Impact of Molecular Subtype on Inflammatory Breast Cancer-Specific Mortality in Adult Women

Murphy John

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Introduction

Inflammatory breast cancer (IBC) is a rare but aggressive subtype of breast cancer, accounting for 2% to 6% of all breast cancer cases in the United States (Devi et al. 2019; Hance et al. 2005). IBC presents differently than other types of breast cancer. It often lacks a breast lump and may not appear on a mammogram, making accurate diagnosis challenging and potentially delaying treatment. IBC causes symptoms of breast inflammation, such as swelling and redness, due to cancer cells blocking lymphatic vessels in the skin, giving the breast an "inflamed" appearance (Menta et al. 2018).

Clinically, IBC is categorized as T4d in the TNM classification for its aggressive biological behavior. In spite of multimodal therapy, IBC has a local recurrence rate of up to 50% and survival rates of only 35% to 40%, significantly lower than those of other types of breast cancer (Robertson et al. 2010). Despite its rarity, IBC disproportionately accounts for up to 10% of all breast cancer-related deaths (Devi et al. 2019; Hance et al. 2005).

Because IBC is rare, the biological characteristics of IBC are not commonly reported and the molecular alterations that result in poor prognosis are not well understood. However, hormone receptors (HR) and human epidermal growth factor receptor-2 (HER2), which define the molecular status of IBC through immunohistochemistry (IHC), are fundamental markers used to demonstrate molecular features, predict prognosis, and optimize therapeutic regimens (Li et al. 2017). IBC tumors are characterized by combinations of hormone receptors and oncogenes, allowing the majority to be characterized as Luminal A (HR+/HER2-), Luminal B (HR+/HER+), HER2 Positive (HR-/HER2+), and Triple Negative by IHC.(Bonito, Cantile, and Botti 2019). Studies have shown that these four molecular subtypes reveal the prognostic discrepancies in both common breast cancers and IBC (Robertson et al. 2010; Le Du et al. 2015; Tolaney et al. 2015; Iwamoto et al. 2011). A previous study examined the association between molecular subtypes and survival outcomes in IBC patients from 2010 to 2013 (Li et al. 2017). However, no updated population-based studies have investigated this relationship.

Therefore, using the most recent Surveillance, Epidemiology, and End Results (SEER) data, this study aims to assess the effect of molecular subtype on IBC-specific mortality in adult females with IBC.

Methods

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is an authoritative source of information on cancer incidence and survival in the United States (https://seer.cancer.gov/). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48% of the U.S. population. This study utilized SEER incidence data from 2010 to 2021.

Study Population

The study population focuses on adult females diagnosed with IBC. Data was extracted from the SEER 17 Registries (2000-2021) using the SEER*Stat software (version 8.4.4; Surveillance Research Program, NCI, Bethesda, MD). The specific criteria used to identify patients with IBC were as follows: (1) Site and Morphology (TNM 7/CS v0204 Schema recode) was limited to "Breast"; (2) Derived TNM classification, AJCC 7th edition (2010-2015) was limited to "T4d", SEER Combined T (2016-2017) was limited to "c2D" and "p4D", and EOD 8th edition (2018+) was limited to "T4D"; and (3) Histology type (ICD-O-3) ranged from 8500 to 8549. Year of diagnosis was limited to 2010 to 2021 because SEER started collecting breast cancer molecular subtype in 2010. To limit our data to adult females, age at diagnosis was limited to patents 20 years and older and sex was limited to "Female".

Variables

For each case, the following information from SEER was obtained: age at diagnosis (20-49, 50-69, and >=70), race (white, black, other), marital status (unmarried, married), N (node) stage (N0, N1, N2, N3), M (metastasis) stage (M0, M1), grade (I/II, III/IV), radiation (no/unknown, yes), chemotherapy (no/unknown, yes), surgery (no/unknown, yes), survival months, cause-specific death classification (Alive or dead of other cause, Dead (attributable to this cancer), Dead (missing/unknown COD)), and other cause of death classification (Alive or dead due to cancer, Dead (attributable to causes other than this cancer), Dead (missing/unknown COD)). Breast cancer subtypes were classified as Luminal A (HR+/HER2-), Luminal B (HR+/HER+), HER2 positive (HR-/HER2+), and Triple Negative. In addition, cases with incomplete information on any of these characteristics and patients who survived less than one month were excluded from the study. To focus on IBC-specific mortality, patients with an unknown cause of death or whose death was attributed to other causes were excluded.

