ejpmr, 2019,6(8), 595-603

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

MODIFIABLE RISK FACTORS OF BREAST CANCER IN YOUNG WOMEN - POLISH EXPERIENCES AND LITERATURE REVIEW

Barbara Kozakiewicz*[1,2], Małgorzata Chądzyńska[3], Małgorzata Czetwertyńska[1], Marta Dulęba[2], Zbigniew Jodkiewicz[1] and Andrzej Deptała[2]

[1]Oncology Center - M. Skłodowska-Curie Institute, 02-034 Warsaw, Wawelska 15.
[2]Medical University of Warsaw, Faculty of Health Sciences, 02-091Warsaw ul. Żwirki i Wigury 61.
[3]Institute of Psychiatry and Neurology, 02-957 Warsaw, ul. Sobieskiego 9.

***Corresponding Author: Dr. Barbara Kozakiewicz**
Medical University of Warsaw. 02-091 Warszawa ul. Żwirki I Wigury 81.
Tel. +48/22 5720702 **Email ID:** barbara.kozakiewicz@wum.edu.pl,

Article Received on 21/06/2019 **Article Revised on 11/07/2019** **Article Accepted on 31/07/2019**

ABSTRACT

Introduction: The rise in the incidence of breast cancer and high mortality of breast cancer patients among adolescents and young women has spurred a search for lifestyle factors correlated with incidence rate and failed treatments. **The goal** is to assess selected lifestyle elements of young breast cancer patients and attempt to evaluate their influence on survival rates. **Material:** A group of 307 women suffering from breast cancer, ages 19-81 years, divided according to age: group A consisted of 37 subjects ages 19-29 years, B - 110 women, 30-35 years, C – 160, 40-81 years. Clinical cancer features and drugs, hormonal medications used as well as BMI were assessed and correlated with the clinical endpoint. **Results:** In the group of younger patients, up to 35 years, a smaller tumor – T1, was identified significantly more often. A similar percentage (16%) of patients up to 29 years of age visited a doctor within a month and after 1 year and 3 years from tumor detection. In this test group, alcohol drinking and tobacco smoking was significantly more prevalent. The total survival rate among the 307 subjects was 74%, and the lowest survival rate of 12% was noted in the youngest group vs. 38% and 49% in the groups of older women. **Conclusions:** Among the lifestyle models for young women currently being propagated, those that have a clearly negative impact on their health are also accepted. This is why it is worth continuing studies on lifestyle factors and to widely educate women about negative factors that are already known.

KEYWORDS: Breast cancer in adolescents and young women, alcohol and breast cancer in adolescents, lifestyle.

INTRODUCTION

Approx. 7% of breast cancer cases are diagnosed in young adult women aged 19-39 years. The individual mean risk of breast cancer incidence in young adult women - BCYW (Breast Cancer Young Women) by the 40th year of age amounts to 1/173, and by the 30th year of age, approx. 1/1,500. Analysis of 184,460 cases of breast cancer conducted by the American Cancer Society demonstrated that, in the USA, BCYW is diagnosed in 6.6% of women under 40 YoA, in 2.4% of patients under 35 YoA, and in 1% under 30 YoA. Predicting breast cancer incidence rate in young Polish women until 2025, it was shown that this incidence rate will have a growth tendency from $16/10^5$ in 2006 roku to $19/10^5$ in 2025 with general predicted growth > 50% for the entire country in 2025 compared to 2006.[1-4]

Assessing incidence among adolescents and young adults 15-35 YoA (AYA – Adolescent and Young Adult) as well as children, oncologists (COG – Children's Oncology Group) determined that a clear increase in breast cancer cases occurred among adolescents and young adults, constituting up to 6% of all breast cancer cases. Meanwhile, in all cases of tumors in children and young adults, 14% are breast cancer cases. During the period of 1975-2000, this cancer in patients under 30 YoA made up less than 0.1% of cases annually. Currently, incidence is equal to 1.3 in the 15-19 age group, 12.1 in the 20-24 age group, and in the 25-29 age group, it reaches up to 81.[5-7]

The results of treating young adult women are worse than for older patients above 40 YoA. The early age at which the cancer occurs increases the risk that cancer will occur in the second breast. In younger patients, local recurrence and formation of distant metastases are observed more frequently, which consequently leads to greater mortality.

Among the distinguished molecular profiles of breast cancer, triple-negative and basal-like (Her+) types are diagnosed more frequently in the BCYW group, 37% vs. 15% in all breast cancer patients. Both of these subtypes, TNBC and HER2 +, are characterized by a more aggressive progression and are overrepresented in the group of young patients. Moreover, expressions of

proliferation marker Ki-67, mutations of gene T53 and protein PTEN occur more frequently among young adult women, and these expressions foster the occurrence of genetic disorders in the form of Li Fraumeni, Muir or Cowden syndrom, which are accompanied by breast cancer.[8,9]

