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TUMOUR SIZE DISTRIBUTION OF INVASIVE BREAST CANCER IN A ONE-YEAR PERIOD: CASE STUDY HERZEGOVINA

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SUMMARY

Background: *To analyse the early stage breast cancer tumour size distribution as an important prognostic factor among the female patients within our local geographic region of Herzegovina.*

Subjects and methods: *This cross-sectional retrospective study included 379 patients who were treated in 2017 at the Oncology Clinic, University Clinical Hospital Mostar. The patients were divided into two groups based on their primary tumour size: early (≤2 cm) and late (>2 cm) stage groups.*

Results: *The number of patients tested for advanced stage tumours surpassing 2 cm was statistically higher (χ^2=106,325; p<0,001). 39,32% (N=149) of the patients presented with tumours ≤2 cm (T1) and 52.24% (N=198) of the total number of the patients presented with tumours >2 cm but ≤5 cm in greatest dimension (T2). The patients' knowledge about breast cancer, availability and adherence of mammography did not show any statistically significant difference with regard to tumour size, while the number of patients with smaller tumours who indicated that they underwent regular mammography was statistically significantly higher (χ^2=13,629; p<0,003).*

Conclusions: *Our data shows that in our region, more women with a diagnosis of breast cancer presented with a larger tumor size. Although there was no statistically significant difference with regard to prior knowledge about breast cancer and availability to mammography, this may be due to a small sample size. Our region does not have a screening mammogram program and this data suggests that the implementation of such a program may improve adherence to existing mammography guidelines which might capture tumors at a smaller size and hence an earlier stage.*

Key words: *breast neoplasms - early detection of cancer – mammography*

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INTRODUCTION

Breast cancer is the most common malignancy and the most common cause of death from malignant diseases in women and as such it still a major public health problem (Bray et al. 2018). According to the International Agency for Research on Cancer (IARC), the incidence and prevalence of this disease are expected to continue to grow in the next 10 years (International Agency for Research on Cancer 2019a). In developed countries, owing to earlier diagnosis, an increasing number of women present with this disease in its earlier stages, which ultimately affects breast cancer survival rates (Bray et al. 2018, Ma & Yu 2006, Parkin et al. 2005, Torre et al. 2015). Self-examination, breast examination and mammography are the most important factors in the early detection of breast cancer, which is directly related to the survival rate of patients with this malignant disease (Harvey et al. 1997, Ma et al. 2012, Oestreicher et al. 2005, Nyström et al. 1993, Provencher et al. 2016). In developing countries, including Bosnia and Herzegovina, due to social and economic transition, breast cancer shows a marked upward trend. Furthermore there is no established centralized registry to foster understanding of the prevalence and incidence of this disease in this region. The breast cancer mortality rate stagnates in developed countries, but it is on the rise in developing countries due to late diagnosis and limited treatment options (Bray et al. 2018, International Agency for Research on Cancer 2019a, Torre et al. 2015). In Europe, breast cancer is detected in more than one-fourth of all newly-diagnosed cancers in women (28.2%) and remains the cause of death in 16.2% of the affected women (Ferlay et al. 2018). According to epidemiological data in Germany 2007/2008, of the total number of newly diagnosed breast cancer cases (excluding patients with carcinoma in situ and patients with unknown stage), 40% are detected in stage T1 and 30% in stage T2. About 4% or, respectively 5% of the newly diagnosed patients are in stages T3 and T4 (Eisemann et al. 2013). According to Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI) in the United States (US), the five-year relative survival rate for women diagnosed with breast cancer is 99% at localized SEER stage, whereas at distant SEER stage, the five-year relative survival rate drops to only 27% (The American Cancer Society medical and editorial content team 2017).

Tumour size is in correlation with the presence and number of involved axillary lymph nodes and it is also an independent prognostic factor (Carter et al. 1989, Foulkes 2012, Michaelson et al. 2003).

