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Original Article

Prostate Cancer Mortality Trend in Montenegro 1990-2018

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Abstract

Background: Prostate cancer is the fifth leading cause of cancer-related death among men worldwide, with an estimated 375,304 deaths in 2020 and a mortality rate of 7.7 deaths per 100,000. It stands as the leading cause of cancer mortality in 48 countries. We aimed to analyze the prostate cancer mortality trend in Montenegro for the period 1990-2018 using regression techniques.

Methods: The data concerning prostate cancer mortality in Montenegro from 1990 to 2018 was collected. Mortality rates were age-standardized to the World Standard Population for estimating both overall and gender-specific trends. The joinpoint, linear and Poason regression were applied for trend assessment.

Results: In Montenegro, during the period from 1990 to 2018, 1,184 individuals died from prostate cancer. The average annual number of deaths was 40.8, with an average age-standardized rate of 8.3. For the period 1990-2018, rates statistically significantly increased on average by 2.4% annually [AAPC (95%CI)=2.4% (1.4-3.4); P<0.001]. An increase in mortality rates was observed among individuals aged 65-74 by 1.1%, which was not statistically significant (P=0.452), and among those aged 75-84 by 2.7%, which was statistically significant [AAPC (95%CI)=2.7% (1.3-4.1); P<0.001]. Almost 50% of all deaths occurred in men aged 75-84, and nearly a third in the age group 65-74.

Conclusion: The rising trend in prostate cancer mortality indicates the need for more effective prevention, screening, early diagnosis, and treatment measures for prostate cancer in Montenegro with special focus on older men.

Keywords: Prostate; Cancer; Joinpoint regression; Mortality; Montenegro

Introduction

Prostate cancer is the fifth leading cause of cancer-related death among men worldwide, with an estimated 375,304 deaths in 2020 and a mortality rate of 7.7 deaths per 100,000. It stands as the leading cause of cancer mortality in 48 countries (1). Global mortality rates from prostate cancer vary depending on geographic location, with a higher prevalence in developed countries (1-3).

Age and family history are the primary risk factors for prostate cancer, with smoking, alcohol consumption, excessive intake of lipids through increased consumption of animal fats, meat, and dairy products, obesity, excessive vitamin E supplementation, diabetes mellitus, dietary patterns, a multitude of variable behavioral, metabolic, and environmental risk factors also identified as contributors (4-11).

Certain countries report a decrease in mortality because of screening (12), cconcurrent with the introduction of PSA screening, widely accepted in many developed countries (13). Since the 1990s, there have been several other changes in diagnosis and treatment, including increased use of computed tomography and high-resolution ultrasound for staging, as well as more refined surgical approaches, the introduction of antiandrogen therapies, chemotherapy, and new radiation treatment methods (14-16).

It is estimated e.g., that 45-70% of the mortality reduction in the United States is due to screening (17). Other explanations for global decrease in mortality include introduction of 'anatomical radical prostatectomy' (18) and radiation therapy combined with endocrine treatment for locally advanced disease (19).

European multicentric screening trial results suggest a mortality reduction due to PSA screening, noticeable 7 years after initiation, with a relative mortality reduction from cancer of up to 9% after 14 years (12), 20% after 16 years (20), and 35% after 18 years of follow-up, while systematic analyses suggest that screening has minimal or no impact on mortality and suggest that the risks and dangers of overdiagnosis and overtreatment outweigh the purported modest benefits (21). Due to these conflicting results, population screening for prostate cancer remains controversial (22-23).

The European Urological Consortium recommends a phased approach, emphasizing the importance of pilot programs to assess the feasibility and effectiveness of screening programs for prostate cancer (24). These programs should include subjects with individual testing intervals, using PSA findings for initial screening and follow-up testing, along with risk calculators and prostate multiparametric MRI (mpMRI), prior to the decision on biopsy (25). As part of these efforts, the European Urological Commission has called for an initiative within the EU4Health program with a specific focus on prostate cancer screening. The European Urological Association (EAU) has initiated the PRAISE project (Prostate cancer awareness and initiative for screening in the European Union). The program was launched on April 1, 2023. It will last for three years (26), with goal to achieve short-term and long-term effects on prostate cancer screening in EU countries.

