



## PILOT STUDY ON THE INCIDENCE OF BREAST CANCER AMONG THE POPULATION OF THE NORTH EAST REGION OF BULGARIA

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### ABSTRACT

**Purpose:** According to the Bulgarian National Cancer Registry of 2017, breast cancer accounted for 26.8% of all malignancies among women. The actual incidence rate was 108.1 per 100 000.

**Materials/ Methods:** An observational retrospective study was conducted among breast cancer patients diagnosed and treated at Dr Marko Markov Specialised Hospital for Treatment of Oncologic Diseases (SHTOD) - Varna, between 2016 and 2019. Descriptive statistics and collected data included demographic characteristics, clinical data (survival rates) and type of pharmacotherapy.

**Results:** In terms of gender distribution, significantly more women were affected, accounting for approximately 99.05%. Patients from cities were almost 7 times more than those from villages. Patients aged between 61 and 70 represented the largest number, which accounted for 28.04% of all included in the study.

**Conclusion:** Taking into consideration not only the efficiency but also the cost-effectiveness of available treatment strategies can lead to considerably better therapeutic outcomes. There is no pharmacoeconomic data analysis in Bulgaria. A further study of all direct and indirect costs is required in order to estimate the cost of premature death, reduced working capacity and disability

**Keywords:** breast cancer, incidence, North East region of Bulgaria, BNCR, NHIF,

### INTRODUCTION:

According to the Bulgarian National Cancer Registry of 2017, breast cancer accounted for 26.8% of all malignancies among women. The actual incidence rate was 108.1 per 100 000. The actual mortality rate was 35.6 per 100 000. 67.3% of patients were diagnosed in the initial stages of the disease. In 27.5%, cancer was in the third and fourth stage, and in the remaining 5.1%, the stage was unspecified. A 2.1% increase in diagnoses at an advanced stage was identified. The five-year relative survival rate for breast cancer in Bulgaria was 72.8% - 11.1% lower than the European average (83.9%). The age-standardized incidence rate of breast cancer in Bulgaria was lower than the European average. However, the age-standardized mortality rate of breast cancer in Bulgaria was higher than the European average - 24.1 and 23.1 per 100,000

women, respectively [1].

The number of malignancies increase due to various factors, including the world population growth and the increase in life expectancy, as well as the socio-economic development of communities and their lifestyles. The five-year relative survival rate for breast cancer in the USA is 89.9%, in the UK - 86.6 and 72.8 in Bulgaria [2]. The age-standardized incidence rate in Europe is 46.3 per 100 000 people. In Bulgaria, this rate is twofold (108.1) [3].

Europe, where only 9.0% of the global population lives, is the second most affected region following Asia, as new cases account for 23.4% of all new cancer cases and 20.3% of all deaths caused by cancer in the world [4]. Breast cancer is among the leading causes of death in women, responsible for 15% of disease-related deaths globally. In countries with a mean life expectancy of over 70 years, approximately one in 8 women will be diagnosed with breast cancer, and about 70% of cases will be observed at age over 60 [3]. Breast cancer accounts for 28.2% of all cancers in women. Newly diagnosed breast cancer patients in Bulgaria in 2018 were 4 016, of which 454.2 in Varna Region, the average number for the country being 435.5 per 100 000 people [5]. Metastatic cancer has a much worse prognosis for the five-year survival rate of about 27%. In comparison, localized breast cancer that can be removed surgically has a five-year survival rate of 98%, while the regionally spread has 85% [6].

According to the Bulgarian National Cancer Registry of 2017, breast cancer (malignant breast neoplasms) is the most common cancer in women and accounts for 26.8% of all malignancies among women. The actual incidence rate was 108.1 per 100 000. The actual mortality rate was 35.6 per 100 000. 67.3% of patients were diagnosed in the initial stage (first and second) of the disease. The five-year relative survival rate for breast cancer in Bulgaria was 72.8% - 11.1% lower than the European average (83.9%). Breast cancer incidence rates increase after 35 and reaches its peak between ages 65-69 (214.2 per 100 000 women) [6].

