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Mortality trend of cutaneous melanoma in Montenegro from 1990-2018

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Abstract. – OBJECTIVE: Every year, melanoma claims over 20,000 lives in Europe. In Montenegro, as in Europe, numerous campaigns have been initiated to raise public awareness about the importance of melanoma prevention and its early detection. Thus, accompanying current diagnostic and therapeutic protocols, new methods of melanoma diagnosis and treatment have been implemented. Studying the trend enables the identification of the groups most burdened by mortality and assesses whether there has been a change in trends based on interventions aiming to reduce mortality. The objective of this study is to evaluate the mortality trend from cutaneous melanoma in Montenegro for the period 1990-2018.

MATERIALS AND METHODS: We have utilized national data on the causes of death from melanoma, code 179 from the ninth and C43 from the tenth revision of the International Classification of Diseases, categorized by gender and age groups. The study utilized various regression techniques, including Joinpoint regression in the Joinpoint Program, Poisson regression, and linear regression in the SPSS 26th Program, to describe the trend.

RESULTS: In Montenegro, during the period from 1990 to 2018, a total of 281 individuals died (51.6% male and 48.4% female). This ranks as the 13th leading cancer in terms of mortality among all cancers. The average age-standardized rate was 1.1 deaths per 100,000 (1.2 for males and 1.0 for females). The number of death cases has been increasing on average by 3.3% annually [average annual percentage change (AAPC) (95% CI) = 3.3 (1.7-4.9); $p<0.001$] on an overall level and by 5.4% annually among males [AAPC (95% CI) = 5.4 (3.6-7.3); $p<0.001$] due to the rises in the age groups 55-64 years and 65-74 years with an average annual percent change of respectively 3.2% [AAPC (95% CI) = 3.2 (0.8-5.8); $p=0.012$] and 5.4% [AAPC (95% CI) = 5.4 (2.7-8.1); $p<0.001$] overall level, and 4.8% [AAPC (95% CI) = 4.8 (2.4-7.3); $p<0.001$] and 7.5% [AAPC (95% CI) = 7.5 (4.9-10.2); $p<0.001$] among males. For females, an increase of 1.1% was recorded, which was not statistically significant [AAPC (95% CI) = 1.1 (-0.8-3.0); $p=0.255$]. Furthermore, there was a noted increase in the rates at an overall level [β (95% CI) = 0.027 (0.008-0.046); $p=0.007$] and in the age group 65-74 years [β (95% CI) = 0.249 (0.090-0.407); $p=0.003$], as well as among males at an overall level [β (95% CI) = 0.052 (0.025-0.079); $p<0.001$] and for age groups 45-54 years [β (95% CI) = 0.102 (0.011-0.193); $p=0.030$] and 65-74 [β (95% CI) = 0.410 (0.144-0.676); $p=0.004$]. In contrast, the rates for females remained constant. The three age groups most burdened by melanoma skin cancer mortality are 65-74 years (23.5%), 55-64 years (21.7%) and 75-84 years (19.2%).

CONCLUSIONS: The results of regression analyses indicate a significant rise in both the number of death cases and mortality rates overall, specifically among males in Montenegro. In females, however, the increase in the number of death cases and rates is not statistically significant. Preventive campaign activities should be redirected towards the most vulnerable groups in terms of mortality, namely males and the elderly population.

Key Words:
Cutaneous melanoma, Mortality trend, Developing country, Montenegro.

Introduction

Melanoma is the most malignant skin cancer, possessing the highest mortality rate[1]. According to GLOBOCAN data[2], in 2020, a total of 57,043

