Original Article

J Breast Health 2014; 10: 209-15
DOI: 10.5152/tjbh.2014.1904

The Outcome of Patients with Triple Negative Breast Cancer: The Turkish Oncology Group Experience

Yeşim Eralp[2], Leyla Kılıç[1], Gül Alço[4], Gül Başaran[3], Mutlu Doğan[5], Dilek Dinçol[5], Senem Demirci[6], Fikri İçli[5], Handan Onur[5], Pınar Saip[2], Ayfer Haydaroğlu[6]

[1]Department of Medical Oncology, Fırat University Hospital, Elazığ, Turkey
[2]Department of Medical Oncology, İstanbul University Faculty of Medicine, İstanbul, Turkey
[3]Department of Medical Oncology, Acibadem University Faculty of Medicine, İstanbul, Turkey
[4]Department of Radiation Oncology, Florence Nightingale Gayrettepe Hospital, İstanbul, Turkey
[5]Department of Medical Oncology, Ankara University Faculty of Medicine, Ankara, Turkey
[6]Department of Radiation Oncology, Ege University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Objective: Triple negative breast cancer (TNBC) is generally considered as a poorer prognostic subgroup, with propensity for earlier relapse and visceral involvement. The aim of this study is to evaluate the outcome of non-metastatic TNBC patients from different centers in Turkey and identify clinical and pathologic variables that may effect survival.

Materials and Methods: Between 1993-2007, from five different centers in Turkey, 316 nonmetastatic triple negative breast cancer patients were identified with follow-up of at least 12 months. The data was collected retrospectively from patient charts. The prognostic impact of several clinical variables were evaluated by the Kaplan-Meier and Cox multivariate anayses.

Results: Mean age at diagnosis was 49 years (range: 24-82). The majority of the patient group had invasive ductal carcinoma (n: 260, 82.3%) and stage II disease (n: 164; 51.9%). Majority of the patients (87.7%) received adjuvant chemotherapy. 5 year overall survival (OS) and disease-free survival (DFS) rates were 84.6% and 71.6%, respectively. Univariate analysis revealed locally advanced disease (p: 0.001), advanced pathological stage (p: 0.021), larger tumor size (T1&T2 vs T3&T4) (p<0.001), nodal positivity (p: 0.006), and extensive nodal involvement (p<0.001) as significant factors for DFS; whereas, advanced pathological stage (p: 0.017), extensive nodal involvement (p<0.001) and larger tumor size (p: 0,001) and presence of breast cancer-affected member in the family (p=0.05) were identified as prognostic factors with an impact on OS. Multivariate analysis revealed larger tumor size (T3&T4 vs T1&T2) and presence of lymph node metastases (node-positive vs node-negative) as significant independent prognostic factors for DFS (Hazard ratio (HR): 3.03, 95% CI: 1.71-5.35, p<0.001 and HR: 1.77, 95% CI: 1.05-3.0, p=0.03, respectively). Higher tumor stage was the only independent factor affecting overall survival (HR: 2.81; 95% CI, 1.27-6.22, p=0.01).

Conclusion: The outcome of patients with TNBC in this cohort is comparable to other studies including TNBC patients. Tumor size and presence of lymph node metastasis are the major independent factors that have effect on DFS, however higher tumor stage was the only negative prognostic factor for OS.

Key words: Triple-negative, breast cancer, prognosis, survival

Introduction

Breast cancer is a heterogeneous disease characterized by different morphological features and genetic abnormalities leading to different clinical behaviour. Triple negative breast cancer (TNBC) which corresponds to approximately 10-24% of all invasive breast cancers; is a special breast cancer subtype lacking expression for estrogen receptor (ER), progesteron receptor (PgR) and human epidermal growth factor receptor-2 (HER-2) (1). Regardless of tumor size or nodal status, triple negativity is an independent negative prognostic factor; reflecting the aggressive nature of this tumor. Risk of recurrence rapidly rises in the first 3 years after diagnosis and the median survival after metastatic relapse was reported as 1 year compared with 2.3 years for the other subtypes (2). TNBC patients are not eligible for hormonal therapies or trastuzumab due to the lack of appropriate targets for these drugs, therefore; primary treatment of this breast cancer subtype relies on standart systemic chemotherapy.