The Specialized Hospital for Treatment of Oncologic Diseases (SHTOD) - Varna provides free examinations of patients for the purposes of early detection and successful treatment of oncologic diseases. In 2019, 671 people visited the outpatient unit at SHTOD, of which 528

women and 143 men; the largest group were aged between 41 and 60 years. In about 1/3 of the people screened, abnormal results were found. Some of them were referred for additional tests or consultations with specialists, while others underwent surgical treatment or pharmacotherapy. Newly registered patients in SHTOD - Varna in 2019 were 2724 people, where 2082 were from Varna Region and 642 from Dobrich Region. A total of 16 000 patients visited the outpatient unit, and 14 685 were treated in the hospital. The leading diagnosis in 2019 was lung cancer, for the first time surpassing prostate cancer which was second. Colorectal cancer was the third most common cancer in men. A worrying trend towards an increase in the new lung cancer cases in women was observed in 2019. Air pollution can be seen as one of the major causes. In 2019 breast cancer was the leader in new cases, followed by colon cancer and uterine cancer.

The above data imply the need for broader prevention of cancers [7].

### MATERIALS/ METHODS:

An observational retrospective study was conducted among breast cancer patients diagnosed and treated at *Dr Marko Markov Specialised Hospital for Treatment of Oncologic Diseases (SHTOD) - Varna*, between 2016 and 2019. Descriptive statistics and collected data included demographic characteristics, clinical data (survival rates) and type of pharmacotherapy.

### RESULTS:

In order to study the incidence rate of breast cancer among the population of the North East region of Bulgaria and provide local authorities with evidence supporting the introduction of breast cancer screening programmes covering a larger population of the region, We conducted an observational retrospective study among breast cancer patients with regards to diagnosis, treatment and follow-up care in the regional oncology outpatient unit at SHTOD between 2016 and 2019. Data included demographic characteristics, clinical data (survival rates) and treatment pattern. The study covered a total of 1,373 breast cancer patients. Data was provided by the outpatient unit of Specialized Hospital for Treatment of Oncologic Diseases (SHTOD) - Varna, which registered all di-

agnosed, consulted, treated, or regularly monitored cancer patients from hospitals in the city of Varna and the North East region of Bulgaria between 2016 and 2019. All patients signed written informed consent at their admission authorizing the use of their anonymized (pseudonymized) data for scientific purposes.

Data included demographic characteristics (age, gender); clinical data (survival rate); stage of the disease; type of pharmacotherapy and other therapy: surgery and/ or radiotherapy; healthcare resource utilization (utilized medicinal products); premature death (in years). Clinical data were collected from the patients' medical records (data in the electronic database and patients' paper files). In terms of gender distribution, significantly more women were affected, accounting for approximately 99.05%. Patients from cities were almost 7 times more than those from villages. Patients aged between 61 and 70 represented the largest number, which accounted for 28.04% of all included in the study.

**Table 1.** Demographic characteristics of breast cancer patients

Category	Sub-group	distribution in %
<b>Age</b>	<30	0.36%
	31-40	7.14%
	41-50	19.81%
	51-60	19.23%
	61-70	28.04%
	>70	25.42%
<b>Gender</b>	Male	0.95%
	Female	99.05%
<b>Region</b>	City	87.18%
	Village	12.6%
	Abroad	0.22%

The mean age of the sample was 60.6 years. The highest survival rate was in patients under 30 years of age, followed by those between 41 and 50 years. The lowest survival rate was in patients above 70.

*The treatment strategy of malignant solid tumours is complex. Surgery, radiation therapy and pharmacotherapy are applied.*

**Table 2.** Clinical characteristics of breast cancer by therapy

	<i>By therapy</i>			
	<b>Chemotherapy + surgical</b>	<b>Surgical + radiotherapy</b>	<b>Surgical + hormone therapy</b>	<b>Other</b>
% survival	92.3%	89.5%	97.1%	78.5%

The individual sequence of these approaches is defined by an Oncology Commission (Tumour Board) consisting of specialists from various medical disciplines based on the Pharmacotherapeutic guideline for oncology diseases [8]. Systemic drug therapy is an acknowledged approach along with the other two treatment patterns (surgery and radiation therapy).