Statistical Analysis

Clinicopathological characteristics were compared between IBC subtype using Pearson's Chi-squared test. Median, 1-year, 5-year, and 10-year survival for IBC is estimated for each variable in using the Kaplain-Meier method and compared using the log-rank test in the subgroups. The proportional hazards assumption was assessed visually with log-log plots and statistically by calculating Schoenfeld residuals and the Pearson's product moment correlation coefficient of the Schoenfeld residuals and ranked survival times. After determining the assumption of proportional hazard was met, univariate and multivariate Cox proportional hazards regressions were used to model the relationship between potential covariates and IBC-specific survival. We obtained hazard ratios (HR) and 95% confidence intervals for each covariate. All statistical analyses were performed using the survival package in R version 4.3.3.

Results

Clinicopathological characteristics

A total of 5969 adult female IBC cases were eligible during 2010-2021 in the SEER database for our study population. Of these, 1829 were excluded; 165 had a survival time less than 1 month, 487 had an unknown or competing cause of death, and 1177 had incomplete information. The remaining 4140 were included in our analysis, as shown in Figure 1.

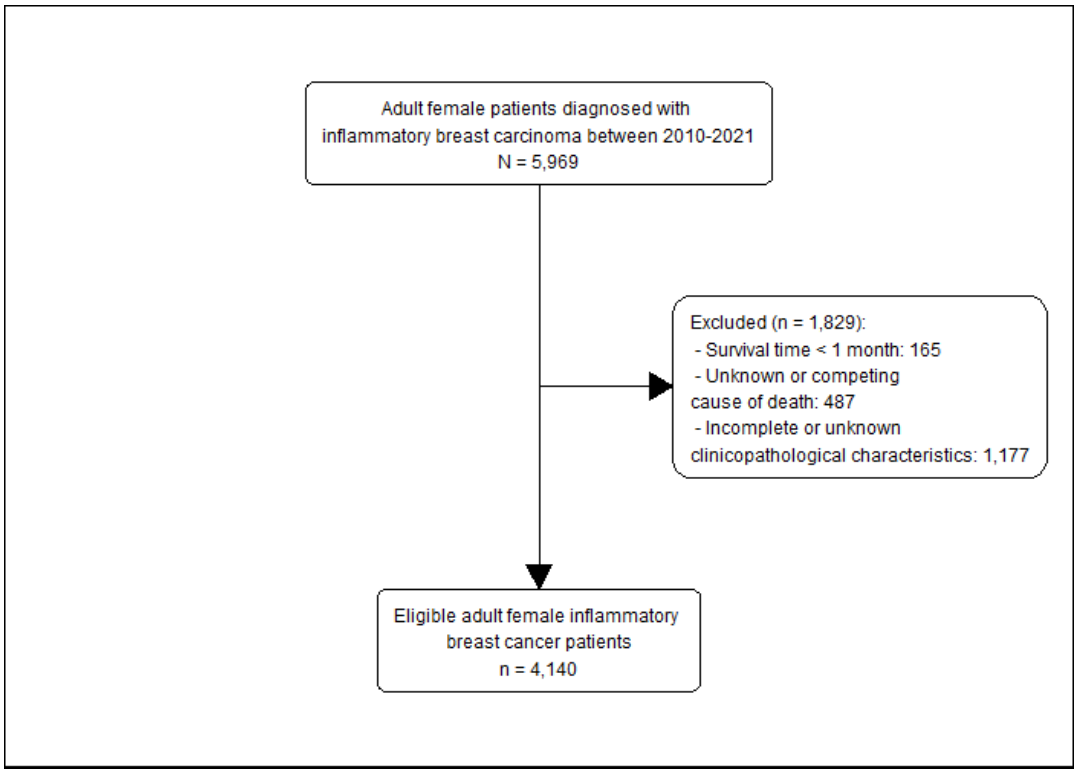

Figure 1: Flowchart of IBC patients screening on SEER database

The clinicopathological characteristics of eligible patients are summarized in Table 1. The age subgroup of 20–49 years accounts for 35.1% of Luminal B cases, a higher proportion compared to other subtypes. Moreover, Luminal B and HER2-positive subtypes appear to affect younger age groups more frequently than Luminal A, with 85.4% and 84.5% of cases, respectively, occurring in patients under 69 years, compared to 76.5% for Luminal A. A higher proportion of Black patients is observed in the Triple-Negative group compared to other subtypes. Marital status analysis shows that the Triple-Negative group has the highest percentage of unmarried women. Triple-Negative cases also have the highest percentage of N3 node stage and exhibit the greatest proportion of grade III/IV cases.

