ORIGINAL ARTICLE

GMJ.2014;3(3):145-52
www.gmj.ir

Histopathological Characteristics of Triple-Negative Breast Cancer: An Iranian Issue

Mehrnoosh Etemadi[1], Mohammad Mahdi Zamani[1,2], Amir Masoud Nazemi[3], Afsaneh Rajabiani[4], Alireza Abdollahi[4]✉

[1]Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Anesthesiology and Critical Care, Tehran University of Medical Sciences, Tehran, Iran
[3]Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Iranian Blood Transfusion Organization, Tehran, Iran
[4]Department of Pathology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: Breast cancer is one of the most frequent malignancies among Iranian women. Triple-negative breast cancer (TNBC) is referred to a type of breast cancer which three biomarkers of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2), are negative. **Materials and Methods:** In this case control study, immunohistopathologic data of patients with TNBC were compared with non-TNBC patients. According to pathological reports, frequency, age, gender, type, size, and tumor grade, involvement and the number of involved lymph nodes, mitosis, Ki-67, necrosis, nuclear grade, tumor side, involvement of the margins, skin involvement, nipple involvement, tumor location, vascular invasion, perineural invasion, presence of in-situ compartment and the benign accompanied tumors, granulomatosis reaction, and calcification were compared between both groups. **Results:** Two hundred fourteen pathological samples of patients with breast cancer were evaluated. TNBC was seen in about 14% of breast cancers in this study on Iranian population. The mean age of TNBC group was 43±12 years and non-TNBC was 50±12 years (p=0.03). TNBC had significantly higher grade, high mitotic indices, more possibility of P53 positivity and higher level of Ki-67. Presence of vascular and nerve invasion and involvement of the margins at the time of diagnosis were seen in the TNBC group comparing with the non-TNBC group. **Conclusion:** Younger age, higher grading, neurovascular invasion, P53 positivity, and high levels of Ki-67, lead clinicians to evaluate the biomarkers of TNBC, and in case of confirming TNBC diagnosis, appropriate treatment methods should be added to the routine ones in breast cancer. **[GMJ.2014;3(3):145-52]**

Keywords: Breast cancer; Epidemiology; Iran; Hormone receptor; Triple-negative breast cancer

GMJ

Fax: +98 731 2227091
PO Box 7461686688
Email:info@gmj.ir

✉ **Correspondence to:**
Alireza Abdollahi, MD, Department of Pathology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Telephone Number: (+98) 21-88269844
Email Address :dr_p_abdollahi@yahoo.com

Introduction

Breast cancer is the second most common cancer worldwide after lung cancer. This cancer accounts for about 10.4% of all cancers and is the fifth leading cause of cancer related mortalities. Breast cancer is the most common cancer in females with a wide comparison gap to other cancers (prevalence rate is twice as colorectal and cervix cancer and three times more than lung cancer) and is the second most common death cause of cancers in females. In 2005, 502000 worldwide deaths were caused by breast cancer, equal to 7% of cancer deaths and approximately 1% of all deaths [1]. According to the latest American cancer society reports on 2010, breast cancer is the most common cancer in women (28%) and is the second cause of cancer mortalities in females [2]. Breast cancer is one of the most frequent malignancies among Iranian women, however; the epidemiological aspects of breast cancer among Iranian patients are uncertain [3].

According to a report of Iranian government in 1994, the highest incidence rates of breast cancer were reported in ages ranged from 45 to 64 and above 80 years old and in three provinces (Yazd, Isfahan and Tehran, respectively). The highest prevalence was in Yazd province (25.46%). The lowest prevalence was in Sistan and Balouchestan province (1.96%). The highest prevalence of breast cancer in men belonged to Kerman province (1.28%) [3].

From 1970, breast cancer incidence in all countries has increased obviously which is assumed to be due to changes in lifestyle. In USA, from 1998, prevalence of this cancer has been declining probably due to less hormone replacement therapy, improved diagnostic methods, and early treatments [2]. The most common types of breast cancer are ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), invasive (or infiltrating) ductal carcinoma (IDC) and invasive (or infiltrating) lobular carcinoma (ILC). Diagnostic evaluation of breast cancers is used commonly with immunohistochemistry (IHC) staining for three biomarkers including estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) [4].

