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Characteristics of Molecular Breast Cancer Subtypes among Uzbekistan's Women

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Abstract In the Republic of Uzbekistan biological characteristics of breast cancer (BC) are published in fragments. In this cohort study included 912 breast cancer patients. Material: Date from Tashkent City Cancer Registry about female BC, diagnosed in 2008-2018 was analyzed. Cohort study included 2 groups of BC: the 1 group of BC is Uzbek native women 500cases, the 2 group-412 cases. Results: Median age of BC in the 1 group is 48,5±11 years, 2 group is 52±11,4 years. Conclusions: Our study findings suggest that the prevalence of triple negative (21,6%) breast cancer in Uzbekistan's.

Keywords Breast cancer, Uzbekistan's women, Biological subtypes, Comorbidity diseases

1. Introduction

An interest to the heterogeneity of breast cancer remains an important issue. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in 2008 [14, 28]. About half the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries. In general, incidence rates are high in Western and Northern Europe, Australia/New Zealand, and North America; intermediate in South America, the Caribbean, and Northern Africa; and low in sub-Saharan Africa and Asia. The factors that contribute to the international variation in incidence rates largely stem from differences in reproductive and hormonal factors and the availability of early detection services [5, 11]. Reproductive factors that increase risk include a long menstrual history, null parity, recent use of postmenopausal hormone therapy or oral contraceptives, and late age at first birth [7]. Alcohol consumption also increases the risk of breast cancer [3, 9]. In many African and Asian countries however, including Uganda, South Korea, and India, incidence and mortality rates have been rising [12, 13], with changes in reproductive patterns, physical inactivity, and obesity being the main contributory factors [5, 4, 8]; increases in breast cancer awareness and screening activity may be partially responsible for the rising incidence in these populations. Maintaining a healthy body weight, increasing physical activity, and minimizing alcohol intake are the best available strategies to reduce the risk of developing breast cancer [10].

According to the Centers for Disease Control and Prevention (CDC), 230.815 women and 2.109 men in the USA were diagnosed with breast cancer in 2013. In the same year, some 40.860 women and 464 men in the USA died from breast cancer. With the exception of skin cancer, breast cancer in the U.S. is the most common cancer in women across all races. However, the rates per 100,000 women differ greatly among certain races and ethnicities: rates per 100,000 women in U.S.: all races: 123.7, white: 124.4, black: 122.9, Hispanic: 92.5, Asian and Pacific Islander: 91.1, American Indian and Alaska Native: 72.3.

The differences among different races could be due in part to reproductive patterns. For instance, white women are more likely to put off childbirth longer and to have fewer children overall. The average body weight of certain ethnicities and the use of menopause hormone therapy may also play a role in these different incident rates [25, 26, 29, 30].

Early detection through mammography has been shown to increase treatment options and save lives, although this approach is cost prohibitive and not feasible in most economically developing countries [1, 27]. Recommended early detection strategies in these countries include the promotion of awareness of early signs and symptoms and screening by clinical breast examination [2].

Over the last decade, gene expression analysis has been extensively submitted in breast cancer research, aiming to elucidate the molecular bases underlying biological features (histological grade, metastasis ability), also finding the specific patterns associated with prognostic and therapy response. Moreover delineating the 5 subtypes (luminal A, luminal B, HER2, basal-like, normal-like) resembled to gene

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expression pattern confirmed - at molecular level - the subsisting concept of breast cancer clinical and morphological heterogeneity.

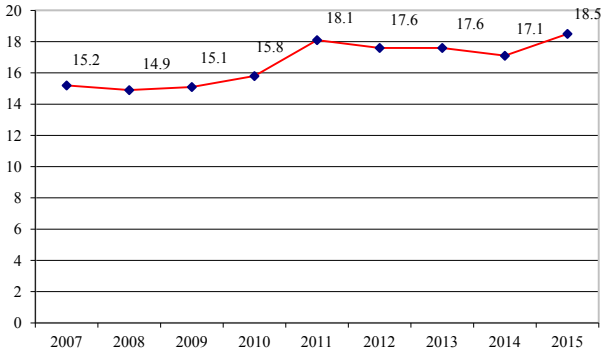

Figure 1. Estimated Age-Standardized Incidence Rates Per 100 000 by Uzbekistan (2007-2015)

