

Trend of breast cancer mortality in Montenegro, 1990-2018 – Joinpoint regression

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Abstract. – OBJECTIVE: In this study, we analyzed breast cancer mortality data overall and by age groups in women in Montenegro, to determine if there were any changes in trend for period 1990-2018.

MATERIALS AND METHODS: The study gathered data on breast cancer mortality in Montenegro obtained from Vital Registration System. Annual data on breast cancer mortality were extracted for period 1990-2018 and analyzed using World Standard Population age-standardized and age-specific rates and Joinpoint regression.

RESULTS: In 2018 in Montenegro, breast cancer accounted for 4.64% of all deaths in women and for 19.78% of all cancer deaths in women. In terms of total cancer mortality, it ranked first among women. Age-standardized rates ranged from 11.41/100,000 in 1990 to 20.46/100,000 in 2016. Joinpoint regression showed no one joinpoint for the entire population of all women and age groups. In the observed period, breast cancer mortality rates significantly increased in the women in Montenegro [average annual percentage change (AAPC) = 1.44%; 95% confidence interval (CI): 0.9-2.0]. The most affected age group was 55-64 years.

CONCLUSIONS: There is a growing breast cancer mortality trend in Montenegro. It is necessary to create specific programs for urgent action, in order to reduce this undesirable trend. At the same time, support from the competent institutions is needed for increasing screening coverage and better prevention of breast cancer in the target population.

Key Words:

Trend, Mortality, Breast cancer, Montenegro.

Introduction

Breast cancer is the leading cause of death in women in many countries worldwide^{1,2}. With near-

ly 700,000 deaths globally, it accounts for 1 in 6 cancer deaths. It ranks as the fifth in the world for cancer deaths¹, with a share of 30% in relation to all cancer in women². Its mortality rate is 17% higher in developing than in developed countries^{1,2}. Taking into account the period from 1990 to the present, there has been a global increase in breast cancer mortality in most age groups and regions³⁻⁵. Despite favorable mortality trends in some developed countries, breast cancer remains a major public health problem^{5,6}. Looking at the European region, there has been a decline in breast cancer mortality with less favorable trends in transition countries⁷⁻⁹.

Breast cancer in women is considered as a multi-etiological disease. It is difficult to understand the contribution of each individual risk factor identified so far⁶. Most risk factors could be addressed through health education, as well as public health initiatives^{5,6}. In general, the most important factors influencing cancer mortality rates are appropriate screening, diagnosis, and treatment of cancers^{10,11}. In the field of breast cancer screening, the World Health Organization recommends population-based mammograms every second year for women with an average risk between 50 and 69 years of age in good health system resources¹². The women who had mammography examinations increased their five-year relative survival rate to 90%¹³. The latest systematic review¹⁴ for Europe has shown that organized mammography breast cancer screening has led to a mortality decrease in the European region.

In Montenegro, breast cancer is the most common cancer in women and is also the leading cause of cancer deaths^{15,16}. Out of the total number of women's deaths because of breast cancer, 58,9% were under 65 years of age and 81,1%

were under 75 years of age¹⁵. 1 out of 5 women cancer deaths was caused by a breast cancer¹⁶. Montenegro recognizes cancer as a major public health problem^{15,17}. A more intensive health policy, aimed at combating breast cancer, has been implemented in recent years with the adoption of the National Breast Cancer Early Detection Program 2010¹⁸ and the National Cancer Program 2011¹⁹. The National Breast Cancer Early Detection Program¹⁸ aims to raise awareness, to identify early signs and symptoms of the disease and to ensure a high percentage of women in the screening program (minimum 70%). The Program also obligate to provide adequate diagnosis and treatment for women with positive/suspicious findings. One of the goals of the Program was to reduce the mortality of women from breast cancer by 15% in the period of 5 years after the Program's implementation. The breast cancer screening in Montenegro began on 23 December 2015, in four municipalities: Podgorica, Danilovgrad, Cetinje and Kolašin. The screening was conducted among women, insured of the Health Insurance Fund of Montenegro, aged 50-69. The screening cycle lasts two years and the screening test is a digital mammography.

In order to better monitor cancer diseases, in accordance with the National Cancer Program¹⁹, a National Cancer Registry was established on 1 January 2013. Cancer surveillance is crucial for making and implementing health care policies aimed at prevention and control of diseases. Without data collection and analysis, there is no adequate assessment whether the set goal is achieved or not^{16,20,21}.