The microscopic features of TNBC are comprised of high histological grade, elevated mitotic count, frequent apoptotic cells and a pushing margin of invasion with stromal lymphocytic infiltration (3, 4). Although TNBCs share similar characteristics with basal-like breast

Address for Correspondence:
Leyla Kılıç, Department of Medical Oncology, Fırat University Hospital, Elazığ, Turkey
Phone: +90 505 455 97 60 e-mail: leylahmet@gmail.com

Received: 28.10.2013
Accepted: 24.06.2014

cancer (BLBC) they are not synonymous as about 5% of ER-positive tumors and between 6 to 35% of HER2- positive tumors may show basal-like gene-expression profile by micro-array analysis (5). In addition TNBCs have similar pathological and biological features with Breast Cancer-1 gene (BRCA-1) related tumors leading to BRCA dysfunction. Since BRCA-1 is involved in deoxyribonucleic acid (DNA) repair, agents targeting either pathway has generated much interest over the past decade. Nevertheless, there is a significant fraction of TNBC that does not overlap with BRCA-1 related cancer; reflecting the heterogeneous structure of this entity.

There are limited reports specifically pointing out the effect of different subsets of races and ethnicities on the prognosis of TNBC. African-American women with TNBC are reported to have a larger tumor with higher grade and mitotic activity at presentation when compared with other racial groups (6). However data concerning the prognosis of Asian or Eastern populations and ethnic subsets is lacking. The aim of the current study was to evaluate the outcome of TNBC in Turkish population from different centers in the country and evaluate the impact of various clinical and pathological prognostic factors that may have influence on survival.

Materials and Methods

Study Population - Patients

From a retrospective registry cohort of TNBC patients followed between 1993-2007, medical records of 316 patients with stage I-III disease were reviewed. Five different centers affiliated to Turkish Medical Oncology Society were involved in the study. Institutional review board approval was obtained from each center prior to the commencement of this retrospective study.

Data on patient's baseline characteristics such as family history of breast cancer, lactation status, history of hormone therapy were extracted from patient charts. All patients underwent surgery including mastectomy and breast conserving surgery which included primary tumor excision, lumpectomy and quadrantectomy. Sentinel lymph node biopsies and/or axillary lymph node dissections were performed for assessment of axillary lymph node status as deemed necessary by the surgeon.

All 316 patients had histological confirmation of invasive breast cancer. Initial breast cancer staging was identified according to the sixth edition of American Joint Committee on Cancer (AJCC). Histological type and grade of primary tumor was assessed depending on Nottingham modification of Bloom-Richardson criteria (7). Baseline estrogen receptor (ER) and progesteron receptor (PR) status were determined by immunohistochemical (IHC) staining and were considered as negative if the percentage of cells staining positive were less than 1%. In case of 2(+) staining by IHC, HER2 gene amplification was analyzed by fluorescent in situ hybridization (FISH). Patients with a history of previous malignancy of breast or other sites and who received neoadjuvant chemotherapy were excluded. Sites of recurrence as locoregional and/or distant metastases and type of treatment at progression (chemotherapy/radiotherapy/surgery) were also recorded. Locoregional recurrence was defined as involvement of the ipsilateral axillary, internal mammarian or supraclavicular lymph nodes and/or skin or subcutaneous tissue with/without ipsilateral breast parenchyma involvement.

