Statistical analysis the development of breast cancer; influencing factors

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Abstract: *The incidence of breast cancer in Romania is about 66.2/100,000 and the mortality around 22.1/100,000. The European Association for the Study of Obesity shows that the prevalence of the obesity is 10-25% for men and 10-30% for women. Data from literature sustain that the costs linked with breast cancer management are about 126 billion euro in 2009, 40% representing medical costs. Increasing of the survival and the prolongation of the time to progression is very important because it means there is a significant decrease inthe cost linked to: oncological medication, the hospitalization days, diagnosis investigation and also a prolongation of the time in wich the patient is integrated socio-economically and also in the family. An important indicator in this disease would be the years of potential life lost.. Material and methods: in this paper, we followed the evolution of 50 patients treated between January 2009 and December 2014 within "Elias" University Emergency Hospital. The above mentioned patients were monitored from diagnosis until the first imagistic documented progression. Several parameters were monitored, amongst which the body mass index, time to progression, age distribution, Ki 67 proliferation index and also the correlation between the parameters.*

Results: The body mass of the majority of the patients (22) was between 30 and 35 kg/m2, thus being considered obese. The average value of the time to progression for the monitored patients was 40,98 months, in concordance with the values found in literature. One particular aspect of the monitored patients was the high frequency of breast cancer within the group of patients under age of 50, followed by 45-50 group and the last was the 35-45 group.

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Conclusions: The excess of adipose tissue could represent a negative prognostic factor in the breast cancer progression. One important aspect is that this prognostic factor could be influenced by creating policies aimed at weight losing and healthy life-style. Breast cancer occurs predominantly with women within the 4-5 age decade, thus, the mortality and the morbidity generated by it determines the loss of many potential life years and a social-economic exclusion of the respective women.

Keywords: *breast cancer, mortality, social-economic insertion, young patients, years of potential life lost, obesity*

JEL Classification: *I1*

Introduction

This article aims at presenting a statistical analysis of a sample of patients diagnosed and treated for breast cancer at the Elias Emergency University Hospital.

The influence of obesity

According to Globocan and WHO (World Health Organization), it is estimated that a number of 522,000 deaths in the female population were determined by breast neoplasm[1]. Epidemiological data assert an increased incidence of breast cancer by almost 20% compared with the 1980s. In Romania, the incidence of breast cancer is of 66.2 / 100,000 and the mortality of 21.6/100,000.[2]

The prevalence of obesity in Romania according to WHO is of 17.7/100,000. This influence of obesity both on the risk of developing breast cancer and the prognosis of this disease is due to some molecular mechanisms with a role in the intra and intercellular signaling.

Currently there is a constant search in order to discover therapeutic means both effective and with minimal side effects and cost-effectiveness favorable. Thus the discovery of molecular mechanisms involved in the development of breast cancer in patients with obesity requires identifying practical issues related to the control

[1] WHO Breast Cancer: prevention and control http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf

[2] WHO EUCAN Breast Cancer: estimated incidence, prevalence and mortality http://eco.iarc.fr/EUCAN/CancerOne.aspx?Cancer=46&Gender=2

of adipose tissue, and the evaluation in terms of economic benefit obtained when applying such measures.

Breast cancer is a major public health problem, being the main neoplasia in women both in Europe and the United States. Since the 1990s the death rate due to breast cancer began to decline, this being due to both mammography screening and adjuvant treatment with chemotherapy and tamoxifen according to a study published in the *New England Journal of Medicine* by Berry D.A. *et a*l1. Although this type of cancer has been classically described as having a lower frequency in the non-industrialized countries, its frequency has started to increase in recent years in these areas. A study published by Metcalfe K.A. claims that industrialization in developing countries has led to rapid increase in the risk of breast cancer.

From epidemiological studies it results that the risk of breast cancer is higher in women who had their first full-term pregnancy at over 30 years of age compared with those who underwent the same event at the age of 18 years or less. Breastfeeding, especially over a prolonged period, decreases the risk of breast cancer. Hormone replacement therapy with estrogen and progestin increases the risk of breast cancer development according to the data of a large study "Women's Health Initiative" .