The traditional model defining the etiology of breast cancer in young adult women is based on initiation of the disease as a result of mutation of BRCA1 and BRCA2 genes as well as on breast cancer or ovarian cancer cases in relatives. Assessing the data from the numerous studies determining the involvement of genetic mutations and family/inherited factors in BCYW cases, it can be stated that they co-exist in less than 10% of breast cancer patients.[3,8,9] Only 1/10 of young breast cancer patients had relatives of the 1st/2nd degree who had breast cancer earlier. In the decided majority of cases, breast cancer in this group is the result of spontaneous genetic mutations that do not occur in other family members.[10,11]

Retrospective assessment of treatment results conducted by SEER (*Surveillance, Epidemiology and End Results)* for over 200 thousand women with breast cancer showed that women aged <40 years die 39% more often due to breast cancer in comparison to patients aged ≥ 40 years. The greatest differences in mortality were observed in women <40 YoA in the early stage of breast cancer (1st, 2nd clinical stage) with respect to older women. Fatalities amounted to 44% vs. 9% under and over 40 YoA, respectively.[12]

The assessment of relative 5-year survival rate depending on age according to SEER's data, for patients diagnosed with and treated for breast cancer during the years 1975-2000, showed a reduction of survival rate as age decreased, equal to 84-86% for the 45-80 age group, 75% for the 35-39 age group, 76% for the 25-29 age group, and 72% for the 20-24 age group.[12-14] Japanese researchers presented similar results in 2016.[15]

In Poland, three trends of incidence and mortality of women aged 19-39 years occurred during the period of 1999-2015. During the years 1999-2003, there was a growth trend of incidence and a reduction in mortality, during the years 2003-2008, stabilized incidence and reduced mortality, and during the period of 2009-2015, a clear increase in both incidence and mortality in the group of young adult women (fig. 1).[16]

Ryc.1. Chart of breast cancer incidence and mortality for women 19-39 YoA, normalized with respect to corresponding values from the start of the interval for the years 1999-2015 according to data from the Oncology Center - M. Skłodowska-Curie Institute (KRN COI).

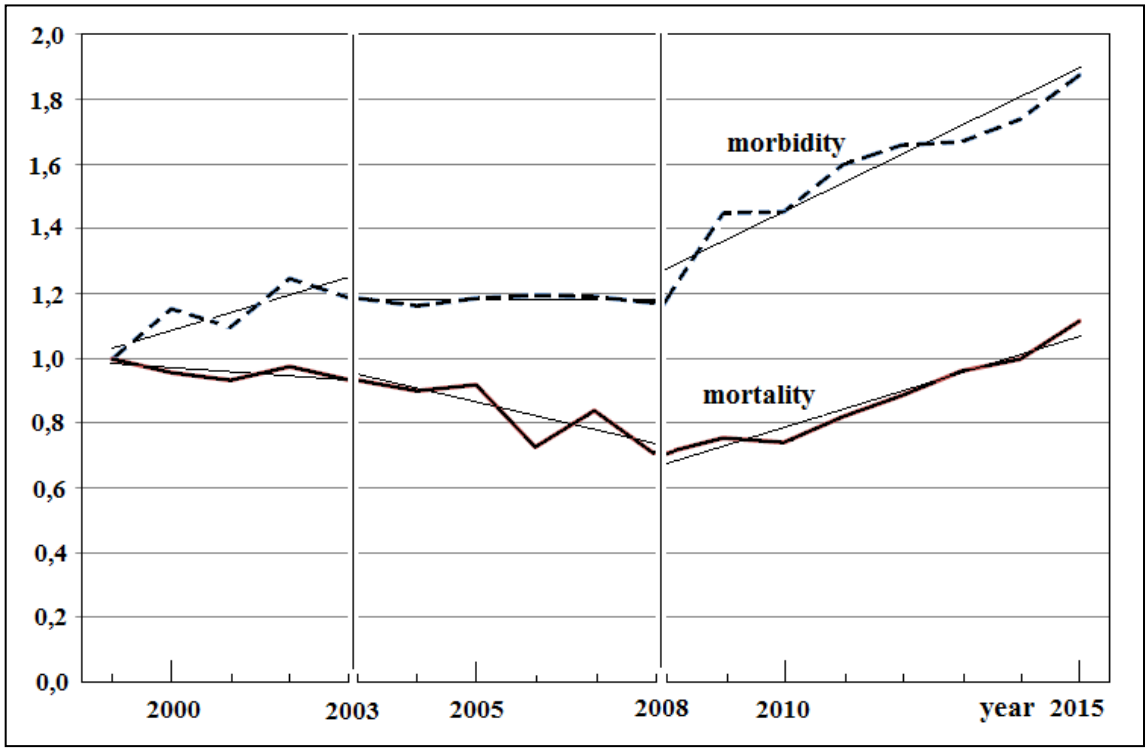

Figure 1: Chart of breast cancer incidence and mortality for women 19-39 YoA, normalized with respect to corresponding values from the start of the interval for the years 1999-2015 according to data from the Oncology Center - M. Skłodowska-Curie Institute (KRN COI).

