$) (**c**)

Results

Median follow-up time was 5.2 years (range, 0–14.9 years). Table 1 shows the distribution of demographic and clinicopathologic features by increasing tumor size. The highest percent of cases (41.8%) were T1c. Women with T3 tumors were younger than women with smaller sized tumors ($F_{4,\ 104{,}494} = 196{,}692$, $p < 0.001$).

The ER+/PR+/HER2−, ER+/PR+/HER2+, ER−/PR−/HER2−, and ER−/PR−/HER2+ subtypes comprised 87.3% of all cases. TNBC and the ER−/PR−/HER2+ subtypes had a higher percent of T2 and T3 tumors when compared with the other subtypes. Black women had the highest percent of T2 and T3 tumors. The two lowest SES categories had the highest percent of the largest tumors. Table 2 shows that for all tumor sizes, the ER+/PR+/HER2− had the best and the TNBC had the worst 5 and 10 year survival. Based on overlapping confidence intervals, the ER+/PR+/HER2+ subtype had the same 5 and 10 year unadjusted survival as the ER+/PR+/HER2− subtype except for the 5-year survival of T1c.

For T1a (Fig. 1a), T2 (Fig. 1d), and T3 (Fig. 1e) tumors, there were no statistically significant differences in unadjusted breast cancer-specific survival between the ER+/PR+/HER2− and ER+/PR+/HER2+ subtypes. The ER+/PR+/HER2− had better survival than the ER+/PR+/HER2+ subtype for T1b ($\chi^2 = 9.24$, $p = 0.002$) (Fig. 1b) and T1c tumors ($\chi^2 = 6.15$, $p = 0.013$) (Fig. 1c). For all tumor sizes, the TNBC and HER2-overexpressing subtypes had statistically significant worse survival than the ER+/PR+/HER2− subtype.

Results of the Cox Regression Analysis (Table 3) indicated that for T1a tumors, the Wald χ^2 was not statistically significant with or without adjustment for treatment. The ER+/PR+/HER2+ subtype was only a risk for mortality in T1b tumors that were unadjusted for treatment. For all other tumor sizes, the ER+/PR+/HER2+ had the same mortality as the ER+/PR+/HER2− subtype regardless of adjustment for treatment. Table 3 also showed that TNBC tumors had an increased risk of mortality for T1b and larger tumors regardless of adjustment for treatment. The HER2-overexpressing subtype had a higher risk of mortality than the ER+/PR+/HER2− subtype except for T1b tumors that were adjusted for treatment. For all tumor sizes, the TNBC had higher hazard ratios than the HER2-overexpressing subtype.

Table 3 Hazard ratios (95% CI) for node-negative ER+/PR+/HER2+, ER−/PR−/HER2+, ER−/PR−/HER2− versus the ER+/PR+/HER2− by increasing tumor size[+]

	T1a and micro (<1–4.99 mm)* $n = 9077$		T1b (5.00–9.99 mm) $n = 23{,}770$		T1c (10.00–19.99 mm) $n = 43{,}688$		T2 (20.00–49.99 mm) $n = 24{,}655$		T3 (50.00+ mm) $n = 3307$	
	Unadjusted for treatment HR (95% CI)	Adjusted for treatment HR (95% CI)	Unadjusted for treatment HR (95% CI)	Adjusted for treatment HR (95% CI)	Unadjusted for treatment HR (95% CI)	Adjusted for treatment HR (95% CI)	Unadjusted for treatment HR (95% CI)	Adjusted for treatment HR (95% CI	Unadjusted for treatment HR (95% CI)	Adjusted for treatment HR (95% CI)
ER+/PR+/HER2−	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
ER+/PR+/HER2+	*	*	1.60 (1.07, 2.40)	1.36 (0.94, 1.97)	1.08 (0.87, 1.34)	1.07 (0.86, 1.27)	1.06 (0.86, 1.29)	1.07 (0.90, 1.27)	1.34 (0.86, 2.08)	1.17 (0.84, 1.60)
ER−/PR−/HER2+	*	*	2.25 (1.38, 3.66)	1.27 (0.78, 2.07)	1.42 (1.12, 1.81)	1.33 (1.05, 1.67)	1.26 (1.03, 1.54)	1.24 (1.04, 1.19)	1.56 (1.06, 2.30)	1.53 (1.11, 2.07)
ER−/PR−/HER2−	*	*	3.47 (2.52, 4.78)	2.24 (1.61, 3.11)	2.05 (1.74, 2.40)	1.84 (1.55, 2.16)	1.99 (1.74, 2.29)	1.83 (1.62, 2.11)	2.11 (1.54, 2.90)	2.02 (1.56, 2.62)

[+] Hazard ratios are adjusted for age, grade, race/ethnicity, and socioeconomic status. Hazard ratios adjusted for treatment also include surgery (lumpectomy, mastectomy), chemotherapy, hormone therapy, and radiation therapy

* Unadjusted and adjusted Wald χ^2 was not statistically significant for T1a tumors ($p > 0.05$)

Discussion

The results of the present study found that for T1a tumors, there is no increased risk of mortality regardless of subtype. However, the treatment-adjusted risk of mortality for the TNBC and HER2-overexpressing subtypes varies by tumor size. For T1a tumors there is no increased risk of mortality for the TNBC but the risk of mortality is increased for all larger sized TNBC tumors with or without adjustment for treatment. In general, this is also true for the HER2-overexpressing subtype.

There is evidence for and against treatment of small, node-negative tumors. Chemotherapy has been shown to have no effect on the risk of mortality in T1a and T1b luminal B tumors after adjustment for age, grade, and lymph node status [8]. The present study is in agreement and provides additional insight on the role of tumor subtype for various sized tumors. We found no increased risk of treatment-adjusted mortality for the node-negative ER+/PR+/HER2+ subtype of any size when compared with the ER+/PR+/HER2− subtype. In addition, 5 and 10 year unadjusted survival of the ER+/PR+/HER2+ subtype is very similar to the ER+/PR+/HER2− subtype.

The unofficial mantra in medical oncology is that HER2 positivity always imparts a dire prognosis. However, the present study suggests that when taking ER and PR into consideration, HER positivity is not always detrimental. In fact, it appears that ER and PR negativity may be more important, supporting previous research [9, 28]. The risk of mortality for the ER+/PR+/HER2+ subtype is very similar to the ER+/PR+/HER2− subtype and the hazard ratios for the TNBC are higher than the HER2-overexpressing subtype for all tumor sizes. Conversely, other investigators have found that HER2-positive T1a and T1b tumors have a significant risk of relapse when compared with HER2-negative tumors and suggests treatment is warranted even for small, HER2-positive tumors regardless of ER and PR status [4, 5].

This retrospective, population-based study using registry data has limitations and cannot provide definitive answers for or against treatment of small tumors of any subtype. These limitations have been amply described [20, 29, 30]. Histologic grading of tumors as well as tests for ER, PR, and HER2 were performed by a wide variety of laboratories without central review. Treatment information from the CCR is quite generic and lacks specific information regarding drug type, dose, and use of anti-HER2 directed therapy. Despite these limitations, the strength of this study is the use of a large number of node-negative breast cancer cases which allowed for stratified analysis of tumor size. Findings obtained from several thousand cases provide real world insight.

Conclusions

This study shows that T1a tumors have the same risk of mortality regardless of ER/PR/HER2 subtype and that ER and PR negativity plays a stronger role in survival than HER2 positivity for tumors of all size.

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Compliance and ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This research study involved analysis of existing data from the CCR without subject identifiers or intervention. Therefore, the study was categorized as exempt from institutional review board oversight.

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