Trend variations reporting of breast cancer helps policymakers to measure its burden, to design health services infrastructure and allocate public health resources^{4,5}. The study of the breast cancer epidemiological trend is partially measurable as highly preventable, in combination with primary and secondary preventive activities^{5,22,23}.

In this study, we analyzed breast cancer mortality data, overall and by age groups, in women in Montenegro in order to determine if there were any changes in trends for the period between 1990 and 2018.

Materials and Methods

Data Sources

The study gathered data on breast cancer mortality among women in Montenegro, obtained

from Vital Registration System, which was first under control of the Statistical Office of Montenegro until 2009, and then under the Institute for Public Health. The personal data of the respondents were protected in accordance with the Law on Personal Data Protection ("Official Gazette of Montenegro", No. 079/08 12/2008, No. 070/09 10/2009, No. 044/12 08/2012, No. 022/17 04/2017) and General Data Protection Regulation (Data Protection Act 2018, c.). The estimated number of people, which we used for calculating mortality rate, was obtained from the website of the Statistical Office of Montenegro (<https://www.monstat.org/eng/page.php?id=234&pageid=48>). We have conducted analyses on breast cancer mortality rates using World Standard Population age-standardized and age-specific rates.

Statistical Analysis

The Joinpoint regression model was used to analyze long-term trends in breast cancer mortality and detect the time points when there was a significant change in the linear time trend. In the Joinpoint regression model, the dependent variable x is the year, and the independent variable y is the logarithmically transformed mortality rate. The models also estimated annual percentage change and average annual percentage change of breast cancer rates. Statistical analysis was carried out with the Joinpoint software (Version 4.9.0.0 - March 25th, 2021, available from the Surveillance Research Program of the US National Cancer Institute <https://surveillance.cancer.gov/joinpoint/>). The selected method for analysis was Grid-search method. The minimum number of observations for the number of points from the end of the time series to the first joinpoint was set to 3. The minimum number of observations between two joinpoints was set to 4. The number of joinpoints was set between 0 and 4. The permutation test was used to choose the best fit joinpoint model, with the total significance level of 0.05. All p -values less than 0.05 were considered significant. We evaluated the models stratified by age groups (aged 35-44, 45-54, 55-64, 65-74 and 75-84). Ages under 35 years and over 85 years were not analyzed, due to small number and 0 value for several years.

Results

Breast cancer mortality data in women for almost 30-year period were analyzed and trends for overall level and for each age groups were examined.

Overall Level

In 2018, breast cancer accounted for 4.64% of all deaths in women and for 19.78% of all cancer deaths in women. In terms of total cancer mortality, it ranked first among women. The total number of deaths from breast cancer increased from 45 in 1990 to 106 in 2018, which equals to an increase of 135%. Age-standardized mortality rates ranged from 11.41/100,000 in 1990 to 20.46/100,000 in 2016 (Table I).

Joinpoint regression model showed no joinpoint for the entire population of all women and age groups. In the observed period, breast cancer mortality rates significantly increased in the women in Montenegro [average annual percentage change (AAPC) = 1.4%; 95% confidence interval (CI): 0.9-2.0] (Table I, Figure 1).

Age Groups

The age group 35-44 showed the lowest mean of age standardized rates, while the highest was recorded in age group 75-84 years. The most af-

ected age group, observed separately by years and also for the entire examined period, was the age group of 55-64 years (Figure 2).

2 of 5 age groups showed decreases in rates over time, statistically significant in age group 35-44 years [AAPC=-3.3%; 95% CI: -6.4-(-0.1)], and not significant in age group 45-54 years (AAPC = -0.7%; 95% CI: -1.6-0.3). The increasing trend was recorded in all older groups with average increases per year of about 3.6% (Table I, Figure 3).

Discussion

According to our knowledge, this is the only study of examining the breast cancer mortality trend in Montenegro. In this study, the breast cancer mortality data in women in Montenegro for over a 28-year period was analyzed. It was found that mortality rates had increased with statistical significance since 1990, showing similarities with a recent study^{3,24} for a similar period globally. The