Table 1: Clinicopathological characteristics by cancer subtype

Characteristic	Overall N = 4,140	Luminal A N = 1,735	Luminal B N = 781	HER2 Positive N = 661	Triple Negative N = 963	p-value
Age						<0.001
20-49 years	1,196 (28.9%)	452 (26.1%)	274 (35.1%)	186 (28.1%)	284 (29.5%)	
50-69 years	2,132 (51.5%)	874 (50.4%)	393 (50.3%)	373 (56.4%)	492 (51.1%)	
>=70 years	812 (19.6%)	409 (23.6%)	114 (14.6%)	102 (15.4%)	187 (19.4%)	
Race						<0.001
White	3,081 (74.4%)	1,332 (76.8%)	594 (76.1%)	494 (74.7%)	661 (68.6%)	
Black	705 (17.0%)	262 (15.1%)	112 (14.3%)	106 (16.0%)	225 (23.4%)	
Other	354 (8.6%)	141 (8.1%)	75 (9.6%)	61 (9.2%)	77 (8.0%)	
Marital Status						0.015
Unmarried	2,218 (53.6%)	936 (53.9%)	387 (49.6%)	345 (52.2%)	550 (57.1%)	
Married	1,922 (46.4%)	799 (46.1%)	394 (50.4%)	316 (47.8%)	413 (42.9%)	
N Stage						<0.001
N0	475 (11.5%)	197 (11.4%)	74 (9.5%)	83 (12.6%)	121 (12.6%)	
N1	1,955 (47.2%)	794 (45.8%)	398 (51.0%)	354 (53.6%)	409 (42.5%)	
N2	723 (17.5%)	342 (19.7%)	123 (15.7%)	95 (14.4%)	163 (16.9%)	
N3	987 (23.8%)	402 (23.2%)	186 (23.8%)	129 (19.5%)	270 (28.0%)	
M Stage						0.023
M0	2,615 (63.2%)	1,056 (60.9%)	488 (62.5%)	434 (65.7%)	637 (66.1%)	
M1	1,525 (36.8%)	679 (39.1%)	293 (37.5%)	227 (34.3%)	326 (33.9%)	
Grade						<0.001
I/II	1,452 (35.1%)	835 (48.1%)	280 (35.9%)	167 (25.3%)	170 (17.7%)	
III/IV	2,688 (64.9%)	900 (51.9%)	501 (64.1%)	494 (74.7%)	793 (82.3%)	
Radiation						0.2
No/Unknown	1,993 (48.1%)	842 (48.5%)	355 (45.5%)	311 (47.0%)	485 (50.4%)	
Yes	2,147 (51.9%)	893 (51.5%)	426 (54.5%)	350 (53.0%)	478 (49.6%)	

Characteristic	Overall N = 4,140	Luminal A N = 1,735	Luminal B N = 781	HER2 Positive N = 661	Triple Negative N = 963	p-value
Chemotherapy						<0.001
No/Unknown	576 (13.9%)	340 (19.6%)	87 (11.1%)	47 (7.1%)	102 (10.6%)	
Yes	3,564 (86.1%)	1,395 (80.4%)	694 (88.9%)	614 (92.9%)	861 (89.4%)	
Surgery						0.056
No/Unknown	1,500 (36.2%)	656 (37.8%)	267 (34.2%)	216 (32.7%)	361 (37.5%)	
Yes	2,640 (63.8%)	1,079 (62.2%)	514 (65.8%)	445 (67.3%)	602 (62.5%)	

Proportional Hazards Assumption

The proportional hazards assumption was assessed for each covariate visually using log minus log plots, as shown in Figure 2.