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death cases from melanoma were reported worldwide, constituting less than 1% of all cancers, with an age-standardized rate of 0.7 in men and 0.4 in women globally. The majority of deaths occurred in Central and Western Europe, East Asia, and South America[3]. Annually, melanoma claims over 20,000 lives in Europe[4]. It is responsible for 1.4% of all cancer-related deaths documented in Europe in 2018[5]. The data from the last decade suggest that, in Montenegro, melanomas account for about 1.4% of all cancer-related deaths[6]. There are pronounced variations in the burden of melanoma across different populations. The analyses suggest that the most substantial melanoma burden is predominantly observed in Australian, North American, and European demographics, with a particular emphasis on the elderly and male cohorts[7-10]. Prolonged exposure to ultraviolet radiation from sunbathing and indoor tanning is identified as a primary risk factor for melanoma onset[11]. Other risk factors for melanoma include having an invasive skin melanoma in one or more first-degree relatives, a history of primary invasive skin melanoma, more than a hundred benign melanocytic nevi, three or more clinically atypical (dysplastic) nevi, fair skin (type 1 or 2), red or blue hair, one or more severe sunburns with blistering, use of tanning beds (especially before the age of 30), and exposure to pesticides[12]. To combat this cancer, population-based strategies have been implemented to reduce its incidence through prevention. The prevention strategies range from primary prevention methods, such as reducing sun exposure and implementing stricter labeling protocols for sunscreens[13,14], to secondary prevention methods like full-body skin visual exams[15].

The disparities in incidence and early diagnosis across Europe are tied to notable differences in public awareness and the availability of primary and secondary prevention campaigns. Nordic and Western European countries have several decades-long traditions of public education campaigns for preventing and detecting skin cancers[15-19].

Early diagnosis of melanoma is pivotal in enhancing survival rates[20,21]. Hence, globally, self-skin examinations are promoted, along with clinics for pigmented lesions that expedite the monitoring of patients suspected of having melanoma[22-24]. Since 2013, Montenegro, as a member of the most famous European melanoma prevention and screening campaign, Euromelanoma[25], has been carrying out actions to raise awareness at the national level about skin malignancies with an emphasis on melanoma. The main goal of these campaigns is to educate the general public about melanoma risk factors and the importance of recognizing abnormal lesions by self-examination. All specialties related to dermatopathology are included in the campaign: dermatologist, plastic surgeon, pathologist, family doctor, general practitioner, oncologist, nuclear medicine specialist. Additionally, with the goal to improve data collection as a part of the Euromelanoma project, the first National Registry of Melanoma Patients is being developed. In recent years, Montenegro has also introduced novel diagnostic and treatment methods for melanoma.

This study aims to assess melanoma mortality (overall, by gender, and by age groups) in Montenegro from 1990-2018 by using regression techniques. Such analyses alert countries experiencing an increasing trend in skin malignancies to take action in mitigating the malignancy load and thereby reducing its overall burden[9]. It can also aid in evaluating the effectiveness of new diagnostic, therapeutic and preventive strategies[26]

Materials and Methods

Data Sources

The data concerning melanoma mortality in Montenegro from 1990 to 2018 were collected. Melanoma was identified using the International Classification of Diseases code 172 from the 9th edition and code C43 from the 10th edition[27]. The primary data source consists of death certificates filled out by physicians who determine the time and cause of death. Ethical approval and consent were not required as this study was based on publicly available data. The data sources until 2009 were from the State Statistical Office (unpublished data until 1999, and for the period 1999-2009 published in the statistical yearbooks of the Institute for Public Health of Montenegro[28]. For the period after 2009, the data source on causes of death is the Institute for Public Health[6]. Population data were sourced from the Statistical Office of Montenegro (available at: https://www.monstat.org/cg/page.php?id=48&pageid=48). Mortality rates were age-standardized to the World Standard Population[29] for estimating both the overall and gender-specific trends.

Statistical Analyses

The joinpoint regression model scrutinized long-term shifts in melanoma mortality and identified significant changes in the linear time trend. In this model, the dependent variable x represents