Given that the success of the therapy and survival rate are greatly affected by the early diagnosis of the disease, the appropriate screening is the secondary prevention measure. Screening is synonymous with secondary prevention. The most common method to detect breast cancer at its early stage is mammography screening. Mammography, as the recommended screening method, can detect breast cancer for up to two years before the tumour becomes large enough to become palpable. Mammography screening for breast cancer has been studied in a number of randomised studies, with the data suggesting a reduction in cancer mortality among women between the ages of 50 and 60 who have undergone screening mammography (Broeders et al. 2012, Coldman et al. 2014, Kolak et al. 2017, Oeffinger et al. 2015, Oestreicher et al. 2005).

According to the report on the health status of the Federation of Bosnia and Herzegovina population published by the Public Health Institute in 2018, the leading causes of death in the Federation of Bosnia and Herzegovina in 2017 were the diseases of the circulatory system (51.6%) and malignant neoplasms (22.3%) of which the later showed a slight increase (Institute for Public Health FB&H 2018). According to a report by GLOBOCAN 2018, in Bosnia and Herzegovina, 1 386 new cases of breast cancer can be expected, with an age-standardized (World) incidence rate of 45.4/100 000. Also, it is estimated that 565 women die each year, with an age-standardized (World) mortality rate of 14.6/100 000 (International Agency for Research on Cancer 2019b).

World Health Organization reported that only a population-based cancer registry can provide a realistic assessment of the movement of malignant neoplasms in a population. In Bosnia and Herzegovina country, the registration process is decentralised due to imprecise guidelines and inadequate training of health professionals. As a result, there is a shortfall in the registration of newly detected cases while the existing data are of relatively poor quality.

The aim of this study was to analyse the distribution of breast tumour size among the female patients in the catchment area of the Clinic for Oncology of the Mostar Clinical Centre and its relationship with the observed characteristics of the subjects. Additionally, the objective was to highlight the importance of early detection as an important prognostic factor. The research was based on the assumption that the share of late stage breast cancer in Herzegovina is higher than in the neighbouring countries such as Croatia, the Netherlands, Denmark and that this is due to insufficient knowledge about breast cancer, inaccessibility of health services/ mammography, as well as the non-implementation of screening programs. The results of such research can contribute to the establishment of the baseline data for the planning and evaluation of mammography screening.

SUBJECTS AND METHODS

Subjects and methods

A cross-sectional retrospective study involved 379 female patients treated in the period from 01 January to 31 December 2017 at the Oncology Clinic of the Mostar Clinical Centre which has a catchment area of about 400,000 inhabitants of the Herzegovina Region.

The study is based on the data concerning a total of 379 female patients with histopathological evidence of invasive breast cancer. According to the size of the primary tumour, the patients were divided into two groups, those with an early stage tumour (tumour ≤2 cm) and those with advanced stage tumours (tumour >2 cm), that is in four groups: T1 stage, which corresponds to an early stage tumour (tumour size ≤2 cm) on the one hand and T2, T3 and T4-late stages (tumour size >2 cm).

The research involved patients who presented for their first examination and breast cancer treatment at the Oncology Clinic during the aforementioned period. All the examinees were familiar with the objective and purpose of the research, and they were asked to sign a prior informed consent to participate. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. A short survey concerning sociodemographic data, the availability of mammography and the practice of mammography examination was used as the primary data source. Data on the stage of the disease according to the TNM classification and the histological classification of breast cancer was collected from hospital documentation.

Statistical Analysis

All the statistical data are given in percentages shown by charts and tables, and calculated in Excel 2007. χ^2-test was used to analyse nominal and ordinal variables. In the absence of the expected frequency, the module of additional exact tests was used in the category variables with multiple subgroups, and Student's t-test was used to test the statistical significance of numerical variables. Differences between the groups were accepted as statistically significant for $p<0.05$. The statistical program SPSS 17 was used for statistical analysis.

RESULTS

Sociodemographic data

The average age of the examinees was 59 years, ranging from the youngest who was 30 to the oldest who was 88 years of age. Patients from rural areas, of low education, unemployed, and with negative family history were more likely to be diagnosed with late stage breast cancer, but the difference is not statistically significant (Table 1).

