Influence of selected prognostic and predictive factors on the survival time of young women treated for breast cancer in 2004-2014

mgr Aneta Radziszewska

Supervisor: prof. dr hab. n. med. Bożenna Karczmarek-Borowska
Co-advisor: dr n. o zdr. Justyna Podgórska-Bednarz

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Summary

Breast cancer (BC) is most often diagnosed in women aged 50-69 due to the natural course of the disease (the highest incidence in the postmenopausal period) and active screening for this group. However, the increase in morbidity in young women is worrying. In Poland, almost 1/3 of cases are reported in women aged 30-49 years, and in the last 3 decades the incidence of breast cancer has almost doubled among women aged 20-49 [2]. BC was the most frequent malignancy among women <45 years of age in the world (13.4 / 105), similarly among young European women - 28.8% of all cancer cases, with a constantly growing incidence [7].

Malignant breast neoplasms in young women have a worse prognosis due to greater aggressiveness and a higher rate of local recurrence in this age group. Higher grades of malignancy, a higher rate of cellular proliferation, and invasion of blood and lymph vessels are significantly more common. The poor prognosis is influenced by a higher percentage of positive HER2 receptor expression and a higher incidence of triple negative cancers compared to postmenopausal women. The above factors also translate into higher mortality rates in the group of young patients with BC [10, 11].

Among the factors that may affect the risk of breast cancer in young women, we can distinguish: individual factors, genetic factors, as well as factors related to food preferences and lifestyle.

The most important factor in response to systemic treatment (predictive) in patients with breast cancer is the state of steroid receptors (ER and PR). Expression of steroid receptors is associated with a better response to treatment and a better prognosis. Over-expression of the HER2 protein or amplification of HER2 gene is an unfavorable prognostic factor and is associated with the indication for anti-HER2 treatment (trastuzumab, lapatinib) [10].

In order to choose a treatment method that will be individually tailored to each patient and thus bring the best treatment results, a number of prognostic factors have been identified that determine the course of the neoplastic disease: age at diagnosis, size of the primary tumor (T feature), presence of metastases in the axilla lymph node and the number of nodes involved (N feature), histological grade G, the presence of estrogen receptor ER, progesterone receptor PR and HER2, the Ki67 proliferation index and the biological subtype of cancer..

Aim: was a retrospective analysis of the influence of selected prognostic and predictive factors in young women in the Podkarpackie province treated for breast cancer in 2004-2014, with the assessment of the time to progression and survival time.

Material and method: The data comes from the resources of the Department of Epidemiology and the Podkarpackie Cancer Registry and the medical history of patients under 45 years of age, treated for breast cancer at the Podkarpackie Oncology Center (POC) in Rzeszów in 2004-2014.

In the retrospective study, the population of young patients included 345 women under 44 years of age at the diagnosis of breast cancer.

Results: There was an increase in the incidence of breast cancer by 59.6% in young patients treated with POC in the years 2004-2014. The youngest respondent was 24 years old, the oldest was 44 years old - median 39 years.

All women menstruated, and 82.3% had their first menarche at the age of 13-15 years. Among the respondents, 76.2% of women gave birth from 1 to 3 times, and 15.9% had never been pregnant. 1-3 miscarriages occurred in 10.1% of the women. Breastfeeding was reported in 75.9% of the respondents, the use of tobacco products was confirmed by 10.7% of patients, while oral hormonal contraception was used by 6.1%. 37.4% of women had the correct body weight at diagnosis, while 12.2% were obese. Inhabitants of rural areas accounted for 54.2%.

Family history predisposing to the development of breast cancer was also examined. In 14.2% of patients, breast cancer was diagnosed among female relatives in the 1st, 2nd, 3rd and 4th degree of kinship. In 2.6% of respondents there was a family history of ovarian cancer, while 63.8% of the respondents did not have a positive family history.

T1 cancers were diagnosed in 31.6% of patients, and T2 in 31.3% of patients. 61.2% of patients had metastases in the lymph nodes, and 5.2% had distant metastases (M). The disease was most often diagnosed at stage II and III, 37.1% and 38.0% of cases, respectively. The most numerous group were moderately differentiated (G2 - 38.8%) and poorly differentiated (G3 - 40.9%) cancers.