Treatment

All patients were treated with multidisciplinary approach. Overall 68% of patients (n=215) received an anthracycline-based (non-taxane) regimen where 6.9% of patients (n=22) received non-antracycline, non-taxane regimens which were mainly CMF and its modifications (Table 1). Fourty patients (12.6%) were administered taxane regimens (due to the approval of taxanes for only node positive disease since 2000 in Turkey). Thirty-nine patients (12.3%) with node negative disease and tumors less than 0.5 cm diameter did not receive adjuvant chemotherapy. Anthracycline-containing regimens included four to eight cycles of one of the following regimens: fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 (FEC_{100}) intravenously (IV) on day 1, every three weeks; doxorubicin 60 mg/m^2, cyclophosphamide 500 mg/m^2 IV on day 1 (AC) every three weeks; fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (FAC) intravenously (IV) on day 1, every three weeks and cyclophosphamide 100 mg/m^2 (days 1-14), methotrexate 40 mg/m^2 days 1 and 8, 5-fluorouracil 600 mg/m^2 IV days 1and 8 (CMF), every 4 weeks. Chemotherapy schedules including taxanes were administered as 4 cycles of docetaxel 100 mg/m^2 or paclitaxel 175 mg/m^2 on day 1 every three weeks, following 4 cycles of AC; and six cycles of docetaxel 75 mg/m^2, doxorubicin 60 mg/m^2, cyclophosphamide 500 mg/m^2 (TAC) IV on day 1 every three weeks.

Table 1. Baseline demographic characteristics and histopathological features

Variables	n (%)
Age	
<35	28 (8.9)
35-50	146 (46.2)
>50	142 (44.9)
Family history	
Present	34 (10.8)
Absent	282 (89.2)
Menstruation status	
Premenopausal	154 (48.7)
Postmenopausal	162 (51.3)
Type of operation	
Mastectomy	178 (56.3)
Breast conserving surgery	138 (43.6)
Pathological stage	
Stage 1	84 (26.6)
Stage 2	164 (51.9)
Stage 3	68 (21.3)
Histological grade*	
Grade 1	6 (1.9)

*Missing information regarding grade is not depicted in the table.
ILC+IDC: Invasive lobular cancer+invasive ductal cancer

Postoperative radiotherapy was administered for patients who had undergone breast conserving surgery, locally advanced disease at presentation and/or four or more axillary lymph node metastases after completion of systemic chemotherapy.

Statistical Analyses

Categorical data were compared using Fisher's exact test and chi squared tests. P values <0.05 were considered statistically significant.

Kaplan Meier analysis was used to estimate the effect of clinical and pathological characteristics on overall survival (OS) and disease-free survival (DFS). OS was defined as the time from diagnosis of the primary breast cancer to death or last contact and DFS was defined as the time elapsing from date of diagnosis to progression at local/regional site or occurence of distant metastases. We fitted Cox proportional hazards model for each survival outcome to determine the simultaneous relationship of patient- and tumor-related variables with each outcome. Age, presence of breast-cancer affected member in the family, histological grade, presence of lymph node metastases, tumor stage and type of operation were included in the Cox model. Pathological stage and presence of locally advanced disease were not considered for inclusion because these terms were correlated with tumor stage and lymph node status. $p< 0.05$ was considered statistically significant and all analysis were performed with the SPSS 16.0 software.

Results

Between 1993 and 2007, 316 patients with stage I-III disease and pathologically confirmed diagnosis of triple negative breast carcinoma were enrolled into this study.

Mean age at diagnosis was 49.7 years (24-82 years). The distribution of menopausal status was roughly equal; 48.7% of patients were premenopausal. Thirty-four patients (10.8%) had a first-degree relative affected by breast cancer ant the rest did not report any family history. Approximately 56% of patients had undergone mastectomy and 44% had undergone breast conserving surgery depending on the surgeon's decision and resectability of the primary tumor. Mean tumor size was 2.6 cm (0.1-11 cm). Pathological staging revealed that the majority of the patients had stage II disease (51.9%, n=164). Stage I disease constituted 26.6% (n=84) of the whole patient group. Invasive ductal carcinoma was the predominant histologic subtype (82.3%, n=260), however rare breast cancer histologies, such as medullary, metaplastic and apocrine carcinoma were also involved. Majority of the tumors were poorly differentiated (grade 3) according to Nottingham modification of Bloom-Richardson criteria. Baseline demographic characteristics and histopathological features of the tumors are summarized in Table 1.

