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Features of triple-negative breast cancer

Analysis of 38,813 cases from the national cancer database

Magdalena L. Plasilova, MD, PhD, Brandon Hayse, BSc, Brigid K. Killelea, MD, MPH, Nina R. Horowitz, MD, Anees B. Chagpar, MD, MSc, MPH, MA, MBA, Donald R. Lannin, MD*

Abstract

The aim of this study was to determine the features of triple-negative breast cancer (TNBC) using a large national database. TNBC is known to be an aggressive subtype, but national epidemiologic data are sparse. All patients with invasive breast cancer and known molecular subtype diagnosed in 2010 to 2011 were identified from the National Cancer Data Base (NCDB). Patients with and without TNBC were compared with respect to their sociodemographic and clinicopathologic features. TNBC was present in 38,628 of 295,801 (13%) female patients compared to 185 of 3136 (6%) male patients ($P < 0.001$). The incidence of TNBC varied by region from 10.8% in New England to 15.8% in the east south central US ($P < 0.001$), as well as by race with the highest rates in African-Americans (23.7%), and lowest in Filipino patients (8.9%). The incidence of TNBC also varied by histology, accounting for 76% of metaplastic cancers, but only 2% of infiltrating lobular carcinomas. TNBCs were significantly larger than non-TNBC (mean 2.8 cm vs 2.1 cm, $P < 0.001$), and more TNBC were poorly differentiated compared to other subtypes (79.7% vs 25.8%, $P < 0.001$). On univariate analysis, TNBC was no more likely than non-TNBC to have node-positive disease (32.0% vs 31.7%, respectively, $P = 0.218$) but in a multivariable analysis controlling for tumor size and grade, TNBC was associated with significantly less node-positivity (OR = 0.59; 95% confidence interval [CI]: 0.57–0.60). TNBC has distinct features regarding age, gender, geographic, and racial distribution. Compared to non-TNBC, TNBC is larger and higher grade, but less likely to have lymph node metastases.

Abbreviations: ER = estrogen receptor, Her2 = human epidermal growth factor receptor 2, NCDB = National Cancer Database, PR = progesterone receptor, TNBC = triple-negative breast cancer.

Keywords: Breast cancer molecular type, national cancer database, triple-negative breast cancer

1. Introduction

Triple-negative breast cancer (TNBC) represents a subgroup of breast tumors defined by lack of expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2). It tends to be biologically aggressive, and with a lack of commonly utilized targeting agents, it is often associated with a worse prognosis.[1] Despite unique identifying features, there is significant heterogeneity among TNBC patient populations and the results of small studies are sometimes contradictory.[2,3] Although many articles have been published describing its biology, behavior, and treatment, large scale epidemiologic studies based on national data are sparse.

The aim of this study was to determine the features of TNBC using a large national dataset. The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society and contains data on about 70% of the cancer cases in the United States. Her2 status has been collected since 2010, allowing determination of molecular type. In this study, 38,813 cases of TNBC diagnosed in 2010 and 2011 were compared to non-TNBC diagnosed in the same years with regard to sex, race/ethnicity, age, geographic distribution, histologic type, stage, pathologic characteristics, and treatment patterns.

2. Methods

The NCDB, established in 1989, is a nationwide, facility-based, comprehensive data set that captures about 70% of all newly diagnosed malignancies in the United States annually. After approval by the NCDB, patient deidentified data were downloaded from the website in January 2014 and analyzed in this study. Given the deidentified and retrospective nature of the data obtained from the NCDB, this study was deemed exempt by the Human Investigations Committee of Yale University.

2.1. Receptor data and study population

The instructions to the tumor registrars in the Collaborative Stage Coding Manual regarding estrogen and progesterone assays were to "record the pathologist's interpretation of the assay value."

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Department of Surgery, and Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, CT.

* Correspondence: Donald R. Lannin, Department of Surgery, Yale University School of Medicine, PO Box 208062, New Haven, CT 06520 (e-mail: Donald.lannin@yale.edu).