Breast cancer patients at regional level were treated following 4EC-4T chemotherapy regimen that included: neoadjuvant (preoperative) systemic treatment, chemotherapy regimen: 4EC-4T *Epirubicin, Cyclophosphamide, Paclitaxel*, anti-HER2 therapy: 4EC-4TH *Epirubicin, Cyclophosphamide Paclitaxel, Trastuzumab*, adjuvant endocrine therapy in pre and perimenopausal patients, LHRH-

agonist *Tamoxifen*. About 18% of all patients underwent only surgery and 95.19% surgery in combination with chemotherapy, hormone therapy, radiation therapy and/or target therapy. Chemotherapy and hormone therapy were part of the therapeutic schemes in 49.45% and 51.81% of the patients, respectively. The most prescribed medicinal products were epirubicin, cyclophosphamide, paclitaxel,

tamoxifen, Zoladex. All patients were women, and their median survival time from diagnosis and treatment was 1.48 years at the end of the study period. Almost half of the patients (48.1%) were in stage 1 or 1a.

Reimbursement levels and the price per unit (DDD) paid by NHIF for all breast cancer medicinal products as per clinical pathway ICD C50 were considered [9].

**Table 3.** Direct costs paid by NHIF for pharmacotherapy

Direct medical costs				
Type of resources	Time period	Price per one cycle	Price per course per patient	Sources of data
<b>Therapy</b>	1 month and 12 months			Positive Drug List, Annex 1, ...
<b>Surgical therapy</b>			1 782.00 BGN	Clinical path 193
<b>Chemotherapy</b>	1 year			
Epirubicin		141.95 BGN	567.80 BGN	
Cyclophosphamide		47.98 BGN	191.90 BGN	
Paclitaxel		32.06 BGN	384.68 BGN	
<b>Hormone therapy</b>				
Tamoxifen		0.17 BGN (per day)	60.83 BGN	
Goserelin		81.08 BGN (per month)	972.12 BGN (per year)	
<b>Radiotherapy</b>			1 945.00 BGN	

Information about the costs was obtained from officially published data in 2019 documents of NHIF and the Pharmacotherapeutic Guideline. Clinical pathway 50 for the treatment of cancer patients is described in the National Framework Agreement. NHIF controls the consumed health resources. In 2019 the number of patients with oncological and onco-hematological diseases who received pharmacotherapy grew by over 3%, and the costs paid by NHIF for their treatment increased by 21% [10].

NHIF pays 97 BGN per day for palliative care which is highly insufficient. According to healthcare professionals, the actual market price for hospice palliative care per bed day is between 150 – 200 BGN [11]. During the last stage of oncologic diseases, doctors' primary duty is pain management. Treatment methods are different depending on the stage at which the disease is diagnosed therefore, early detection multiplies the chances for a full recovery. In the early stages, however, malignancies rarely have apparent warning signs. Unfavourable statistics for our country (high percentage of late diagnoses, high mortality and low five-year survival rates) come to show the importance of screening and early detection of breast cancer.

#### DISCUSSION:

This study presents the demographic characteristics of breast cancer patients and treatment patterns in the studied group of patients from the North East region of Bulgaria. Costs associated with breast cancer were calculated from the perspective of NHIF, whereas indirect costs were not calculated. The study revealed that the majority of affected patients were women (99.02%), which is in line with statistical data at both national and global level. We

found that patients between ages 61 and 70 prevailed – 28.04%, the mean age at diagnosis for breast cancer was 60.6 years in the North East region of Bulgaria, which supported literature data. Data collected by our study matched national data. Male patients affected by breast cancer accounted for 0.95%; the highest rate of breast cancer incidence was in cities – more than 87%, while in rural areas, it was about 13%. The highest breast cancer incidence rate 28% was in the age group from 61 to 70 years, followed by 25% in the age group above 70, 19.8% were patients aged 41 to 50 and 7.5% in the 30-40 years range. Our data showed that the highest mortality rate was in patients above the age of 70. During the four-year period of the study, the highest survival rate of 100% was registered in the first age group up to 30 years of age, followed by 94% in the age range between 41-50, and the lowest rate of 81% was in patients over 70. Surgical treatment was preferred in more than 95 % of all diagnosed patients. More than half of the surveyed patients received radiotherapy, hormone therapy and chemotherapy, whereas target therapy was preferred in only 4.73% of the cases. Our study confirmed that hormone therapy dominated chemotherapy which is similar to other publications [12, 13, 14]. In other studies, hormone therapy is an efficient and cost-effective alternative of chemotherapy treatment strategies [15, 16]. The prescribed treatment protocols were in accordance with those approved in the respective pharmacotherapeutic guideline for oncology diseases available in Bulgaria in 2019. Treatment patterns varied among the surveyed patients due to cancer stage, comorbidities and other determinants. Bulgarian breast cancer patients have been provided with financial access