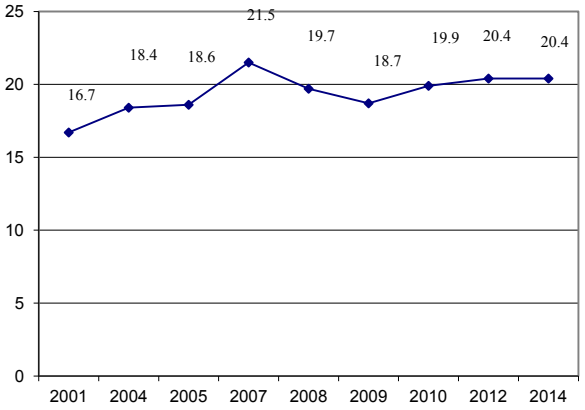

Figure 2. Estimated Mortality Rates Per 100 000 by Uzbekistan (2001-2014)

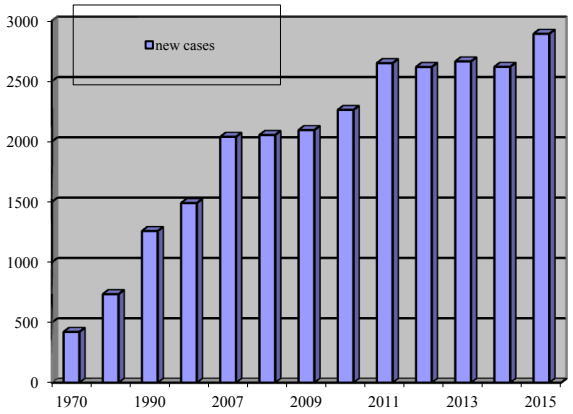

Figure 3. New breast cancer cases in Uzbekistan (1970-2015)

The epidemiology of BC has been extensively studied in developed countries; however, epidemiological data is scarce in the Central Asia. Breast cancer ranks the first place in the structure of morbidity and mortality from malignant tumors of the female population of the Republic of Uzbekistan (Fig.1, 2). It is 2892 new cases of BC in 2015 (Fig. 3). However molecular classification and its prognostic significance in Uzbekistan women with breast cancers have not been studied.

We present epidemiological analysis and molecular subtypes of BC in Uzbekistan in an attempt to aid continuously evolving strategies for cancer surveillance and control. The 5 year survival rate in BC patients over the past decades does not exceed 50% on the territory of Uzbekistan (Fig.4) [6].

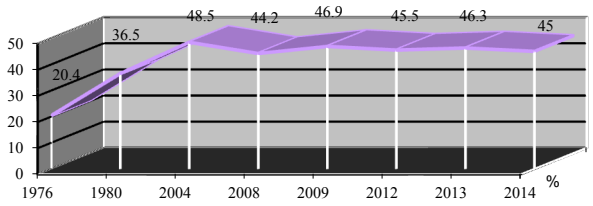

Figure 4. Five-year survival (females only) 1976-2014, the Republic of Uzbekistan

At the present stage of clinical oncology treatment of BC is based not only on the "classic" date as stage of diseases, grade, and histology but molecular-biological characteristics studies in different populations. In the Republic of Uzbekistan these characteristics of BC are published in fragments, which was the purpose of carrying out a large-scale study to obtain reliable comprehensive data on the issue.

Furthermore, we highlight the temporal changes of cancer care delivery over the period of this study.

2. Methods

Date from Tashkent City Cancer Registry about female BC, diagnosed in 2008-2018 was analyzed. Estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor Receptor type 2 (Her2) expressions and Ki 67 status were assessment, using immunohistochemistry (IHC) in 912 breast cancer patients. The IHC analysis is significant, yet it is almost impossible to pass in Uzbekistan. Cohort study included 2 groups of female BC: the 1 group of BC is Uzbek native women (500cases-54,8%), the 2 group of BC is women from another ethnics group (412-45, 2% cases).

