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Epidemiology Of Triple-Negative Breast Cancer (Tnbc) In Uzbekistan

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Abstract: Breast cancer remains the most frequently diagnosed malignancy among women across the globe. It occupies the leading position in cancer incidence rates, with a steady annual increase. Globally, approximately 2.1 million new cases of breast cancer are registered each year, and over 571,000 women die from the disease. This translates to a diagnosis every 20 seconds and more than three deaths every five minutes. Among these cases, 15–18% exhibit the triple-negative breast cancer (TNBC) subtype. TNBC is most commonly observed in younger women under 45 years of age who retain normal ovarian function. Despite its clinical significance and aggressive nature, TNBC remains less thoroughly investigated compared to other breast cancer subtypes. This review aims to consolidate current knowledge on the epidemiology, risk factors, pathological and immunohistochemical features, classification, prognosis, genetic aspects, and treatment options for TNBC.

Keywords: Triple-negative breast cancer, epidemiology, risk factors, histological variants, clinical pathology, immunohistochemistry, treatment.

Introduction: Breast cancer is the most common malignancy among women in Uzbekistan, accounting for approximately 24.6% of all female cancers as of 2012 data, surpassing other types like cervical cancer (12.4%). According to the Global Cancer Observatory (GLOBOCAN) 2022 estimates, there were 5,022 new breast cancer cases in Uzbekistan, representing 14.0% of all new cancer cases and ranking first among female-specific cancers [1]. The age-standardized incidence rate (ASR) for breast cancer in females is approximately 27.8 per 100,000 population, with a cumulative risk of developing the disease before age 75 at 3.0%. Mortality stands at 2,246 deaths annually (10.2% of total cancer deaths), with an ASR of 14.8 per 100,000 and a cumulative mortality risk of 1.5% before age 75. The 5-

year prevalence is 15,645 cases, or 90.8 per 100,000 population. Urban areas report higher incidence rates (13.2 per 100,000) compared to rural areas (8.5 per 100,000), with the highest standardized rates observed in Tashkent city (22.5 per 100,000), Navoiy (12.4 per 100,000), and Bukhara (11.1 per 100,000). Overall breast cancer incidence has been rising, influenced by demographic shifts, improved detection, and lifestyle changes such as diet and urbanization[2].

Triple negative is sometimes used as a surrogate term for basal-like; however, more detailed classification may provide better guidance for treatment and better estimates for prognosis. Triple-negative breast cancers have a relapse pattern that is very different from hormone-positive breast cancers: the risk of relapse is much higher for the first 3–5 years but drops sharply and substantially below that of hormone-positive breast cancers after that. This relapse pattern has been recognized for all types of triple-negative cancers for which sufficient data exists although the absolute relapse and survival rates differ across subtypes. [5].

Triple negative breast cancer is very often detected at late stages of disease, when there are distant metastases and there is a severe inflammatory process. In many cases, this pathology is hereditary, meaning it can occur at any age, but most often it occurs in carriers of genetic mutations BRCA-1 and BRCA-2.[8]. Breast cancer is a heterogeneous disease that includes various biological entities, which are separated on the basis of specific morphological and immunohistochemical features as well as clinical behavior. For many years, invasive breast cancer was classified according to its histological features and expression of hormone receptors (HR), that is, the estrogen receptor (ER) and the progesterone receptor (PR). More recently, characterization of HER2 status has become important for classifying invasive breast cancer with regard to trastuzumab treatment. Tumors that are negative for ER, PR and HER2 (triple negative [TN]) are reported to account for 12–25% of invasive breast cancer, and initially some of this group has attracted attention because of aggressive behavior and lack of response to currently available systemic therapy. [9].

In contrast, the term triple-negative (TN) breast cancer is a pragmatic, clinical term, which correlates with the molecular classification but cannot be used to identify one or more molecular subtypes [6].