the year, while the independent variable y symbolizes the log-transformed mortality rate. These models also offered insights into the estimated annual percentage change (EAPC) and the average annual percentage change (AAPC) of melanoma mortality rates. Analyses were executed using the Joinpoint Software, version 5.0.2-May, 2023, freely available on the website of the National Cancer Institute of the United States of America[30]. The natural logarithm of the Age standardized death rate (ASDR) was fitted to a regression line, ln ASDR = $\alpha + \beta x + \varepsilon$, where x denotes the calendar year. The EAPC was computed as $100 \times [\exp(\beta)-1]$, and its 95% confidence interval (CI) was also derived from the linear regression model[9,30]. To determine the EAPC, the regression line was adjusted to the natural logarithm of rates, using the calendar year as an independent variable. The Grid-search method was chosen for the analysis. The minimum number of observations for points from the end of the series to the first joinpoint was established as 3 and between two joinpoints as 4. The number of joinpoints was set between 0 and 4. The permutation test facilitated the selection of the most fitting joinpoint model with an overall significance level of 0.05. Gender differences were assessed using the parallelism test[31]. Beyond the joinpoint regression, both linear and Poisson regressions were applied. They were executed in the Statistical Software for Social Sciences SPSS 26 (IBM Corp., Armonk, NY, USA).

Results

From 1990 to 2018, Montenegro recorded a total of 281 deaths (145 males or 51.6% and 136 females or 48.4%) from melanoma, making it the 13th most common cause of cancer-related mortality for the observed period. The average annual death count was 9.7 (5.0 males and 4.7 females), with the average age-standardized rate being 1.1 (1.2 for males and 1.0 for females). The rates were approximately 1.07 times higher among males (Table I).

Due to low values, with certain years recording rates of 0 or close to 0, the joinpoint regression could not have been executed for age-standardized rates, neither overall nor gender-specific.

The outcomes derived from the joinpoint regression analysis pertaining to death cases indicate an average annual increase of 3.3% [AAPC (95% CI) = 3.3 (1.7-4.9); $p<0.001$] at an overall level and 5.4% annually among males [AAPC (95% CI) = 5.4 (3.6-7.3); $p<0.001$]. The increase was recorded within age groups 55-64 years and 65-74, with average annual percent changes of 3.2% [AAPC (95% CI) = 3.2 (0.8-5.8); $p=0.012$] and 5.4% [AAPC (95% CI) = 5.4 (2.7-8.1); $p<0.001$] respectively for the overall population, and 4.8% [AAPC (95% CI) = 4.8 (2.4-7.3); $p<0.001$] and 7.5% [AAPC (95% CI) = 7.5 (4.9-10.2); $p<0.001$] among males. Among females, an increase of 1.1% has been recorded, which is not statistically significant [AAPC (95% CI) = 1.1 (-0.8-3.0); $p=0.255$]. For males in the age group 45-54 years, a breakpoint emerged in 2011. From 1990-2011, the mortality count increased annually by an average of 7.5% [AAPC (95% CI) = 7.5 (3.5-11.7); $p=0.001$], subsequently followed by a pronounced decline of 13.2% from 2011-2018. While this decrease was not statistically notable for the observed period, it rendered the trend for this overall age group statistically insignificant (Table I, Figures 1 and 2). The parallelism test results suggest that the mortality trend by gender is not parallel and that male mortality rates escalate 4.3 times faster [final selected model: AAPC difference (95% CI) = 4.3 (1.8-6.9); $p=0.001$].

Employing linear regression, we observed an increase in rates at an overall level [β (95% CI) = 0.027 (0.008-0.046); $p=0.007$] and in the age group 65-74 years [β (95% CI) = 0.249 (0.090-0.407); $p=0.003$], as well as among males at an overall level [β (95% CI) = 0.052 (0.025-0.079); $p<0.001$] and for age groups 45-54 years [β (95% CI) = 0.102 (0.011-0.193); $p=0.030$] and 65-74 years [β (95% CI) = 0.410 (0.144-0.676); $p=0.004$]. Conversely, the female rates remained stable (Table I).

Poisson regression allows us to discern the trend pattern in contexts where there is a limited number of cases per unit of time, as is the case with mortality due to skin melanoma. By utilizing this method, we additionally recorded an increase in mortality cases among women aged 65-74 years [β (95% CI) = 0.047 (0.004-0.090); $p=0.032$]. Similar increases were observed in the age group 35-44 years [β (95% CI) = 0.080 (0.009-0.151); $p=0.028$] and 45-54 for males [β (95% CI) = 0.066 (0.012-0.121); $p=0.018$] (Table I).