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However, it was noted that the College of American Pathologists had issued guidelines in late 2009 that if 1% or more of tumor cells stained positive, the ER/PR value was considered positive.[4]

With regard to Her2 assays, the NCDB contains data on immunohistochemistry, fluorescence in situ hybridization, and chromogenic in situ hybridization, but the field we used for this study was one where the individual local tumor registrars determined the best assay result for each individual patient. The registrars were instructed to use gene amplification assays first, and then use immunohistochemistry assay for cases where the amplification assay was borderline or not performed.

The population used for this study consisted of all patients with invasive breast cancer diagnosed in 2010 and 2011 whose ER, PR, and Her2 were known to be positive or negative. This represented 88.4% of all invasive breast cancers in the database for those years. Cases were categorized as triple negative (TNBC) if all 3 receptors were known to be negative, and non-TNBC if any one of the receptors was known to be positive.

2.2. Tumor size

The NCDB variable, "tumor size," is a combination of clinical and pathological size. If surgery was performed before any other treatments, the pathological size was used, but if neoadjuvant therapy was employed, the clinical tumor size before treatment was used. The size is coded in 1 mm increments, but for this study the size was converted to 1 cm increments, that is, from 1 to 10 mm, 11 to 20 mm, 21 to 30 mm, etc, so that positive lymph node rates could be calculated for each size interval.

2.3. Race, histology, and treatment variables

The NCDB classified race and histology into many categories, with relatively few cases in each group. To allow a valid analysis, only racial categories with greater than 400 cases and histology categories with greater than 200 cases were included; categories with less than 400 and 200 cases, respectively, were recoded as "other." For determination of surgical treatment, only cases that had definitive surgery, either mastectomy or lumpectomy, were included. For patients who had neoadjuvant chemotherapy, pathologic complete response was defined as no remaining invasive tumor in either the breast or the axillary lymph nodes.

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS version 22, Chicago, Ill. USA. Bivariate comparisons were performed with chi-square tests, and multivariable analysis was performed with binary logistic regression. Statistical tests were 2-sided, and P values <0.05 were considered significant.

3. Results

3.1. Completeness of data

The Her2 variable was complete for 91% of the 2010 to 2011 cases, and was positive in 14.2%, negative in 83.1%, and borderline in 2.7%. The cases of borderline Her2 expression were excluded, resulting in 88% of all invasive cancers being positive or negative for Her2. Essentially all of the cases with complete data on Her2 also had complete data for ER and PR. It appears that the 2009 guidelines changing the definition of hormone

Table 1

Incidence of triple-negative tumors by sex, race/ethnicity, age, and geographic region.