Ductal carcinomas accounted for over 79% of the neoplastic lesions. Among ductal carcinomas not otherwise specified (NOS), more than half of the cases 52.5% were HER (-) luminal subtype, basal type, triple negative 11.9%, and HER2 overexpression - 10.4%. In 70.4% of patients, positive estrogen receptors (ER) were found in cancer cells, and in 50.4% of cases demonstrated also the expression of the progesterone receptor (PR). The presence of the HER2 receptor was found in 25.5% of the respondents. The value of the Ki67 marker <20% was noted in 30.1% of patients. BRCA1 mutation was confirmed in 17.4% of patients.

The median follow-up was 132 months (11 years from 2004-2014) - minimum 0.5 months, maximum 180 months.

When analyzing the collected material, no influence of the age of the examined patients on the time to diagnosis, progression-free survival and overall survival was shown.

The only difference between the time of cancer diagnosis was the presence of the BRCA1 mutation ($p = 0.0011$). It was found that genetically burdened women (17.4%) developed BC at a younger age than patients without the mutation.

Breast cancer was reported at an earlier age among women who started menstruating between the ages of 13-15, smoked and lived in rural areas. Patients who did not give birth, miscarried 2 or 3 times, did not breastfeed, used hormonal contraception, smoked, were underweight or obese also had a higher risk of developing BC. It has also been proven that in patients with a family history of cancer of the breast (C50), ovary (C56) and endometrium (C54), as well as in the second group, where there was cancer of the lung (C34), stomach (C16) and colon (C18), the incidence of breast cancer was earlier. However, the desired statistical significance was not achieved for the above factors.

Progression-free survival (PFS) in the studied patients was differentiated by the following variables: M feature, clinical stage, presence of progesterone receptors and the use of neoadjuvant therapy, depending on the stage of advancement. On the other hand, overall survival (OS) was significantly influenced by: BMI, feature T, N, M, number of removed lymph nodes, clinical advancement, histological malignancy (G), biological subtype of the tumor, ER and PR receptors, Ki67, tumor localization in breast, type of surgery, chemotherapy and hormone therapy, and recurrence ($p <0.005$).

Depending on the prognostic factors, it was noticed that 5-year PFS and OS decreased with increasing T, N, M, stage and histological malignancy, and the shortest 5-year PFS and OS were observed in patients with tri-negative cancer.

Depending on the predictive factors, it was estimated that the higher 5-year survival rates were achieved by patients with ER (+) and PR (+) > 20%. In the case of HER2, statistical significance was not achieved, however, patients with HER (-) had longer OS.

Significantly longer PFS and OS were noted in the case of neoadjuvant treatment and hormone therapy.

The multivariate analysis showed that the following factors were important for the assessment of survival: histological malignancy, positive estrogen receptor status, expression of the HER2 receptor as well as T, N and M features.

Conclusions:

1. The presence of the BRCA1 mutation differentiated the time of cancer diagnosis (p = 0.0011). It was found that genetically burdened women (17.4%) developed BC at a younger age than patients without the mutation.

2. The presence of risk factors such as: date of the first menstruation, number of pregnancies, number of miscarriages, breastfeeding, use of hormonal contraception, smoking, place of residence and family history, determined the earlier occurrence of neoplastic disease, but the data were not statistically significant.

3. In the studied group, the age of the patients at diagnosis did not significantly differentiate any of the examined factors. Therefore, the analysis was not divided into patients <36 years>.

4. Progression-free survival (PFS) in the studied patients was differentiated by the following variables: M feature, clinical advancement, presence of progesterone receptors and the use of neoadjuvant therapy depending on the stage of advancement (p <0.005).

5. Overall survival (OS) was significantly influenced by: BMI, T, N, M feature, number of removed lymph nodes, clinical advancement, histological grade (G), biological tumor subtype, ER and PR receptors, Ki67, location breast tumor, type of surgery, chemotherapy and hormone therapy, and recurrence (p <0.005).

6. When assessing the 5-year PFS and OS, depending on the prognostic factors, it was noticed that with the increase in T, N, M, stage and histological malignancy, the percentage of PFS and OS decreased, and the shortest 5-year PFS and OS had patients with tri-negative cancer.

7. When analyzing 5-year survival, depending on predictive factors, it was estimated that higher survival rates were achieved by patients with ER (+) and PR (+)> 20%. In the case of HER2, statistical significance was not achieved, however, patients with HER (-) had longer OS.

8. By assessing the time to progression, depending on the treatment used, a much longer PFS and OS was achieved in the case of neoadjuvant treatment and hormone therapy.

9. The multivariate analysis showed that the following factors were important for the assessment of survival: histological grade, positive estrogen receptor status, expression of the HER2 receptor as well as T, N and M features.