Triple-negative breast cancer (TNBC) is referred to a type of breast cancer in which none of these three biomarkers are positive. Indeed, in TNBC patients, genes of these three biomarkers are not expressed. Despite the similarity in the basics of diagnosis of TNBC and other types of breast cancers, different factors distinguish this type of cancer from the other types. Some of these factors are age, race, risk factors, pathologic and molecular properties, normal course of this disease, sensitivity, and response to chemotherapy [5]. Prevalence of this type is higher in younger population and African-American individuals who are in pre-menopausal ages [6]. This type of cancer often has a more aggressive nature compared to other types and routine hormonal treatments are mostly ineffective. It is estimated that about 10-20% of breast cancers are TNBC [7]. Recently, TNBC has attracted the attention of therapeutic and counseling cancer centers in different countries and valuable studies have been assigned on issues like recognition, comparison, screening, prevention, and treatment of this type of breast cancer [7].

According to high prevalence of breast cancer in Iranian women and probable differences in distribution and other clinical and pathological specifications of this cancer compared to other countries, the aim of this study is to evaluate the demographic and histopathological specifications of this special type of breast cancer (TNBC) in Iran as a developing country and also comparing that to non-TNBC (N-TNBC).

Materials and Methods

Study population

This is a retrospective cross-sectional study that was conducted in 2012. All pathological samples being evaluated were from the breast cancer patients collected from pathology ward's archieve of the first referral center of the Iranian people, Imam Khomeini Hospital, Tehran,Iran,from July 2010 to June 2011.

Inclusion criteria for this study were all pathological samples of patients with breast mass

which were diagnosed as a malignant breast tumor. Exclusion criteria were the absence or incomplete immunohistopathologic report for the respective pathological sample. There was no age or sex restriction to enter the study. Patients' name were written as a code in the data collection questionnaires.

Malignant breast tumors with negative ER, PR and HER2, IHC biomarkers were defined as TNBC group and were considered as the case group. Other patterns were labeled as N-TNBC and were considered as the control group. According to pathological reports, frequency, age, sex, cancer type, tumor size, tumor grade, tumor side, tumor location, the benign accompanied tumors, presence of lymph node involvement and the number of involved lymph nodes, presence or absence of in-situ involvement, skin involvement, nipple involvement, involvement of the margins, vascular invasion or perineural invasion, mitosis, Ki-67, necrosis, nuclear grade, calcification, and granulomatosis reaction were compared between the two groups.

Grading of the tumors is as follows, grade I- both form and cellular division of the cells are similar to normal (well differentiated), grade II- tumoral cells are between grade I and III (moderately differentiated), and grade III- abnormal tumoral cells with rapid growth (poorly differentiated).

Data analysis

The statistical package of social science, version 19.0 (SPSS, Chicago, Illinois, USA) was used for data analysis. Statistical significance was noted for $P \leq 0.05$. Chi-Square test was used to find the associations between qualitative variables. while independent sample t-test and ANOVA test were applied for comparison of quantitative variables.

Results

Two hundred and fourteen pathological samples of the patients with breast cancer were evaluated. Thirty patients (14%) were negative for all three receptors (TNBC group) and 184 patients (86%) belonged to N-TNBC group. The mean age of patients in TNBC group was 43±12 years (26 to 85 years old). The mean age in N-TNBC group was 50±12 years (24 to 91 years old) (P=0.03). Of the patients, 181 (98.4%) were females and 3 patients (1.6%) were males in N-TNBC group. TNBC group were all females. Significant sex difference was not seen between the two groups (P=0.48).

Mean tumor size in the TNBC group was 3.83±1.88 cm3 ranging from 1 to 10 cm3 and was 2.98± 2.22 cm3 in N-TNBC group, within the 0.2-13 cm3 range. Significant difference in tumor sizes was not seen between the two groups (P=0.72).

The number of lymph nodes in the TNBC group was 3±3 and in N-TNBC was 2±2 (P=0.058). TNBC group had significantly, younger age, higher grade, high mitotic indices, more possibility of P53 positivity, and higher level of Ki-67 at the diagnosis time. Presence of vascular and nerve invasion and involvement of the margins at the time of diagnosis were more significant in TNBC compared to N-TNBC, also. Table-1 shows the other pathological specifications of breast tumors in two groups.

TNBC had more Significantly DCIS and LCIS types than N-TNBC. Grade III of cellular and nuclear grading was significantly higher in TNBC. Left lower quadrant (LLQ) involvement was significantly higher than other locations in TNBC. Microscopic and macroscopic characteristics of breast tumors of the two groups are compared in Table-2.