Survival Analysis

Patients with at least follow-up period of 12 months were analyzed and the median follow-up time was 52.2 months. The overall 5-year survival (OS) rate was 84.6% and disease-free survival rate (DFS) was 71.6%. During follow-up, 75 patients (24.1%) had relapse documented as locoregional recurrence or as distant metastases or both. Thirty-eight patients (12%) died because of breast cancer-related reasons during follow-up. The sites of initial progression are listed in Table 2. Median survival after initial recurrence was 20.6 months (SD: ±2.7 months, range: 15.3-25.9 moths) and median time elapsed from diagnosis to first occurence of distant metastases was 24.4 months (SD: ±1.8 months, range: 5.3-103.3 moths). Median time from distant metastases to death was estimated as 9.8 months (±1.6 months, range: 1.0-74 months).

The effect of clinical and histopathological parameters on disease-free survival and overall survival were also evaluated (Table 3). Univariate analysis revealed advanced pathological stage (stage 1 vs stage 2 and 3), higher tumor stage (T1&T2 vs T3&T4), tumor size >2 cm, presence of lymph node metastases, extensive nodal involvement (number of metastatic lymph node >10) and presence of locally advanced disease as indicators of worse overall and disease free survival. The presence of breast cancer-affected member in the family was associated with an improved OS (p=0.05) but not with DFS. First recurrence as distant metastases rather than locoregional relapse was also associated with poorer overall survival (p=0.003). When the analysis was restricted to patients who had only systemic recurrence during follow-up, presence of brain metastases was found to be a significant factor for worse overall survival when compared with other metastatic sites such as liver, lung or bone (Table 4).

Table 2. Sites of progression

Site of progression	n	%
Locoregional	16	5.1
Contralateral breast	6	1.9
Locoregional+distant	2	0.6
Distant metastases	51	16.1
Total	75	24.1

To evaluate the prognostic impact of the type of adjuvant treatment received, we stratified the patients into matching subgroups according to presence of node (+) disease. Patients who received non-taxane based regimes (n=113) showed a tendency for improved DFS compared to the remaining (n=40) treated with taxane-based combinations (5 year DFS rate 65.5% vs 59.3%, p=0.06). Nevertheless; there was no OS difference noted between the two treatment groups.

In the multivariate analysis, after controlling for patient and tumor characteristics, higher tumor stage (T3&T4 vs T1&T2) and presence of lymph node metastases (node- negative vs node-positive) were independently associated with worse DFS (Hazard ratio (HR):3.03, 95% CI: 1.71-5.35, p<0.001 and HR: 1.77, 95% CI: 1.05-3.0, p=0.03, respectively). However higher tumor stage was the only independent factor affecting overall survival (HR: 2.81; 95% CI, 1.27-6.22, p=0.01) (Table 5).

Discussion and Conclusions

Triple negative breast cancer (TNBC) is a recently identified subtype of breast cancer characterized by aggressive clinical behaviour and predilection for visceral metastasis. Lack of effective systemic therapy options following recurrence is another major factor contributing to the poor survival rate in this patient subset. Nevertheless; reports regarding survival differences in outcome among TNBC with respect to patient and tumor characteristics have revealed conflicting results (8, 9). The goal of this study was to examine outcome of non-metastatic TNBC patients from different centers in Turkey and investigate the influence of clinical and histopathological variables on survival.

According to our analysis the 5-year overall and disease free survival rates were 84.6% and 71.6%, respectively. When compared with African-American counterparts the survival rates for our TNBC patients seems to be higher than expected (10). There are conflicting reports about the effect of race on survival of TNBC patients. Data supporting the role of ethnic influence on survival comes from studies that have documented a higher prevalance and higher mortality of TNBC among African American women compared with white women. (11).

