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ORIGINAL PAPER

Differences in clinicopatholgic characteristics and risk of mortality between the triple positive and ER+/PR+/HER2− breast cancer subtypes

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Abstract

Purpose This study compared the demographic and clinicopathologic characteristics and risk of mortality between the triple positive (TP) and ER+/PR+/HER2− breast cancer subtypes.

Methods Cases of first primary female invasive TP and ER+/PR+/HER2− breast cancer were obtained from the California Cancer Registry. Logistic regression analysis was used to compare differences in factors associated with the TP versus the ER+/PR+/HER2− subtype. Cox regression was used to compute the adjusted risk of breast cancer-specific mortality of the TP versus ER+/PR+/HER2−.

Results The odds of TP versus ER+/PR+/HER2− were higher with advanced stage, high grade, low SES, ≤45 years of age (OR 1.48; CI 1.40–1.55), black (OR 1.11; CI 1.02–1.21), Asian/Pacific Islander (OR 1.15; CI 1.09–1.22), and uninsured (OR 1.42; CI 1.15–1.73). Unadjusted survival analysis indicated worse survival for the TP when compared with the ER+/PR+/HER2− subtype. However, adjusted risk of mortality for the TP subtype was not statistically significantly worse than the ER+/PR+/HER2− subtype.

Conclusions Young age, advanced stage and grade, low SES, black and API race, and lack of health insurance are more common in the TP subtype than in the ER+/PR+/HER2− subtype. However the risk of mortality between these two subtypes is similar.

Keywords Breast cancer · Luminal B · Triple positive · Mortality · Risk factors · Population-based registry

Introduction

Breast cancer has been traditionally classified as luminal A, luminal B, triple negative, and HER2-overexpressing based estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). However, when considering each individual tumor marker, eight subtypes of breast cancer can be defined. Differences in incidence and survival have been noted among these eight subtypes [1, 2]. For example, the clinicopathologic characteristics and survival of triple negative breast cancer (TNBC) have been amply described [3–5]. TNBC has been shown to have the worst survival and is more common in young women, black and Hispanic women, and women of lower socioeconomic status (SES) when compared with the ER+/PR+/HER2− subtype, the most common breast cancer subtype [3, 6, 7].

Without consideration of ER and PR, HER2-positive tumors have poorer survival than HER2-negative tumors [1, 8]. However when all three markers are utilized to categorize breast cancer, the ER+/PR+/HER2+ or triple positive (TP) subtype has relative and breast cancer-specific survival quite similar to the ER+/PR+/HER2− subtype [1, 2]. The TNBC subtype comprises approximately 12% of breast cancer cases and has been extensively investigated [3, 4, 9, 10]. In contrast, The TP subtype, a subset of the luminal B classification, makes up between 9% and 11% of all breast cancer cases and there are few epidemiologic studies that have provided a comprehensive evaluation of risk of mortality and the factors associated with this subtype.

The purpose of this study was to compare the demographic, clinicopathologic characteristics, and risk of

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mortality between the triple positive (TP) and ER+/PR+/HER2− breast cancer subtypes.

Materials and methods

The study utilized the California Cancer Registry (CCR) to identify 106,758 cases of first primary female TP and ER+/PR+/HER2− breast cancer diagnosed between January 1, 2000 and December 31, 2015 and reported to the CCR as of December 31, 2016. (ICDO-3 sites C50.0–C50.9) [11]. Cases included in the study had complete data for tumor size, grade, American Joint Commission on Cancer (AJCC) stage of diagnosis, surgery (lumpectomy, mastectomy), chemotherapy, hormone therapy, radiation therapy, cause of death, age, socioeconomic status (SES), Charlson Comorbidity Index (CCI), insurance status, and race/ethnicity. 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.

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]. Mortality information was obtained from the Vital Records Division of the California Department of Public Health and was complete through December, 2015. 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].

ER and PR status were recorded according to pathologists' interpretation of the assays. Prior to the year 2010, ER and PR were considered negative if immunoperoxidase staining of tumor cell nuclei was less than 5%. Beginning in 2010, this was changed to less than 1%. ER and PR status may also have been determined by examining cytosol protein. ER was considered negative if there were fewer than three femtomoles per milligram of cytosol protein and PR was considered negative if there were fewer than five femtomoles per milligram of cytosol protein [11].

HER2 was assessed through 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 two copies of the HER2 gene classified as negative and two or more copies as positive [15].