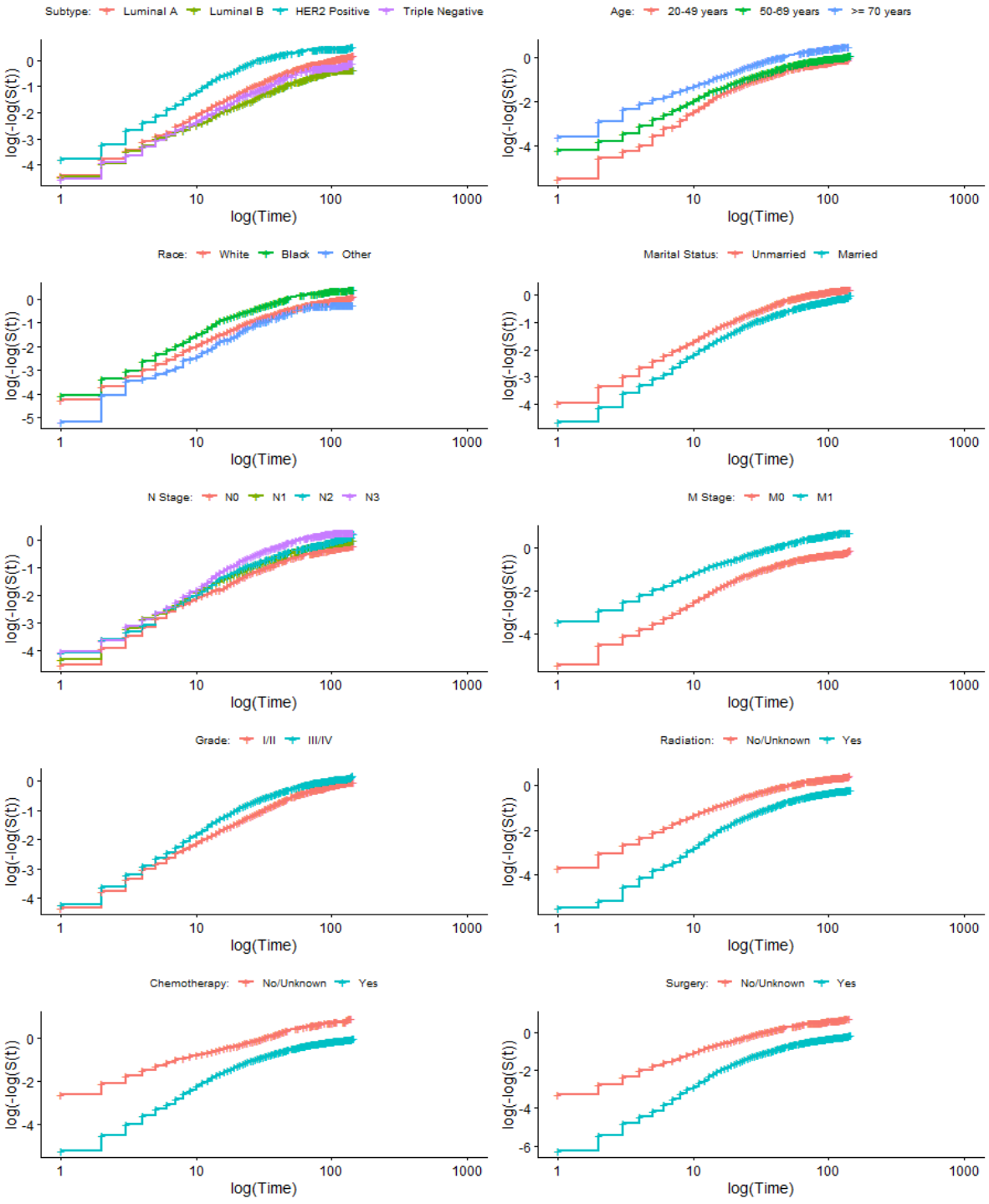

Figure 2: Log minus log plots

Upon inspection, slight deviations from parallelism were observed for the covariates subtype, grade radiation, chemotherapy, and surgery. Therefore, the full Cox proportional hazards model was fitted to the data, and Schoenfeld residuals were extracted. The correlation between Schoenfeld residuals and ranked survival times for each covariate is presented in Table 2.