IHC assessments were grouped into five phenotypic subtypes: Luminal A (97cases), Luminal B Her2 negative (195cases), Luminal BC without Ki 67 score identification Her2 negative (246cases), Luminal B Her2 positive (79cases), triple negative (197cases) and non-luminal Her2 positive (98cases) (Fig. 5).

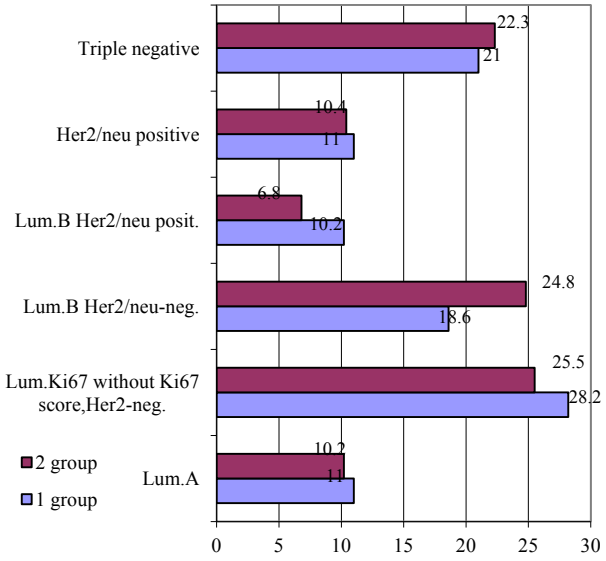

Figure 5. Breast cancer molecular subtypes in two ethnic groups (n=912), %

2.1. Results

Most of Uzbekistan women with breast cancer are diagnosed relatively at young age and mostly have locally advanced stages and are treated with multimodality approach (Fig.8). Median age of BC in the 1 group is 48,5±11 years, 2 group is 52±11,4 years.

Median age of Luminal A BC in the 1 group is 51,8±11 years, 2 group is 53,8±11,3 years. Median age of Luminal B Her2 negative BC in the 1 group is 49,6±12years, 2 group is 51,5±10years. Median age of Luminal B Her2 positive BC in the 1 group is 49,5±13,2years, 2 group is 49,5±13,5years. Median age of non-luminal Her2 positive BC in the 1 group is 46,6±7,4years, 2 group- is 53±8,3years. Median age of triple negative BC in the 1 group is 48,4±12 years and in the 2 group is 52,4±10,6 years.

High nuclear grade (high nucleus-to-cytoplasmic ratio), high mitotic index and poorly differentiated all connote poor prognosis. Infiltrating ductal carcinoma is by far the most common type of invasive breast cancer, with relatively poorer survival. Tubular, medullary, mucinous, and papillary cancers have a more favorable prognosis, but account for only 6% of invasive cancers [18].

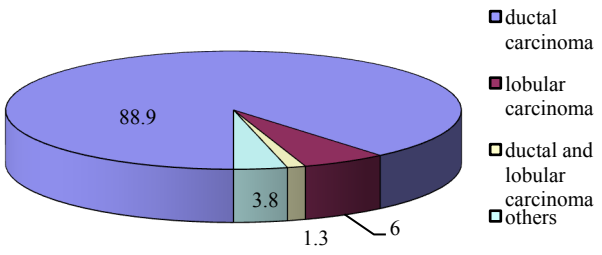

Figure 6. The histological types of breast cancer (n=912)

The histological type of BC tumor was invasive carcinoma in 88,9% cases (Fig.6).

Majority of tumors were moderately differentiated (GII): 1 group was 62,1%, 2 group of BC patients- 56,4% (Fig.7) [16, 24, 31].

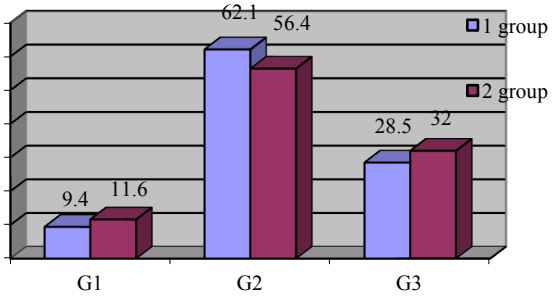

Figure 7. Bloom-Richardson System With Nottingham Modification Scoring (n=912)

Among patients with Her2/neu-positive BC the patients of the indigenous ethnos (1 group) were 54%, the average level of Ki67 was 47,1%.