Race was 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. For the present study, race/ethnicity was classified into five mutually exclusive categories: non-Hispanic white, African American or black, Hispanic, Asian/Pacific Islander, and American Indian.

SES was derived using data from the 2000 US census for cases diagnosed from 2000 to 2005, and the American Community Survey was used for cases diagnosed from 2006 to 2015 [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 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 [3, 18–25].

Insurance status was classified private, uninsured, Medicaid, Medicare, and Other which included Military, Veterans Administration, Indian Public Health, and County.

Treatment with surgery included lumpectomy or mastectomy. Chemotherapy, hormone therapy, and radiation therapy were classified as given or not given without regard to specific agents. The CCI is a weighted index that takes into account the number and seriousness of comorbid diseases [26]. For this study, the CCI was categorized as a score of 0, 1, and 2 or greater.

Statistical analysis

Contingency tables were used to evaluate the distribution of age, stage, tumor grade and size, race/ethnicity, treatment, SES, insurance status, and CCI, between the TP and ER+/PR+/HER− subtypes. The difference in mean age between the subtypes was compared using analysis of variance.

Logistic regression analysis was used to compute the adjusted odds of age, stage, tumor grade, race/ethnicity, SES, insurance status, and CCI, of being associated with TP versus the ER+/PR+/HER− subtype. All variables were entered simultaneously and odds ratios (OR) and 95% confidence intervals (CI) were computed. The expected probability of the TP subtype was computed for various combinations of risk factors [27].

Kaplan–Meier survival analysis and the Log-Rank test were used to compare unadjusted survival between the two subtypes. Five and ten year cumulative survival and 95% confidence intervals were computed.

Cox Proportional Hazards modeling was used to compute the risk of mortality for the TP subtype when adjusted for age, stage, tumor grade, SES, insurance status, CCI, and treatment. All variables were entered simultaneously. Tumor size was excluded from the analysis because of its strong correlation with AJCC stage.

Table 1 Demographic and tumor characteristics of the ER+/PR+/HER2− and ER+/PR+/HER2+ subtypes in women with invasive breast cancer from the California Cancer Registry 2000–2015

	ER+/PR+/HER2− *n* = 93,984 *n* (%)	ER+/PR+/HER2+ *n* = 12,774 *n* (%)
Age at diagnosis		
≤45	11,528 (12.3)	2,886 (22.6)
46–69	55,990 (59.6)	7,439 (58.2)
70+	26,466 (28.2)	2,449 (19.2)
AJCC stage at diagnosis		
Stage 1	51,340 (54.6)	5,048 (39.5)
Stage 2	32,059 (34.1)	5,379 (42.1)
Stage 3	8,425 (9.0)	1,797 (14.1)
Stage 4	2,160 (2.3)	550 (4.3)
Tumor grade		
Well differentiated; grade I (low)	30,094 (32.0)	1,374 (10.8)
Moderately differentiated; grade II (low)	47,405 (50.4)	5,648 (44.2)
Poorly differentiated; grade III (high)	16,031 (17.1)	5,570 (43.6)
Undifferentiated; grade IV (high)	454 (0.5)	182 (1.4)
Tumor size		
T1a + micro ≤ 5 mm	6,542 (7.0)	747 (5.8)
T1b 6–10 m	18,327 (19.5)	1,456 (11.4)
T1c 11–20 mm	37,006 (39.4)	4,458 (34.9)
20–50 mm	25,737 (27.4)	4,713 (36.9)
T3 50 mm +	6,372 (6.8)	1,400 (11.0)
Race/ethnicity		
White	62,729 (66.7)	7,606 (59.5)
Black	4,554 (4.8)	800 (6.3)
Hispanic	14,899 (15.9)	2,341 (18.3)
Asian/Pacific Islander	11,399 (12.1)	1,968 (15.4)
American Indian	403 (0.4)	59 (0.5)
Socioeconomic status (SES)		
SES 1—low	10,000 (10.6)	1,580 (12.4)
SES 2	15,080 (16.0)	2,238 (17.5)
SES 3	18,812 (20.0)	2,629 (20.6)
SES 4	22,805 (24.3)	3,035 (23.8)
SES 5—high	27,287 (29.0)	3,292 (25.8)
Insurance status		
Private	57,868 (61.6)	8,085 (63.3)
Uninsured	545 (0.6)	129 (1.0)
Medicaid	10,118 (10.8)	1,884 (14.7)
Medicare	24,474 (26.0)	2,501 (19.6)
Other	979 (1.0)	175 (1.4)
Charlson Comorbidity Index		
0	70,898 (75.4)	9,975 (78.1)
1	15,719 (16.7)	2,005 (15.7)
2+	7,367 (7.8)	794 (6.2)
Chemotherapy		
No	66,077 (70.3)	4,731 (37.0)
Yes	27,907 (29.7)	8,043 (63.0)
Hormone therapy		
No	39,039 (41.5)	6,565 (51.4)
Yes	54,945 (58.5)	6,209 (48.6)