Breast cancer is the most frequently diagnosed neoplasm in the life of women, but also among adolescents in the AYA group, as confirmed by data from SEER. The aggressiveness of the cancer's progression is greater the younger the patients are, and it seems that it is related not only to the biological features of BCYW tissue but also

to factors currently modifying the lifestyle of young people. These factors are an early start in alcohol consumption, tobacco smoking, obesity and use of hormonal contraceptives. The age at which exposure occurs and its duration are significant to the risk of incidence. Currently, young people are not aware of the impact of their lifestyle on their health. In the assessment of IARC (International Agency for Research on Cancer) approx. 700 thousand new cases of malignant neoplasms around the world every year are linked to drinking alcohol.[17] Unsatisfactory results of treating neoplastic diseases in the AYA group are the subject of numerous medical and social actions. In 2006, the AYA Oncology Progress Review Group was appointed with the goal of acquiring knowledge about factors influencing the end result of treating malignant neoplasms. The result of these activities was the development of the LIVESTRONG Young Adult Alliance, a program that was to raise the curability of this group of patients. In 2009, the National Cancer Institute (NCI) and the Lance Armstrong Foundation (LAF) organized and conducted workshops with the goal of investigating the current status of basic and translational studies concerning neoplasms among AYA for the purpose of taking further measures to limit the mortality of young patients.[18]

The goal of the study is to assess the frequency of the presence of modifiable risk factors of breast cancer in adolescents and young adult women as well as their influence on survival rate.

MATERIAL AND METHOD

Retrospective analysis of disease progression in 307 women suffering from breast cancer, 19 to 81 YoA, treated at the Oncology Center – Marie Skłodowska-Curie Institute in Warsaw during the years 1990 to 2012, was conducted. The studied group was divided into 3 age subgroups: group A, 19-29 YoA, consisted of 37 of the youngest patients; group B, 30-35 YoA, consisted of 110 young women, and group C, 40-81 YoA – 160 women. In each group, family medical history, tumor observation time and its size at the time of visiting a doctor, clinical structure, prognostic and predictive factors were evaluated. In addition, the presence of risk factors was estimated, i.e. alcohol consumption, tobacco smoking, use of hormonal contraceptives, and BMI, as well as total survivals and failures of treatment. The clinical status of the studied group is characterized in table 1.

Tab. 1: Characteristics of studied group – 307 breast cancer patients.

Features of neoplastic tissue	**Group A 19-29 N=37** **N %**	**Group B 30-35 N=110** **N %**	**Group C Ages 40-81 (mean age 59.8) N =160** **N %**	**Differences between groups**
Tumor size				
T1	17 46	60 54	45 28	A-B: (λ^2=6.32; p=0.097) A-C: (λ^2=11.31; p=0.01)* B-C: (λ^2=28.8; p<0.001)*
T2	18 48	32 29	91 57	
T3	1 3	14 13	24 15	
T4	1 3	4 4	0 0	
Lymph node infiltration				
N0	20 54	38 35	30 19	A-B: (λ^2=11.71; p=0.02)* A-C: (λ^2=36.7; p<0.001)* B-C: (λ^2=14.57; p=0.006)*
N1	12 33	48 44	67 42	
N2	0 0	7 6	23 14	
N3	2 5	16 14	40 25	
Nx	3 8	1 1	0 0	
Microscopic form Ductal carcinoma	24 65	71 65	101 63	A-B: (λ^2=0.001; p=0.97) A-C: (λ^2=0.04; p=0.84) B-C: (λ^2=0.06; p=0.81)
Lobular carcinoma	5 13	11 10	29 18	A-B: (λ^2=0.35; p=0.55) A-C: (λ^2=0.45; p=0.50) B-C: (λ^2=3.41; p=0.06)
Other forms	8 22	28 25	30 19	A-B: (λ^2=0.22; p=0.64) A-C: (λ^2=0.16; p=0.69) B-C: (λ^2=1.74; p=0.19)

*- statistically significant differences between groups - Chi-squared test

The microscopic form of the neoplastic tumor and its size (T feature) did not differ in young patients up to 35 YoA. In the group of the oldest women, tumor T1 was diagnosed the least frequently (28%), compared to 46% and 54% in groups A and B, respectively. High advancement, T3 and T4 was diagnosed, on average, in 15% of the oldest women and 6% of the youngest women (tab.1).

Among the studied subjects, breast tumor observation time ranged from 1 month to three years. Younger women from groups A and B did not differ in terms of

tumor observation time, while older women observed changes in breasts for a significantly longer period of time than women from group B (tab.2).

The 3 studied groups of patients differed between each other in terms of lymph node infiltration, where the frequency of metastases increased with age, respectively, A-46%, B-65%, C-81%.

Table 2: Observation time of breast tumor growth among the studied subjects.

Observation time of breast tumor	**Group A 19-29 N=37**** **N %**	**Group B 30-35 N=110**** **N %**	**Group C Ages 40-81 (mean age 59.8) N =160**** **N %**	**Differences between groups*****
Up to 1 month	5 16	14 14	-	A-B: (λ^2=9.35; p=0.096) A-C: (λ^2=0.71; p=0.70) B-C: (λ^2=6.51 p=0.04)*
More than 1 month up to 2 months	9 29	13 13	-	
3-5 months	8 26	44 45	59 37	
6-11 months	4 13	19 20	50 31	
1 year	3 10	7 7	24 15	
more than 1 year	2 6	1 1		

*- statistically significant differences between groups

**Among the 147 subjects in groups A and B, 18 (12%), and among the 160 subjects in group C, 27 (17%), did not know the observation time.