	Total cancer number	Nontriple-negative number (%)			Triple-negative number (%)	*P*
		HR+ Her2−	HR+ Her2+	HR− Her2+		
Sex						<0.001
Female	295,801	214,052 (72.4%)	29,794 (10.1%)	13,327 (4.5%)	38,628 (13.1%)	
Male	3,136	2587 (82.5%)	315 (10.0%)	49 (1.6%)	185 (5.9%)	
Race/ethnicity						<0.001
Non-Hispanic white	235,082	175,760 (74.8%)	22,870 (9.7%)	9669 (4.1%).1%)	26,783 (11.4%)	
Non-Hispanic black	33,970	20,255 (59.6%)	3744 (11.0%)	1904 (5.6%)	8,067 (23.7%)	
Non-Hisp Asian/P.I.	9,294	6519 (70.1%)	1091 (11.7%)	639 (6.9%)	1,045 (11.2%)	
Hispanic	15,536	10,476 (67.4%)	1847 (11.9%)	907 (5.8%)	2,306 (14.8%)	
Other/unknown	5,055	3629 (71.8%)	557 (11.0%)	257 (5.1%)	612 (12.1%)	
Age						<0.001
≤30	2,059	1014 (49.2%)	411 (20.0%)	155 (7.5%)	479 (23.3%)	
31–40	15,094	8439 (55.9%)	2494 (16.5%)	978 (6.5%)	3,183 (21.1%)	
41–50	51,793	34,894 (67.4%)	6422 (12.4%)	2627 (5.1%)	7,850 (15.2%)	
51–60	72,543	49,920 (68.8%)	8051 (11.1%)	4149 (5.7%)	10,423 (14.4%)	
61–70	77,870	59,173 (76.0%)	6724 (8.6%)	3061 (3.9%)	8,912 (11.4%)	
>70	79,578	63,199 (79.4%)	6007 (7.5%)	2406 (3.0%)	7,966 (10%)	
Geographic region						<0.001
East South Central	17,319	11,844 (68.4%)	1850 (10.7%)	888 (5.1%)	2,737 (15.8%)	
West South Central	23,951	16,634 (69.5%)	2693 (11.2%)	1150 (4.8%)	3,474 (14.5%)	
South Atlantic	65,180	46,520 (71.4%)	6502 (10.0%)	3035 (4.7%)	9,123 (14.0%)	
East North Central	52,707	38,085 (72.3%)	5162 (9.8%)	2301 (4.4%)	7,159 (13.6%)	
Middle Atlantic	46,259	33,908 (73.3%)	4699 (10.2%)	1982 (4.3%)	5,670 (12.3%)	
West North Central	21,923	16,223 (74.0%)	2121 (9.7%)	949 (4.3%)	2,630 (12.0%)	
Mountain	14,382	10,682 (74.3%)	1377 (9.6%)	619 (4.3%)	1,704 (11.8%)	
Pacific	38,647	28,794 (74.5%)	3842 (9.9%)	1699 (4.4%)	4,312 (11.2%)	
New England	18,569	13,949 (75.1%)	1863 (10.0%)	753 (4.1%)	2,004 (10.8%)	

HR = hormone receptor, Her2 = human epidermal growth factor receptor 2.

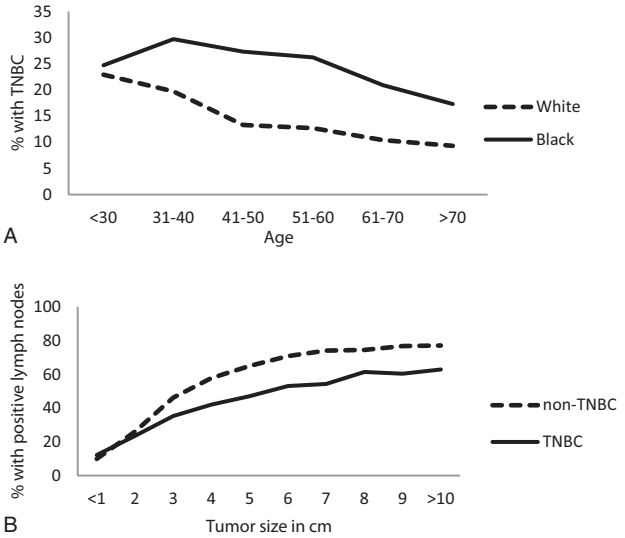

Figure 1. (A) Percentage of cancers that are triple negative by patient age and race. (B) Percentage of cancers that are lymph node positive by tumor size and molecular type.

receptor positivity from 10% to 1% were adopted fairly quickly. Out of all invasive cancers diagnosed in 2010 and 2011, 79.1% were positive for ER, 18.0% were negative, and 2.9% were unknown/not done; whereas for 2004 to 2009, only 73.6% were positive, 20.1% negative, and 6.3% unknown/not done.

3.2. Incidence of triple-negative tumors by sex, race/ethnicity, age, and geographic region

Table 1 shows incidence data for TNBC based on sex, race/ethnicity, age, and geographic region. TNBC was present in 38,628 of 295,801 (13%) female patients compared to 185 out of 3136 (6%) male patients ($P < 0.001$). Non-Hispanic black and Hispanic patients had higher incidence of TNBC, and TNBC was more common amongst younger patients ($P < 0.001$ for both). Across all age groups, African-American women were more likely to have TNBC than their white counterparts; however, at the youngest ages (< 30), the 2 racial groups had roughly equivalent proportions of TNBC (Fig. 1A). Based on 9 geographic regions of the United States, TNBC was highest in the east south central (15.8%), the west south central (14.5%), and the south Atlantic regions (14.0%) and lowest in New England (10.8%, $P < 0.001$).