Table 1 (continued)

	ER+/PR+/HER2− $n = 93,984$ n (%)	ER+/PR+/HER2+ $n = 12,774$ n (%)
Radiation therapy		
No	46,017 (49.0)	7,056 (55.2)
Yes	47,967 (51.0)	5,718 (44.8)
Surgery		
None	2,299 (2.4)	577 (4.5)
Lumpectomy	55,370 (58.9)	6,049 (47.4)
Mastectomy	36,315 (38.6)	6,148 (48.1)
Mean age at diagnosis(± SD)	61.3 ± 13.3	56.7 ± 13.7

Percents are computed using total number of cases within the ER+/PR+/HER2− and ER+/PR+/HER2+ subtypes

American Indian race was excluded from multivariable analyses due to an insufficient number of cases. All analyses were performed using IBM SPSS 21.0 [28].

Results

Women with the TP subtype were approximately 5 years younger than women with the ER+/PR+/HER2− subtype ($F_{1,106,756} = 1,347.14$, $p < 0.001$) (Table 1). Table 1 shows that women 45 years of age and younger were more likely to have the TP subtype. Advanced stage, high grade, and large tumor size were associated with the TP subtype whereas the reverse was true for the ER+/PR+/HER2− subtype. A higher percent of black, Hispanic, and API women had the TP subtype when compared with the ER+/PR+/HER2− subtype. In contrast, the majority of white women had the ER+/PR+/HER2− subtype. A lower percent of women with the TP subtype had a CCI of 1 or 2 +.

Results of the logistic regression analysis showed that when compared with the ER+/PR+/HER2− subtype, the TP subtype was associated with young age, advanced stage and grade, black and Asian/Pacific Islander race, lower SES, and being uninsured or having Medicaid (Table 2). A CCI Score of 2+ was associated with reduced odds of the TP subtype when compared with the ER+/PR+/HER2− subtype.

The expected probability of an woman who was uninsured, Asian/Pacific lslander 45 years of age or younger, in the lowest SES with a stage 4, grade 4, tumor, and CCI of 1 had a 54% expected probability of the TP subtype versus the ER+/PR+/HER2− subtype. In contrast, a white woman who was 70 + years of age, in the highest SES with private insurance, a stage 1, grade 1 tumor, and CCI of 2 + had only a 4% probability of being TP rather than the ER+/PR+/HER2−.

Survival analysis (Fig. 1) shows that the TP subtype had worse overall survival than the ER+/PR+/HER2− subtype. ($X^2 = 206.05$, $p < 0.001$). Table 3 shows the 5 and 10 year survival and 95% confidence intervals for each of the subtypes. At both 5 and 10 years, the TP had worse survival than the ER+/PR+/HER2− subtype and the confidence intervals did not overlap.

Table 4 shows that older age, higher stage, grade, SES, and CCI, as well as being black, uninsured, or having Medicaid or Medicare insurance were associated with increased risk of mortality. Hispanic and API race, as well as treatment with chemotherapy, radiation, hormone therapy, or surgery decreased the risk of mortality. When adjusted for all of these factors, risk of mortality for the TP subtype was not statistically significantly higher than the ER+/PR+/HER2− subtype (HR = 1.04, 95% CI 0.98, 1.10).

Discussion

The present investigation found that when compared with the ER+/PR+/HER2− subtype, women with TP breast cancer are diagnosed at a higher stage, advanced grade, and are approximately 5 years younger. These results are consistent with the findings of Alqaisi et al. [29] who reported that the TP subtype had a younger age of diagnosis than all other ER-positive subtypes. In contrast, Alwan and colleagues [30] reported that only 20% of TP cases

Table 2 Odds ratios and 95% confidence intervals (CI) from logistic regression analysis for the ER+/PR+/HER2+ breast cancer subtype when compared with the ER+/PR+/HER2− subtype