The three age groups most burdened by skin melanoma mortality are 65-74 years (23.5%), 55-64 years (21.7%), and 75-84 years (19.2%). Notably, a significant percentage of melanoma skin cancer deaths is recorded among the age group 35-44 (11.0%) and 25-34 years (4.3%) (Figure 3). The average rates for these groups are detailed subsequently (Table I).

Table I. Descriptive statistics of death cases and mortality rate and results of regression analyses of skin melanoma mortality in Montenegro for the period 1980-2018.

C43	Joinpoint regression for death cases	Linear regression for mortality rate	Poisson regression for death cases	Mortality rate mean±sd	Death cases mean±sd	Death cases overall number for 1980-2018
	AAPC (95%CI)	β (95% CI)	β (95% CI)			
Male	5.4* (3.6-7.3)	0.052* (0.025-0.079)	0.060* (0.039-0.081)	1.2±0.7	5±3.5	145
25-34						6
35-44		0.067 (-0.009-0.143)	0.080* (0.009-0.151)	1.22±1.73	0.52±0.74	15
45-54	1.9 (-3.2-7.4)	0.102* (0.011-0.193)	0.066* (0.012-0.121)	1.85±2.14	0.76±0.91	22
55-64	4.8* (2.4-7.3)	0.133 (-0.007-0.273)	0.053* (0.014-0.093)	3.99±3.22	1.34±1.23	39
65-74	7.5* (4.9-10.2)	0.410* (0.144-0.676)	0.104* (0.055-0.153)	5.55±6.71	1.17±1.51	34
75-84		(-0.209) (-0.790-0.371)	0.026 (-0.02-0.073)	10.64±12.64	0.93±0.99	27
85+						2
Female	1.1 (-0.8-3)	0.003 (-0.018-0.024)	0.013 (-0.006-0.034)	1.0±0.5	4.7±2.1	136
25-34						6
35-44		(-0.014) (-0.087-0.059)	0.000 (-0.061-0.062)	1.27±1.58	0.55±0.69	16
45-54		(-0.015) (-0.120-0.091)	0.018 (-0.037-0.074)	1.77±2.28	0.69±0.89	20
55-64		0.011 (-0.095-0.115)	0.030 (-0.021-0.082)	2.14±2.27	0.76±0.83	22
65-74		0.118 (-0.082-0.318)	0.047* (0.004-0.090)	4.21±4.43	1.10±1.17	32
75-84	0.2 (-2.2-2.6)	(-0.02) (-0.305-0.266)	0.018 (-0.026-0.064)	6.98±6.16	0.93±0.75	27
85+		(-0.115) (-0.982-0.752)	0.006 (-0.062-0.074)	13.48±18.71	0.45±0.63	13
All	3.3* (1.7-4.9)	0.027* (0.008-0.046)	0.036* (0.022-0.051)	1.1±0.5	9.7±4.7	281
25-34	1.1 (-0.8-3.1)	0.011 (-0.017-0.040)	0.017 (-0.050-0.086)	0.45±0.80	0.03±0.49	12
35-44	2.8 (-0.2-5.9)	0.027 (-0.026-0.080)	0.018 (-0.023-0.061)	1.24±1.50	0.75±0.85	31
45-54	2.5 (-0.5-5.5)	0.043 (-0.028-0.113)	0.034 (-0.002-0.071)	1.81±1.99	0.99±1.09	42
55-64	3.2* (0.8-5.8)	0.072 (-0.021-0.165)	0.039* (0.008-0.070)	3.05±2.66	1.44±1.36	61
65-74	5.4* (2.7-8.1)	0.249* (0.090-0.407)	0.071* (0.038-0.102)	4.85±5.16	1.53±1.68	66
75-84	0.5 (-1.8-2.8)	(-0.082) (-0.374-0.209)	0.019 (-0.012-0.051)	8.68±8.93	1.26±1.06	54
85+	0.3 (-1.8-2.5)	0.071 (-0.494-0.635)	0.009 (-0.051-0.070)	9.16±16.43	0.37±0.58	15

*Statistically significant change in mortality trend.

