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Is the biology of breast cancer different in patients ≥ 80 years old?

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ABSTRACT

Introduction. The highest incidence of cancer occurs in the seventh and eighth decades of life, hence with the lengthening of human life, the number of seniors diagnosed with cancer is increasing. For years, breast cancer has remained the most commonly diagnosed cancer in women in Poland. There is a belief that breast cancer in elderly women has a milder course, grows more slowly, and is biologically less aggressive compared to younger patients.

Material and methods. This study presents characteristics of the biology of 240 breast cancers diagnosed in 232 patients aged ≥ 80 years and compares them with the biology of 295 breast cancers diagnosed in 291 patients in other age groups.

Results. Evaluating breast cancer biology in patients ≥ 80 years of age compared to patients < 80 years of age in our data showed no statistically significant differences.

Conclusions. The belief that breast cancers are less aggressive in the elderly was not confirmed in our study.

Key words: breast cancer at age ≥ 80 years, breast cancer, breast cancer biology
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Introduction

The highest incidence of cancer occurs in the seventh and eighth decades of life due to the relationship between aging and carcinogenesis [1]. As human life expectancy increases, so does the number of elderly people diagnosed with cancer. The prognosis by the Central Statistical Office indicates that in 2030 there will be 2.2 million people in Poland aged ≥ 80 years, while in 2021 there were 1.64 million people in this age group. At the same time, it is known from demographic analyses that the average life expectancy of 80-year-olds in Poland projected for 2020 was about 9 years for a woman and about 7 years for a man [2]. These data indicate that cancer in the elderly is an important and growing social problem.

Breast cancer has remained for years the most frequently diagnosed cancer in women in Poland (Fig. 1 [3]). In 2019, there were more than 19000 new cases of breast cancer in women (22.9% of total cancer incidence), and nearly 7000 women died from the disease (15.1% of cancer deaths). In men, the incidence of breast cancer has remained at a similarly low level for years (about 150 new cases per year) [4]. From the mid-1970s to 2010, breast cancer was the most common malignant cause of death among women in Poland, but mortality from the disease, unlike incidence, remained constant and even showed a slight downward trend in the first decade of the 21st century (Fig. 1). This "divergence" between incidence and mortality trends observed in Poland and other developed countries of the world results from progress in early detection and treatment of this cancer. In recent years, in contrast to most European countries, breast cancer mortality in Poland has been gradually increasing. Data from the National Cancer Registry indicate that this increase has been most related to women over 65 years of age (Fig. 1). Similar observations come from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry in the US, where the smallest decrease in breast

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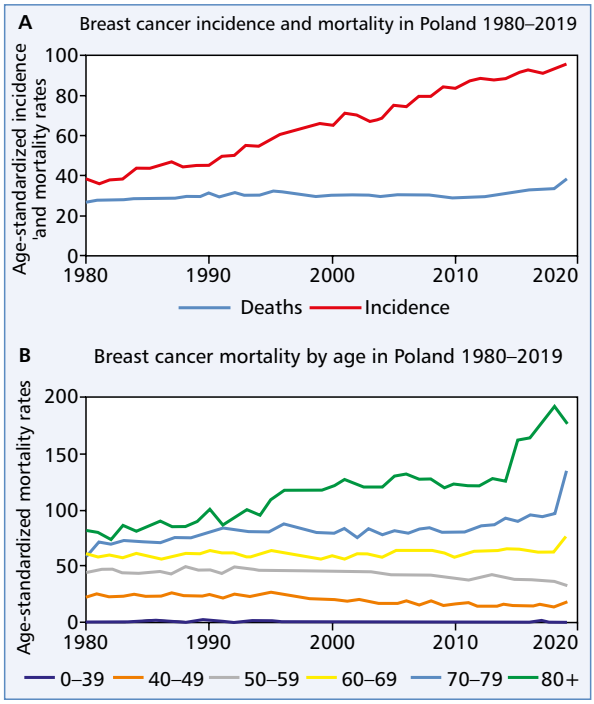

Figure 1A–B. Trends in incidence and mortality of breast cancer in women in Poland from 1980 to 2019 (based on:[3])

cancer mortality was observed in a group of women over 75 years of age [5]. This is all alarming because this group of patients is growing most rapidly.