Table 1. Distribution of breast tumour size in relation to the sociodemographic characteristics of the examinees

Variable	T size								χ^2	p
	T1		T2		T3		T4			
	N	%	N	%	N	%	N	%		
Residence									5.601	0.469
Urban	83	55.7	101	51.0	5	31.2	8	50.0		
Rural	47	31.5	78	39.4	8	50.0	6	37.5		
Sub-urban	19	12.8	19	9.6	3	18.8	2	12.5		
Living condition									1.734	0.934*
With family	125	83.9	165	83.3	13	81.2	14	87.5		
Living alone	21	14.1	31	15.7	3	18.8	2	12.5		
Others	3	2.0	2	1.0	0	0.0	0	0.0		
Marital status									6.262	0.671*
Married	111	74.5	130	65.7	11	68.8	12	75.0		
Single	9	6.0	23	11.6	1	6.2	1	6.2		
Widowed	28	18.8	40	20.2	4	25.0	3	18.8		
Divorced	1	0.7	5	2.5	0	0.0	0	0.0		
Education									6.911	0.846*
No qualification	10	6.7	14	7.1	2	12.5	2	12.5		
Primary school (8 yrs)	44	29.5	64	32.5	4	25.0	8	50.0		
Secondary school (12 yrs)	69	46.3	89	45.2	9	56.2	6	37.5		
Higher school (14 years)	12	8.1	13	6.6	0	0.0	0	0.0		
More than 14 yrs	14	9.4	17	8.6	1	6.2	0	0.0		
Occupation									14.058	0.094*
Employed	52	34.9	42	21.2	6	37.5	3	18.8		
Unemployed	33	22.1	44	22.2	6	37.5	4	25.0		
Retired	59	39.6	101	51.0	4	25.0	8	50.0		
Others	5	3.4	11	5.6	0	0.0	1	6.2		
Income									16.437	*0.038**
Retirement	68	45.6	114	57.6	6	37.5	9	56.2		
Salary	60	40.3	51	25.8	7	43.8	3	18.8		
Social care support	1	0.7	3	1.5	1	6.2	1	6.2		
Others	20	13.4	30	15.2	2	12.5	3	18.8		
Family history									2.449	0.481
No	105	70.5	149	75.3	12	75.0	14	87.5		
Yes	44	29.5	49	24.7	4	25.0	2	12.5		

*Fisher's exact test

Women whose principal source of income is retirement money are diagnosed with late stage cancer in a statistically higher number ($p<0.038$), while a positive family history of breast cancer and married status both have a positive effect on early breast cancer diagnosis but that wasn`t statistically significant.

During the research period, a statistically significantly higher number of patients who presented for treatment at the Oncology Clinic were treated for an advanced stage tumour greater than 2 cm ($\chi^2=106.325$; $p<0.001$) (Figure 1).

More than a third of our patients (39.32%) had a tumour ≤2 cm (T1), 52.24% of the total number of patients had a T2 tumour (tumour >2 cm but ≤5 cm in greatest dimension), and 4.22% of patients presented with stages T3 and T4 tumours ($\chi^2=274.478$; df=3; $p<0.001$) (Table 2).

Patients with T2 tumours i.e. breast tumours over 2 cm and less than or equalling 5 cm in size account for the biggest share in the investigated sample. These tumours fall within the category of larger size tumours which are associated with a poorer disease prognosis.

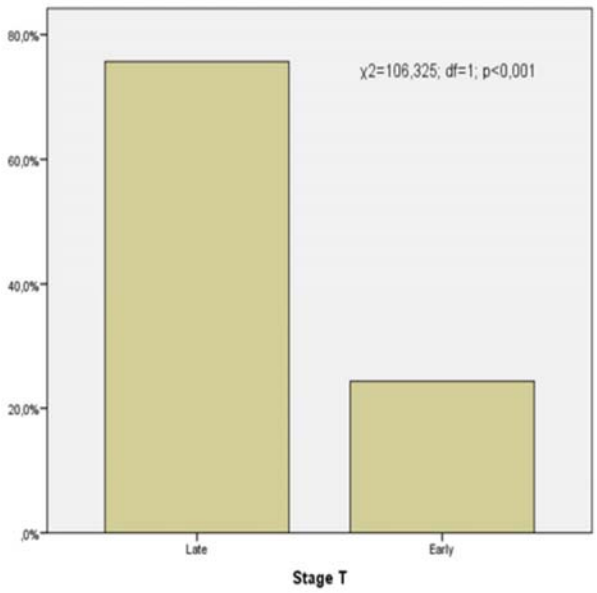

Figure 1. Analysis based on the primary breast cancer size

Table 2. Sample distribution with regard to the stages of the disease according to the TNM classification - T stage