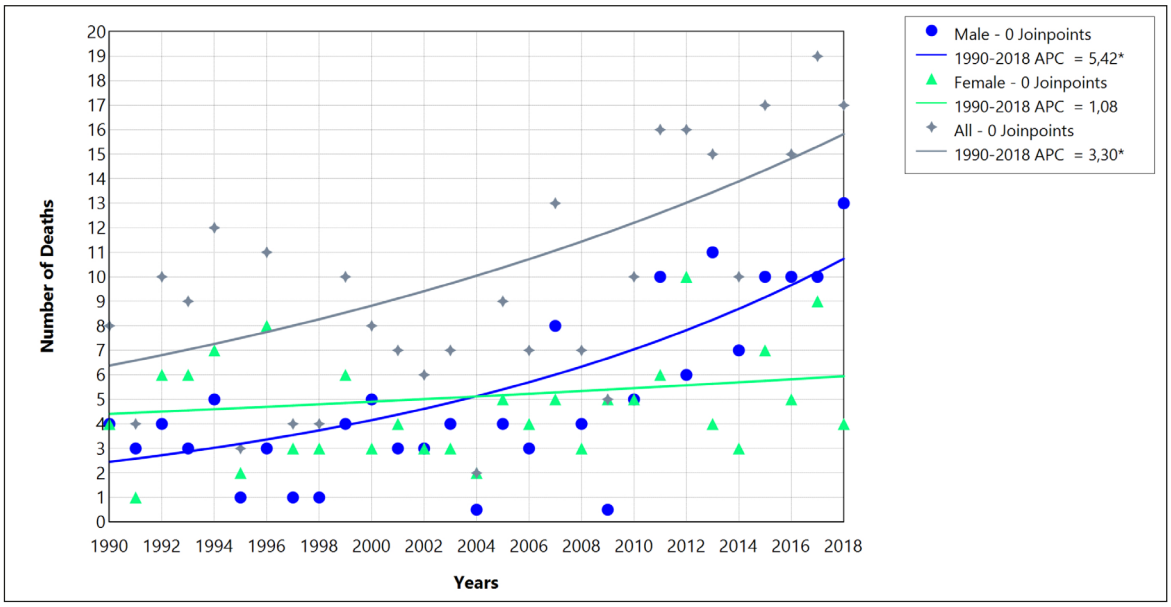

Figure 1. Joinpoint regression analysis of overall and gender skin melanoma mortality in Montenegro from 1990 to 2018. APC-Annual Percentage Change; *APC was significantly different from zero $p<0.001$.

Discussion

This study outlines the mortality trends from melanoma in Montenegro for the period from 1990 to 2018. The results of regression analyses indicate that there is a significant increase in both the number of deaths and mortality rates for the entire population and males in Montenegro as well. However, for females, neither the growth in the number of cases nor the rate proves statistically significant. On a global level, while the number of cases is increasing by 90% compared to 1990,