to the latest innovative therapies

Along with surgical treatment and radiation therapy, chemotherapy currently remains the main approach for tumour cells treatment. An essential drawback of conventional chemotherapeutic agents is their poor selectivity for neoplastic over healthy cells, which leads to many side effects and low effectiveness of the treatment.

The rapidly increasing number of patients with neoplastic diseases and the high mortality rate among them put scientists and pharmacists in a situation of need for the development of a new, adequate treatment [17].

Neurotensin (NT) is a 13 amino acid containing neuropeptide expressed in both the central nervous system (CNS) and periphery (gastrointestinal tract and the cardiovascular system)<sup>[18]</sup>. Like other neuropeptides, Neurotensin has different functions. It is a neurotransmitter and neuromodulator in the central nervous system and a local paracrine hormone in the periphery, particularly in the gastrointestinal tract[19]. In the brain, NT plays a role in naloxone-independent antinociception and appears to be an important modulator of nociceptive regulation. The biological activity of the new NT(8-13) analogues is currently under investigation [17]. Opioid peptides are promising in terms of clinical application and use as analgesics.

The biological effect results from specific interactions of the peptide with three different receptors (NTS1, NTS2 and NTS3/sortilin). The basic sequence for modifications was its C-terminal hexapeptide NT(8–13) (Arg8-Arg9-Pro10-Tyr11-Ile12-Leu13). Besides their numerous central and peripheral functions, it was reported that NTRs are over expressed in various human tumours. NT peptides are known to influence cell proliferation and pass through the blood-brain barrier. Like many other neuropeptides, the main drawback in using NTs is their extremely short half-life as a result of their rapid degradation by peptidases. To overcome this problem, various neurotensin analogues were synthesized. The biological activity of the new NT (8-13) analogues is currently under investigation. Received preliminary data from MTT assay of the parent molecule tested in a wide concentration range (2 - 0.03 mM) on MCF-7 (breast cancer cells) and 3T3 (non-cancerous cells) after 72 hours, showed slight influence on viability over both 'normal' and cancer cell lines.

Neurotensin (8-13)-based drug design is a hopeful perspective for drug development. Using Neurotensin (8-13)-sequences does not endanger drug interactions at the cytochrome P450 3A4 level [20]

RGD- and Neurotensin(8-13)-based drug design is a hopeful perspective for drug development. There is a great deal of data on the observed therapeutic effects of both sequences (e.g. anticancer, analgesic etc.), but little is known about the pharmacokinetics of these peptides and the possible drug interactions in which they can be involved. Hydrolytic stability of the peptides is one of the most important properties regarding their application in practice. Early information on the stability is essential for the pharmacokinetic behavior in the body, for the storage conditions, the occurrence of toxic effects associated with its degradation products. Using Neurotensin (8-13)-sequences does not endanger drug interactions at the cytochrome P450 3A4 level [20]

It is necessary to calculate not only direct costs paid by NHIF but also indirect costs paid by the patient and society so as to estimate the real value of disability and premature death. This will serve as an initial step for further national and regional studies of the cost of illness for a better understanding of the real impact of breast cancer from different perspectives: society, patients and their families. Economic evidence should be considered an important tool for decision-making in the healthcare sector. Thus, the financial impact of specific innovative therapies could be identified, and scarce resources could be re-distributed better [21].