Montenegro has yet to implement a screening program. Efforts are underway to include Montenegro in the PRAISE project, which would offer valuable insights into the effectiveness of PSA screening and its effect on the overall survival of patients with newly diagnosed prostate cancer. In Montenegro for the last two years is the mandatory mpMRI of the prostate before deciding on a prostate biopsy has been implemented, based on the results of the PRECISION study (27), which influenced mpMRI to become a mandatory part of patient preparation for the initial prostate biopsy (28).

Trend analyses provide significant information on the patterns of the studied phenomenon and the success of preventive strategies.

We aimed to analyze the prostate cancer mortality trend in Montenegro for the period 1990-2018 using regression techniques.

Materials and Methods

The data concerning prostate cancer mortality in Montenegro from 1990 to 2018 was collected. Prostate cancer was identified using the International Classification of Diseases code 185 from the 9th edition and code C61 from the 10th edition (29). The primary data source consists of death certificates filled out by physicians who determine the time and cause of death. Until 2009, data were sourced from the State Statistical Office (with unpublished data available until 1999, and for the period 1999-2009 published in the

statistical yearbooks of the Institute for Public Health of Montenegro (30). For the period after 2009, the data source on causes of death is the Institute for Public Health (31). Population data were sourced from the Statistical Office of Montenegro (https://www.monstat.org/cg/page.php?id=48&pageid=48). Mortality rates were age-standardized to the World Standard Population (32) for estimating both the overall and gender-specific trends.

The joinpoint regression model scrutinized long-term shifts in prostate cancer 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 prostate cancer mortality rates. Analyses were performed using the Joinpoint Software, version 5.0. 2-May, 2023 from the Surveillance Research Program of the US National Cancer Institute. The natural logarithm of the ASR was fitted to a regression line, ln (ASR) = $\alpha + \beta x + \varepsilon$, 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 (33). To determine the estimated annual percentage change (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 5. The permutation test facilitated the selection of the most fitting joinpoint model with an overall significance level of 0.05 (34). Beyond the joinpoint regression, both linear and Poisson regressions were applied. They were both performed in the Statistical Software for Social Sciences SPSS 26 (IBM Corp., Armonk, NY, USA).

Ethical approval and consent were not required as this study was based on publicly available data.

Results

In Montenegro, during the period from 1990 to 2018, 1,184 individuals died from prostate cancer. This cancer is the second leading cause of death among men, following lung cancer. The average annual number of deaths was 40.8, with an average age-standardized mortality rate of 8.3 (Table 1).

Compared to 1990, the rate increased by 163.4%, representing the largest rate increase after bladder cancer. For the period 1990-2018, rates statistically significantly increased on average by 2.4% annually [AAPC (95%CI)=2.4 (1.4-3.4); $P<0.001$](Table 1, Fig. 1).

Table 1: Descriptive statistics for prostate cancer death cases and mortality rate in Montenegro and results of regression analyses for period 1990-2018

C61(yr)	Joinpoint regression for death of cases	Joinpoint regression for mortality rate	Linear regression for mortality rate	Poisson regression for death cases	Mortality rate	Number of death cases	Overall death cases
	AAPC (95%CI)		β (95%CI)	β (95%CI)	Mean±SD		
	4.6* (3.6-5.6)	2.4* (1.4-3.4)	0.213* (0.139-0.286)	0.045* (0.038-0.052)	8.3±2.4	40.8±17.1	1184
0-4							
5-14							
15-24							
25-34							1
35-44							2
45-54			-0.020 (-0.109-0.068)	0.015 (-0.033-0.064)	0.2±1.9	0.9±0.7	25
55-64	2.1* (0.1-4.2)		0.212 (-0.113-0.538)	0.027* (0.007-0.048)	14.9±7.3	4.8±2.3	138
65-74	6.3* (2.1-10.7)	1.1 (-1.7-4.0)	1.244* (0.414-2.075)	0.030* (0.018-0.043)	58.7±20.8	12.3±4.9	358
75-84	5.9* (4.3-7.4)	2.7* (1.3-4.1)	5.840* (3.408-8.273)	0.059* (0.048-0.070)	194.1±72.3	18.6±10.6	540
85+	3.4 (-1.3-8.2)		9.813* (4.876-14.75)	0.058* (0.035-0.081)	204.9±135.3	4.1±3.2	120