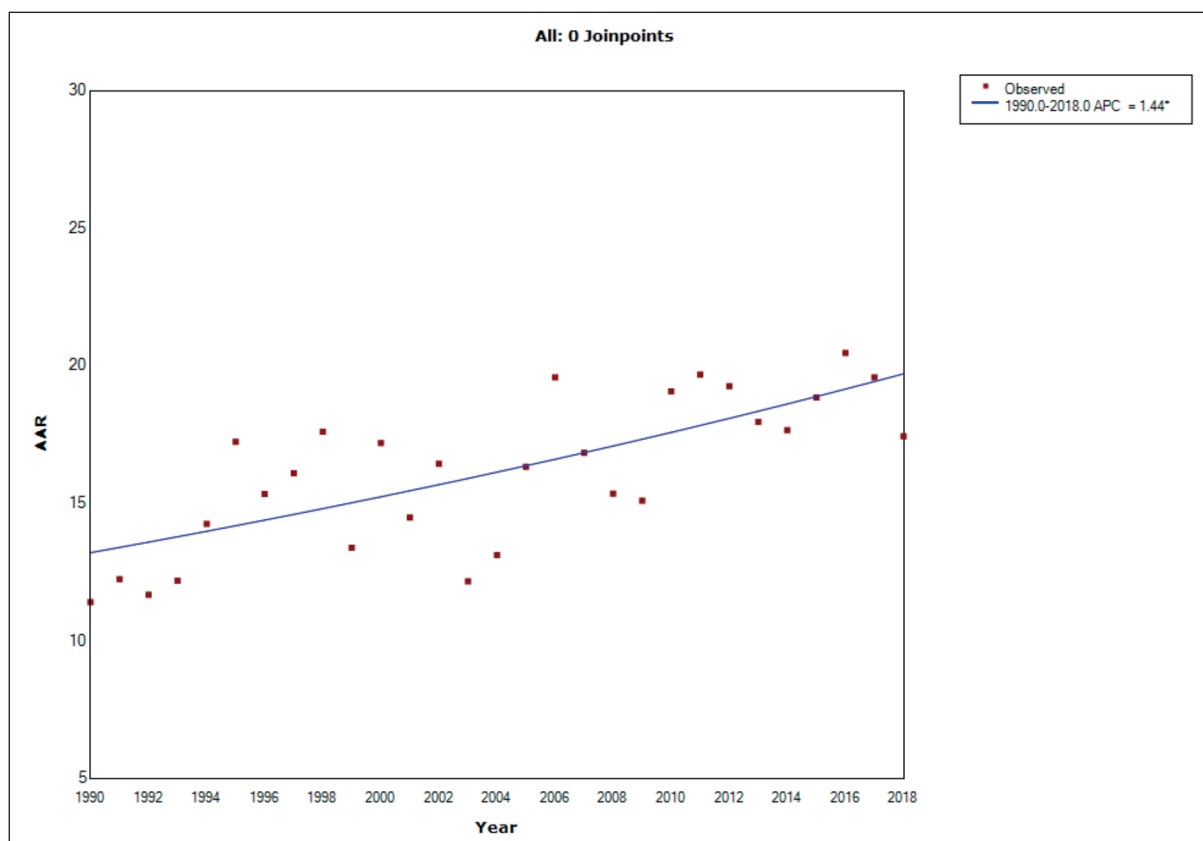


Figure 1. Joinpoint regression analysis of overall women breast cancer mortality in Montenegro from 1990 to 2018. AAR-age adjusted rate standardized to World Standard Population. APC-Annual Percentage Change, *APC was significantly different from zero $p < 0.001$.

average annual increase was 1.4%, with a higher increase in older women. That was significantly higher than the global growth of 0.23% per year in the same period (1990-2017)³.