3.3. Incidence of triple-negative tumors by detailed racial groups

The NCDB included detailed information on racial group distribution. Table 2 shows the incidence of triple-negative tumors for all racial groups that contained more than 400 individuals. Compared to the white population, black, American Indian/Eskimo, and Asian Indian patients had a higher incidence of TNBC, and Filipino patients had a lower incidence of TNBCs.

3.4. Incidence of triple-negative tumors by detailed histologic type

Table 3 shows the incidence of TNBC among all histologic types with more than 200 cases. Infiltrating ductal carcinoma was the most common histologic type and contained 14.6% TNBC. However, there was an extremely wide range from adenoid cystic, which was 78% TNBC to tubular that was 0.3%. Histologic types with a higher percent TNBC compared to infiltrating ductal were adenoid cystic, metaplastic, medullary, apocrine adenocarcinoma, and inflammatory carcinoma. Carcinoma not otherwise specified (NOS) and adenocarcinoma NOS were also more likely to be TNBC, probably because these categories are used for very undifferentiated cancers. Histologic types with a lower percent of TNBC than infiltrating ductal included tubular carcinoma, mucinous carcinoma, infiltrating lobular, infiltrating ductal and infiltrating lobular, infiltrating lobular mixed with other types, cribriform carcinoma, micropapillary and papillary carcinoma, Paget's disease with infiltrating ductal, intraductal papillary with invasion, and infiltrating ductal mixed with other types. To see whether differences in histological type may account for the racial and age differences observed, Table 4 shows histology by race and age for triple-negative cancers. The racial and age differences were mainly due to infiltrating ductal cancers and not due to the very small contribution of other histologic types.

Table 2

Incidence of triple-negative tumors by detailed racial groups*.

	Total cancer number	Nontriple-negative number (%)			Triple-negative number (%)	P#
		HR+ Her2−	HR+ Her2+	HR− Her2+		
White	249,185	185,265 (74.3%)	24,556 (9.9%)	10,497 (4.2%)	28,867 (11.6%)	Ref
Black	34,380	20,529 (59.7%)	3790 (11.0%)	1926 (5.6%)	8,135 (23.7%)	<0.001
Asian Indian	576	383 (66.5%)	61 (10.6%)	42 (7.3%)	90 (15.6%)	0.003
American Indian/Eskimo	808	548 (67.8%)	95 (11.8%)	47 (5.8%)	118 (14.6%)	0.008
Korean	679	435 (64.1%)	90 (13.3)	62 (9.1%)	92 (13.5%)	0.111
Asian Indian or Pakistani	849	592 (69.7%)	100 (11.8%)	55 (6.5%)	102 (12.0%)	0.696
Chinese	1,448	1003 (69.3%)	167 (11.5)	105 (7.3%)	173 (11.9%)	0.667
Vietnamese	497	325 (65.4%)	63 (12.7%)	52 (10.5%)	57 (11.5%)	0.936
Japanese	903	696 (77.1%)	74 (8.2%)	31 (3.4%)	102 (11.3%)	0.787
Pacific Islander, NOS	576	419 (72.7%)	66 (11.5%)	29 (5.0%)	62 (10.8%)	0.539
Other Asian, NOS	2,266	1621 (71.5%)	253 (11.2%)	157 (6.9%)	235 (10.4%)	0.072
Filipino	1,579	1102 (69.8%)	226 (14.3%)	111 (7.0%)	140 (8.9%)	0.001
Other	2,030	1396 (68.8%)	248 (12.2%)	112 (5.5%)	274 (13.5%)	0.007
Unknown	3,161	2325 (73.6%)	320 (10.1%)	150 (4.7%)	366 (11.6%)	0.992

* Where $N > 400$.