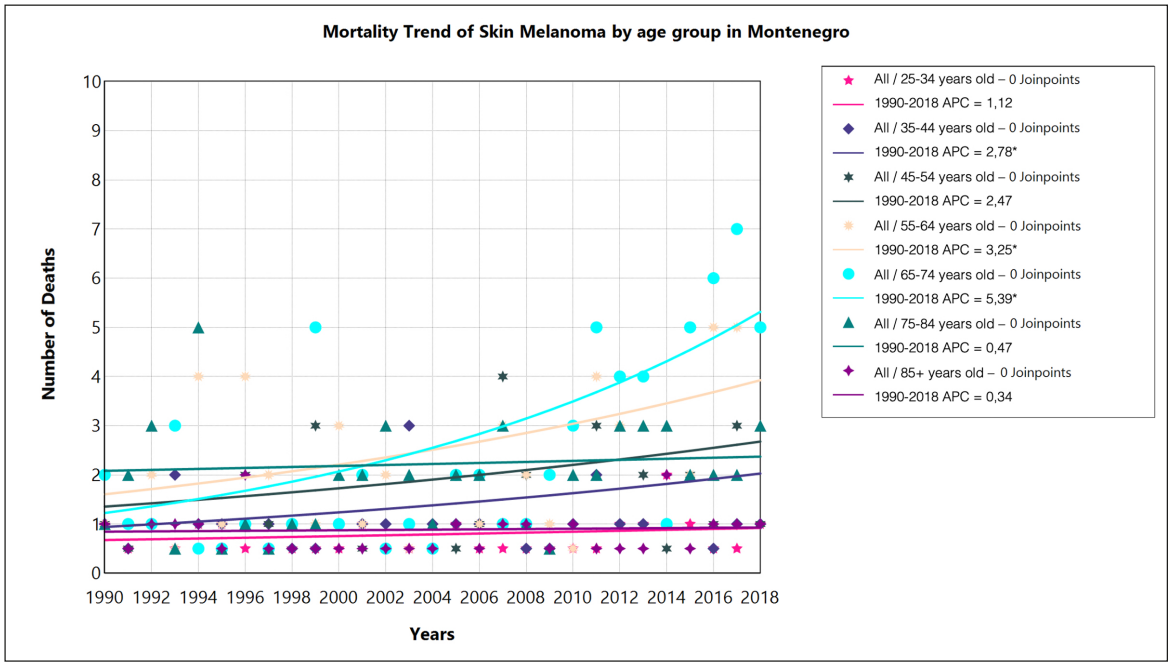

Figure 2. Joinpoint regression analysis of skin melanoma mortality by age groups in Montenegro from 1990 to 2018. APC-Annual Percentage Change, *APC was significantly different from zero $p<0.001$.

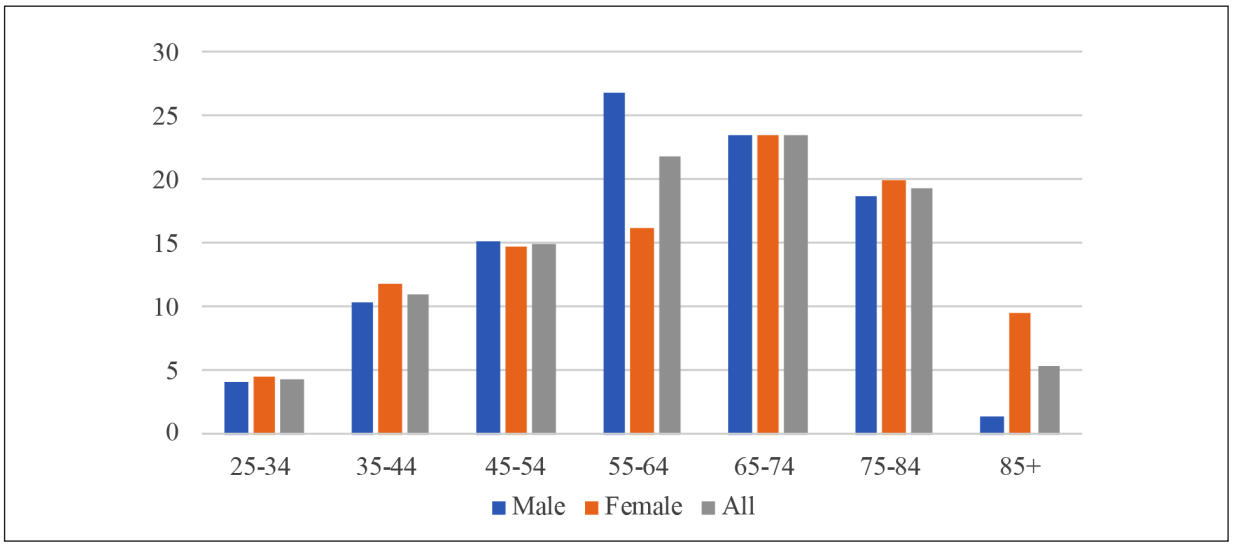

Figure 3. Distribution of skin melanoma mortality by age groups in Montenegro, 1990-2018.

age-standardized rates reveal a declining trend from 1990 to 2019 (EAPC in ASDR = -0.27). These rates are decreasing for the entire population, males and females alike[9].