Table 2: Schoenfeld Residual and Ranked Survival Time Correlation

Variable	Correlation	p.value
Luminal B	-0.034	0.128
Triple Negative	-0.128	<0.001
HER2 Positive	-0.043	0.054
50-69 years	-0.033	0.142
>=70 years	-0.031	0.161
Black	0.009	0.692
Other	0.008	0.703
Married	-0.003	0.876
N1	-0.004	0.856
N2	-0.004	0.84
N3	0.016	0.459
M1	-0.006	0.797
Grade: III/IV	-0.042	0.062
Radiation: Yes	0.070	0.002
Chemotherapy: Yes	0.110	<0.001
Surgery: Yes	0.074	0.001

While the p-values for the covariates triple negative subtype, grade, radiation, chemotherapy, and surgery are statistically significant at the 0.05 level, the observed correlations are not of large magnitude. Specifically, the correlations are -0.128, -0.042, 0.070, 0.110, and 0.074, respectively. Given that these values are relatively small in magnitude, we proceed with the Cox proportional hazards regression model.

Survival Analysis

Table 3 presents the median survival in years, along with 1-, 5-, and 10-year survival percentages, stratified by clinicopathological characteristics, all of which show statistically significant differences based on the log-rank test. Survival outcomes differ significantly by subtype, with the Triple-Negative subtype showing the poorest prognosis, including a median survival of 1.7 years and 1-, 5-, and 10-year survival rates of 67%, 24%, and 21%, respectively. Conversely, the Luminal B subtype has the most favorable outcomes, with a median survival of 9.4 years and a 10-year survival rate of 50%. Racial disparities are evident, as Black patients have the poorest survival outcomes, with a median survival of 2.4 years compared to 4.6 years for White patients and 5.4 years for patients of other races. Unmarried women experience poorer survival compared to married women. Although 1-year survival is similar across all node stages, nodal involvement significantly affects long-term outcomes, with the N3 stage showing the lowest median survival of 2.7 years and the poorest 5- and 10-year survival rates. Survival differences are also pronounced by distant metastasis (M stage), with M1 stage associated with worse outcomes. Additionally, higher cancer grades correlate with poorer survival. In terms of treatment, patients who receive radiation, chemotherapy, or surgery exhibit better survival outcomes across all measurements.

We conducted univariate and multivariate analyses based on the data in Table 3, with the results of the Cox proportional hazards regression presented in Table 4.

Univariate Analysis

In the univariate analysis, subtype, age, race, marital status, N stage, M stage, grade, radiation, chemotherapy, and surgery were all significantly associated with IBC-specific survival. These variables were therefore included in the multivariate analysis.

Multivariate Analysis

The multivariate analysis revealed that subtype, age, race, marital status, N stage, M stage, grade, radiation, chemotherapy, and surgery were independent predictors of IBC-specific survival. The Luminal B subtype was associated with better survival (aHR=0.72, 95%CI: 0.56-0.74, P<0.0001), whereas the Triple-Negative subtype showed the poorest survival outcomes (aHR=2.51, 95%CI: 1.79-2.21, P<0.0001). In terms of treatment, our results find that the existing therapies are effective in improving survival, that is radiation (aHR=0.76, 95%CI: 0.69-0.85, P<0.0001), chemotherapy (aHR=0.50, 95%CI: 0.44-0.57, P<0.0001), and surgery (aHR=0.59, 95%CI: 0.52-0.66, P<0.0001).