Tumor size	N	%
T1	149	39.32
T2	198	52.24
T3	16	4.22
T4	16	4.22

χ^2=274.478; df=3; p<0.001

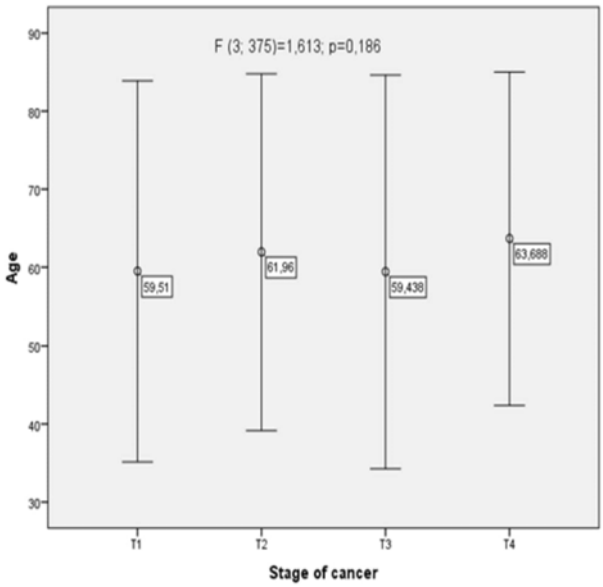

Figure 2. Tumour size with respect to age

As shown in the Table 3, a substantial number of patients (over 60%) in all of the T stage groups did not have the necessary knowledge about breast cancer; this knowledge is even poorer in patients with larger tumours, but the difference is not statistically significant. Over one half of the patients (52%) indicate that they do not have access to mammography while 42% report regular mammography exams.

The examinees' knowledge about breast cancer and the availability of mammography did not show statistically significant difference with regard to tumour size, whereas there is a statistically significant difference in the number of examinees with smaller tumours who report regular mammography exams (χ^2=13.629; p<0.003).