Table 3. Kaplan Meier survival estimates for overall survival and disease-free survival

Factor	n event/ n total	5 yr OS† rate (%) (±SD)	p	n event/ n total	5 yr DFS¥ rate (%) (±SD)	p
Age						
<50	2/28	88 (7.5)	0.324	8/28	66.4 (9.8)	0.756
>50	36/288	84 (2.7)		67/288	72.0 (3.2)	
Family history						
(+)	1/34	97.4 (2.6)	0.050	6/34	79.4 (7.7)	0.195
(-)	37/282	82.9 (2.8)		69/282	70.6 (3.3)	
Menopause status						
premenopausal	14/154	89 (3.0)	0.336	42/154	69.1 (4.4)	0.309
postmenopausal	19/162	85.5 (3.4)		29/162	74.3 (4.4)	
Pathological stage						
Stage 1	4/84	95.5 (2.6)	0.017	12/84	80.4 (5.5)	0.021
Stage 2&3	34/232	80.7 (3.4)		63/232	68.4 (3.6)	
Histological grade						
Grade 1&2	8/76	81.7 (6.3)	0.256	18/76	68.4 (6.6)	0.515
Grade 3	27/200	82.9 (3.3)		48/200	70.9 (3.9)	
Tumor stage						
T1&T2	27/280	88.5 (2.4)	0.001	52/280	76.3 (3.1)	<0.001
T3&T4	9/36	61.1 (10.4)		20/36	39.4 (9.5)	
Nodal positivity						
node (-)	14/163	88.8 (3.0)	0.07	27/163	79.4 (3.8)	0.006
node (+)	23/153	81 (4.0)		45/153	64.4 (4.7)	
Extensive nodal involvement						
positive node≤ 10	29/293	87.2 (2.5)	<0.001	60/293	74.9 (3.0)	<0.001
positive node>10	8/23	58.7 (11.6)		12/23	41 (12.7)	
Tumor size						
≤2 cm	9/128	93.7 (2.5)	0.038	20/128	77.3 (4.8)	0.01
>2 cm	27/188	81.4 (3.4)		52/188	68.4 (4.0)	
Locally advanced disease						
(-)	16/177	88.4 (3.0)	0.063	29/177	78.7	0.001
(+)	22/139	79.7 (4.2)		46/139	63.1	
Site of progression						
Locoregional	3/22	88.4 (3.0)	0.003	22/22	9.1 (1.1)	0.572
Distant metastases	32/55	79.7 (4.2)		55/55	5.7 (3.2)	
Taxane regimens*						
(+)	6/40	72.1 (10.2)	0.157	13/40	59.3 (9.9)	0.068
(-)	16/113	83.4 (4.4)		31/113	65.5 (5.4)	
Type of operation						
Mastectomy	26/178	82.0 (3.5)	0.181	52/178	67.8 (4.1)	0.031
Breast conserving	12/138	88.6 (3.3)		23/138	77.1 (4.4)	

Among node (+) patients.
†OS: Overall survival
¥DFS: Disease-free survival

It has been found that breast cancer among black women usually present with higher grade and hormone-receptor negative phenotype (12). In addition, African-American women with late stage TNBC had significantly worse 5-year survival rates compared with non-Hispanic Caucasian patients (14% for African-American and 36% for non-Hispanic Caucasian women) (8). However a single center study which included African-American and Caucasian TNBC patients, reported that race did not effect the clinical presentation and outcome of disease where patients received similar therapy and follow-up (13). Besides, the evaluation of approximately 15,000 breast cancer patients pre-

Table 4. Kaplan Meier overall survival estimates for patients with disease progression