	OR (95% CI)
Age	
≤45	1.48 (1.40, 1.55)
46–69	Reference
70+	0.75 (0.71, 0.80)
AJCC stage	
1	Reference
2	1.18 (1.13, 1.24)
3	1.28 (1.20, 1.36)
4	1.56 (1.12, 1.71)
Grade	
Well differentiated; grade I (low)	Reference
Moderately differentiated; grade II (low)	2.41 (2.27, 2.56)
Poorly differentiated; grade III (high)	6.29 (5.90, 6.71)
Undifferentiated; grade IV (high)	7.07 (5.91, 8.46)
Charlson Comorbidity Index	
0	Reference
1	0.96 (0.91, 1.01)
2+	0.87 (0.81, 0.95)
Race/ethnicity[a]	
White	Reference
Black	1.11 (1.02, 1.21)
Hispanic	1.01 (0.95, 1.06)
Asian/Pacific Islander	1.15 (1.09, 1.22)
Socioeconomic status	
SES 1—low	1.12 (1.04, 1.20)
SES 2	1.13 (1.06, 1.20)
SES 3	1.08 (1.02, 1.14)
SES 4	1.06 (1.01, 1.12)
SES 5—high	Reference
Insurance status	
Private	Reference
Uninsured	1.42 (1.15, 1.73)
Medicaid	1.17 (1.10, 1.24)
Medicare	1.01 (0.95, 1.06)
Other	1.08 (0.91, 1.28)

All variables entered simultaneously and mutually adjusted

[a]American Indians excluded from multivariable analysis due to an insufficient number of cases

were under the age of 40 and that over 67% were diagnosed in stages 1 and 2.

The present study also found that when compared with the ER+/PR+/HER2− subtype, women with the TP subtype are more likely to be black or API and of lower SES, factors commonly associated with the TNBC subtype [3, 6, 7]. In addition, the TP subtype has worse unadjusted survival than the ER+/PR+/HER2− subtype. But when adjusted, there is no difference in risk of mortality between the TP and ER+/PR+/HER2−, the most common subtype and the one with the best survival. These findings are consistent with a previous study in node negative T1, T2, and T3 breast cancer where the adjusted risk of mortality was computed for both the TP and TNBC subtypes. For all sizes of tumors, after adjusting for age, grade, race/ethnicity, SES, and treatment, the risk of mortality was still higher for TNBC but not the TP when compared with the ER+/PR+/HER2− subtype [31].

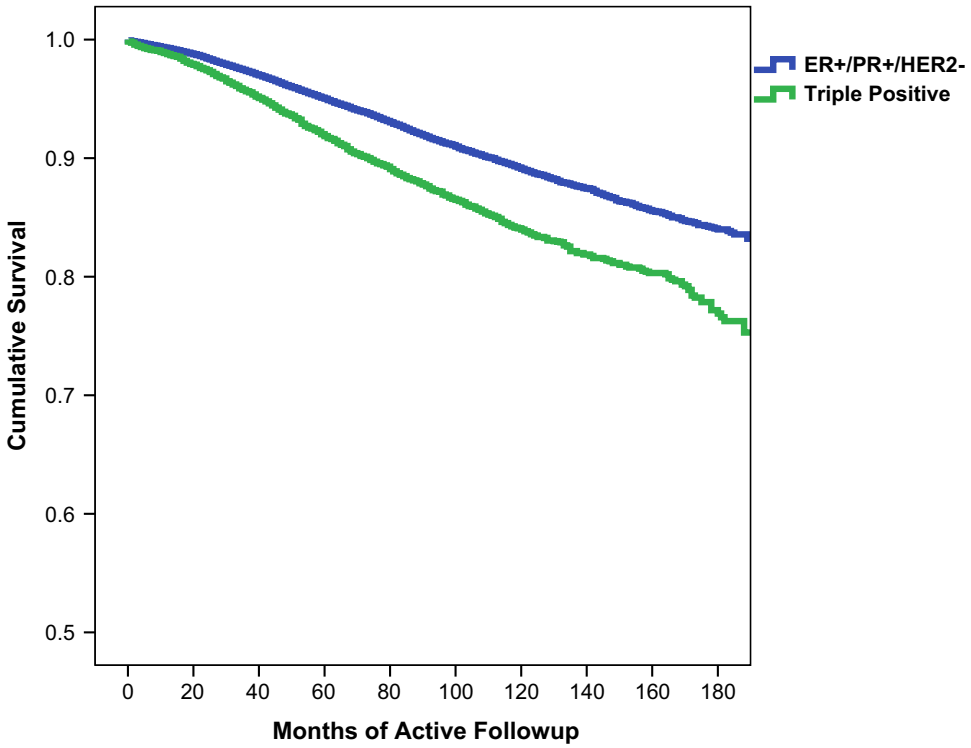

Fig. 1 Unadjusted Kaplan–Meier breast cancer-specific survival of the ER+/PR+/HER2− (blue line) and the triple positive (green line) breast cancer subtypes over 180 months of follow-up. (Color figure online)