In 2018, the melanoma mortality rate in Montenegro was 1.6/100,000. The average rate for the studied period was around 1.1 cases per 100,000, which is significantly lower than the highest rates recorded in countries like New Zealand (5.2/100,000) and Australia, Norway, North Macedonia, and Sweden (greater than 3/100,000). Conversely, it is considerably higher than the world's lowest rates found in Mongolia, Egypt, Sri Lanka, and India (less than 0.2/100,000)[9].

Although globally, age-standardized mortality rates exhibit a declining trend, 102 countries have shown an upward trajectory in ASDR. Guatemala witnessed the most significant increase in ASDR (EAPC = 3.9, 95% CI: 3.1-4.6), followed by Belarus and Greece[9].

In Montenegro, the rates among men in 2019 were 3.7 times higher than women, which is double the global rate, where the ratio was at 1.56 for the same year. Age-specific melanoma mortality rates in Montenegro peak in individuals aged above 75 years. This partially aligns with global findings, wherein the prominent mortality rates manifest in those aged over 70 years, particularly among males[9].

In Montenegro, the number of deaths is increasing in the 55-74 age group, with a particularly pronounced increase in both the number of cases and rates for those aged 65-74 years, encompassing the total population and males. Globally, for the observed period from 1990 to 2019, mortality rates demonstrate a declining trend for age groups younger than 80 years, especially among individuals aged 30 to 49 years. However, there is an upward trend among the population older than 80.

Over the past decade, public health systems have promoted multiple primary and secondary prevention strategies that might be responsible for the mild reduction in mortality rates, especially in younger age groups[9].

The further decrease may be associated with advancements in healthcare and medical technology, such as early detection through skin cancer examinations using superior diagnostic tools and the approval of immunotherapy and molecularly targeted treatments for advanced melanoma[32-34].

Mortality trends from melanoma vary significantly worldwide[9] and depend on geographical location, ethnicity, age, and gender[35-38].

Considering the global burden of melanoma, Europe remains one of the most affected regions[9,39,40]. Mortality rate estimates in Europe show minimal variations among countries, ranging from the lowest at 1.1 ASDR in Malta to 3.5 ASDR in Norway, with an average of 1.7 for EU + EFTA countries. Mortality rates are universally higher for males than females, spanning Europe from 0.9 to 2.8 for females and 1.3 to 4.2 for males. Nordic countries and Switzerland display the most substantial gender disparity in mortality rates, peaking in Finland (1.1 for females *via* 2.9

for males). Mortality due to melanoma claims over 20,000 lives in Europe annually. From 1985 to 2015, the countries manifesting a consistent rise in ASDR from melanoma for both genders in Europe were Estonia, Latvia, Lithuania, Norway, the UK, the Republic of Moldova, Serbia, Slovakia, Croatia, Italy, Slovenia, Belgium, Japan and the Republic of Korea.

The Czech Republic, Macedonia, and Switzerland displayed a decreasing trend in male mortality rates. Austria, Denmark, Finland, Hungary, Switzerland, and Macedonia exhibited declining trends in female mortality rates. For men, the highest AAPC in mortality rates from 2005-2015 was recorded in Ireland (+5.3%), the Republic of Korea (+4.4%) and Lithuania (+3.0%), whereas the negative AAPC was observed in Australia, the Czech Republic, Macedonia, Romania, and Switzerland. Among women, Croatia registered the highest AAPC (+1.8%), whereas the negative AAPC was noted in the Czech Republic, Macedonia, Sweden, Hungary, Switzerland, Austria, Finland, Spain, and Denmark.