Obesity is characterized by hypertrophy of fat cells which causes the occurrence of hypoxic zones, hypoxia being a well-known factor in stimulating neoangiogenesis, cell motility and invasion. In neoplastic leptin breast pathology and its receptor can be activated in response to hypoxia and hyperinsulinemia.[2]

Estrogen plays a key role in the development and progression of breast cancer, which is proven by numerous studies3. For breast cancer4 patients a level of correlation has been shown between serum levels of leptin and receptors' expression for estrogen and progesterone in immunohistochemistry.

As the prevalence of obesity is growing and represents an important health issue, there is a possible increase in the incidence of breast cancer, a reason for which

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[1] Berry DA, Cronin KA, Plevritis SK *et al*. "Effect of screening and adjuvant therapy on mortality from breast cancer" *N. Engl J Med* 2005;353(17):1784

[2] Bartella V *et al*–"Insulin–dependent leptin expression in breast cancer cells" *Cancer Res* 68,4919-4927(2008)

[3] Yager J.D.&Davidson N.E. –Estrogen carcinogenesis in breast cancer.N. Engl.J.Med354, 270-282

[4] TessitoreL, et al - Adypocite expression and circulating levels of leptin increase in both gynecological and breastcancer patients, Int. J. Oncol. 24, 1529-1535 (2004)

further studies are needed in order to explore the link between these two types of pathologies. In this context it is possible to explore future therapies targeted towards leptin and the molecular mechanisms in which it is involved, and various components of the tumor microenvironment.

Diagnosis, monitoring and treatment of breast cancer are, in the context of an increasing prevalence, the subject of numerous Phase I, II, III or IV studies. In the treatment of this malignancy the concept of personalized therapy appeared for the first time in the context of using tamoxifen in patients with estrogen receptor present in immunohistochemistry and subsequently the trastuzumab in those tumors with HER2 overexpression.

Due to the increased incidence of this malignancy in socio-economically and family active patients and in the context of an increase of survival in patients with metastatic breast cancer, a very important aspect is the identification of those types of treatments that could both prolong survival with no signs of disease and ensure the life quality of these patients in order to allow maintaining the social, economic and family insertion of those patients for a longer period of time.

As according to WHO (World Health Organization) the breast cancer-related costs are approximated to around Euro 15 million per year, an important issue raised relates to the cost-effectiveness of different types of treatments and the development of reduction strategies in the incidence of this disease, the implementation of optimal screening method in order to detect this treatable cancer in its early stages and the identification of subgroups of patients for which breast cancer could be prevented or for which the evolution of this pathology may be modified by changing style life.

According to the World Health Organization, the prevalence of obesity almost doubled compared to the 1980s. Approximately 35% of adults aged over 20 are overweight and 11% are obese. The statistics show that 65% of the population is overweight. Although obesity is an important cause of morbidity caused by complications thereof, obesity and overweight can still be prevented. Obesity is a risk factor for breast cancer, but it causes also an increase in mortality in patients diagnosed with this pathology. The overweight patients who accumulate extra kilos have also a poor prognosis, thus explaining the necessary steps to prevent excess adipose tissue becoming a very important issue. Numerous epidemiological studies support the role of obesity in breast cancer occurrence as well as its association with aggressive tumor phenotypes.

A recently published British prospective study (POSH) that has followed the evolution of 2956 patients under 40 years of age diagnosed with breast cancer in

2001-2007 demonstrated the negative impact of obesity on the overall survival. Thus, although obesity is associated with a decrease in efficacy of both chemotherapy and hormonal therapy in these patients, a way to optimize the treatment of this subgroup of patients require further research.

Disability-Adjusted Life Years is the indicator used in medical statistics consisting of adding years of life lost by premature death and years lived with incapacity caused by illness.

As the breast cancer shows a rising incidence in patients in the 4-5 decade of life, this indicator has a significant value and is extremely useful in assessing the socio-economic impact of this disease.

Material and Methods

In this paper we present the evolution of 50 patients diagnosed and treated for breast cancer at the Elias Emergency University Hospital. A separate database in which more variables were included related to: age, menopausal status, immunohistochemical features of tumor aggressiveness, time to progression, body mass index used to assess excess of adipose tissue, presence or absence of diabetes.