***The comparison of observation time for groups A-B concerns 1 month-more than 1 year, and for groups A-C and B-C, the period of 3 months - 1 year.

RESULTS

During the period under discussion, steroid receptors and the HER-2 receptor were not yet determined in every patient, and they were tested in 39% among the 147 younger patients. The differences in occurrence among these patients were not statistically significant. The absence of the HER-2 receptor was determined in 74% of young subjects, without differences between group A and B. Triple-negative breast cancer (TNBC) was diagnosed in 38% among all young patients. It was present in 52% of subjects from group A and in 32% of subjects from group B. The differences in these proportions are not statistically significant (Chi-squared test = 2.30; p=0.129). Among TNBC patients in group B, 31% died, and all were daughters of mothers who also had breast cancer. The total survival rate in group A and B was, respectively, 77% and 69%, and the survival rate for the entire TNBC group was 72%. Although these percentages pertain to small groups, they reflect the trend of lower survival rates among younger patients.

Analyzing tumor observation time above 1 year with recognized prognostic features of cancer tissue and total survival time, it was determined that long observation of changes is not a negative prognostic factor in young women (tab.3).

Table 3: Long breast tumor observation time (1-3 years) and clinical features of cancer with respect to end result among the youngest patients, up to 29 YoA.

Age	**Years of tumor observation**	**Tumor size (mm)**	**Clinical stage**	**Hist-path**	**Lymph nodes**	**ER PR**	**Her2**	**Cancer cases among relatives**	**End result**
27 years	1	20	T1NxM0	Tumor phylodes	0/0	+	?	?	Living 8 years
29 years	1	30	T2N0M0	Ca ductale	0/24	+	?	-	up to 7
29 years	3	20	T1N0M0	Ca ductale	0/7	-	+	Mother, sister- breast	Living 6 years After 5 years, cancer of second breast
29 years	2	10	T1N0M0	Ca ductale	0/14	+	+	Aunt- stomach	Living 6 years
29 years	1	20	T1N1M0	Ca ductale	6/15	-	+	-	Living 6 years

Among the modifiable risk factors of breast cancer, the influence of drugs was assessed to be significant: alcohol, when consumed in the form of two drinks or two beers twice a week, tobacco if more than 5 cigarettes were smoked daily, use for at least 6 months of hormonal contraception, and in addition, BMI (body mass index) was also assessed as significant.

Table 4: Frequency of using drugs, hormonal contraception and BMI of studied group.

Modifiable risk factors	Group A 19-29 N=37 N %	Group B 30-35 N=110 N %	Group C Ages 40-81 (mean age 59.8) N =160 N (N_{group})** %	Significant differences between groups A, B, C*
Smoking	27 73	63 57	27(98) 27	A-B: (λ^2=2.9; p=0.08) A-C: (λ^2=27.7; p<0.001)* B-C: (λ^2=12.3; p<0.001)*
Alcohol consumption	29 78	29 26	45(120) 37	A-B: (λ^2=31.4; p<0.001)* A-C: (λ^2=20.4; p<0.001)* B-C: (λ^2=1.6; p=0.2)
Contraception	23 62	78 71	59(73) 81	A-B: (λ^2=0.99; p=0.32) A-C: (λ^2=4.51; p=0.03)* B-C: (λ^2=2.29; p=0.13)
BMI- norm overweightness/obesity	30 80 2 5	90 82 14 13	84(160) 52 70(160) 44	A-B: (λ^2=0.01; p=0.92) A-C: (λ^2=10.07; p=0.002)* B-C: (λ^2=24.45; p<0.001)*

*- statistically significant differences between groups, **among older subjects, (N_{group}) - the number of persons providing a response, was placed in parentheses.

In group C, significantly less (27%) patients smoked cigarettes in comparison to 73% and 57% in groups A and B. In the group of the youngest women, 78% of adolescent girls drank alcohol significantly more frequently in comparison to 26% and 37% in groups B and C. Significant differences appeared in the use of contraception between the group of the youngest (A-62%) and oldest women (B-81%). Overweightness or obesity was determined among the oldest women C-44% while groups A and B presented with approx. 80% within weight norms.

Among the 307 patients, fatalities were declared in 79 cases (26%), and differences in mortality rates were not statistically significant, however the tendency of a greater number of fatalities among the oldest women in comparison to group B was marked. Among the studied subjects, distant metastases were identified in 17% (53) of subjects, and local recurrence in 8% (25). Differences between groups are not statistically significant (tab. 5).

Table 5: Assessment of treatment result in 307 breast cancer patients.