Age-standardized rates for the observed period ranged from 11.41/100,000 to 20.46/100,000, similar to those in many low middle-income countries, which are also considered to have the highest mortality rates in the world²⁵⁻²⁸. In the last 30 years, the number of deaths from breast cancer in women has globally increased. In 2019, China, India and the USA were the countries with the highest number of deaths in the world (93.50×10^3 , 82.10×10^3 , 54.40×10^3 ; respectively)^{4,6}. With a rate of 17.3 per 100,000 population registered in the last observed year, Montenegro had a rate above the global average for the same year, which was 16.3 per 100,000. The highest mortality rates in the same year were recorded in Melanesia (ASR = 25.5), Polynesia (ASR = 21.6), Northern Africa (ASR = 18.4), Caribbean (ASR = 18.1), and Western Africa (ASR = 17.8). The lowest estimated death rates were found in Eastern Asia (ASR = 8.6), Central America (ASR = 10.1), Australia and New Zealand (ASR = 12.6), North America (ASR = 12.6), and South America (ASR = 13.4)⁵. Compared to European countries, Montenegro also had a higher rate⁷, followed by Serbia, which, despite high rates, has reported a declining trend in breast cancer mortality in recent years²⁹. In Europe, in 2017, the highest mortality rates were observed in Serbia (20.6/100,000 women), followed by other Eastern European countries and Ireland (16.6/100,000). The lowest rate was reported in Spain (10.9/100,000 women), followed by Norway (11.2), Sweden (11.3), Belarus (11.4) and the Czech Republic (12.1)⁷. The average annual percentage change of the breast cancer mortality trend in women was much higher in the Philippines (4.36% for the period 1992-2011) and Thailand (4.35% for the period 1979-2016) than in Montenegro, and lower in Colombia (0.75% for the period 1984 to 2015) and Brazil (0.44% for the period 1979-2015). There was a significant decrease in the following countries: Denmark (-3.38%, 1994-2015), Norway (-2.61, 1986-2015), Estonia (-2.58%, 1981-2015), Canada (-2.46%, 1979-2013) and the United Kingdom (-2.32%, 1979-2015)⁵. In the countries of the European region, a more favorable situation than in Montenegro is recorded in Croatia (+0.3%, 2003-2016) and in Slovenia (-1.9%, 1993-2015)³⁰. Breast cancer death rates have declined over time in most high-income countries, while it has remained

high and increasing in many middle income and low income countries²⁵.

There is a limited knowledge about the main drivers of mortality rates changes in different geographical areas and different time periods globally³¹. Recent patterns of mortality for Europe point to a decline in the last three decades. These reductions are higher in Northern than in Eastern Europe^{7,8}. Such favorable trends are the result of introducing breast cancer screening and improvements in diagnosis and treatments³²⁻³⁵. The exceptions are Poland and Romania. A possible reason for the unfavorable trend in these countries is the ineffective early breast detection program, as well as the long average time from the diagnosis to the start of the treatment, which is about 9.5 weeks for Poland^{7,36}, up to 38 weeks in extreme cases^{7,37}. In Romania, this period is on average 20.5 weeks^{7,36}, while in the United Kingdom the average waiting time for treatment does not exceed a week⁷. There are no precise data on waiting time from diagnosis to treatment in Montenegro. Due to the pandemic, about 2,000 women in Montenegro, whose screening revealed a change in breast tissue, have been waiting for clarification since January 2020.

There are several factors that could influence the mortality trend, and none of them has been singled out as particularly dominant⁷. Researches indicate the importance of adequate screening, diagnosis, and treatment as the most important factors influencing cancer mortality rates in general^{7,10,11}. It is encouraging to conclude that in countries (North America and Central Europe) that have introduced adequate screening, mortality rates have had declining trend^{138,39}. In contrast, increasing mortality in low-income and low-middle-income countries may be due to a lack of screening programs, and thus too late-stage diagnoses, as well as obstacles to cancer treatment⁴⁰. It is assumed that about two-thirds of the decline in breast cancer deaths in Western Europe and North America is due to the introduction of new treatments, and one-third is due to early detection and better diagnosis⁷.

There is no research in Montenegro that could contribute to explain the high percentage of deaths from breast cancer. In general, a large percentage can be attributed to relatively poor surveillance of cancer diseases in the country. Efforts for improving cancer control have been made in recent years^{15,17-19} and we can expect possible effects in a few years. Montenegro has introduced a screening program⁴¹ that began on 23 December 2015. It used to cover only a total of 30-40% (an excep-