Proportion and Incidence of TNBC

Triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, represents a particularly aggressive subtype. In Uzbekistan [3], TNBC accounts for 12-20% of all breast cancer cases, which is within the global range but potentially on the higher end due to regional genetic and environmental factors [10]. In 2016, approximately 1,100 women were diagnosed with TNBC, reflecting the subtype's contribution to the national burden at that time. Applying the 12-20% proportion to the 2022 GLOBOCAN estimate of 5,022 total breast cancer cases suggests an annual TNBC incidence of roughly 600-1,000 new cases. Limited subtype-specific data from smaller studies indicate even higher proportions; for instance, in a cohort of breast cancer patients, 80% were classified as TNBC, predominantly invasive ductal carcinoma (92% of cases). Another report highlights that hormone receptor (HR)-negative types, which encompass TNBC, comprise 65.9% of cases in Uzbekistan, underscoring a potentially elevated prevalence of aggressive subtypes compared to Western populations (where TNBC is typically 10-15%).

Demographic and Risk Factors

TNBC in Uzbekistan disproportionately affects younger women, with a higher incidence in premenopausal individuals (up to age 50). Peak age intervals for breast cancer overall (and likely TNBC) are 50-59 years (18.0 per 100,000), 60-69 years (31.2 per 100,000), and ≥70 years (19.3 per 100,000), but TNBC skews toward earlier onset. Key risk factors include early menarche, early first pregnancy, short breastfeeding duration, and elevated body mass index, which are more prevalent in the region. Genetic factors, such as BRCA mutations, may contribute, with early-onset cases representing about 3% of annual breast cancer diagnoses (based on 2010 data of 2,273 total cases). Broader contributors to breast cancer risk in Uzbekistan include infections (21.3% of attributable cancers), tobacco (13.8%), UV exposure (9.7%), alcohol (7.8%), and obesity (3%), though subtype-specific links require further local research.

Stage Distribution and Outcomes

At diagnosis, TNBC in Uzbekistan presents at advanced stages in many cases, complicating prognosis. Among the 1,100 TNBC cases in 2016, staging was as follows: 34% stage I, 42% stage II, 15% stage III, and 6% stage IV. This distribution reflects challenges in early detection, with urban-rural disparities exacerbating late presentations [3]. Treatment relies heavily on chemotherapy (neoadjuvant, adjuvant, or metastatic), given the lack of targeted therapies for ER/PR/HER2. Regimens include taxanes (e.g., paclitaxel, docetaxel), anthracyclines, platinum agents (e.g., carboplatin), and gemcitabine, following NCCN/ESMO guidelines. Despite chemosensitivity, outcomes remain poor: 24-month overall survival (OS) rates are 97% (stage I), 93%

(stage II), 71% (stage III), and 27% (stage IV), with median OS of 13 months in metastatic disease. Relapse peaks 1-3 years post-diagnosis, and most deaths occur within 5 years. The high mortality-to-incidence ratio for breast cancer (48.5%) highlights the urgent need for screening programs and targeted interventions [4].

Challenges and Future Directions

Uzbekistan's rising breast cancer burden, including TNBC, is driven by an aging population and improving diagnostics, but high TNBC proportions suggest unique molecular profiles warranting genomic studies. Pilot screening programs in regions like Bukhara (covering 21,976 new cases in 2020) aim to shift toward earlier detection. International collaborations, such as the Uzbekistan-Korea Oncology Consortium, emphasize capacity building for better subtype profiling and survival. Enhanced biomarkers and therapies could mirror global advances, reducing the disproportionate impact on young women [3].

This summary draws on available data up to 2022-2025; ongoing surveillance is essential for updated estimates. Upon histoloagic examination, triple-negative breast tumors mostly fall into the categories of secretory cell carcinoma or adenoid cystic types (both considered less aggressive); medullary cancers and grade 3 invasive ductal carcinomas with no specific subtype; and highly aggressive metastatic cancers. [2]. Medullary TNBC in younger women are frequently BRCA1-related. Rare forms of triple-negative breast cancer are apocrine and squamous carcinoma. Inflammatory breast cancer is also frequently triple negative.