This study has confirmed national and international trends regarding breast cancer incidence at a regional level. Early diagnosis and regular follow-up of breast cancer patients and the choice of the best treatment strategy would ensure the desired therapeutic outcomes, would reduce the social burden and save healthcare resources. All these aspects need to be researched in further studies for the North East region of Bulgaria.

#### CONCLUSION:

Taking into consideration not only the efficiency but also the cost-effectiveness of available treatment strategies (surgery, radiation therapy, medicinal products with different mechanism of action) can lead to considerably better therapeutic outcomes. There is no pharmacoeconomic data analysis in Bulgaria of whether the increase in costs leads to better survival rates and better quality of life as NHIF monitors only quantitative and not qualitative indicators. A further study of all direct and indirect costs is required in order to estimate the cost of premature death, reduced working capacity and disability [11].

## REFERENCES:

1. State of Health in the EU. Bulgaria: Country Health Profile 2017. European Commission. [\[Internet\]](#)
2. [Roche Bulgaria: Breast cancer. HER2-negative breast cancer] [in Bulgarian] rochemd.bg. 27. 11. 2020. [\[Internet\]](#)
3. Breast cancer statistics: World Cancer Research Fund. 2018 [\[Internet\]](#)
4. [Healthcare 2018.] [in Bulgarian] NSI, Sofia. 2019. [\[Internet\]](#)
5. [Breast cancer incidence in Bulgaria, 2014 & 2015.] [in Bulgarian] BNCR. [\[Internet\]](#)
6. American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2019-2021. Atlanta: American Cancer Society. 2019. [\[Internet\]](#)
7. [Annual report of the Municipality of Varna.] [in Bulgarian] [\[Internet\]](#)
8. [Pharmacotherapeutic guideline for oncology diseases in Bulgaria.] [in Bulgarian] 2019. [\[Internet\]](#)
9. [ICD-10 C50 Malignant neoplasm of breast.] [in Bulgarian] Mediately. [\[Internet\]](#)
10. [Annual report on the activities of the National Health Insurance Fund for 2019.] [in Bulgarian] NHIF Sofia. 2020. [\[Internet\]](#)
11. [Our treatment of cancer is more costly than in Germany.] [in Bulgarian] Clinica.bg. [\[Internet\]](#)
12. American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society. 2017. [\[Internet\]](#)
13. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015 Mar 1;136(5): E359-86. [\[PubMed\]](#)
14. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. *CA Cancer J Clin*. 2016 Jan-Feb;66(1):31-42. [\[PubMed\]](#)
15. Hormone Therapy More Cost-Effective Than Chemotherapy for Patients With HR +/HER2- Metastatic Breast Cancer. JCP Editors. *J Clin Pathways*. 2016; 2(4):10-13. [\[Internet\]](#)
16. Dimitrova M, Lakic D, Petrova G, Bešlija S, Culig J. Comparative analysis of the access to healthcare services and breast cancer therapy in 10 Eastern European countries. *SAGE Open Med*. 2020 May 20;8: 2050312120922029. [\[PubMed\]](#)
17. Mihaylova S. [Synthesis and Biological Evaluation of SMAC-NT Peptide Conjugates with Combined Antineoplastic and Analgesic Effect.] [Dissertation] Varna (Bulgaria): Medical University-Varna. 2019. 3p. [in Bulgarian] [\[Internet\]](#)
18. Michailova S, Georgieva M, Bruckdorfer T, Pajpanova T. Influence of arginine mimetics on the biological effects of NT(8-13) analogues. *European Peptide Society & PSP*. 2018; 257-258. [\[Crossref\]](#)
19. Michailova S, Dzimbova T, Kalikova K, Tesarova E, Pajpanova T. Chemical stability of new neurotensin (8-13) analogues. *Bulg Chem Commun*. 2017; 49(E):113-117. [\[Internet\]](#)
20. Georgiev K, Radeva M, Balacheva A, Michaylova S, Pajpanova T. Modulation of CYP3A4 by the RGD- and Neurotensin(8-13)-analogues. *European Peptide Society & PSP*. 2018. pp.215-216. [\[Crossref\]](#)
21. Public Health. Non-communicable diseases. Cancer. European Commission. [\[Internet\]](#)

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