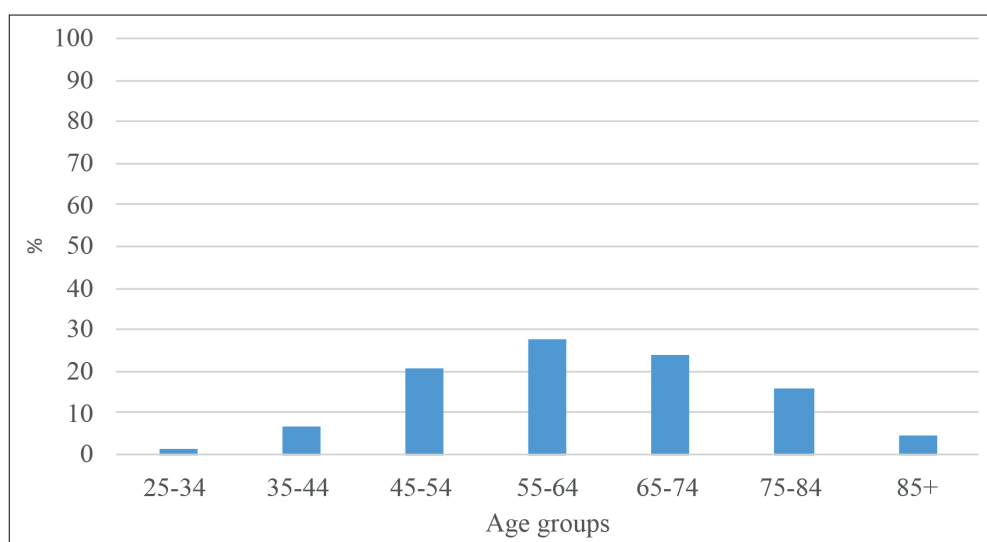


Figure 2. Distribution of breast cancer mortality by age groups in women in Montenegro, 1990-2018.

tion was made in 2020 in which the percentage was only 17.49%, due to the COVID-19 pandemic) of the target population. Early detection rate of breast cancer was 11 per 1,000 screened women, according to the screening department of the Institute of Public Health. The effect of screening program can be expected within 3-5 years from its beginning^{42,43}. Unfortunately, we have not received promising results up to now. One of the

goals of the National Breast Cancer Program in Montenegro¹⁸ was to reduce breast cancer mortality by 15% in 5 years from its implementation. It has not been achieved so far. In order to have effective Early Breast Detection Program, a country must have adequate facilities to manage all new cases detected with the screening, as well as the resources to ensure their follow-up⁴¹. The postponement of screening in 2020 in Montene-

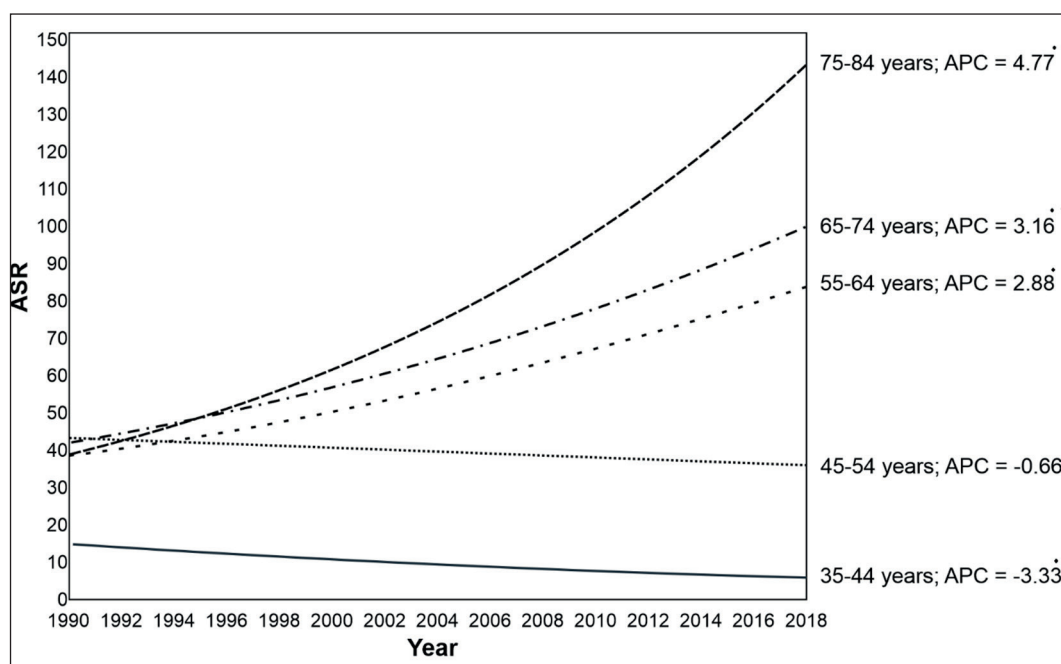


Figure 3. Joinpoint regression analysis of women breast cancer mortality by age groups in Montenegro from 1990 to 2018, ASR-Age Specific Rate. APC-Annual Percentage Change, *APC was significantly different from zero $p < 0.001$.

Table I. Mortality Rate per 100,000 population for women breast cancer in Montenegro and Average Annual Percentage Change of Rates for period 1990-2018.