Site of progression	n event/n total	median OS¥ (mo)	SD(±)	95% CI*	p
Brain					
(-)	32/69	61.0	9.7	(41.8-80.0)	0.041
(+)	5/7	32.0	10.4	(11.6-52.3)	
Liver					
(-)	29/63	61.0	9.5	(42.3-74.6)	0.400
(+)	8/13	47.0	15.2	(17.0-76.9)	
Lung					
(-)	24/52	59.0	8.4	(42.5-75.4)	0.332
(+)	13/24	48.0	10.9	(26.4-69.5)	
Bone					
(-)	29/58	52.0	10.1	(32.0-71.9)	0.647
(+)	8/18	59.0	11.4	(36.5-81.4)	

OS¥: Overall survival
CI*: Confidence Interval

Table 5. Independent prognostic variables on DFS and OS: Cox regression analysis results

	Overall survival			Disease-free survival		
Variable	HR*	95% CI†	p	HR	95% CI	p
Family history of breast cancer (+) vs (-)	0.23	0.03-1.69	0.15	0.75	0.29-1.90	0.54
Histological grade (Grade 1&2 vs 3)	1.68	0.73-3.88	0.21	1.15	0.65-2.01	0.61
Age >50 vs <50 yrs	1.98	1.47-8.34	0.35	0.88	0.39-1.96	0.76
Lymph node (+) vs (-)	1.73	0.85-3.51	0.13	1.77	1.05-3.0	0.03
T stage T3+T4 vs T1+T2	2.81	1.27-6.22	0.01	3.03	1.71-5.35	<0.001
Type of operation (BCS¥ vs mastectomy)	0.87	0.35-1.94	0.74	0.81	0.44-1.49	0.51

*HR: Hazard ratio
†CI: Confidence interval
¥BCS: Breast conserving surgery

sented to National Cancer Network centers revealed that triple negative subtype was associated with worse breast cancer-specific survival however inclusion of race into the cox regression model did not alter survival estimates. This finding suggests that the worse overall survival for TNBC patients may not be mediated by the effect of race, at least for African-American patients (14).

There has been limited data on this disease entity among Asian populations. A retrospective analysis by Kurebayashi et al. (15) has revealed 86.2% five-year survival rate in a Japanese cohort of breast cancer patients (n=793) which TNBC constituted 7% of the whole patient population. In addition data from a single institution series including some of the patients that constitutes a fraction of the patient group in this study; have reported a 5-year survival rate of 82.4% which was comparable to other hormone receptor negative disease when adjusted for known clinical factors such as age, stage, grade and nodal status (16). A recently published article from a single center in Turkey which included early triple-negative breast cancer patients also revealed a 81% five-year overall survival rate which was in concordance with our results (17). The major weakness of our study is the inability to compare the survival rates and clinicopathologic characteristics with other breast cancer subtypes. Nevertheless, in another study by Turkey which compared TNBC and non-TNBC patients have pointed at similar DFS rates for both patient groups (18). Median overall survival rates could not be obtained but the 5-year DFS rates for TNBC and HER-2 positive patients were reported to be 67% and 66%, respectively which were slightly lower than our results. Moreover another retrospective series from Turkey has also stated that these tumors displayed similar clinicopathological characteristics and overall survival rates were comparable with non-TNBC variants (19).

These reported discrepancies in outcome within different triple-negative patient populations may be related to many factors including genetic polymorphisms, epigenetic differences or distinct tumor-host interactions leading to distinctive clinical behaviour. In addition pharmacogenomic differences may also be a confounding factor for the outcome accounting for variances in efficacy of systemic treatment (20,21). In concordance with these clinical observations, data from molecular array-based analysis support the heterogeneous nature of TNBC. An analysis from Rody et al.(22) has revealed a favorable subgroup within their TNBC cohort who display a high B-cell and low IL-8 metagene expression.

In our analysis, tumor stage was an independent prognostic factor for both OS and DFS. Additionally presence of lymph node metastasis was associated with worse disease-free survival. Similarly other studies from different populations underscore the influence of tumor size on survival for TNBC patients (23,24). A recent Asian study have demonstrated that tumor size and axillary lymph node status were the main prognostic indicators for 7-year DFS and OS in multivariate Cox's regression analysis (25). The effect of pathological stage and lymph node status on survival for Turkish TNBC patients have also been established in the previous study (18).