End result	Group A 19-29 N=37 N %	Group B 30-35 N=110 N %	Group C Ages 40-81 (mean age 59.8) N =160 N %	Significant differences between groups A, B, C*
Recurrences	4 11	10 9	11 7	A-B: (λ^2=0.1; p=0.76) A-C: (λ^2=0.66; p=0.42) B-C: (λ^2=0.45; p=0.5)
Metastases	10 27	17 15	26 16	A-B: (λ^2=2.47; p=0.12) A-C: (λ^2=2.34; p=0.13) B-C: (λ^2=0.03; p=0.86)
Fatalities	9 24	22 20	48 30	A-B: (λ^2=0.31; p=0.58) A-C: (λ^2=0.47; p=0.49) B-C: (λ^2=3.39; p=0.065)
5-year survivals	28 76	88 80	112 70	as above

*- statistically significant differences between groups

Among the 31 fatalities of young women, 8 (26%) had mothers and/or sisters with breast cancer. Assessing the total 5-year survivals among 228 of the subjects, the lowest percentages were obtained for the youngest group – 12% (28 patients), and in the older groups, B and C - 38% (88) and 49% (112) of patients, respectively.

DISCUSSION

The subject literature shows that differences between the results of breast cancer treatment for adolescents and young adults <40 YoA and older women are dependent on the microscopic and molecular features of cancer tissue, epidemiological factors and optimal treatment strategies. Despite accounting for these data, in cases of proper selection of the treatment method and application

of treatment with equal diligence, younger patients have worse prognoses, and their survival rates are lower than for patients over 40 YoA. In patients below 35 YoA, the risk of fatality increases by 5% with every year of age by which the patient is younger at the time of breast cancer incidence.[19]

There are no standards of diagnostic procedure for adolescent breast cancer patients. The sensitivity of the USG test is approx. 58%, and that of the mammographic test is lower, at 45-55%, while sensitivity is 94% for older patients, above 39 YoA. False negative results for ultrasonographic testing of young women's breasts fluctuate from 0.3% to 47%. The American Cancer Society recommends mammography as the basic diagnostic tests for AYA, and in cases of images that are difficult to interpret, magnetic resonance with contrast. This procedure increases the sensitivity of imaging diagnostics to over 90%.[20,21] The sensitivity of magnetic resonance is 93-100%, specificity is lower 37-97%. Diagnostic difficulties are caused by the diversity of changes occurring in young women's breasts and their varied reaction to enhancement with contrast. The density of mammary gland tissue is the mammographic index of glandular and connective tissue with respect to fatty tissue. It depends on genetics, age, but also on modifiable factors, e.g. body weight, use of hormonal medications and alcohol consumption.[22] Flom et al. demonstrated elevated mammographic breast density in women who initiated alcohol consumption early, before their 18th YoA, and drank alcohol regularly during puberty.[23]

Breast self-testing allows for identifying a neoplastic tumor in approx. 85% of regularly self-testing women over 40 YoA, and in young women, palpable changes are determined in 37% of cases. The most sensitive test in the AYA group is biopsy, the efficacy of which is 78%. In women >40 YoA, the sensitivity of integrated imaging methods and self-testing amounts to 100%. In young women, diagnostic difficulties are based on the diversity of images and intensities related to the influence of risk factors and the fact that adolescents rarely test their breasts or not at all. Radiologists prefer microscopic verification in diagnostics of young women's breasts.[21,24] Among the studied subjects, a tumor with a size above 2 cm was identified in 54% of the youngest patients vs. 29% in older patients. T3 and T4 advancement was determined in 14% of young and 15% of older and the oldest subjects. Greater advancement at the time at which breast cancer was diagnosed in young women results from lack of self-control and awareness of breast cancer incidence. Lymph nodes were infiltrated at the time of diagnosis in 38% of subjects in group A, 64% of subjects in group B, and 81% of subjects in group C. The presence of metastases to lymph nodes is a more frequent phenomenon among the AYA group with respect to infiltration of lymph nodes in women >40 YoA as described in the literature.[25]

In our study, breast tumor observation time did not differ significantly and did not have a negative impact on survival among the studied young patients up to 35 YoA. This is why the opinion that the aggressiveness of neoplasms in adolescents and young adults is linked to the tumor's biological features rather than its size at the time of detection seems to be justified. The lack of diversity in microscopic types of cancer in the tested group can be explained by the lack of significant differences in survivals. The negative prognosis for adolescent and young adult patients is also linked to more frequent incidence of secondary neoplasms, i.e. cancer of the second breast, leukemia, lung cancer and ovarian cancer.[25,26] Among the studied group, a secondary neoplasm was identified in one among the youngest patients, and this was cancer of the second breast. An early age of incidence also increases the risk of local recurrence and distant metastases. Studies by the European Organisation for Research and Treatment of Cancer (EORTC) demonstrated a risk index (HR) at the level of 2.8 (confidence interval 95% [CI] 1,4-5,6) of cancer recurrence in patients below 35 YoA in comparison to patients above 50 YoA.[28]

Triple-negative breast cancer has a much worse prognosis in terms of progression and survival, regardless of age. Among the studied AYA patients, TNBC was diagnosed in 22 cases (38%), 9 (24%) of them from group A and 13 (12%) from group B. 5-year survivals of patients from both groups A and B amounted to, respectively, 76% and 80%. This percentage was 70% in the group of older women. All deceased patients, from both groups, were daughters of mothers who had breast cancer. In many authors' assessment, TNBC is determined more often in BCYW, in approx. 26% of cases in comparison to 12% of all breast cancer patients. The most recent studies suggest that the occurrence of TNBC is correlated with lifestyle, which may worsen treatment results.[28-30]