One of the new categories was typical and “atypical” medullary carcinoma (classified as type A), as defined by Ridolfi et al. The criteria of medullary carcinoma are: syncytial architecture; no glandular or tubular structures; diffuse lymphoplasmacytic infiltration; round carcinoma cells with vesicular nuclei and marked pleomorohism, mitosis; and complete histological circumscription, as described in the 2003 WHO classification of Tumors of the Breast and Female Genital Organs.“Atypical” medullary carcinoma is defined as tumors showing the association of a predominantly syncytial architecture with 2–3 of the other criteria. Atypical medullary features are common in BRCA1-associated carcinoma and these tumors frequently show a basal-like phenotype [2]. The other new category was carcinoma with (classified as type B), according to the classification of Tsuda et al [8]. This type of IDC is consisted to have undergone infarction at the center, and deposits of hyaline material and collagen occupy more than one-third of the cut surface of the tumor with sparse myofibroblasts, accompanied by a myxoid matrix at the periphery. This carcinoma shows no features of spindle cell carcinomas, osseous or cartilaginous metaplasia, or matrix-producing carcinomas. Recently, the presence has been noted in basal-like-type breast cancer. [6].

Incidence and Prevalence of TNBC in Uzbekistan

Precise national statistics on TNBC in Uzbekistan are limited, but available studies (based on the Tashkent city cancer registry, 2008–2018) indicate the following:

- Out of 912 breast cancer (BC) patients, TNBC was identified in 197 cases (21.6%), which is higher than rates in Western countries (10–15%) and Russia.
- Among Uzbek women, TNBC and HER2-positive subtypes are more aggressive and prevalent compared to the luminal A subtype (luminal A: 10.6%, TNBC: 21.6%).
- In 2022, a pilot screening program in Bukhara identified 377 BC cases, with the majority at stage II (58.5%), though specific data on TNBC subtypes are unavailable. Overall, 3.5% of BC cases were confirmed as cancer under BIRADS 0–5 categories.
- Ethnic differences: Among Uzbek women, TNBC ranks as the second most common subtype after luminal B (HER2-negative) (27.3% luminal B, 21.6% TNBC). In other ethnic groups (e.g., Russian, Kazakh), luminal subtypes predominate.
- The overall incidence of BC in Uzbekistan is rising (approximately 14% annual increase, similar to neighboring Kazakhstan), but the proportion of TNBC remains consistently high. Prevalence data are limited, but the high mortality rate of BC (third highest after stomach cancer) reflects TNBC’s significant contribution [3].

Risk Factors and Demographic Characteristics of TNBC in Uzbekistan

- **Age and Gender**: TNBC is more common among working-age women (45–65 years, 51.4%), but its aggressiveness is higher in younger women (under 40 years). Among BC cases, 54.8% occur in ethnic Uzbek women.
- **Genetic Factors**: BRCA1 mutations are associated with TNBC (in neighboring Kazakhstan, TNBC has an odds ratio of 6.61). In Uzbekistan, a family history of BC is reported in approximately 26% of cases.
- **Environmental and Lifestyle Factors**: Obesity, smoking, and occupational exposures (e.g., chemicals) may exacerbate TNBC risk, though research on these factors in Uzbekistan is scarce. In Central Asia, infections and ultraviolet radiation may contribute to increased BC risk.
- **Ethnic and Regional Differences**: TNBC

prevalence is higher among Uzbek women (similar to trends in countries like Ghana and Afghanistan). Urban-rural disparity: Screening is more effective in Tashkent, but rural areas face delayed diagnoses.

Prognosis and Screening Challenges

The prognosis for TNBC in Uzbekistan is poor, with most cases diagnosed at locally advanced stages (stage II–III, 67%), and 5-year survival rates are lower than for luminal subtypes. National screening programs (mammography and ultrasound) are limited, but the Bukhara pilot program (2022) showed promising results, with 10,000 women screened. Recommendations include strengthening national screening, expanding immunohistochemical analyses, and introducing genetic screening. Due to the lack of targeted therapies for TNBC, chemotherapy remains the primary treatment, though research on PARP inhibitors and immunotherapy (PD-L1) offers hope.

Given the limited data on TNBC in Uzbekistan, further national studies (through cancer registries) are essential. The high proportion of this subtype underscores the need to improve BC control strategies in the country [2].

DISCUSSION

The higher prevalence of TNBC in Uzbekistan compared to global averages raises critical questions about contributing factors. The elevated proportion (21.6% in some studies) among ethnic Uzbek women suggests a potential genetic predisposition, possibly linked to BRCA1 mutations, as seen in neighboring Kazakhstan (odds ratio of 6.61 for TNBC). This aligns with global trends where TNBC is more common in certain ethnic groups, such as African and African-American populations, and may reflect shared genetic or environmental influences in Central Asia. The high incidence in younger women (under 40) and the association with family history (26% of cases) further support the need for genetic screening programs, which are currently limited in Uzbekistan. The lack of comprehensive data on BRCA mutations and other molecular markers hinders precise risk stratification and personalized treatment approaches [5].