AAPC-Average annual percentage change; β -regression coefficient; CI -confidence interval; SD-standard deviation; * indicated that AAPC and β are statistically significantly different from zero at a *P*-value less than 0,05

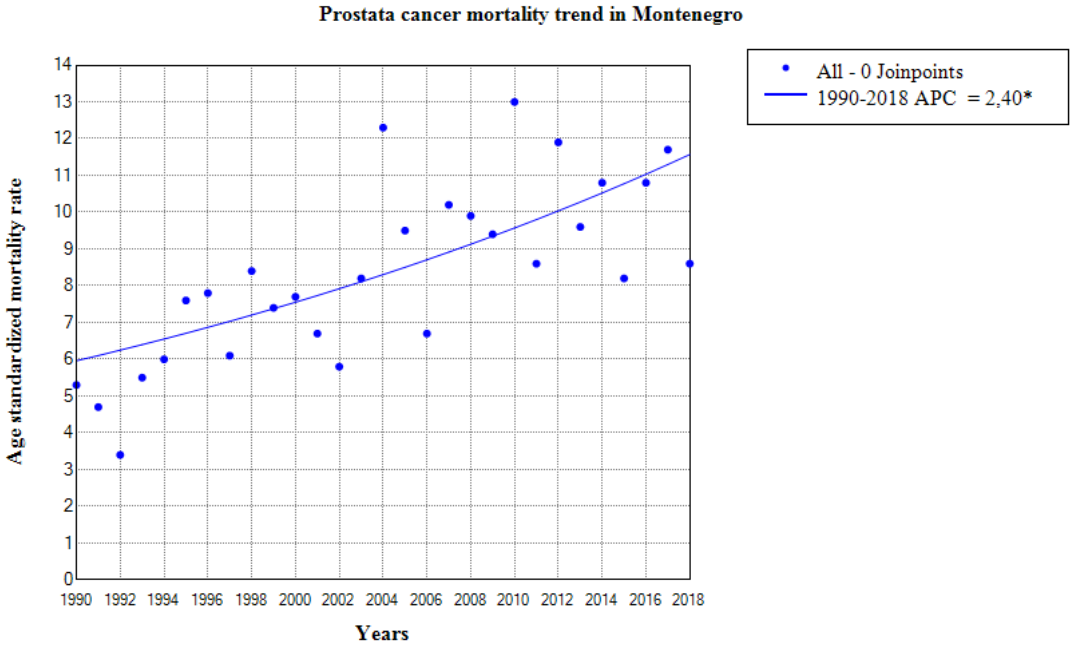

Fig. 1: Joinpoint regression analysis of prostate cancer mortality rate in Montenegro from 1990 to 2018. APC-Annual Percentage Change, *-APC was significantly different from zero for $P < 0.05$

Joinpoint regression did not reveal points in time at which there was a significant change in mortality rate trends. For the age groups that could be analyzed with joinpoint regression, an increase in mortality rates was observed among individuals aged 65-74 by 1.1%, which was not statistically significant (*P*=0.452), and among those aged 75-84 by 2.7%, which was statistically significant [AAPC (95%CI)=2.7% (1.3-4.1); *P*<0.001] (Table 1). Linear regression confirmed similar changes in trend, with an increase in all older age groups (Table 1).

Joinpoint regression indicated that the number of deaths from prostate cancer also significantly increased, averaging 4.6% annually [AAPC (95%CI)=4.6% (3.6-5.6); *P*<0.001] for the overall level (Table 1, Fig. 2).