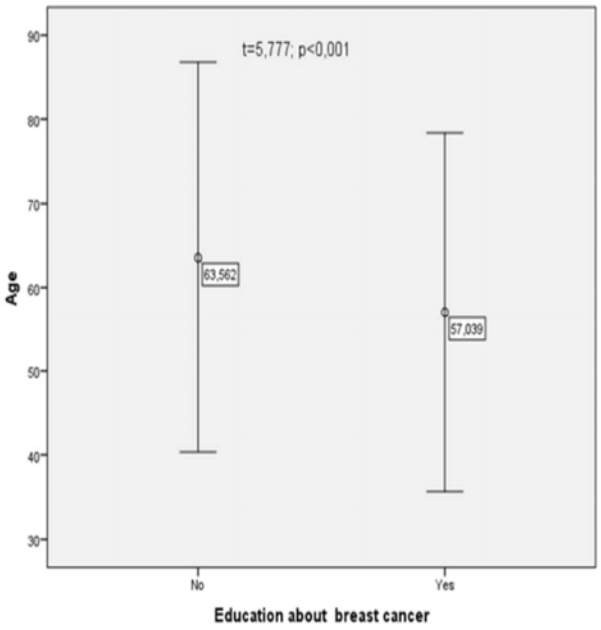

Figure 3. Knowledge about breast cancer according to age

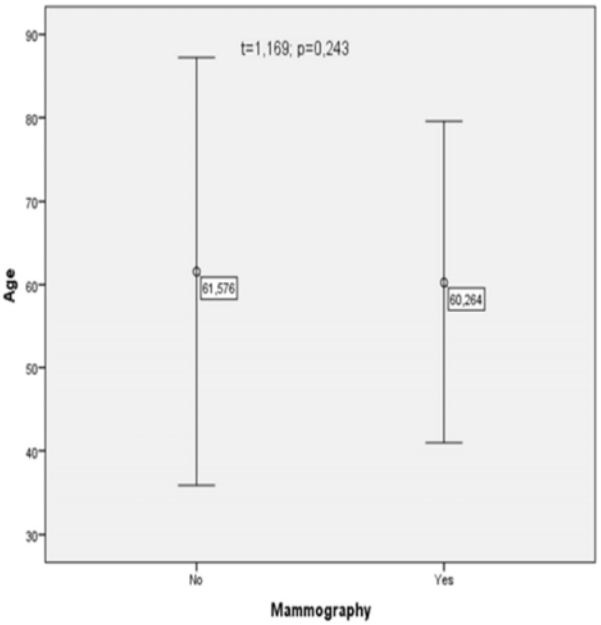

Figure 4. Mammography practice with regard to the patients' age

Table 3. Knowledge, availability and regularity of mammography with respect to tumour size

Variable	Tumour size T1		T2		T3		T4		χ^2	p
	N	%	N	%	N	%	N	%		
Knowledge									6.749	0.080
No	81	54.4	127	64.1	11	68.8	13	81.2		
Yes	68	45.6	71	35.9	5	31.2	3	18.8		
Availability of mammography									5.375	0.146
No	64	43.0	107	54.0	9	56.2	6	37.5		
Yes	85	57.0	91	46.0	7	43.8	10	62.5		
Regularity of mammography									13.629	*0.003*
No	76	51.0	124	62.6	13	81.2	14	87.5		
Yes	73	49.0	74	37.4	3	18.8	2	12.5		

Advanced tumour stages are somewhat more common in older patients, however tumour size does not show a statistically significant difference with regard to the examinees' age (Figure 2).

The older patients' group shows poorer knowledge about breast cancer in comparison with younger patients, i.e. there is a statistically significant difference (p=0.001) (Figure 3).

The patients who report regular mammography are somewhat younger but there is no statistically significant difference in mammography with regard to age (t=1.169; p=0.243) (Figure 4).

DISCUSSION

Breast cancer is the most common cancer and one of the main causes of cancer mortality in women (Bray et al. 2018). Late diagnosis is associated with poor survival (The American Cancer Society medical and editorial content team 2017), therefore the identification of factors that influence late detection of the disease can be an effective step in reducing breast cancer mortality. Reducing the mortality of women with this disease is only possible by early detection of breast cancer through screening methods, appropriate diagnostics and an adequate therapeutic approach. The earlier the disease is diagnosed, the better the chances for successful treatment (Burton & Bell 2013, Caplan 2014, Mandelblatt et al. 2013).

As mentioned before, according to SEER database of the NCI in the US, the five-year relative survival rate for women diagnosed with breast cancer is 99% at localized SEER stage, whereas at distant SEER stage, the five-year relative survival rate drops to only 27% (The American Cancer Society medical and editorial content team 2017).

The fifteen-year survival rate in patients with tumours 0.1-1 cm in size is 91.8% (node-negative), respectively 80.4% (node-positive), for tumours of 2.1-5 cm it is 78.5% (node-negative), respectively 47.1% (node positive) (Narod 2012).

In our study, 4.22 % of the patients presented for their first appointment with tumours larger than 5 cm.

Tumour size is a prognostic indicator which correlates both with the number of affected lymph nodes and the survival rate. If the lymph node findings are negative, the tumour size is used as an independent prognostic factor and an indicator for decision on adjuvant treatment (Carter et al. 1989, Elder et al. 2011, Foulkes 2012, Michaelson et al. 2003, Narod 2012)

The experience of many countries shows that screening mammography increases the number of early-stage breast cancer detections (Bleyer & Welch 2012, Miller et al. 2014, Shaevitch et al. 2017).

Many studies have demonstrated the importance of screening mammography; for example a Danish study shows that the introduction of screening for breast cancer has reduced mortality by as much as 40% (Olsen et al. 2005).