In 2019, 1921 women aged ≥ 80 were diagnosed with breast cancer in Poland, accounting for 9.8% of the total incidence, and 2054 women died of the disease, accounting for 29.5% of breast cancer deaths in this age group. Similar relationships (3 times higher percentage of deaths than incidence) were observed in the male population, with 23 occurrences at age ≥ 80 (15.4% of total incidence) and 36 deaths (43.3% of breast cancer deaths). It is believed that breast cancers in older women have a milder course, grow more slowly, and are more often of a favorable histopathological type than in younger people [6]. This may suggest potential for a less aggressive treatment in this group of patients. Some investigators believe that the biology of breast cancer is age-dependent [7]. Some retrospective studies suggest that cancers with estrogen receptor (ER) expression are more common in the elderly than in the rest of the patient population, accounting for up to more than 80% of cases in the former [8]. In contrast, HER2-positive [overexpression of human epidermal growth factor receptor type 2 (HER2) or amplification of the encoding this protein *HER2* gene] and triple-negative cancers are relatively less common in the elderly. It has also been shown that poorly differentiated tumors are less common in seniors, and triple-negative tumors have lower Ki67 proliferation index values and are more differentiated than in the younger patient population [9, 10]. Analyses of histologic subtypes indicate that in elderly patients, infiltrating not otherwise specified carcinoma (NOS, formerly called NST — no special type), is the most common diagnosis, but compared to younger patients, other less common subtypes, such as mucinous carcinoma, lobular carcinoma, and intrahepatic papillary carcinoma, are more often to be found [7, 8, 11].

Material and methods

This study aimed to retrospectively analyze the biology of breast cancer in patients aged ≥ 80 years diagnosed at the Breast Cancer Unit (BCU) in Prof. Tadeusz Koszarowski Opole Cancer Center and to compare it with younger patients.

A total of 523 patients were included in the analysis, of whom 232 patients aged ≥ 80 years diagnosed between 2016 and 2020 formed the study group (hereafter referred to as the 80+ group), and 291 patients aged < 80 years diagnosed with breast cancer in 2019 formed the control group (hereafter referred to as the < 80 group). There were 240 breast cancers diagnosed in the study group and 295 in the control group (8 patients in the 80+ group and 4 patients in the < 80 group were diagnosed with synchronous cancers of both breasts). There were 2 males in each group.

Biological characteristics of the disease were assessed and included:

- histologic type (classified as NOS, lobular carcinoma, and other subtypes);
- histologic grade;
- biological subtype — defined based on estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 status — luminal A, luminal B HER2-negative, luminal B HER2-positive, non-luminal HER2-positive, and triple-negative.

The diagnosis of invasive breast cancer in each patient was based on histopathologic examination of material obtained using core needle breast tumor biopsy (most commonly) or surgical excision in cases of extensive infiltration. Almost all examinations were performed in the Department of Pathomorphology of the Opole Cancer Center. Each result included information on the histologic type of the cancer and its grade. The biological subtype of the cancer was determined according to the recommendations of the 2015 and 2017 St. Gallen consensus conferences. Except for one patient, the percentage of cells with ER, PR expression, and the degree of this expression was determined in each case. Any ER or PR response present in ≥ 1% of cancer cells was considered positive. HER2 status was determined by assessing HER2 receptor expression by immunohistochemistry,

and in cases of equivocal results, HER2 gene amplification was additionally assessed by in situ hybridization (ISH). The Ki-67 proliferation index, expressed as a percentage, was assigned to one of two categories — low (values < 20%), or high (values ≥ 20%). Such categorization is in accordance with the Polish Guidelines for Diagnostic and Therapeutic Procedures of Breast Cancer [12]. The St. Gallen recommendations also allow categorization based on the median Ki-67 value, which raises the threshold to 25% in the Department of Pathomorphology of the Opole Cancer Center [13]. The choice of the 20% threshold was dictated by the fact that, generally, this is the accepted threshold in BCU daily practice.

Statistical methods

The statistical package R version 3.3.2 in RStudio version 2022.07.0 was used for calculations. The study used a significance level of $p = 0.05$. The results presented here, including the analysis of the biological characteristics of the cancers, are part of a larger research effort involving many statistical tests. For this reason, Bonferroni's correction was applied to all analyses and a significance level of $p = 0.001$ was assumed for individual tests. The Wilcoxon test, Pearson chi-squared concordance, and Fisher's exact test were used for analysis.