1. Distribution by age group

The distribution by age groups is an important issue in terms of socio-economic impact of diagnosis and management of this disease**.**

Within the group analyzed, the average age for the patients included is 54 years with a confidence level varying between 51 and 57. This average age overlaps the literature stating an increased incidence of breast cancer in patients during postmenopausal stage, the breast cancer in women under 50 representing only a quarter of all the cases. These results are also consistent with ESMO guidelines that support a benefit of performing mammography in terms of decreased mortality within an age interval ranging between 50-691. Another aspect is related to numerous studies that have shown the influence of excess fat on breast neoplasm occurrence in postmenopausal patients.

A particular aspect of the group of patients analyzed is the increased frequency of breast camcer. The second group from the point of view of frequency is the group 45-50. This distribution age group has important significance in terms of

[1] Association of European Cancer League. European Union Council Recommendation on Cancer Screening.

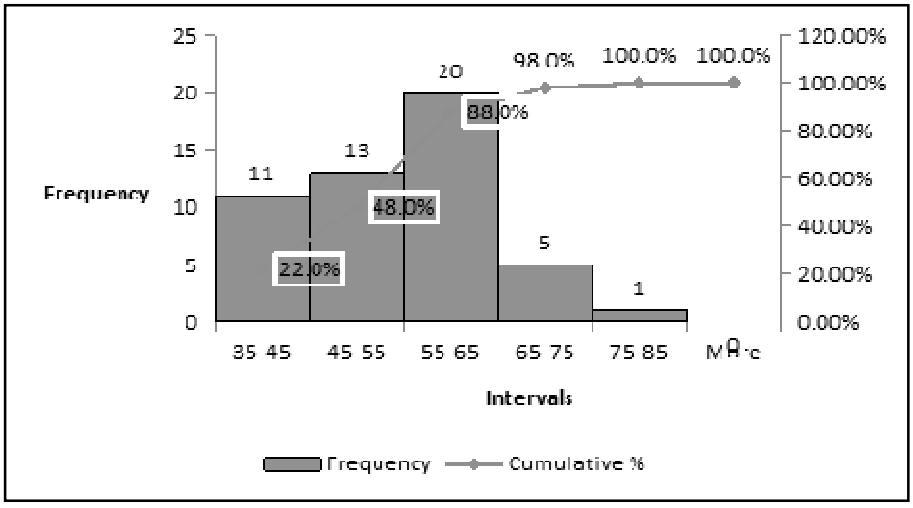
Disability-Adjusted Life Years. Thus, within this age group the number of years lost due to early mortality is as important as the number of years of life in which these patients live with some degree of disability as a result of both the metastatic disease-related symptoms and the side effects of different types of cancer therapies.

Therefore, depending on the aggressiveness of the disease and the treatment, these patients will be temporarily or permanently disrupted from the socio-economic environment.

From the statistical analysis of the age variable (Annex 1) the following values result:

- The age average at which these patients were diagnosed is 54.58, a value consistent with the data in the literature stating an increased incidence of this pathology in 5-6 decade of life
- The standard deviation in the group analyzed is 9.83
- The range length for this variable in the group analyzed is 50
- The maximum age at diagnosis for breast cancer in the group analyzed is 85
- The minimum age at diagnosis of this pathology in the group analyzed is 35. The reliable range for the age variable having the mean of 54.58 [44.65; 64.31]

Figure 1. Distribution by age group



2. Distribution by body mass index

As the prevalence of overweight in Romania is 17.7 / 100,000, the histogram below analyzes the structure of the group in terms of body mass index and therefore of excess fat. Thus the average ratio of the body mass index in the analyzed group is 27.42kg/m^2 . It is particularly important in the histogram below that the majority of patients (22) had a body mass index of 30-35 kg/m^{2,} and therefore being considered obese. In this context, the excess fat can represent both a risk factor for breast cancer occurrence and a prognostic or predictive factor in the context in which we have analyzed a group of patients who experienced a reversal of progression after initial treatment.

Between 0-18kg / m^2 we find 2% of the patients included in the study. In the following range (18-25kg/m^2) there are 10 patients which represent 20% of the total.