In conclusion, our study gives an idea about the outcome of early TNBC patients and underlines the major prognostic factors that may have influence on survival. Relatively higher survival estimates when compared with African-American counterparts, suggest that there may be a subset of TNBC patients with a more favorable outcome. Whether this difference is due to racial and ethnic factors is still a subject of debate. Our findings support the fact that TNBC is a heterogeneous disease and highlights the requirement for identification of molecular sub-classifications that may lead to the identification of new pathways of tumor progression and new targets.

Ethics Committee Approval: The study is approved individually by each local ethical committees of the centers involved.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.E.; Design - Y.E., L.K., G.A.; Supervision - Y.E., G.B., D.D., S.D., F.I., H.O.; Data Collection and/or Processing - Y.E., L.K., G.A., G.B., M.D., D.D., S.D., F.I., H.O., P.S., A.H.; Interpretation - Y.E., L.K.; Literature Review - Y.E., L.K., P.S.; Writing - Y.E., L.K.; Critical Review - G.A., G.B., D.D., F.I, H.O., P.S.; Other - S.D., A.H., M.D.

Acknowledgements: The authors thank to Dr Rian Disci for reviewing the statistical analysis of the report.

Financial Disclosure: The authors declared that this study has received no financial support.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Viale G, Rotmensz N, Maisonneuve P, Bottiglieri L, Montagna E, Luini A, Veronesi P, Intra M, Torrisi R, Cardillo A, Campagnoli E, Goldhirsch A, Colleoni M. Invasive ductal carcioma of the breast with the 'triple-negative' phenotype: prognostic implications of EGFR immunoreactivity. Breast Cancer Res Treat 2009; 116:317-328. (PMID: 18839307) [CrossRef]
2. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Pusztai L. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008; 26:1275-1281. (PMID: 18250347) [CrossRef]
3. Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, Perou CM. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod. Pathol 2006; 19:264-271. (PMID: 16341146) [CrossRef]
4. Dabbs DJ, Chivukula M, Carter G, Bhargava R. Basal phenotype of ductal carcinoma in situ: recognition and immunohistologic profile. Mod Pathol 2006; 19:1506-1511. (PMID: 16941011)
5. Liu H, Fan Q, Zhang Z, Yu H, Meng F. Basal-HER2 phenotype shows poorer survival than basal-like phenotype in hormone receptor-negative invasive breast cancers. Hum Pathol 2008; 39:167-174. (PMID: 18045647) [CrossRef]
6. Lund M, Eley JW, O'Regan RM, Gabram SS, Saavedra HI, Liff JM, Brawley OW et al. Molecular differences between triple-negative tumors of African-American women with white women (abstract) San Antonio Breast Cancer Symp 2008; a2087.
7. Elston CW, Ellis IO. Pathological prognostic factors in breast cancers. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991; 19:403-410. (PMID: 1757079) [CrossRef]
8. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative and HER-2 negative invasive breast cancer, the so-called triple-negative phenotype. Cancer 2007; 109:1721-1728. (PMID: 17387718) [CrossRef]
9. Dawood S, Broglio K, Kau SW, Green MC, Giordano SH, Meric-Bernstam F et al. Triple receptor-negative breast cancer- the effect of race on response to primary systemic treatment and survival outcomes. J Clin Oncol 2009; 27:220-226. (PMID: 19047281) [CrossRef]
10. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006; 295:2492-2502. (PMID: 16757721) [CrossRef]
11. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, Dolan NC, Paskett ED, McTiernan A, Hubbell FA, Adams-Campbell LL, Prentice R. Ethnicity and breast cancer: Factors influencing differences in incidence and outcome. J Natl Cancer Inst 2005; 97:439-448. (PMID: 15770008) [CrossRef]
12. Ihemelandu CU, Leffall LD Jr, Dewitty RL, Naab TJ, Mezghebe HM, Makambi KH, Adams-Campbell L, Frederick WA. Molecular breast cancer subtypes in premenopausal and ppostmenopausal African-American women: Age-specific prevelance and survival. J Surg Res 2007; 143:109-118. (PMID: 17950079) [CrossRef]
13. Pacheco JM, Gao F, Bumb C, Ellis MJ, Ma CX. Racial differences in outcomes of triple-negative breast cancer. Breast Cancer Res Treat 2013; 138:281-289. (PMID: 23400579) [CrossRef]
14. Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, Wong YN, Blayney DW, Niland JC, Winer EP, Weeks JC. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer 2012; 118:5463-5472. (PMID: 22544643) [CrossRef]
15. Kurebayashi J, Moriya T, Ishida T, Hirakawa H, Kurosumi M, Akiyama F, Kinoshita T, Takei H, Takahashi K, Ikeda M, Nakashima K. The prevalance of intrinsic subtypes and prognosis in breast cancer patients of different races. Breast 2007; 16:72-77. (PMID: 17714947) [CrossRef]
16. Derin D, Eralp Y, Ozluk Y, Yavuz E, Guney N, Saip P, Igci A, Ozmen V, Kücücük S, Aslay I, Aydiner A, Topuz E. Lower level of MAPK expression is associated with anthracycline resistance and decreased survival in patients with hormone receptor negative breast cancer. Cancer Invest 2008; 26:671-679. (PMID: 18608215) [CrossRef]
17. Varol U, Cakar B, Yildiz I, Dalgic C, Ozisik H, Ozisik M, et al. Survival analysis of Triple negative and Her-2 positive breast cancer patients: single center report. J Breast Health 2014; 10: 42-46. [CrossRef]
18. Bulut N, Aksoy S, Dizdar O, Dede D, Arslan C, Dogan E, Gullu I, Ozisik Y, Altundag K. Demographic and clinico-pathological characteristics in patients with triple-negative and non-triple-negative breast cancer. Med Oncol 2011; 28:75-79. (PMID: 20963641) [CrossRef]
19. Mersin H, Yildirim E, Berberoglu U, Gülben K. The prognostic importance of triple negative breast carcinoma. Breast 2008; 7:341-346. (PMID: 18450442) [CrossRef]
20. Martin DN, Boersma BJ, Yi M, Reimers M, Howe TM, Yfantis HG et al. Differences in the tumor microenvironment between African-American and European-American breast cancer patients. PLoS One 2009; 4:e4531. (PMID: 19225562) [CrossRef]