The highest ASDR for both genders was documented in Norway (4.55 per 100,000 for men and 3.02 per 100,000 for women) and Slovenia (3.86 per 100,000 for men and 2.58 per 100,000 for women)[26]. Norway, Sweden and the Netherlands rank among the top five for ASDR of melanoma in Europe[9]. In Eastern and Southeastern European countries, including Montenegro, mortality rates are relatively consistent, but mortality trends vary. For the middle age group (50-69 years), mortality trend investigations display disparity among countries, with decreasing trends in countries like the Czech Republic and Slovakia but ascending trends in others, peaking for men in Serbia (AAPC 3.6%) and for women in Slovenia (AAPC 6.0%). The oldest age groups consistently show significant mortality increases in both genders, up to an 8% AAPC in Serbia[41].

Across Europe, a significant increase in survival rates has been recorded[42,43]. It has exceeded 90% for a five-year relative rate in Nordic or Western countries but remains below 60% in Eastern Europe for individuals diagnosed in this decade[44].

This can be partly attributed to novel advanced melanoma treatment modalities[45,46]. A study[47] conducted in the US demonstrates an association between the introduction of new systemic therapies and a sudden decline in melanoma mortality. Countries that approved this therapy later, such as Spain, subsequently recorded a decline in mortality[48]. Although innovative, effective therapies were introduced in European countries from 2012 to 2015, access to them is highly inconsistent across the continent[49].

In Montenegro, therapeutic options have been expanded. Both immunotherapy and combination therapy are being used. As a first-line treatment in immunotherapy, Pembrolizumab has been utilized since 2017. Depending on the *BRAF* status, combination therapy is also employed (drugs: Trametinib used from 2017, Dabrafenib used from 2017 Vemurafenib used from 2013, Cobimetinib used from 2017). The combination therapy can also be considered as a first-line treatment. If the BRAF status is negative, chemotherapy is administered following immunotherapy. Numerous primary and secondary prevention campaigns were initiated in the 1980s or at the beginning of the 21st century[50-52]. The most renowned campaign for Europe is the Euromelanoma Plan, which commenced in 1999[25]. Germany launched a national melanoma screening program (the SCREEN Project) in 2008[53], but its implementation has yet to achieve significant shifts in mortality rates[44,54,55].

In recent years, Montenegro has been conducting national-level awareness-raising initiatives. Annually, in May, as part of the Euromelanoma campaign, free skin examinations for the public are organized under various slogans (for 2023, the slogan was "Are you protected from the sun"). Additionally, the Montenegrin population has access to the Euromelanoma website at https://www.euromelanoma.eu/cnr-me/, translated into the native language, providing information on melanoma prevention, detection and treatment.

Globally, fervent research efforts are underway to advance diagnosis to earlier stages, prevent the onset, and develop groundbreaking treatments. One objective of analyzing epidemiological data and trends is to capture the early indications of the success of these initiatives through changes in melanoma incidence or mortality[44].

Conclusions

Despite the measures undertaken in recent years aimed at mitigating melanoma, no change in the mortality trend has been observed. In Montenegro, both the number of melanoma death cases and the mortality rates are significantly increasing, both at the overall level and among males. However, the increase in the number of death cases and the mortality rate is not statis-

tically significant for females. Preventive campaign efforts should be redirected towards the most vulnerable groups in terms of mortality, namely males and the older population.

Authors' Contributions

Conceptualization: M. Nedovic Vukovic, Z. Bukumiric. Data curation: M. Nedovic Vukovic, Z. Terzic. Formal analysis: M. Nedovic Vukovic, M. Golubovic, Z. Terzic. Investigation M. Nedovic Vukovic, M. Golubovic. Methodology: M. Nedovic Vukovic, Z. Bukumiric. Supervision: Z. Terzic, M. Golubovic. Visualization: M. Bojic. Writing – original draft: M. Nedovic Vukovic. Writing – review & editing: M. Nedovic Vukovic, Z. Terzic, M. Golubovic.

Conflict of Interest

The authors have no conflict of interest to declare.

Data Availability

All data generated or analyzed during this study are included in this published article.

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Ethics Approval and Informed Consent

No ethical approval or consent was necessary, as this study relied on publicly available data.

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