Year	AAR [†]	ASR [‡]				
	All women	35-44 age group	45-54 age group	55-64 age group	65-74 age group	75-84 age group
1990	11.41	14.09	33.77	22.39	57.37	72.09
1991	12.24	14.28	38.98	38.39	34.16	40.25
1992	11.68	6.94	42.39	40.34	50.04	20.02
1993	12.19	11.33	48.47	39.82	37.07	30.41
1994	14.25	29.16	36.15	45.08	39.39	20.27
1995	17.24	22.31	38.57	47.28	71.70	50.24
1996	15.34	6.61	52.46	58.73	41.01	78.83
1997	16.09	17.46	48.23	52.96	56.08	87.39
1998	17.60	17.36	49.24	62.55	54.45	37.97
1999	13.39	4.33	39.38	48.50	60.64	72.97
2000	17.19	18.66	56.57	45.58	73.43	72.02
2001	14.48	13.93	37.55	61.59	51.18	79.66
2002	16.44	18.51	32.78	64.77	80.13	94.91
2003	12.16	13.83	32.62	28.97	61.70	79.10
2004	13.12	6.93	30.11	60.56	42.92	100.64
2005	16.32	2.34	55.36	44.07	77.03	82.26
2006	19.58	21.25	43.57	73.93	69.26	80.33
2007	16.84	21.35	34.10	71.96	48.42	114.18
2008	15.35	2.38	40.75	69.49	48.80	90.16
2009	15.09	11.98	40.82	55.33	70.93	53.69
2010	19.07	4.79	38.87	82.14	87.67	148.93
2011	19.68	2.39	53.03	76.79	93.42	124.89
2012	19.26	14.26	30.11	77.38	71.29	78.85
2013	17.96	4.72	42.06	66.07	101.02	94.38
2014	17.66	4.69	23.57	72.57	118.19	119.58
2015	18.84	11.62	35.68	86.67	82.94	127.39
2016	20.46	6.92	33.68	83.75	112.74	136.79
2017	19.58	9.18	31.49	73.69	119.98	125.54
2018	17.43	0.00	46.20	61.58	78.80	116.71
AAPC [§] (95%CI [¶] of AAPC [§])	1.4 (0.9-2.0)	-3.3 [-6.4-(-0.1)]	-0.7 (-1.6-0.3)	2.9 (1.9-3.9)	3.2 (2.1-4.3)	4.8 (3.1-6.5)
<i>p</i>	< 0.001	< 0.001	0.200	< 0.001	< 0.001	< 0.001

[†]Age adjusted rate, [‡]Age specific rate, [§]Average Annual Percentage Change, [¶]Confidence interval.

gro, due to the COVID-19 recommendations⁴⁴, has extended the waiting period for clarification of changes observed by screening, and thus for treatment. It could further increase mortality from breast cancer in the future in Montenegro, which is difficult to assess now^{7,45}.

In addition to all the above, we cannot exclude the risk factors for the development of breast cancer that have been identified so far. These factors are: alcohol consumption, obesity, younger age for menarche, older age for menopause, fewer births, less breastfeeding, lack of physical activi-

ty and unhealthy lifestyles, such as fat consumption and low intake of fruits, vegetables and grains and others⁴⁶. Alcohol use, obesity, diabetes, and lack of physical activity jointly contribute to tumor mortality of about 30%. According to estimates, Montenegro is among the countries with the highest mortality rate attributable to tobacco use, along with Serbia and Lebanon⁶. Approximately one third of breast cancers can be avoided by appropriate lifestyle modifications and mentioned risk factors⁴⁷. Considering the latest research on the prevalence of risk factors in Montenegro, the situation is not very promising: 35.4% of adults in Montenegro are active smokers, while the average alcohol consumption per year is 10.3 liters per person older than 15 years⁴⁸. Obesity and physical inactivity are also present in the Montenegrin population: 40% of the adult population in Montenegro is overweight, 15% is obese, only 13% exercises more than three times a week, of which only 8.6% daily¹⁶. However, it is difficult to estimate the contribution of these already known risk factors to breast cancer mortality in Montenegro.

Conclusions

There is a growing trend of breast cancer mortality in Montenegro. The age group 55-65 is the most affected. It is necessary to create specific programs (to ensure that women do not wait for expert examinations of suspected mammograms and to shorten the waiting time from the moment of diagnosis to appropriate treatment) for urgent action, in order to reduce this undesirable trend. At the same time, support is needed from the competent institutions to increase the coverage of screening and to prevent breast cancer in the target population.

Conflicts of Interest

The authors declare no conflicts of interest.

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