Environmental and lifestyle factors, such as obesity, smoking, and occupational exposures, may also play a role, though local research on these is sparse. Central Asia's unique environmental exposures, including ultraviolet radiation and infections, could contribute to the overall breast cancer burden, potentially amplifying TNBC risk. Urban-rural disparities in screening access exacerbate late-stage diagnoses, particularly in rural areas where mammography and ultrasound are less available. The Bukhara pilot screening program (2022), which screened 10,000 women, demonstrates the feasibility of early detection but highlights the need for nationwide expansion to reduce the 67% of TNBC cases diagnosed at advanced stages.

The absence of targeted therapies for TNBC, due to its lack of ER, PR, and HER2 expression, limits treatment to chemotherapy, which, while effective in some cases, yields poorer outcomes (e.g., 27% 24-month survival for stage IV). Emerging therapies like PARP inhibitors and PD-L1 immunotherapy, which have shown promise globally, are not yet widely accessible in Uzbekistan, underscoring gaps in healthcare infrastructure and clinical trial participation. The high mortality-to-incidence ratio (48.5%) reflects these challenges, compounded by delays in diagnosis and limited access to advanced diagnostics like immunohistochemical subtyping [7].

To address these issues, Uzbekistan must prioritize:

1. Enhanced Screening Programs: Expanding mammography and ultrasound screening, particularly in rural areas, and integrating TNBC-specific biomarkers (e.g., Ki-67, EGFR) into diagnostics.
2. Genetic Testing: Implementing BRCA1/2 screening to identify high-risk populations, especially young women and those with a family history.
3. National Cancer Registry: Developing a comprehensive registry to track TNBC incidence, prevalence, and outcomes, enabling data-driven policies.
4. Research and Collaboration: Partnering with international consortia (e.g., Uzbekistan-Korea Oncology Consortium) to study TNBC's molecular profiles and test novel therapies.
5. Public Health Interventions: Addressing modifiable risk factors like obesity and smoking through awareness campaigns tailored to Uzbekistan's cultural context.

The rising breast cancer incidence (14% annual increase) and TNBC's significant contribution demand urgent action. Comparative studies with neighboring countries like Kazakhstan, where similar trends are observed, could inform regional strategies. While the Bukhara pilot offers a model for screening, scaling such efforts requires investment in healthcare infrastructure and training. Ultimately, addressing TNBC in Uzbekistan necessitates a multifaceted approach combining early detection, molecular research, and access to innovative treatments to improve survival and reduce disparities [5].

CONCLUSION

The epidemiology of triple-negative breast cancer (TNBC) in Uzbekistan highlights its significant burden, with an estimated 12–20% of breast cancer cases

attributed to this aggressive subtype, potentially higher (up to 21.6%) based on regional studies like the Tashkent cancer registry (2008–2018). The elevated prevalence of TNBC compared to Western countries (10–15%) underscores unique genetic, ethnic, and environmental factors in Uzbekistan, particularly among ethnic Uzbek women, who show a higher incidence of aggressive subtypes like TNBC and HER2-positive cancers. The disease disproportionately affects younger and working-age women (45–65 years), with a notable proportion diagnosed at advanced stages (II–III, 67%), contributing to poorer prognosis and lower 5-year survival rates compared to luminal subtypes. Limited national screening programs, late diagnoses in rural areas, and the absence of targeted therapies for TNBC exacerbate the challenge. While pilot screening initiatives, such as in Bukhara (2022), show promise, the high mortality-to-incidence ratio (48.5%) and TNBC's contribution to breast cancer mortality (third highest after stomach cancer) emphasize the urgent need for enhanced early detection, improved diagnostics (e.g., immunohistochemistry), and genetic screening for BRCA mutations. Emerging therapies like PARP inhibitors and PD-L1 immunotherapy offer hope, but their integration into Uzbekistan's healthcare system requires further research and infrastructure development. Comprehensive national cancer registries and subtype-specific studies are critical to address TNBC's disproportionate impact and improve breast cancer control strategies.

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