Starting from the value of 25 kg/m^2, there are the patients considered overweight and obese. In the overweight category of patients there are 13 while the obese patients are 26.

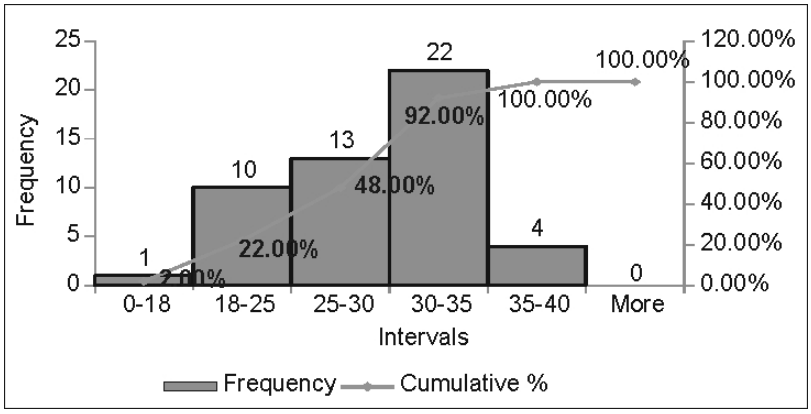
From this analysis of the group of patients it results that 78% of the patients in the group analyzed, *i.e.* 39 patients, were overweight or obese. This percentage is significant and might suggest that breast cancer occurs more frequently in patients with excess fat.

In Romania, the percentage of female population affected by obesity is 8%. In the group of patients studied, the percentage of patients with obesity is 51%. This situation is a first proof of the hypothesis that breast cancer is favored by excess fat.

From the statistical analysis of data on body mass index variable (Annex 2) the following values resulted:

- The mean of values is 28.76 kg/m^{2,} which shows the large share of overweight people (the mean is close to the value of 30 kg/m^2)
- The standard deviation within the group analysed is 4.48.
- The interval length in the patients analyzed is 17.74.
- The minimum value of the body mass index is 17.51 kg/m^{2,} *i.e.* in the overweight category.
- The maximum value of the body mass index is 35.26 kg/m^2, a value falling in the category II degree obesity.
- The confidence level for the body mass variable with a mean of 28.76 has a confidence level of: [27.40; 30.13]

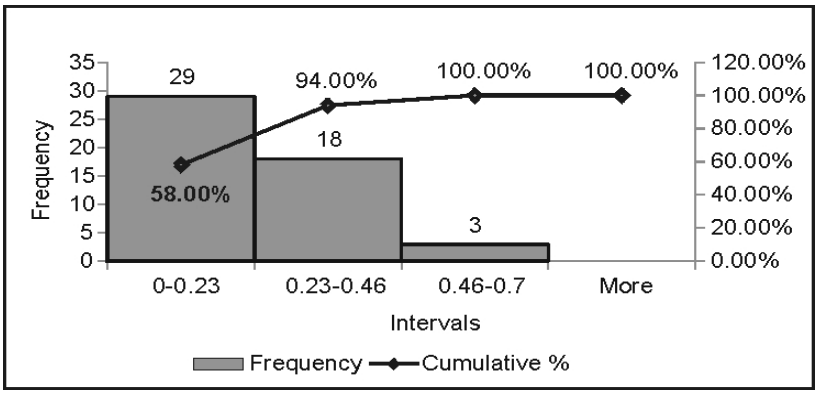
Figure 2. Distribution of patients according to body mass



3. Distribution by Ki67 proliferation index

Ki67 index has a particularly important prognostic value in breast cancer diagnosis. The literature data support the association between obesity and the presence of aggressive tumors with a high proliferation index. In the group of patients analyzed the Ki67 tumor proliferation index had an average value of 23.1% which means an intermediate value. The European guidelines included this index in the intrinsic subtypes classification of breast cancer, using the threshold value of 20%. One possible explanation for this value could be the presence of a high percentage of overweight or obese patients. This classification into intrinsic subtypes has a great importance in selecting patients receiving chemotherapy.

Figure 3. Distribution of patients according to Ki67 proliferation index



In the group of patients analyzed, a total of 28 patients, 58% respectively, have had during immunohistochemistry a ki67 index between 0-23%.