Table 3: Survival for IBC by Clinicopathological Characteristics

Characteristic	Median Survival (years)	1 Year	5 Year	10 Year	p-value[7]
Subtype					<0.001
Luminal A	4.3	86%	47%	33%	
Luminal B	9.4	90%	63%	50%	
Triple Negative	1.7	67%	24%	21%	
HER2 Positive	5.8	88%	53%	44%	
Age at diagnosis					<0.001
20-49 years	5.8	89%	53%	42%	
50-69 years	4.3	83%	47%	37%	
>=70 years	2.2	72%	30%	21%	
Race					<0.001
White	4.6	84%	48%	37%	
Black	2.4	75%	30%	23%	
Other	5.4	89%	51%	45%	
Marital Status					<0.001
Unmarried	3.2	79%	39%	30%	
Married	5.8	86%	53%	41%	
N Stage					<0.001
N0	7.8	86%	56%	46%	
N1	4.7	83%	48%	38%	
N2	4.1	84%	47%	34%	
N3	2.7	80%	34%	25%	
M Stage					<0.001
M0	7.7	90%	57%	47%	
M1	2.1	70%	26%	14%	
Grade					<0.001
I/II	5.4	86%	52%	39%	
III/IV	3.4	81%	42%	33%	
Radiation					<0.001
No/Unknown	2.4	73%	33%	24%	
Yes	7.4	92%	57%	45%	
Chemotherapy					<0.001
No/Unknown	1.6	60%	18%	11%	
Yes	5	86%	50%	39%	
Surgery					<0.001
No/Unknown	1.8	65%	23%	15%	
Yes	7.3	92%	57%	46%	

[7] Log-rank test

Table 4: Cox Proportional Hazards Regression Model for Survival in Adult Women with IBC

	Crude			Adjusted		
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**	**HR**[1]	**95% CI**[1]	**p-value**
Subtype						
Luminal A	—	—		—	—	
Luminal B	0.65	0.56, 0.74	<0.001	0.72	0.63, 0.83	<0.001
Triple Negative	1.99	1.79, 2.21	<0.001	2.51	2.24, 2.82	<0.001
HER2 Positive	0.80	0.69, 0.91	0.001	0.92	0.80, 1.06	0.3
Age at diagnosis						
20-49 years	—	—		—	—	
50-69 years	1.21	1.09, 1.35	<0.001	1.10	0.99, 1.23	0.074
>=70 years	2.02	1.78, 2.29	<0.001	1.55	1.35, 1.77	<0.001
Race						
White	—	—		—	—	
Black	1.57	1.41, 1.75	<0.001	1.24	1.11, 1.39	<0.001
Other	0.81	0.68, 0.97	0.021	0.81	0.68, 0.97	0.021
Marital Status						
Unmarried	—	—		—	—	
Married	0.70	0.64, 0.76	<0.001	0.88	0.80, 0.96	0.005
N Stage						
N0	—	—		—	—	
N1	1.26	1.08, 1.47	0.004	1.27	1.08, 1.48	0.003
N2	1.34	1.13, 1.59	<0.001	1.51	1.27, 1.80	<0.001
N3	1.78	1.51, 2.10	<0.001	1.75	1.48, 2.06	<0.001
M Stage						
M0	—	—		—	—	
M1	2.56	2.35, 2.80	<0.001	1.95	1.76, 2.16	<0.001
Grade						
I/II	—	—		—	—	
III/IV	1.32	1.20, 1.45	<0.001	1.20	1.09, 1.32	<0.001
Radiation						
No/Unknown	—	—		—	—	
Yes	0.47	0.43, 0.51	<0.001	0.76	0.69, 0.85	<0.001
Chemotherapy						
No/Unknown	—	—		—	—	
Yes	0.37	0.33, 0.42	<0.001	0.50	0.44, 0.57	<0.001
Surgery						
No/Unknown	—	—		—	—	
Yes	0.34	0.32, 0.38	<0.001	0.59	0.52, 0.66	<0.001

[1] HR = Hazard Ratio, CI = Confidence Interval

Discussion

In this large population-based cohort of women diagnosed with IBC, we found a better survival in Luminal B molecular subtype and poorer in Triple Negative. We found that Black patients made up the smallest percentage of Luminal B subtype and the greatest of Triple Negative. Similar findings were observed for patients who were unmarried at diagnosis.

Take things that ive noted from other study and compare results here. It would be interesting to look at the combination of treatments (radiation, chemo, surgery) Also comparing subtype to broader range of breat cancer not just IBC.

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