Among patients with triple negative BC the patients of the 1 group were 53,3%, the average level of Ki67 was 59,8%.

The risk of developing BC was higher in women aged 40-60 years with the most adverse prognostic biological subtypes of breast cancer (Fig.9). Along with this increasing in new patients under age of 35 years is marked.

Among patients with Luminal B Her2/neu-positive BC in the 1 group were 10,2% patients, the average level of Ki67 was 54,8%.

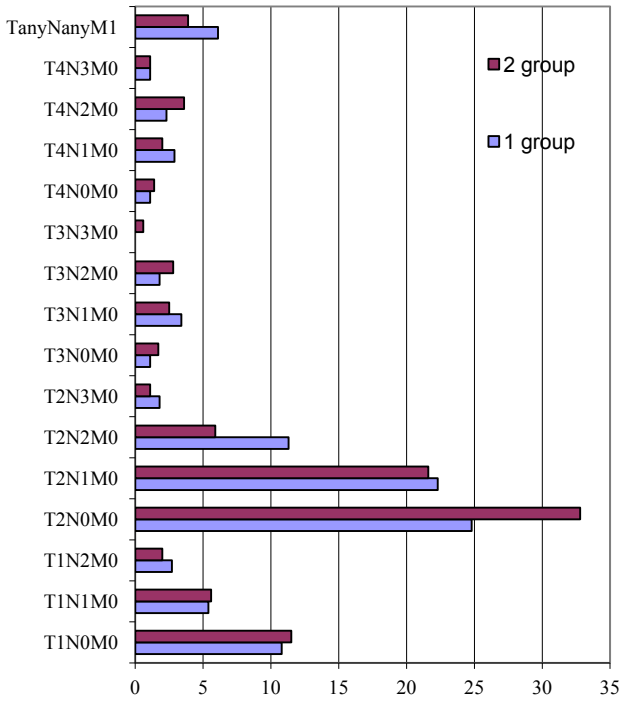

Figure 8. Clinical characteristics of patients (n=912)

Luminal A BC in 1 group is noted predominance of infiltrative BC with Grate II-III, in the 2 group is noted

predominance of infiltrative BC with Grate I-II.

Among patients with Luminal A BC the patients of the 1 group level of Ki67 was 17%, in the 2 group Ki67 was 18,9%.

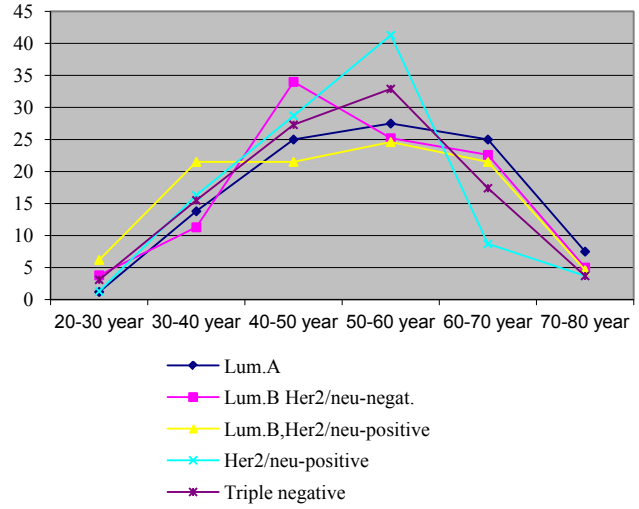

Figure 9. Age and breast cancer subtypes in two groups of patients (n=666)

Luminal A BC in 1 group is noted predominance of infiltrative BC with Grate II-III, in the 2 group is noted predominance of infiltrative BC with Grate I-II. Among patients with Luminal A BC the patients of the 1 group level of Ki67 was 17%, in the 2 group Ki67 was 18,9%.

Luminal B Her2-negative BC in 1 group is noted predominance of infiltrative BC with Grate II-III like in the 2 group. Among patients with Luminal B BC the patients of the 1 group level of Ki67 was 34,2%, in the 2 group Ki67 was 47,1%.