Triple negative vs nontriple negative compared to whites.

HR = hormone receptor, Her2 = human epidermal growth factor receptor.

Table 3

Incidence of tripl-negative tumors by histologic type*.

	Total cancer number	Nontriple-negative number (%)			Triple-negative number (%)	P#
		HR+ Her2−	HR+ Her2+	HR− Her2+		
Infiltrating ductal	224,844	155,060 (69.0%)	25,170 (11.2%)	11,788 (5.2%)	32,826 (14.6%)	Ref
Adenoid cystic	220	45 (20.5%)	1 (0.5%)	2 (0.9%)	172 (78.2%)	<0.001
Metaplastic	1,221	227 (18.6%)	18 (1.5%)	45 (3.7%)	931 (76.2%)	<0.001
Medullary	643	178 (27.7%)	33 (5.1%)	43 (6.7%)	389 (60.5%)	<0.001
Apocrine adenocarcinoma	480	97 (20.2%)	41 (8.5%)	70 (14.6%)	272 (56.7%)	<0.001
Carcinoma NOS	2,186	1179 (53.9%)	252 (11.5%)	154 (7.0%)	601 (27.5%)	<0.001
Inflammatory	934	357 (38.2%)	144 (15.4%)	191 (20.4%)	242 (25.9%)	<0.001
Adenocarcinoma NOS	1,598	926 (57.9%)	200 (12.5%)	154 (9.6%)	318 (19.9%)	<0.001
Neoplasm, malignant	615	440 (71.5%)	56 (9.1%)	23 (3.7%)	96 (15.6%)	0.479
Adenocarcinoma with mixed subtypes	259	195 (75.3%)	19 (7.3%)	5 (1.9%)	40 (15.4%)	0.701
Infiltrating ductular	490	339 (69.2%)	61 (12.4%)	23 (4.7%)	67 (13.7%)	0.562
Inf ductal mixed with other types	9,501	7502 (79.0%)	728 (7.7%)	273 (2.9%)	998 (10.5%)	<0.001
Intraductal papillary with invasion	546	445 (81.5%)	36 (6.6%)	11 (2.0%)	54 (9.9%)	0.002
Pagets with infiltrating ductal	345	116 (33.6%)	96 (27.8%)	108 (31.3%)	25 (7.2%)	<0.001
Papillary carcinoma	970	861 (88.8%)	43 (4.4%)	8 (0.8%)	58 (6.0%)	<0.001
Micropapillary	600	461 (76.8%)	74 (12.3%)	30 (5.0%)	35 (5.8%)	<0.001
Cribriform carcinoma	550	493 (89.6%)	27 (4.9%)	5 (0.9%)	25 (4.5%)	<0.001
Inf lobular mixed with other types	1,060	951 (89.7%)	52 (4.9%)	10 (0.9%)	47 (4.4%)	<0.001
Infiltrating ductal and inf lobular	15,040	13,239 (88.0%)	1197 (8.0%)	162 (1.1%)	442 (2.9%)	<0.001
Infiltrating lobular carcinoma	27,799	25,756 (92.7%)	1382 (5.0%)	121 (0.4%)	540 (1.9%)	<0.001
Mucinous carcinoma	5,608	5216 (93.0%)	314 (5.6%)	45 (0.8%)	33 (0.6%)	<0.001
Tubular carcinoma	1,756	1710 (97.4%)	39 (2.2%)	1 (0.1%)	6 (0.3%)	<0.001
Other/unknown	1,672	846 (50.6%)	126 (7.5%)	104 (6.2%)	596 (35.6%)	<0.001

* Where $N > 200$.

Triple negative vs nontriple negative compared to infiltrating ductal.

HR = hormone receptor, Her2 = human epidermal growth factor receptor.