A value of the Ki67 proliferation index between 23-46 was evidenced in 18 patients that represented 36% of all patients.

An ki 67 index with a value of over 46% was identified in a total of 3 patients, 6% respectively.

Ki 67 is a protein whose expression is increased in cells undergoing division. A proliferation value of the ki 67 index <10% is considered low, 10-20% is considered borderline, while over 20% is considered high.

A study by Inwald E.C. and collaborators demonstrated that the Ki 67 proliferation index has a predictive value in terms of overall survival and survival without signs of disease1.

From the statistical analysis of data on the Ki67 proliferation index variable (Annex 3) the following values resulted:

- The mean of values is 23.1%, which, according to data from the literature, characterizes highly proliferative tumors with a high degree of aggression. This is consistent with the literature that states that excess body fat is associated with aggressive tumor phenotypes.
- The standard deviation in this group of patients is 13.54%.
- The minimum value of Ki67 proliferation index in this group of patients is 0%.
- The maximum value of the ki 67 index in the group of patients analyzed is 70%.
- The confidence level for the variable of the body mass index with a mean of 23.1% has a range of [26.95; 19.26].

4. Distribution by time to progression

It is a commonly used indicator to assess the effectiveness of treatment. It is commonly used in clinical trials with overall survival, but it is considered a more accurate indicator in assessing the response to a given treatment evaluated in a clinical trial.

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[1] Inwald E.C. *et al* **–"**Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry". *Breast Cancer Res Treat*. 2013 Jun;139(2):539-52. doi: 10.1007/s10549-013-2560-8. Epub 2013 May 16

In our case it we reviewed the time from diagnosis until first progression regardless of treatment type, the time being measured in months.

The average time value to progression for the patients analyzed is of 40.98 months. These data are consistent with the literature stating an increased risk of relapse within the first 5 years after diagnosis.

In the group of patients analyzed, a total of 33 patients, i.e. 66% of the patients, progressed in the first 24 months after diagnosis. These data are in agreement with the literature.

From the statistical analysis of data on the time variable to progression (Annex 4) the following values resulted:

- The mean of values within the group analyzed is 40.98 months;
- The standard deviation within this group is 46.50;
- The minimum amount of time to progression was 2 months;
- The maximum amount of time to progression is 168 months;
- The confidence level for the time variable to progression with mean 40.98 months is [54.19].

Figure 3. The distribution by time to progression of desease

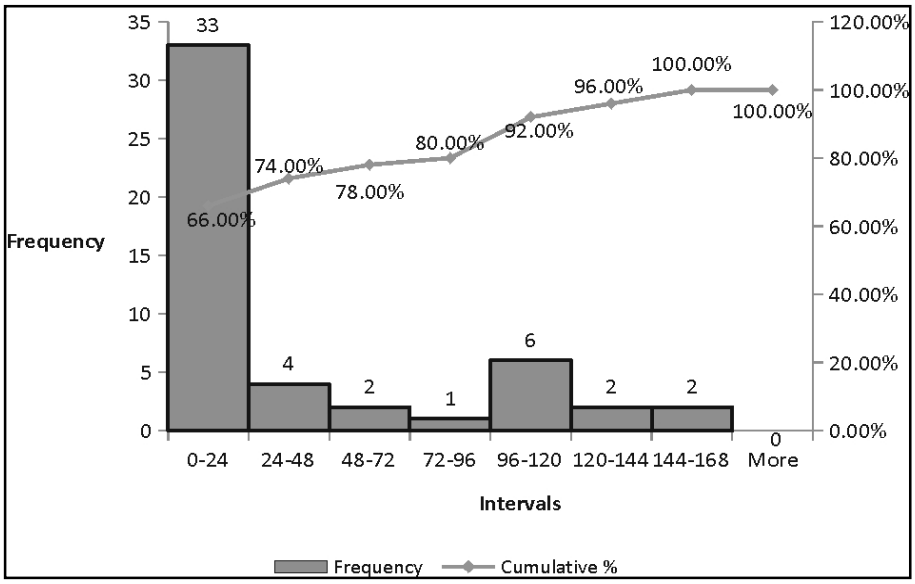

Table. 1. The centralized statistical parameters

Variables	UM	Average	Standard Deviation	Average confidence level	Minimum	Maximum
V1(Age)	years	54.58	9.83	[44.65; 64]	35	85
V2 (IMC)	Kg/m^2	28.76l	4.48	[27.40; 30.13]]	17.51	35.26
V3 (Ki67%)	%	23.1%	13.54	[26.95; 19.26]	0%	70%
V4 (Time to Progression)	months	40.98 l	46.50	[27; 54]	2	168

Source: Data from Annexes 1-4.