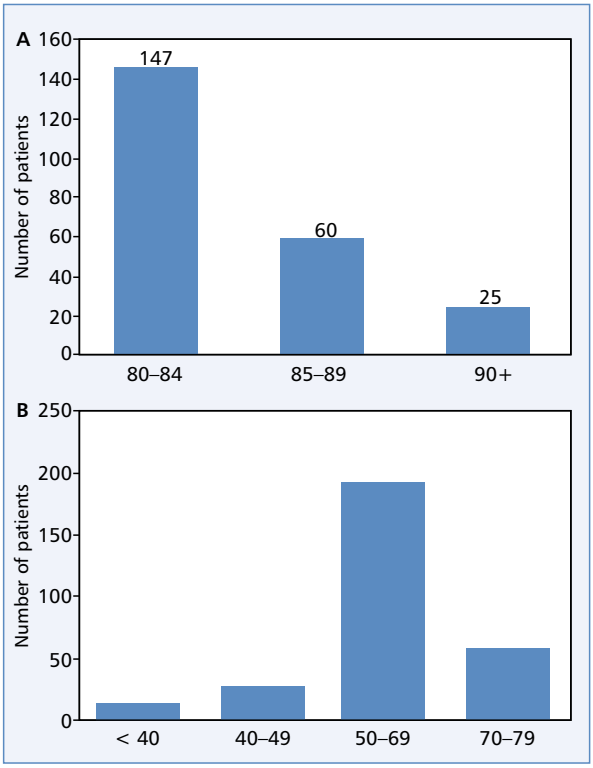

Figure 2. Age distribution of breast cancer patients at the time of diagnosis; **A.** The study group, 80+; **B.** The control group, < 80

Results

The median age in the study group was 82.7 years (range 80.0–97.0) and 63.6 years (range 27.3–79.6) in the control group. The study group had a significant majority of patients aged from 80 to 84 years and the control group had patients aged from 50 to 69 years, the age for population-based screening (Fig. 2).

In both groups, NOS-type cancer was most commonly diagnosed (75.8% in the 80+ group and 83.4% in the < 80 group). Less common histologic types (including lobular, mucinous, and papillary carcinoma) were diagnosed slightly more frequently in the 80+ group than in the control group (24.2% *vs*. 16.6%, respectively). Poorly differentiated tumors were more common in the < 80 group (32.9% *vs*. 26.7% in patients 80+), but this was not a significant difference either (Tab. 1).

The biology of the tumors was similar in both groups (Tab. 1). ER expression was present with a similar frequency (83.3% in the 80+ group and 84.1% in the < 80 group), as was PR (74.6% and 70.2%, respectively). HER2 positivity was slightly more common in the < 80 group (28.8% *vs*. 17.5% in the 80+ group), but the difference was not significant. The median Ki67 index was 26 in the 80+ group and 25 in the < 80 group (range in both groups 1–100). There were no differences in the percentage of cancers with high (≥ 20%) and low (< 20%) Ki67 in the study groups either. This resulted in a similar distribution of biological subtypes of breast cancer in both groups. Luminal B HER2-negative cancers predominated (42.5% in the 80+ group and 34.9% in the < 80 group), and the largest differences between the groups were in the percentage of luminal B HER2-positive cancers (12.9% and 23.4% of patients, respectively). These differences were not significant.

Cancer focality was assessed by a pathomorphological report and, in patients who did not undergo surgery, based on imaging studies. Multifocal tumors were found more frequently in patients < 80 years (18.4% *vs*. 12% in the 80+ group), but the difference was not significant. In addition, this difference may be due to the higher number of surgical procedures in the control group. In both groups, lobular cancers were more common in the multifocal tumor cohorts; that is 28% in the 80+ group (13.8% in the total group) and 17.7% in the < 80 group (9.8% in the total group).

Discussion

The most commonly diagnosed histologic type of breast cancer, regardless of age, is NOS, but many

Table 1. Characteristics of the tumors

Characteristics	80+ group n = 240 (%)	< 80 group n = 295 (%)	p
Histologic type			
Not otherwise specified carcinoma (NOS)	182 (75.8)	246 (83.4)	0.092
Lobular	33 (13.8)	29 (9.8)	
Other	25 (10.4)	20 (6.8)	
Grading			
G1	50 (20.8)	44 (14.9)	0.114
G2	126 (52.5)	154 (52.2)	
G3	64 (26.7)	97 (32.9)	
Tumor focality			
Unifocal	184 (88.0)	227 (81.6)	0.055
Multifocal	25 (12.0)	51 (18.4)	
Estrogen receptor (ER) status			
ER-negative	39 (16.3)	47 (15.9)	0.998
ER-positive	200 (83.3)	248 (84.1)	
No data	1 (0.4)	0 (0.0)	
Progesterone receptor (PR) status			
PR-negative	60 (25.0)	88 (29.8)	0.264
PR-positive	179 (74.6)	207 (70.2)	
No data	1 (0.4)	0 (0.0)	
HER2			
Negative	196 (81.7)	210 (71.2)	0.004
Positive	42 (17.5)	85 (28.8)	
Unknown	2 (0.8)	0 (0,0)	
Ki67 index (%)			
Median	26	25	0.854
Range	1–100	1–100	
Ki67 by category			
Low (< 20%)	78 (32.8)	102 (34.6)	0.662
High (≥ 20%)	160 (67.2)	193 (65.4)	
No Data	2 (0.8)	0 (0.0)	
St. Gallen* sub-type			
Luminal A	68 (28.3)	76 (25.7)	0.069
Luminal B HER2-negative	102 (42.5)	103 (34.9)	
Luminal B HER2-positive	31 (12.9)	69 (23.4)	
Non-luminal HER2-positive	11 (4.6)	17 (5.8)	
Triple-negative	26 (10.9)	30 (10.2)	
Unknown	2 (0.8)	0 (0.0)	