3.5. Tumor characteristics of triple-negative and nontriple-negative cancers

Tumor characteristics for TNBC and non-TNBCs are shown in Table 5. TNBC and Her2 positive patients had larger tumors than HR+ Her2− patients and were more likely to be high grade, have lymphovascular invasion, and to present with clinically metastatic disease.

In unadjusted analysis TNBC were more likely than HR+ Her2− patients but less likely than Her2+ patients to have positive nodes. However, when stratified by tumor size, as seen in Fig. 1B,

Table 4

Histology of triple-negative cancers by race and age.

	Race number (%)		Age number (%)	
	White	Black	≤50	>50
Infiltrating ductal	24,262 (84.0%)	7,036 (86.5%)	9,398 (87.2%)	21,900 (83.5%)
Adenoid cystic	150 (0.5%)	18 (0.2%)	38 (0.4%)	130 (0.5%)
Metaplastic	738 (2.6%)	159 (2.0%)	192 (1.8%)	705 (2.7%)
Medullary	265 (0.9%)	106 (1.3%)	161 (1.5%)	210 (0.8%)
Apocrine adenocarcinoma	214 (0.7%)	42 (0.5%)	25 (0.2%)	231 (0.9%)
Carcinoma NOS	431 (1.5%)	145 (1.8%)	186 (1.7%)	390 (1.5%)
Inflammatory	184 (0.6%)	47 (0.6%)	66 (0.6%)	165 (0.6%)
Adenocarcinoma NOS	239 (0.8%)	63 (0.8%)	80 (0.7%)	222 (0.8%)
Neoplasm, malignant	76 (0.3%)	14 (0.2%)	20 (0.2%)	70 (0.3%)
Adenocarcinoma with mixed subtypes	34 (0.1%)	6 (0.1%)	8 (0.1%)	32 (0.1%)
Infiltrating ductular	44 (0.2%)	20 (0.2%)	17 (0.2%)	47 (0.2%)
Inf ductal mixed with other types	743 (2.6%)	199 (2.4%)	229 (2.1%)	713 (2.7%)
Intraductal papillary with invasion	40 (0.1%)	14 (0.2%)	10 (0.1%)	44 (0.2%)
Pagets with infiltrating ductal	22 (0.1%)	2 (0%)	6 (0.1%)	18 (0.1%)
Papillary carcinoma	35 (0.1%)	22 (0.3%)	18 (0.2%)	39 (0.1%)
Micropapillary	23 (0.1%)	9 (0.1%)	10 (0.1%)	22 (0.1%)
Cribriform carcinoma	21 (0.1%)	4 (0%)	6 (0.1%)	19 (0.1%)
Inf lobular mixed with other types	41 (0.1%)	3 (0%)	7 (0.1%)	37 (0.1%)
Infiltrating ductal and inf lobular	350 (1.2%)	64 (0.8%)	103 (1.0%)	311 (1.2%)
Infiltrating lobular carcinoma	446 (1.5%)	69 (0.8%)	78 (0.7%)	437 (1.7%)
Mucinous carcinoma	27 (0.1%)	4 (0%)	2 (0%)	29 (0.1%)
Tubular carcinoma	5 (0%)	1 (0%)	0 (0%)	6 (0%)
Other/unknown	477 (1.7%)	88 (1.1%)	121 (%)1.1%)	444 (1.7)

Table 5

Tumor characteristics of triple-negative and nontriple-negative cancers.