A comparison of mortality rates between young women and women >40 YoA conducted by Gnerlich et al. indicates that younger women have a higher mortality rate of 44% vs. 9% for older women, even in early stages of the disease. In our study, 24% of women up to 29 YoA died vs. 20% in the group up to 35 YoA. Meanwhile, mortality was 30% in the group of 38-81 YoA. No significant differences in 5-year survival were observed between the studied groups. Perhaps the effects described in the literature did not occur in our observation of survival due to differences between the groups of the youngest and oldest women: tumor size (T1 feature less numerous) in group C, longer time of tumor observation, more frequent use of contraception (than in group A) and more frequent problems with overweightness. Among the deceased young patients, 26% had relatives of the 1st degree with breast cancer. The presence of the disease in just one relative of the first degree of consanguinity increased the risk of breast cancer two-fold. This risk increases 3- to 4-fold as the

number of incidences among 1st-degree relatives rises.[31,32]

Younger patients are less frequently affected by co-existing illnesses and present better tolerance to the toxicity of treatment, which they undergo more and more frequently due to detection of a more aggressive form of cancer than in patients >40 YoA. There are no recommendations for performance of mastectomy in the guidelines of the National Cancer Network (NCCN) from 2015 concerning treatment of breast cancer in AYA. Despite this, assessing the need for bilateral cancer treatment, bilateral mastectomy was performed in this group four times more often than in patients 50-64 YoA (OR 3.81; 95% CI 3.55-4.08).[33,34]

Lifestyle and the influence of modifiable breast cancer risk factors are features that strongly differentiate the group of young and the youngest patients. It is important to distinguish the factors that improve survival results in this group of patients in light of the rate at which the incidence rate is rising. Statistics in the USA indicate that, from 1975 to 2000, the number of breast cancer cases among the youngest patients – adolescent girls and young adult women (up to 35 YoA) – has increased by 1 million. In 2017, 252,710 American women developed breast cancer, including 11,160 (4%) under 40 YoA, and 2% among them died for this reason.[3] The trend of growing incidence and mortality rates among young women (fig.1) is also being observed in Poland. In estimating the risk of carcinogenesis, the aim is to identify factors influencing the occurrence of cancer and its progression. It seems that, thanks to conscious modification of their lifestyle, young women can guard against such frequent incidence of breast cancer. They should be educated that starting smoking prior to the birth of their first child increases the risk of breast cancer by 21%.[35]

In the assessment of ACS, physical exercise and sports activity at least once a week reduces the risk of breast cancer by 10-20% in comparison with women who are not physically active.[36,37] Moreover, Abrahamson et al. demonstrated that physical exercise in the form of recreational activities with a minimum duration of 5 hours per week reduced the risk of mortality in 717 breast cancer patients <40 YoA in comparison to young but physically inactive women (HR = 0.78 (95% CI 0.45-1.34)).[38] A positive energy balance resulting from excessive calorie consumption and/or insufficient energy expenditure leads to enlargement of fatty tissue and obesity. Both of these factors increase the risk of breast cancer development in older women and cause progression of cancer in patients of every age. In women before menopause, larger tumor sizes in breasts as well as elevated mortality due to breast cancer are linked to obesity (HR = 1.75, 95% CI 1.26-2.41) in comparison to women after menopause without obesity (HR = 1.34, 95% CI 1.18-1.53).[39] Breastfeeding reduces the risk of breast cancer by 4% for every 12 months.[40]

The results of studies assessing the influence of tobacco smoking on breast cancer incidence indicate that smoking slightly increases the risk of breast cancer. Long-term smoking of over 10 cigarettes per day is particularly dangerous to women who start smoking before their first pregnancy.[41] Scientists from the American Cancer Society identified the dependency between smoking and the time of first birth. They determined that women who started smoking prior to the birth of their first child are at 21% greater risk of breast cancer with respect to non-smokers. Moreover, they suggest that secondhand smoking increases the risk of breast cancer, particularly in young women.[42] Among our group of subjects, the youngest patients, up to 29 YoA, smoked most often (73%), and this percentage decreased significantly as patient age increased ($\lambda 2=27.7$; $p<0.001$), with 27% of patients in group C being smokers.

In the assessment of IARC, alcohol has the strongest influence on the incidence of breast cancer, and it is linked to 1/4 of new cases every year. When assessing the influence of alcohol on the development of breast cancer, the amount of its consumption by patients must be determined, and this information is variously evaluated. In a meta-analysis covering over 8 thousand breast cancer patients, moderate consumption was recognized as 14 U = 112g/week (1U= 0.8 g or 1 oz. = 28 g, or 1 drink = 12.5 g of alcohol).[43] In the assessment of Polish authors, consumption of 1.5 portions/day, (1 portion = 10g or 12.5 ml of ethanol) increases the risk of breast cancer by 1.5x with respect to non-drinkers. The risk of breast cancer in young women who consume alcohol regularly, regardless of the form of alcohol, increases by 7.1% with respect to non-drinking patients and grows as alcohol consumption increases.[44] Based on a study by Gou et al., alcohol consumption by young women increases the rate of breast cancer recurrences, particularly among patients who drink regularly.[45,46] In addition, among the subjects of this study, the youngest group had the highest percentage of alcohol drinkers, 78%, and consumed alcohol significantly more often with respect to the other subjects. In assessment of the end result of breast cancer treatment, a slight drop in total mortality linked to moderate alcohol consumption in receptor-positive patients and reduction of case fatality rate among patients with moderate alcohol consumption with receptor-negative breast cancer were described. The authors of this study recommend further clarification of results in light of the growing frequency of alcohol drinking among the population of young women (18-44 YoA), which exceeds 54.6% in the USA.[47,48]