21. Phan VH, Moore MM, McLachlan AJ, Piquette-Miller M, Xu H, Clarke SJ. Ethnic differences in drug metabolism and toxicity from chemotherapy. Expert Opin Drug Metab Toxicol 2009; 5:243-257. (PMID: 19331590) [CrossRef]
22. Rody A, Karn T, Liedtke C, Pusztai L, Ruckhaeberle E, Hanker L, Gaetje R, Solbach C, Ahr A, Metzler D, Schmidt M, Müller V, Holtrich U, Kaufmann M. A clinically relevant gene signature in triple negative and basal-like breast cancer. Breast Cancer Res 2011; 13:R97. (PMID: 21978456) [CrossRef]
23. Lin C, Chien SY, Kuo SJ, Chen LS, Chen ST, Lai HW, Chang TW, Chen DR. A 10year followup of triple negative breast cancer patients in Taiwan. Jpn J Clin Oncol 2012; 42:161-167. (PMID: 22287721) [CrossRef]
24. Nishimura R and Arima N. Is triple negative a prognostic factor in breast cancer? Breast Cancer 2008; 15:303308. (PMID: 18369692) [CrossRef]
25. Yuan N, Meng M, Liu C, Feng L, Hou L, Ning Q, Xin G, Pei L, Gu S, Li X, Zhao X. Clinical characteristics and prognostic analysis of triplenegative breast cancer patients. Mol Clin Oncol 2014; 2:245-251. (PMID: 24649341)