	Nontriple-negative number (%)			Triple-negative number (%)	P^*
	HR+ Her2−	HR+ Her2+	HR− Her2+		
T stage					
cT1	129,150 (68.0%)	13,787 (52.9%)	4,860 (42.9%)	15,923 (46.4%)	<0.001
cT2	46,109 (24.3%)	8,677 (33.3%)	4,024 (35.5%)	13,090 (38.1%)	
cT3	8,384 (4.4%)	1,846 (7.1%)	1,091 (9.6%)	2,893 (8.4%)	
cT4	6,356 (3.3%)	1,774 (6.8%)	1,358 (12.0%)	2,432 (7.1%)	
N stage					
cN0	164,877 (84.6%)	19,425 (71.9%)	7,644 (63.4%)	25,202 (72.0%)	<0.001
cN1	22,921 (11.8%)	5,726 (21.2%)	3,150 (26.1%)	7,021 (20.1%)	
cN2	4,535 (2.3%)	1,173 (4.3%)	731 (6.1%)	1,630 (4.7%)	
cN3	2,501 (1.3%)	704 (2.6%)	530 (4.4%)	1,139 (3.3%)	
M stage					
cM0	192,356 (96.0%)	25,643 (92.6$)	11,227 (90.8%)	33,682 (94.1%)	<0.001
cM1	8,052 (4.0%)	2,047 (7.4%)	1,131 (9.2%)	2,104 (5.9%)	
Grade					
1	61,993 (30.1%)	2,397 (8.5%)	210 (1.7%)	888 (2.4%)	<0.001
2	102,929 (50.0%)	12,129 (42.9%)	2,996 (24.2%)	6,562 (17.8%)	
3	40,741 (19.8%)	13,733 (48.6%)	9,187 (74.1%)	29,353 (79.8%)	
LVI					
Yes	33,864 (19.0%)	6,847 (29.1%)	3,240 (32.0%)	7,643 (25.0%)	<0.001
No	144,162 (81.0%)	16,649 (70.9%)	6,897 (68.0%)	22,881 (75.0%)	
Mean tumor size (cm ± SE)	2.04 ± 0.004	2.48 ± 0.012	2.78 ± 0.021	2.78 ± 0.012	<0.001
Positive nodes					
>0	57,327 (30.3%)	9,820 (38.2%)	4,502 (40.0%)	10,768 (32.0%)	0.218
0	131,798 (69.7%)	15,874 (61.8%)	6,749 (60.0%)	22,852 (68.0%)	
OR unadjusted (95% CI)	Reference	1.42 (1.38–1.46)	1.53 (1.48–1.59)	1.08 (1.06–1.11)	<0.001
OR adjusted for tumor size and grade (95% CI)	Reference	1.06 (1.02–1.09)	0.95 (0.91–1.00)	0.59 (0.57–0.61)	<0.001
Surgery					
Lumpectomy	117,468 (58.2%)	12,951 (47.7%)	4,713 (39.5%)	17,809 (50.0%)	<0.001
Mastectomy	84,405 (41.8%)	14,182 (52.3%)	7,224 (60.5%)	17,776 (50.0%)	
OR unadjusted (95% CI)	Reference	0.66 (0.64–0.67)	0.47 (0.45–0.49)	0.72 (0.70–0.74)	<0.001
OR adjusted for tumor size, nodal status and grade (95% CI)	Reference	0.78 (0.76–0.81)	0.62 (0.60–0.65)	0.96 (0.94–0.99)	0.009
Chemotherapy					
Yes	67,007 (34.9%)	20,622 (75.2%)	10,407 (84.5%)	28,460 (81.4%)	<0.001
No	125,018 (65.1%)	6,799 (24.8%)	1,916 (15.5%)	6,490 (18.6%)	
OR unadjusted (95% CI)	Reference	5.7 (5.5–5.8)	10.1 (9.6–10.6)	8.2 (7.9–8.4)	<0.001
OR adjusted for tumor size, nodal status and grade (95% CI)	Reference	5.7 (5.5–5.9)	7.6 (7.1–8.2)	5.6 (5.4–5.8)	<0.001

* Triple negative compared to nontriple negative except the rows with odds ratios, where the *P* value represents triple negative compared to the reference, HR+ Her2−.
CI = confidence interval, HR = hormone receptor, Her2 = human epidermal growth factor receptor, OR = odds ratio, SE = standard error.

patients with TNBC were significantly less likely to have positive nodes than their non-TNBC counterparts ($P < 0.001$). Adjusting for tumor size and grade in a multivariable logistic regression model, TNBCs had a much lower rate of lymph node positivity than any other molecular type (OR = 0.59; 95% CI: 0.57–0.61).