Discussion

This study revealed 14% of TNBC cases in Iranian women who had younger age, higher grade, high mitotic indices, positive P53, and higher level of Ki-67at the diagnosis time, and moreover had more noticeable invasion to the margins, vascular and nerve invasion at the time of diagnosis comparing with N-TNBC. The DCIS and LCIS types were considerably more at risk of TNBC. In Canada, Dent et al. conducted a study to compare clinical characteristics, medical history, recurrence pattern and the course of the disease in women with TNBC, with other types of breast cancer. This cohort study was done on 1601 patients who were diagnosed with breast cancer in Toronto

hospitals, from January to December 1987. TNBC was diagnosed in 11.2% of patients. Comparing TNBC to others, the mortality of TNBC was higher in first 5 years after the diagnosis. The maximum risk of remote metastasis in TNBC was in the first 3 years after diagnosis; afterward this risk was rapidly declined while in the other groups, this risk was almost stable during the time. This study showed that TNBC has a more aggressive clinical course [8]. In 2008, Liedtke et al. performed a cohort study on 255 patients with TNBC and the responses to chemotherapy with neoadjuvant therapy were evaluated. According to this research, higher relapse rates in visceral organs and soft tissue and lesser bone involvement were seen in patients with TNBC compared to other types. Moreover, survival rate after relapse time was lower in TNBC patients. Pathologically complete re-

Table-1. Pathologic characteristics of breast cancer in each group

Variables	Number of Mitosis	P53 (neg/pos)	Ki-67
TNBC (n=30)	3.60±2.13	11/19	0.16±0.06
N-TNBC (n=184)	2.90±1.31	123/61	0.18±0.05
P-value	0.01	0.002	0.25

TNBC: triple-negative breast cancer, N-TNBC: non-triple-negative breast cancer.

Continued of Table-1 (2). Pathologic characteristics of breast cancer in each group

Variables	Necrosis (neg/pos)	Vascular Invasion (neg/pos)	Calcification (neg/pos)	Nerve Invasion (neg/pos)	Nipple Involvement (neg/pos)
TNBC (n=30)	20/10	18/12	22/8	23/7	29/1
N-TNBC (n=184)	136/48	119/65	154/30	163/21	170/14
P-value	0.40	0.04	0.16	0.03	0.39

TNBC: triple-negative breast cancer, N-TNBC: non-triple-negative breast cancer.

Continued of Table-1 (3). Pathologic characteristics of breast cancer in each group

Variables	Insitu Component (neg/pos)	Associated Benign Tumor (neg/pos)	Involvement of The Margins (neg/pos)	Granulomatosis Reaction (neg/pos)	Skin Involvement (neg/pos)
TNBC (n=30)	19/11	24/6	17/13	30/0	27/3
N-TNBC (n=184)	118/66	150/34	161/23	180/4	170/14
P-value	0.93	0.84	0.001	0.41	0.65

TNBC: triple-negative breast cancer, N-TNBC: non-triple-negative breast cancer.

Table-2. Microscopic and macroscopic characters of tumor in each group

Series	Variable	TNBC	N-TNBC	P-value
	Tumor Type			
	IDC or ILC	27 (90%)	167 (90.8)	**0.80**
1	DCIS	3 (10%)	6 (3.3%)	**0.04**
	LCIS	-	10 (5.4%)	**0.001**
	MC	-	1 (0.5%)	**-**
	Tumor Grading			
2	I	3 (10%)	15 (8.2%)	**0.87**
	II	26 (86.7%)	152 (82.6%)	**0.66**
	III	1 (3.3%)	17 (9.2%)	**0.02**
	Nuclear Grading			
3	I	4 (13.3%)	14 (7.6%)	**0.05**
	II	24 (80%)	147 (79.9%)	**0.91**
	III	2 (6.7%)	23 (12.5%)	**0.01**
	Tumor Side			
4	Right	17 (56.7%)	108 (58.7%)	**0.79**
	Left	13 (43.3%)	75 (40.8%)	**0.65**
	Bilateral	-	1 (0.5%)	**-**
	Tumor Location			
	RUQ	21 (70%)	108 (58.7%)	**0.09**
	RLQ	3 (10%)	25 (13.6%)	**0.76**
5	LUQ	3 (10%)	16 (8.7%)	**0.87**
	LLQ	1 (3.3%)	26 (14.1%)	**0.01**
	Subareol	2 (6.7%)	8 (4.3%)	**0.06**
	All Sides	-	1 (0.5%)	**-**

TNBC: triple-negative breast cancer, N-TNBC: non-triple-negative breast cancer, DCIS: ductal carcinoma in situ, LCIS: lobular carcinoma in situ, IDC: invasive (or infiltrating) ductal carcinoma, ILC: invasive (or infiltrating) lobular carcinoma, MC: medullary carcinoma, RUQ: right upper quadrant, RLQ: right upper quadrant, LUQ: left upper quadrant, LLQ: left lower quadrant.