*In 2 patients diagnosed outside the Opole Oncology Center due to incomplete immunohistochemical examination, the biological subtype of the cancer could not be determined. Due to their poor general condition and their failure to undergo oncological treatment, the re-diagnosis was abandoned

authors emphasize an increase in the proportion of lobular and mucinous carcinomas with patient age [9, 14, 15]. Retrospective studies differ in their assessment of the prevalence of histologic types other than NOS in older patients. In the population we analyzed, NOS was predominant in both 80+ and younger patients, as expected. Although lobular carcinoma was diagnosed slightly more frequently in patients 80+ than in controls

(13.8% *vs*. 9.8%), as were other histologic types (10.3% *vs*. 6.8%), these differences were not significant. The percentage of histologic types other than NOS in patients 80+ reported in the literature ranges from 16% to 31.5% [5, 16, 17]. In our study, this was true for 24% of cancers in the 80+ group, which is consistent with literature data and confirms the increasing prevalence of rarer histologic types of breast cancer with age [18].

Analysis of our data showed no significant differences in the incidence of multifocal tumors between the study and control groups. Such differences between older and younger patients were not shown in Weissenbacher's analysis, although some researchers suggest a higher incidence of multifocal tumors in younger patients, especially those < 40 years of age. [19, 20]. The absence of this difference in our data may be due to the small number of patients < 40 years of age in the study group (14 patients).

Well-differentiated (G1) carcinomas were diagnosed more often in patients 80+ compared to the control group, while poorly differentiated (G3) carcinomas were diagnosed in the < 80 group, but the difference was not significant. This observation is consistent with data reported in the literature [6, 21–23]. However, some investigators have shown significant differences in tumor differentiation, suggesting a more favorable biology of breast cancer in the elderly [24, 25].

Estrogen is known to play an important role in the pathogenesis of breast cancer. During menopause, estrogen levels gradually decline, while adrenal and ovarian androgen levels remain constant or begin to decline slowly, resulting in the relative dominance of androgens. Considering that the hormonal balance in older women is different from that of premenopausal ones, the biology of 80+ breast cancer is even more interesting. The expression of hormone receptors in the tumor, including ER alpha (ER-a) and beta (ER-b), PR, and androgen receptor (AR), indicates the type of sex hormones on which the tumor is dependent. However, the pattern of expression of these receptors in relation to menopausal status or age is still controversial.

In our study, we did not observe differences in ER and PR expression or median Ki67, and in the analysis of HER2 status, the differences were not significant, which is consistent with the results of other authors [15, 16, 21, 23, 24, 26]. This resulted in a similar distribution of biological subtypes (according to St. Gallen) in the 80+ and < 80 groups, which is also consistent with data in the literature [22]. In both study groups, the majority of HER2-positive cancer patients showed ER expression (74% in the 80+ group and 80% in the < 80 group). It would be interesting to evaluate the AR expression in the study population; unfortunately, it is not a routine practice [27].

Breast cancers in patients aged ≥ 80 years evaluated in our study were characterized by different combinations of biological and pathomorphological features, with no significant differences compared to younger patients. Therefore, assessment of prognosis and therapeutic management in older patients should be individualized and take into account the biology of the disease, rather than generalized rules based on the age of patients, as suggested by other authors [28].

Conclusions

The results of our evaluation of breast cancer biology in patients ≥ 80 years of age compared with patients < 80 years of age showed no statistically significant differences. The belief that breast cancer is less aggressive in the elderly than in the general population was not confirmed in our study.

Article Information and Declarations

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None.

Author contributions
J.H.-K.: should be considered the major author, author of the concept, methods, research, data analysis, manuscript preparation; P.Z.: data collection, data analysis, manuscript preparation; A.S. statistical analysis; B.R.: should be considered the senior author, author of the concept, methods, research, data analysis, manuscript preparation.

Conflict of interest
None conflict of interest related to the article.

Data availability statement
All analyzed data is included in this article. Further inquiries may be directed to the corresponding author.

Ethics statement
A positive opinion was obtained from the Bioethics Committee at the Opole Medical Chamber in Opole.

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Supplementary material
None.

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