Oral contraceptives, which stimulate the proliferation of epithelial cells of the mammary gland, are another significant etiological factor of breast cancer. There is no unambiguous assessment of which ingredient in these contraceptives causes this effect. However, scientists' assessment that the use of hormonal contraception increases the risk of breast cancer significantly, by up to

24%, is unequivocal. This risk grows further still if patients used such contraception prior to the birth of their first child or before their 20th YoA. After the passage of ten years from the time at which this method of contraception was discontinued, the risk is comparable to that of the general population of women who do not use contraceptive pills.[49,50]

Studies of the influence of protective factors and risk as well as of their mutual relationships have become the foundation for creating the most effective prophylactic programs, e.g. NREP (National Registry of Effective Programs), which made it possible to evaluate addiction to psychotropic substances among adolescents in the United States.[51] Identifying risk factors and their influence on the number of breast cancer cases, as well as propagation of methods of eliminating these adverse factors, may be the simplest way to limit breast cancer incidence, particularly among the youngest group in the population.

Conflict of interest

The authors do not report any financial or personal relations with third parties or organizations that could have a negative impact on the contents of this publication or claim rights to this publication.

LITERATURE

1. Didkowska J, Wojciechowska U, Zatoński W.: Prognozy zachorowalności i umieralności na nowotwory złośliwe w Polsce do 2025 roku. KRN COI Warszawa, 2009.
2. Canadian Cancer Society/National Cancer Institute of Canada (2015) Canadian Cancer Statistics 2015. Toronto, Canada.
3. Breast Cancer Facts & Figures 2017-2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf
4. Anders CK, Johnson R, Litton J, Phillips M i wsp.: Breast Cancer Before Age 40 Years. Semin Oncol, 2009 June; 36(3): 237–249.
5. Lewis DR, Seibel NL, Smith AW i wsp. MR: Adolescent and Young Adult Cancer Survival. J Natl Cancer Inst Monogr, 2014; 2014(49): 228–235.
6. Smith EC, Ziogas A, Anton-Culver H.: Delay in Surgical Treatment and Survival After Breast Cancer Diagnosis in Young Women by Race/Ethnicity. JAMA Surg, 2013 Apr; 24: 1-8.
7. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. Semin Oncol, 2009; 36: 237.
8. Yelland A, Graham MD, Trott PA, Ford HT, Coombes RC, Gazet JC et al.: Diagnosis breast cancer in young women. BMJ, 1991; 302: 618-620.
9. Nelen MR, van Staveren WC, Peeters EA iwsp. Localization of the gen for C owden disease to chromosome 10q22-23. Nat Genet, 1996; 13: 114-116.
10. Zbucka M, Leśniewska M, Knapp P, Wołczyński S: How we can modify the risk of breast cancer? Prz Menopauz, 2005; 6: 70 – 75.
11. King MC, Marks JH, Mandell JB: Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science, 2003; 302(5645): 643-6.
12. Gnerlich JL, Deshpande AD, Jeffe DB i wsp. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg., 2009; 208: 341–347.
13. Bleyer A, O'leary M, Barr R i wsp.: Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975–2000. Bethesda: National Cancer Institute, NIH, 2006.
14. Keegan TH, Press DJ, Tao L i wsp. : Impact of breast cancer subtypes on 3-year survival among adolescent and young adult women. Breast Cancer Res., 2013; 15(5): R95.
15. Kataoka A, Iwamoto T, Tokunaga E et al.: Young adult breast cancer patients have a poor prognosis independent of prognostic clinicopathological factors: a study from the Japanese Breast Cancer Registry. Breast Cancer Res Treat, 2016; 160: 163–172.
16. http://onkologia.org.pl/nowotwory-piersi-kobiet/ (pobrano 22.01.2018r.)
17. Shield KD, Soerjomataram I, Rehm J.: Alcohol Use and Breast Cancer: A Critical Review Alkoholism. Clinical and Experim, 2016; 40: 1166–1181.
18. Tricoli JV, Seibel NL, Blair DG i wsp.: Unique characteristics of adolescent and young adult acute lymphoblastic leukemia, breast cancer, and colon cancer. J Natl Cancer Inst., 2011, 20; 103(8): 628-35.
19. de Deus Moura R, Carvalho FM, Bacchi CE. Breast cancer in very young women: clinico-pathological study of 149 patients ≤25 years old. Breast, 2015; 24: 461-467.
20. Salem DS, Kamal RM, Mansour SM i wsp.: Breast imaging in the young: the role of magnetic resonance imaging in breast cancer screening, diagnosis and follow-up. J Thorac Dis., 2013; 5(Suppl 1): S9–S18.
21. Warner E.: The role of magnetic resonance imaging in screening women at high risk of breast cancer. Top Magn Reson Imaging, 2008; 19(3): 163-9.
22. Byrne C, Ursin G, Martin CF i wsp.: Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk. J Natl Cancer Inst., 2017; 109.
23. Flom JD, Ferris JS, Tehranifar P i wsp.: Alcohol intake over the life course and mammographic density. Breast Cancer Res. Treat., 2009; 117(3): 643–651.
24. Ashley S, Royle T, Corder N i wsp.: Clinical, radiological and cytological diagnosis of breast cancer in young women. Br J Surg, 1989; 76.