sponse (PCR) rate was higher in TNBC and this group had a good survival after chemotherapy with neoadjuvant. However, if the patients remained with residual disease after chemotherapy with neoadjuvant and they were diagnosed as TNBC type, the prognosis was very bad [9]. In the same year, Lin et al. in United States performed a study with the purpose of defining metastasis risk and determining disease course in metastatic TNBC patients including those with central nervous system (CNS) metastasis. From January 2000 to June 2006, 116 patients were selected by obtaining their pathological and drug history in a cancer institute. According to this study, from the time that the metastasis was diagnosed, the mean survival time was estimated 13.3 months. Once the metastasis was diagnosed, 14% of the patients had CNS involvement. Overall, in 46% of the patients, CNS metastasis was diagnosed before death. Mean survival time after diagnosing CNS metastasis, was 4.9 months. By excluding race and age parameters, mortality in patients whose CNS involvement was their first sign, was 3.4 times higher than other patients with TNBC. Results of this study showed that the survival of TNBC after relapsing, is infrequent and new therapeutic strategies are needed. This study revealed that high rates of CNS involvement are not seen in TNBC [10]. In addition, Anders et al. in North Carolina, performed a cross-sectional study to evaluate the age, race, subtype and prognosis of breast cancer patients with brain metastasis. According to this survey, while investigating brain relapses, extra-cranial metastasis was diagnosed in 83% of the patients which indicated the systemic nature of this disease. Mean survival time of TNBC patients after CNS metastasis was less than 6 months [11]. In 2010, a good review by Foulkes et al. on etiologic factors and clinical and molecular characteristics and the treatment of TNBC stated that the relapse rate of TNBC compared to other types, was higher and its prognosis was poorer [12]. De Laurentiis et al. in Italy reviewed the current TNBC therapeutic choices. According to this survey, TNBC is sensitive to anthracycline-taxane-based neoadjuvant chemotherapy, which should be considered as the treatment method of TNBC [13]. At the same year, Santana-Davila et al. in Florida published an article about different available choices for TNBC treatment. Platinum agents, anti-tubulin agents, antiangiogenic agents, and multikinase inhibitors, were the studied and confirmed regimen for TNBC chemotherapy. Moreover, neoadjuvant chemotherapy is the preferred regimen in patients with TNBC but there is no preferred agent in neoadjuvant chemotherapy method [14].

By reviewing several studies from different countries,it was found that TNBC accounts for 10-20% of all breast cancers [7-8, 15-16] based on the thresholds that are/were defined for ER and PR positivity and the methods for HER2 assessment. The main characteristics of TNBC that is found in several related studies include the fact that TNBC affect younger patients (<50 years) [8,17] , is more prevalent in African-American race [16], and almost always TNBC is significantly more aggressive than tumors with other immunohistopathologic charasteristics [15]. Patients with TNBC [8] have a significantly poorer and shorter survival after the first metastasis occurred, compared with non-triple-negative breast cancers. TNBC is often diagnosed in high histological grade [18], but according to a study, about 10% of TNBC cases have been reported to be in grade I [8]. There are controversial results on the prevalence of lymph node metastasis in patients with TNBC; Dent et al. reported higher prevalence of lymph node metastasis in TNBC compared with N-TNBC [8], but other studies did not find any differences between TNBC and N-TNBC in this regard [17-19]. It has been reported that, unlike N-TNBC, there is no correlation between tumor size and presence of lymph node metastasis in the TNBC [8].

Ragarding epidemiological studies in Asia, Suresh et al. study investigated the epidemiological and clinical profile of TNBC at their institute in India. Characteristic data on 171 patients with TNBC were from 2008 to 2010. The mean age was 49 years (22-75 years old). Just eight patients (5%) had a family history of breast or ovarian cancer. One hundred and six patients (62%) were in stage II, 26 (15%) in stage III, 21 (12%) in stage I and 18 pa-

tients (10%) were in stage IV [20].

Our study was designed to look at the demographic profile and histopathological data of TNBC in the Iranian setting. To our knowledge, this is possibly the largest investigation on TNBC performed in Iran which was done as a case control study. Our TNBC population was slightly younger (median age of 43 years old) than the ones described in western data [8] (median age of 53 years old). This finding most likely reflects that the general trend of breast cancer was occurring a decade earlier, in Iran. In our study, average age of TNBC group was reported 43 years old, which is 2 years younger compared to the N-TNBC group.