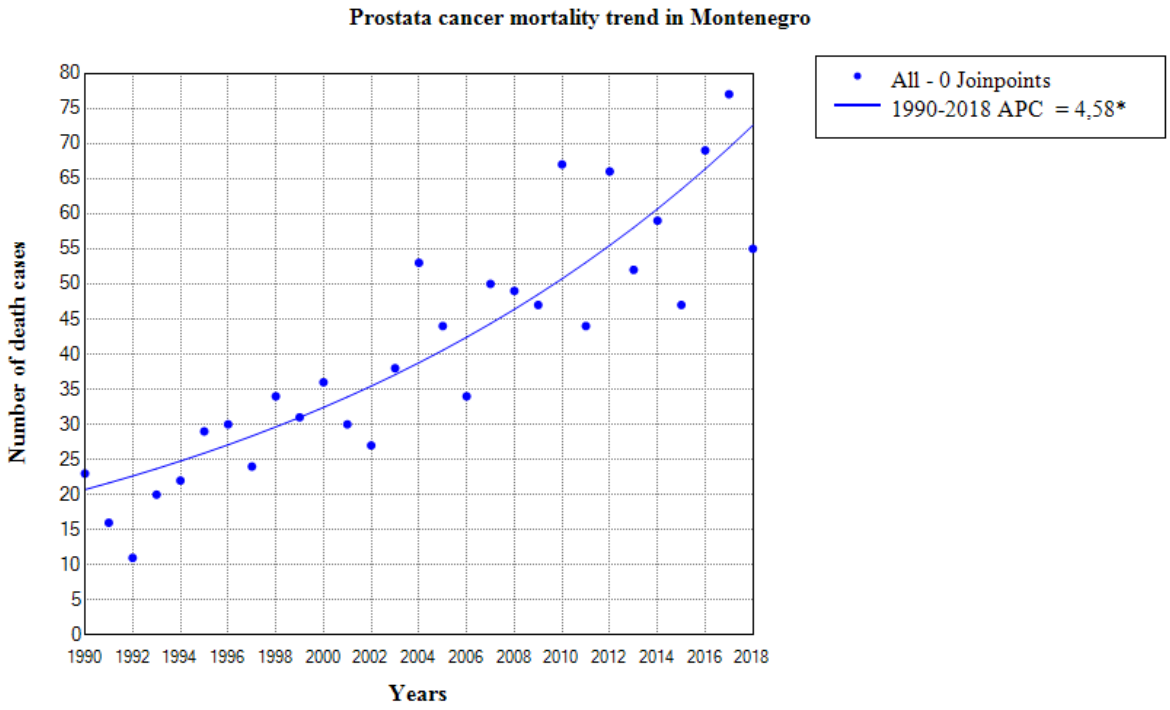

Fig. 2: Joinpoint regression analysis of prostate cancer death cases in Montenegro from 1990 to 2018. APC-Annual Percentage Change, *-APC was significantly different from zero for *P* < 0.05

2.1% [AAPC (95%CI)=2.1 (0.1-4.2); *P*=0.004] for the age group 55-64, 6.3% [AAPC (95%CI)=6.3% (2.1-10.1); *P*=0.003] for the age group 65-74, and 5.9% [AAPC (95%CI)=5.9% (4.3-7.4); *P*<0.001] for the age group 75-84. The increase in mortality for men aged 65-74 was particularly pronounced during the period 1990-1996 when joinpoint regression recorded an annual increase of 27.4%. After this period, the rate increase of 1.2% annually was not statistically significant (*P*=0.197). Also, for the age group 85+ during the period 1990-2003, there was a decrease in the number of cases by -5.2%, but without statistical significance (*P*=0.224), followed by a sharp increase in the number of deaths averaging 11.4% annually for the period 2003-2018 [AAPC (95%CI)=11.4% (6.3-16.8); *P*<0.001]. Poisson regression confirmed the same increase in the number of deaths among men, as well as for all individuals older than 55 years (Table 1). Almost 50% of all deaths occurred in men aged 75-84, and nearly a third in the age group 65-74 (Table 1, Fig. 3).