The morbidity rate and prevalence of breast cancer during last year we were analyzed with the main contributory factors. A woman's hormonal history appears to be a risk factor, as the relative risk of breast cancer seems to be related to the breast's cumulative exposure to estrogen and progesterone [17, 18].

Thyroid function has been associated with breast cancer risk, and breast cancer cell growth and proliferation. It is not clear whether thyroid function affects prognosis following breast cancer but, if so, this could have an important clinical impact. In patients with breast cancer a high prevalence of benign thyroid diseases (BTD) has been described, Hashimoto's thyroiditis accounting to a large extent for this association. In patients with BTD the prevalence of BC is significantly higher than the expected, showing the usefulness of screening for breast malignancy of patients with BTD [19-23].

In this cohort study from Uzbekistan we found that the high incidence of hypothyroidism along with established epidemiological risk factor for breast cancer, such as metabolic syndrome, was investigated (Table 1).

Table 1. Comorbidity disease in two groups of breast cancer patients

Subtype/ disease	1 group (%)	2 group (%)
Luminal A BC		
Heart and vessel dis.	29,1	28,6
M. diabetes	2,1	0
Hypothyroidism	21,8	21,4
Mild liver dis.	41,8	23,8
Metabolic syndrome	0	4,8
Luminal B Her2-negative BC		
Heart and vessel dis.	44	31,4
M. diabetes	2,2	2,9
Hypothyroidism	10,8	7,8
Mild liver dis.	29	20,6
Metabolic syndrome	8,6	17,6
Luminal B Her2-positive BC		
Heart and vessel dis.	9,8	39,3
M. diabetes	3,9	7,1
Hypothyroidism	15,7	10,7
Mild liver dis.	47,1	35,7
Metabolic syndrome	9,8	0
Non-Luminal B Her2-positive BC		
Heart and vessel dis.	20	27,9
M. diabetes	3,6	0
Hypothyroidism	12,7	30,2
Mild liver dis.	36,4	25,6
Metabolic syndrome	9,1	7
Triple negative BC		
Heart and vessel dis.	15,2	25
M. diabetes	7,6	2,2
Hypothyroidism	14,3	20,7
Mild liver dis.	43,8	17,4
Metabolic syndrome	7,6	2,2
Luminal BC without Ki67 score		
Heart and vessel dis.	34	35,2
M. diabetes	2,1	5,7
Hypothyroidism	6,4	4,8
Mild liver dis.	36,2	41
Metabolic syndrome	3,5	0

Breast cancer patients with comorbidities have poorer survival than cancer patients without comorbidity [15]. Successful treatment of the comorbid daises or the breast cancer can delay mortality causes by this interaction in BC patients.

In two groups of BC patients more than 2 comorbidity diseases were in 92 cases: 1 group is 47 (9,4%) cases, 2 group is 45 (10,9%) cases.

2.2. Discussion

In this cohort study from Uzbekistan, including more than 900 breast cancer patients, we found that subtypes of BC are heterogenic in ethnic groups. The breast cancer morbidity rate in Uzbekistan is constantly increased with the prevalence of locally advanced breast cancer. It is connected with no-effective working of national screening program.

3. Conclusions

In this study, we first demonstrated heterogenic of breast cancer subtypes among Uzbekistan's women.

Our study findings suggest that the prevalence of triple negative (21,6%) breast cancer in Uzbekistan's subjects is not similar to that among Western and Russian cohorts. Age is important risk factor for breast cancer, but it has also been suggested that age at diagnosis is related to breast cancer survival. Our findings hypothesize a positive association between Her2/neu-positive breast cancer tumors and hypothyroidism in breast cancer patients. These findings may have implications, and Her2/neu-positive breast cancer and thyroid's function should be focused in larger breast cancer studies. In conclusion, there was a remarkable difference in tumor characteristics and biomarkers between Uzbek and other ethnic's group cohorts. Uzbek women with breast cancer had a higher proportion of aggressive tumor types (triple negative and HER2-positive) than did other ethnic's group. This study represents the first comprehensive assessment of the epidemiological features of breast cancer in Uzbekistan basing a framework for enhancing strategic health plans regarding breast cancer control in Uzbekistan.

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