Table 3 Kaplan–Meier unadjusted 5 year and 10 year breast cancer-specific survival and 95% confidence intervals (CI) for the ER+/PR+/HER2− and ER+/PR+/HER+ breast cancer subtypes

	5-year (95% CI)	10-year (95% CI)
ER+/PR+/HER2−	94.7% (94.5–94.8%)	88.8% (88.4–88.9%)
ER+/PR+/HER2+	91.3% (90.7–91.6%)	83.1% (82.2–83.6%)

Traditionally, the luminal B subtype been defined as any HER2-positive tumor that is ER-positive and/or PR-positive [6, 32]. However, gene expression profiling has indentified heterogeneity within the luminal B subtype [33, 34]. Two luminal B subtypes have been defined, one that is HER2-negative with a high proliferation index as determined by Ki67, and one that is HER2-positive [8, 35, 36]. Regardless of how it is defined, the luminal B subtype has poorer survival than the more common luminal A subtype [37–40]. However, TP breast cancer, a subset of the luminal B subtype, had not been extensively studied which was the impetus for current investigation. This study was conducted using data from the California Cancer Registry. Population-based registries are a valuable and underappreciated resource but we acknowledge that they have limitations. For example, the determination of ER, PR, and HER2 was performed by a wide variety of laboratories without inter-rater reliability testing. In addition, treatment data from the CCR lack specific information regarding drug type. Finally, there is no exact method of determination of race/ethnicity and therefore misclassification is possible. Despite the limitations of studies utilizing population-based registries, results obtained from over 100,000 cases provide real world generalizability and should not be overlooked.

Our study concludes that the women with the TP subtype are more likely to be younger, diagnosed at an advanced stage and grade, black, API, and of low SES when compared

Table 4 Risk of mortality of clinicopathologic characteristics of the ER+/PR+/HER2+ and ER+/PR+/HER2− breast cancer subtype subtypes

	HR (95% CI)
Age	
≤45	1.07 (1.00,1.15)
46–69	Reference
70+	1.70 (1.60, 1.82)
AJCC stage	
1	Reference
2	3.15 (2.92, 3.40)
3	9.35 (8.58, 10.19)
4	41.91 (38.35, 45.81)
Grade	
Well differentiated; grade I (low)	Reference
Moderately differentiated; grade II (low)	1.82 (1.67, 1.98)
Poorly differentiated; grade III (high)	3.13 (2.87, 3.41)
Undifferentiated; grade IV (high)	2.77 (2.25, 3.41)
Charlson Comorbidity Index	
0	Reference
1	1.20 (1.13, 1.28)
2+	1.67 (1.54, 1.82)
Race/ethnicity[a]	
White	Reference
Black	1.16 (1.06, 1.27)
Hispanic	0.87 (0.81, 0.94)
Asian/Pacific Islander	0.81 (0.74, 0.88)
Socioeconomic status	
SES 1—low	1.34 (1.22, 1.46)
SES 2	1.31 (1.22, 1.42)
SES 3	1.24 (1.15, 1.33)
SES 4	1.34 (1.06, 1.22)
SES 5–high	Reference
Treatment	
Chemotherapy	0.95 (0.89, 1.00)
Radiation therapy	0.79 (0.78, 0.83)
Hormone therapy	0.93 (0.89, 0.98)
Lumpectomy or mastectomy	0.86 (0.83, 0.90)
Insurance status	
Private	Reference
Uninsured	1.68 (1.36, 2.08)
Medicaid	1.48 (1.38, 1.59)
Medicare	1.24 (1.16, 1.32)
Other	1.55 (0.26, 1.90)
Subtype	
ER+/PR+/HER2−	Reference
ER+/PR+/HER2+	1.04 (0.98, 1.10)

All variables entered simultaneously

[a]American Indians excluded from analysis due to an insufficient number of cases

to women diagnosed with ER+/PR+/HER2−, the most common breast cancer subtype. However, there is no difference in the adjusted risk of mortality between these two subtypes.

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Compliance with ethical standards

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

Research involving human participants and/or animals 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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