Narod (2012) has shown that cancer is detected at an earlier stage in women who are regularly screened and that as a result they may look forward to a significantly longer survival period (15 years).

A screening program for breast cancer reduces the incidence of advanced tumours. Tumours surpassing 2 cm are categorised as large since the purpose of screening mammography is to detect much smaller, non-palpable tumours which cannot be established by a clinical exam (American Joint Committee on Cancer 2002, Autier et al. 2011, Harding et al. 2015, Gøtzsche et al. 2012, Smith 2003).

Also, the Henrietta Banting database in Toronto was used to evaluate the relationship between tumour size and survival rates in women with breast cancer, and the best results were found in the treatment of tumours smaller than 2 cm which are detected on screening mammograms. This would be especially important in the environments where large tumours are rather common, as was the case in our clinic (Narod 2012).

The results of this study show that at the Oncology Clinic a statistically significant number of patients were treated at a late stage; when the tumour was greater than 2 cm (χ^2=106.325; p<0.001), which may be due to the lack of screening programs, insufficient knowledge of breast cancer, non-compliance with recommendations for breast cancer screening due to distance/inaccessibility of medical care. In that, the educational background and age of the population, a high proportion of those with a lower level of education combined with social, economic and psychological conditions, may be the reasons why women fail to respond to screening drives.

This is corroborated by the results of our research: tumours greater than 2 cm prevail among women from rural areas, with lower education, unemployed, with negative family history of breast cancer.

The results obtained show that late-stage tumours are somewhat more common in older patients; however, tumour size does not show a statistically significant difference in relation to the age of the subjects (p=0.186). Women who live on income from retirement (which is an indicator of age as well as a lower financial status) show a statistically significant difference in the frequency of late-stage cancer diagnosis (p<0.038), while the positive family history of breast cancer and marriage have a positive effect on the early diagnosis of breast cancer.

The finding of this study suggests that specific factors are of particular importance in certain patient groups. Research and better understanding of the nature of health beliefs and attitudes towards breast cancer among the general female population are crucial in reducing late detection of the disease (Lostao et al. 2001). A significant number of patients (over 60%) in all T stages do not have the necessary knowledge about breast cancer; even poorer knowledge is shown by the examinees with larger tumours, but without a statistically significant difference. The older patient group is less familiar with breast cancer, and there is a statistically significant difference in relation to the younger patients (p=0.001).

More than half of the patients (52.2%) report that mammography is not available to them, while 42% of them state that they are regularly screened. Patients who report mammography examinations are somewhat younger, but without a statistically significant difference in mammography examinations with regard to age ($t=1.169$; $p=0.243$).

The examinees' knowledge of breast cancer or the availability of mammography did not show statistically significant differences when it came to their tumour sizes, but there was a statistically significantly higher number of smaller-size tumours among those who underwent regular mammography ($\chi^2=13.629$; $p<0.003$). The fact that a large number of our patients lacked in knowledge about breast cancer and did not have regular mammography exams show how significant it is to raise awareness of the importance of screening for breast cancer and its acceptance by the female population.

In Croatia, the percentage of cancer detected at a localised (early) stage increased from 40 to over 60% over the past 15 years owing to early diagnosis (Croatian National Institute of Public Health 2018). In contrast, the results of our study show that almost 2/3 of our patients arrive late with their tumours ranging in size from 2 cm to 5 cm. Because tumour size is an important factor in diagnostics, choice of treatment and survival rates, there is an indisputable argument in favour of the development of a national program of raising awareness among women about the benefits of screening as a secondary breast cancer prevention method.

Of the 28 EU Member States, 25 have developed programs and registers, while some have just launched pilot projects or programs. In most countries, screening is conducted every two years (every three years in Malta and the United Kingdom). Bulgaria, Greece and Slovakia have just started their screening programs and Romania currently has a small pilot project (Altobelli & Lattanzi 2014, International Agency for Research on Cancer 2017).