Conclusions

In the group of patients analyzed it is found that that the majority of patients (78%) are overweight or obese, so in these patients there is an excess of adipose tissue. In Romania, 8% of the female population suffer from obesity, this increased percentage within the analyzed group conform the increased risk induced by the excess of fat tissue for breast cancer occurrence. This excess fat, through multiple intra- and intercellular signaling pathways, has an effect both on the increased risk of developing breast cancer and the tumor aggressiveness.

The aggressiveness of these tumors is evaluated by Ki 67 proliferation index, with a percentage in the analyzed group having an average of 23.1%, and this value was above the 20% threshold value for a tumor to be regarded as a highly proliferative one and therefore highly aggressive.

In the examined group, the age at diagnosis was frequently in the group of 55-65 years (20) followed by 45-55 group. Therefore that breast cancer patients are diagnosed at an age when they are still active in the professional field and have an important economic contribution. It is very important to identify the risk factors for breast cancer occurrence, in particular the risk factors that may be influenced. Also, for the patients diagnosed with breast cancer it is of major importance to increase the overall survival and the time to progression, thus enabling these patients to remain active both in socio-economic and family fields.

In this study, the percentage of patients identified as overweight or obese is great. The average value of the Ki67 proliferation index is suggestive for high proliferative, aggressive tumors. In the context of these results, the hypothesis that the evolution of the breast cancer is influenced by the excess fat seems to be true. Further studies are necessary for personalizing the treatment for this subset of patients.

Another extremely useful approach is the implementation of strategies to reduce excess fat in overweight and obese patients diagnosed with breast cancer such as: physical activity supported by regular visits to the nutritionist in order to lose weight.

These measures could lead to an increase in the overall survival and in the time to progression of the disease, having a significant impact on the disability-adjusted life years, these patients enjoying socio-economice and familial integration a longer period of time.

ANNEXES

Annex 1. Statistical parameters of the variable AGE

V3	
Mean	54.58
Standard Error	1.391546
Median	56
Mode	57
Standard Deviation	9.839715
Sample Variance	96.82
Kurtosis	0.851061
Skewness	0.295955
Range	50
Minimum	35
Maximum	85
Sum	2729
Count	50
Confidence Level(95.0%)	2.796416
min	51.78358
max	57.37642

Source: own calculations.

Annex 2. Statistical parameters of the variable IMC

IMC	
Mean	28.76815
Standard Error	0.680644
Median	30.07561
Mode	29.29688
Standard Deviation	4.812883
Sample Variance	23.16384
Kurtosis	-0.2537
Skewness	-0.53557
Range	20.26315
Minimum	17.51463
Maximum	37.77778
Sum	1438.407
Count	50
Confidence Level(95.0%)	1.367806

Source: own calculations.

Annex 3. Statistical parameters of the variable Ki67

V4	
Mean	0.231
Standard Error	0.01916
Median	0.2
Mode	0.2
Standard Deviation	0.135485
Sample Variance	0.018356
Kurtosis	2.598429
Skewness	1.178953
Range	0.7
Minimum	0
Maximum	0.7
Sum	11.55
Count	50
Confidence Level(95.0%)	0.038504
min	0.192496
max	0.269504

Source: own calculations.

Annex 4. Statistical indicators of the variable TIME (time to progression)

V7	
Mean	40.98
Standard Error	6.576736366
Median	16
Mode	24
Standard Deviation	46.50454882
Sample Variance	2162.673061
Kurtosis	0.505045218
Skewness	1.369113349
Range	165
Minimum	3
Maximum	168
Sum	2049
Count	50
Confidence Level (95.0%)	13.21644654

Source: own calculations.

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