Amirikia et al. analyzed patients with breast cancer, from the California Cancer Registry (CCR) between 1988 and 2006. In their study, white Americans were identified as non-Hispanic whites (NHWs) and African Americans were identified as non-Hispanic blacks (NHBs). Epidemiologic data of 375,761 invasive breast cancers were investigated (containing 276,938 in NHWs and 21,681 in NHBs). Patients from NHBs were younger than NHWs (median age of 57 years and 64 years, respectively). NHBs had higher incidence of stage III and stage IV and a higher incidence of TNBC in all age categories [21]. Overall, there is now evidence emerging from several epidemiological studies regarding major characteristics of this group of breast cancer which have a relatively poorer prognosis than the other breast cancer sub-types. Boyle et al. gathered available data about TNBC in their review article in 2012. Boyle reported TNBC as the 10%–20% of invasive breast cancers which has been shown more in younger age, deprivation status, African-American race, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer and BRCA1 mutations [22].

Any size or stage of breast cancer will have poorer prognosis, if its grade is higher, so in our study cellular and nuclear grading were both evaluated and higher cellular grading were seen in TNBC in Iran. Cellular grading report showed grade II in 82.6% of patients and the second most common was grade III (9.2%). Also the common nuclear grading was grade II (79.9%) and the second most common was grade III (12.5%). Our report also indicated the higher grades of breast cancer in TNBC, while in NTNBC group, grade I was in second position, in both cellular and nuclear grading.

Conclusion

This study revealed the following characteristics for TNBC in Iranian race: younger age at diagnosis, higher grades, high mitotic indices, more possibility of P53 positivity and higher levels of Ki-67. Presence of vascular and nerve invasion and involvement of the margins at the time of diagnosis were seen in TNBC patients comparing to N-TNBC as well.

TNBC included DCIS and LCIS types significantly more than N-TNBC but not about IDC and ILC types of breast cancer. Grade III of cellular and nuclear grading was significantly higher in TNBC and finally LLQ involvement was significantly higher than other regions in TNBC.

Acknowledgments

This study has been granted by Tehran University of Medical Sciences and Health Services.

Conflicts of Interest

None declared.

References

1. Muñoz M, Estévez LG, Alvarez I, Fernández Y, Margelí M, Tusquets I, et al. Evaluation of international treatment guidelines and prognostic tests for the treatment of early breast cancer. Cancer Treat Rev. 2008;34(8):701-9.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.
3. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, et al.

Breast cancer in Iran: an epidemiological review. Breast J. 2007;13(4):383-91.
4. Abd El-Rehim DM, Pinder SE, Paish CE, Bell J, Blamey R, Robertson JF, et al. Expression of luminal and basal cytokeratins in human breast carcinoma. J Pathol. 2004;203(2):661-71.
5. Rubovszky G, Udvarhelyi N, Horváth Z, Láng I, Kásler M. Triple-negative breast carcinoma--rewiev of current literature]. Magy Onkol. 2010;54(4):325-35.
6. Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, et al. Differences in breast carcinoma characteristics in newly diagnosed African–American and Caucasian patients. Cancer. 2007;110(4):876-84.
7. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750.
8. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15):4429-34.
9. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008;26(8):1275-81.
10. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer. Cancer. 2008;113(10):2638-45.
11. Anders CK, Deal AM, Miller CR, Khorram C, Meng H, Burrows E, et al. The prognostic contribution of clinical breast cancer subtype, age, and race among patients with breast cancer brain metastases. Cancer. 2011;117(8):1602-11.
12. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010;363(20):1938-48.
13. De Laurentiis M, Cianniello D, Caputo R, Stanzione B, Arpino G, Cinieri S, et al. Treatment of triple negative breast cancer (TNBC): current options and future perspectives. Cancer Treat Rev. 2010;36:S80-S6.
14. Santana-Davila R, Perez EA. Treatment options for patients with triple-negative breast cancer. J Hematol Oncol. 2010;3:42.
15. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007;13(8):2329-34.
16. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. Cancer. 2007;109(9):1721-8.
17. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol. 2006;24(36):5652-7.
18. Tischkowitz M, Brunet J-S, Bégin LR, Huntsman DG, Cheang MC, Akslen LA, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC cancer. 2007;7(1):134.
19. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer. 2007;109(1):25-32.
20. Suresh P, Batra U, Doval D. Epidemiological and clinical profile of triple negative breast cancer at a cancer hospital in North India. Indian J Med Paediatr Oncol. 2013;34(2):89.
21. Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women. Cancer. 2011;117(12):2747-53.
22. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol. 2012;23(suppl 6):vi7-vi12.