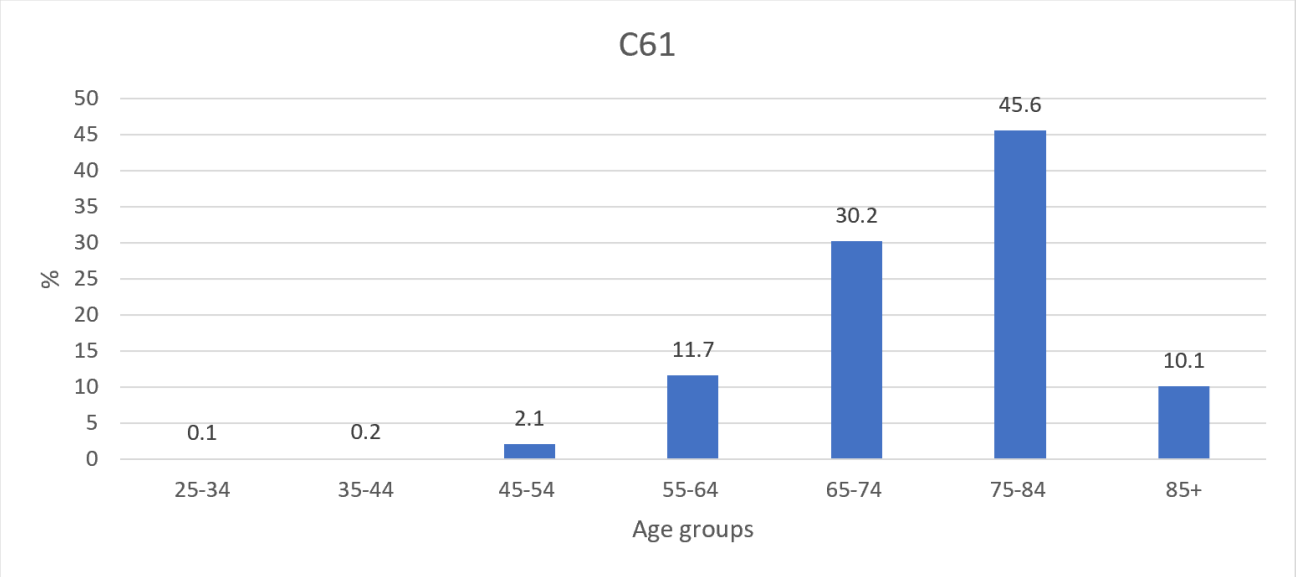

Fig. 3: Distribution of prostate cancer mortality by age groups in Montenegro, 1990-2018

There were only three deaths recorded in individuals younger than 45 years.

Discussion

This study examines prostate cancer mortality trends in Montenegro, using national mortality data from 1990 to 2018. Both mortality rates and cases have increased, with rates growing by an average of 2.4% annually, in contrast to a global decrease of -0.75% annually. Mortality trends vary globally, with 119 countries showing increasing rates, led by Georgia and Cape Verde with an average annual increase of +2.53%, while 57 countries experienced a decrease, with Canada showing the largest decline at -2.3% (3).

The Age-Standardized Mortality Rate (ASMR) for prostate cancer is rising in countries, mostly from Asia and Central and Eastern Europe (15), while a decrease is noted in countries with a very high Human Development Index (HDI), including Canada, Austria, France, Iceland, Luxembourg, New Zealand, Sweden, Switzerland, and the United States (2).

In Montenegro, prostate cancer is the second leading cause of death among men, and according to GLOBOCAN 2020 data, is the leading cause of death among men in 48 countries (1). The average age-standardized mortality rate in Montenegro for the studied period was 8.3, with a rate of 8.6 recorded in the last year of observation, which is lower than in countries in the region (35-37). For example, in Serbia for the period 1991-2010, the average annual standardized mortality rate was 9.92 per 100,000 (37). According to 2020 data, rates worldwide vary drastically, ranging from the lowest of 0.54 per 100,000 men recorded in Bhutan, to the highest of 41.7 per 100,000 men recorded in Zimbabwe (2).

From countries in the region, Croatia show a steady increase in mortality from the 1960s, with a stabilization of the trend in the recent period (35). In the period from 1960 to 2010, Croatia experienced a significant annual increase of +1.2%, followed by a statistically non-significant decrease from 2010-2014 (APC -1,2%) (36). In Serbia, prostate cancer mortality has continuously risen from 1991 to 2010, with a slightly lower average annual increase than Montenegro (AAPC 2.2%) (37).