25. Brenner DR, Brockton NT, Kotsopouloset J i wsp.: Breast cancer survival among young women: a review of the role of modifiable lifestyle factors. Cancer Causes Control, 2016; 27: 459–472.
26. Ashley S, Royle GT, Corder A i wsp.: Clinical, radiological and cytological diagnosis of breast cancer in young women. Br J Surg, 1989; 76: 835-837.
27. Li N, Huang M, Yang Y i wsp.: Case Report. Secretory breast cancer in a 7-year-old girl. Int J Clin Exp Pathol, 2017; 10(5): 6006-6010. www.ijcep.com. (pobrano 12.02.2018r.)
28. de Bock GH, van der Hage JA, Putter H i wsp.: Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer, 2006; 42: 351–356.
29. Shah SP, Roth A, Goya R i wsp.: The clonal and mutational evolution spectrum of primary triple-negative breast cancers. Nature, 2012; 486: 395–399.
30. Howlader N, Altekruse SF, Li CI i wsp.: US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst., 2014, 28; 106(5).
31. Gnerlich JL, Deshpande AD, Jeffe DB i wsp.: Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg, 2009; 208: 341–347.
32. Bleyer A, Barr R, Hayes-Lattin B, Thomas D i wsp.: The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer, 2008; 8: 288–298.
33. Early Breast Cancer Trialists' Collaborative Group. Peto R, Davies C, Godwin J i wsp.: Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet, 2012; 379: 432–444.
34. Gradishar WJ, Anderson BO, Balassanian, R i wsp.: Breast cancer version 2.2015: Clinical practice guidelines in oncology. JNCCN, 2015; 13(4): 448-475.
35. Gaudet MM, Gapstur SM, Sun J i wsp.: Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst., 2013; 105: 515-525.
36. Hildebrand JS, Gapstur SM, Campbell PT i wsp.: Recreational physical activity and leisure-time sitting in relation to postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev., 2013; 22: 1906-1912.
37. Pizot C, Boniol M, Mullie P, Koechlin A, Boniol M, Boyle P i wsp.: Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. Eur J Cancer, 2016; 52: 138-154.
38. Abrahamson PE, Gammon MD, Lund MJ i wsp.: Recreational physical activity and survival among young women with breast cancer. Cancer, 2006; 107: 1777–1785.
39. Chan DS, Vieira AR, Aune D i wsp.: Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol, 2014; 25: 1901–1914.
40. Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. Lancet, 2002; 360: 187-195.
41. Macacu A, Autier P, Boniol M i wsp.: Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat., 2015; 154: 213-224.
42. Gaudet MM, Gapstur SM, Sun J i wsp.: Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst., 2013; 105: 515-525.
43. Abrahamson PE, Gammon MD, Lund MJ i wsp.: Recreational physical activity and survival among young women with breast cancer. Cancer, 2006; 107: 1777–1785.
44. Malczyk E, Majkrzak Ż.: Wybrane elementy stylu życia a ryzyko rozwoju raka piersi. Problemy Higieny i Epidemiologii, 2014; 95(4): 827 -830.
45. Gou YJ, Xie DX, Yang KH i wsp.: Alcohol consumption and breast cancer survival: a meta-analysis of cohort studies. Asian Pac J Cancer Prev., 2013; 14: 4785–4790.
46. Flatt SW, Thomson CA, Gold EB i wsp.: Low to moderate alcohol intake is not associated with increased mortality after breast cancer. Cancer Epidemiol Biomarkers Prev., 2010; 19: 681–8.
47. de Gelder R, Draisma G, Heijnsdijk EA i wsp.: Population-based mammography screening below age 50: balancing radiation-induced vs prevented breast cancer deaths. Br J Cancer, 2011; 104: 1214-1220.
48. Brawley OW. Risk-based mammography screening: an effort to maximize the benefits and minimize the harms. Ann Intern Med., 2012; 156: 662-663.
49. Tkaczuk- Włach J, Sobstyl M, Jakiel G. Rak piersi – znaczenie profilaktyki pierwotnej i wtórnej. Prz Menopauz, 2012; 4: 343- 347.
50. Makowski M, Połać I, Pertyński T. Estrogeny a rak sutka. Prz Menopauz, 2007; 3: 150–154.
51. Kataoka A, Iwamoto T, Tokunaga E et al.: Young adult breast cancer patients have a poor prognosis independent of prognostic clinicopathological factors: a study from the Japanese Breast Cancer Registry. Breast Cancer Res Treat, 2016; 160: 163–172.