3.6. Treatment of triple-negative and nontriple-negative cancers

Table 5 also shows differences in treatment. On univariate analysis, TNBC and Her2 positive patients received less breast-conserving surgery compared with HR+ Her2− patients. However, after adjusting for tumor size, nodal status, and grade, Her2+ patients continued to have significantly less breast conservation whereas the difference largely disappeared for TNBC patients. TNBC and Her2+ patients were also much more likely to receive chemotherapy; and among patients who received chemotherapy, they were more likely to receive neoadjuvant chemotherapy (28% vs 22%, $P < 0.001$) and to have a pathologic complete response (40% vs 28%, $P < 0.001$).

4. Discussion

To our knowledge, this is the largest study regarding the epidemiology, tumor characteristics, and treatment patterns of TNBCs in the United States. We found that the incidence of TNBC was 13% among females and 6% among males. The incidence of TNBC was highest among non-Hispanic black and Hispanic patients (23.7% and 14.8%). These data are in agreement with previously published smaller studies.[1,5,6,7] In addition, however, we found an increased incidence of TNBC in American Indian/Eskimo (14.6%) and Asian Indian patients (15.6%). Interestingly, the incidence of TNBC was lowest in Filipino patients (8.9%). It has been previously reported that

Filipino woman have an increased risk of Her2 positive breast cancers, regardless of ER and PR status.[8] In addition, we found that the highest incidence of TNBC is in the southern regions of the United States, which might reflect the racial/ethnic distribution of the population.

In all racial/ethnic groups, TNBC was associated with increased incidence among young patients. However, as seen in Fig. 1A, the shape of the curves differs by race. In white patients, TNBC was highest under age 40, whereas in black patients, it did not really drop off until after age 60.

The data illustrate the broad histological heterogeneity of TNBCs. There were 7 different histologic subtypes where TNBC was more prevalent and 12 types where it was less prevalent than infiltrating ductal carcinoma. This is consistent with smaller studies that showed TNBC was associated with some special histologic subtypes such as adenoid cystic,[9,10] medullary or metaplastic subtypes,[11,12] and not with other subtypes such as tubular or lobular carcinoma.[13]

This study clarifies the relationship between TNBC and lymph node metastases. Although the overall percentage of positive nodes for TNBC and non-TNBC is equivalent, TNBC tends to be larger and of higher grade; hence, it would be predicted to have a higher incidence of lymph node metastases. When adjusted for these factors, however, the incidence of positive nodes with TNBC is considerably less than non-TNBC. This is in agreement with other recent studies.[14–16] However the finding in this study of increased lymphovascular invasion in TNBCs is contrary to previously published reports.[15,16]

We found that TNBC and Her2+ patients were treated more frequently with mastectomy than were HR+ Her2− patients. However, upon adjusting for larger tumor size, nodal status, and grade, TNBCs had about the same breast conservation rate as HR + Her2− patients. While TNBC patients have a higher risk for both local and distant recurrence, histologic or molecular subtype is not an indication for mastectomy and standard criteria should be applied to select the surgical approach in TNBC.[1,2,7,17]

The majority (80%) of TNBC patients received systemic chemotherapy and the odds of receiving chemotherapy were much greater for TNBC than for non-TNBC even when adjusted for stage and grade. Furthermore, TNBC was more likely to be treated with neoadjuvant chemotherapy, and more likely to have a pathologic complete response. This is what we would expect based on the biology and clinicopathologic features of TNBC.[18,19] More detailed analyses of neoadjuvant chemotherapy use in the NCDB have recently been published.[20,21]

In summary, TNBC has distinct features regarding age, gender, geographic, and racial/ethnic distribution. Compared to non-TNBC, TNBC is larger and higher grade, but less likely to have lymph node metastases. When the stage is taken into account, the surgical treatment is similar to that of non-TNBC, but treatment with chemotherapy is much more common.

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