Participation in screening programs varies across Member States. The largest was in Denmark (84%) (Mikkelsen et al. 2016). On average, the EU has not reached the target population coverage level of 70%, with a few countries falling short of the goal due to educational, organisational and other barriers. Let us mention the example of Ireland, which started the National Breast Cancer Screening Program in 2000. From 2010 to 2014, the coverage rate among the target population increased from 73.9% to 76.5% (Altobelli & Lattanzi 2014, Johnston et al. 2017), thus exceeding the program target of 70%. In addition, the key challenge is how to reach socially and economically vulnerable women.

Breast cancer is more common in Low and Middle Income Countries (LMICs) like ours, and in these countries, breast cancer is more common in younger women, with 23% of new cases of breast cancer detected among women aged between 15 and 49 compared to the 10% in developed countries. According to the WHO analysis (2003), only 2.2% of women aged between 40 and 69 in the LMIC were covered by a national screening program for breast cancer, while in our country there is no such program at all. Besides the insufficient early detection rate, there are other contributing factors to later diagnosis. They include poverty, cultural and religious beliefs, misconceptions about disease, and fear of illness. The other reasons may be low education levels of women in rural areas, no access to health care and a very low income (Gutnik et al. 2016). All of this should be taken into account in the planning and implementation of screening for breast cancer, especially given the unreliable cancer statistics, difficulties resulting from decentralised data collection - the Cancer Registry that does not give a realistic picture of the magnitude of the problem, and also the absence of a national strategy to combat cancer and a coordinated program at the national level.

There is evidence and meta-analyses of a large number of randomised studies suggesting that mammography screening of women between the ages of 50 and 69 is associated with a 25% reduction in breast cancer mortality, while benefits in women aged 40 to 49 years are less certain (Kerlikowske 1997).

We believe that measures should be put in place for the implementation of a screening program accompanied by promotional activities and health education, i.e. awareness raising, provision of guidance and advice and education of the entire population, especially persons of a lower educational status, those who live in remote areas and in precarious economic conditions.

The National Early Breast Cancer Detection Program should include family physicians as they would find it easiest to reach out to people who do not respond to calls for examination and for whom guidance and advice provided by a professional are of special significance (Chamot et al. 2004).

The results of this study may contribute to the study of factors related to late-stage breast cancer diagnosis in women in Herzegovina.

CONCLUSIONS

In view of the high percentage of late stage cancer detected in women treated at our Oncology Clinic, their insufficient knowledge about cancer and the fact that the outcome of treatment is more favourable in breast cancer detected at an early stage, and also bearing in mind the limited access to health services/mammography, and the lack of proper implementation of screening resources available, it is safe to conclude that there is a need to improve attitudes towards health and to develop and expand health culture in Bosnia and Herzegovina. This could be part of a successful program which should include a practical component in addition to theoretical knowledge. In educating the population about health, the emphasis should be put on prevention; they should be made aware of the risk factors which contribute to the onset of the disease in order to awaken

"oncological awareness". Therefore, secondary prevention, acceptance of the importance of preventive screening, and making women aware that early detection can make a difference in the outcome, all play a role. People's health, their attitude, habits and behaviour should be changed and improved. It is very important for people to bear in mind the following: preventive examination is not just an exercise in looking for a disease, but also a health check.

Women can play an active role in cancer detection by undergoing regular clinical breast examinations and mammography screenings. A breast self-exam and mammography are the most effective procedures for early detection of the disease. For each woman, breast status control should become both a routine and an obligation.

We believe that the results presented in this can be used in practice in local communities in our region where there is no screening program or a National Cancer Plan. We are among those rare countries which have neither of the two.

This is especially important for a country where health indicators are poor and intervention measures either substandard or non-existent.

Our findings are a key step in providing intial data in this region within Bosnia and Herzegovina on what stage women present with breast cancer. We also provide information on what factors relate to the later stage presentation. This can be thus used futher to help develop a screening program and can help guide investment into resources that can ensure early diagnosis and ultimately timely treatment of breast cancer.

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Contribution of individual authors:

Inga Marijanović, Marija Kraljević, Josipa Jović Zlatović, Teo Buhovac & Gordana Pavleković all made substantial contributions to the design of the study, and/or data acquisition, and/or the data analysis and its interpretation.

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