Prostate cancer is predominantly a disease of older men (1,4,5). In Montenegro, about 85% of deaths occur in individuals older than 65 years, and in Serbia, 73% of deaths were in patients

aged 70 years and older (37). In Montenegro, mortality is increasing in all age groups over 55, with the most significant increase in the number of cases observed in the age group 65-74, and for rates, the largest increase is recorded in the age group 75-84, corresponding with findings in neighboring countries (36,37) and globally (16,38).

Global studies suggest that significant heterogeneity in mortality within regions and nations indicates differences in screening policies, access to healthcare, genetic susceptibility, socioeconomic factors, and lifestyle (3).

PSA screening's impact on reducing prostate cancer mortality has been extensively studied. Initially introduced in Canada in 1986 for diagnosis and monitoring, PSA later became a widely recommended screening method globally (13,16). Wherever PSA screening has been applied, it led to an artificial increase in incidence and in most countries with frequent use of PSA testing, a decrease in prostate cancer mortality was also observed shortly after the incidence increased (16). For example, the introduction of PSA screening in Croatia was followed by an increase in the incidence of prostate cancer by 8.5% in the decade after screening introduction (1998-2007) (39).

Contradictory results regarding the benefits of screening (12,20,40,41) and concerns about overdiagnosis and overtreatment of the disease (16,21), which outweigh the benefits in terms of mortality (21), led to frequent changes in recommendations for its application (42-47). For example, in the United States, the US Preventive Services Task Force recommended in 2008 not to conduct PSA screening for men aged 75 years and older (42), and then expanded this recommendation in 2012 for all age groups (43). New recommendation in 2017 suggested individual decision-making about prostate cancer screening after discussion with a clinician for men between 55-69 years (45). Then, in 2018, the same task force recommended that men aged 55 to 69 discuss the potential benefits and harms of screening with their clinician (48).

The most recent recommendations suggest an MRI-first strategy based on age and risk that would not only result in fewer prostate cancer deaths, biopsies, and overdiagnoses but would also be cost-effective (49). Clinical guidelines from public health organizations in developed countries and regions, e.g. American Urological Association, Canadian Task Force on Preventive Health Care, Japanese Urological Association, and European Urological Association, have provided more specific recommendations for prostate cancer screening. These guidelines advise that average-risk men above a certain age with a long-life expectancy should make an informed decision about undergoing PSA testing (13). Recent studies found that men who participated in any PSA screening over the past 19 years experienced a 40% decrease in prostate cancer mortality compared to unscreened men (50).

The reason for the increase in mortality in Montenegro is not clear. Given that there is still no official prostate cancer screening in Europe (PRAISE study ongoing), in Montenegro, we are guided by EAU recommendations aimed at early detection of clinically significant prostate cancer in patients at increased risk (28). This includes a urologist's examination for individuals older than 50 years (or 45 if there is a positive family history) with a PSA finding and PSA ratio and digital rectal examination. If PSA is elevated, the finding is repeated after 4-6 weeks, and then, if necessary, prostate mpMRI is indicated, followed by targeted and systematic biopsy. Currently, Montenegro lacks a dedicated strategy for enhancing men's health, except for initiatives by NGOs like the Men's Health organization. Plans for establishing a Prostate Center are underway, but the project is still in its early developmental stage.

The increase in mortality from prostate cancer in countries of Asia, and Central and Eastern Europe, is partially explained by increased intake of energy, animal fats, and red meat (11).

Scientists suggest that recommendations against screening might be a reason for the increase in mortality in Canada and the United States in recent years (2,51). A significant role in reducing mortality is also attributed to changes in diagnostic and treatment methods (16,19). In Montenegro, prostate mpMRI has been introduced as a

mandatory diagnostic method before deciding on a possible prostate biopsy. As for the therapeutic approach, active surveillance has been introduced for patients with low-grade tumors, who are actively monitored according to EAU recommendations and mandatory prostate mpMRI.

Research on trends according to geographic regions suggests that the highest mortality in less developed regions is associated with limited access to diagnosis and treatment, as well as with lower quality of health services and information (52). Smoking is identified as one of the most important factors for the development of this cancer, and the habit of smoking at the time of diagnosis and treatment of the disease showed a negative impact on patient prognosis in a meta-analysis, which is associated with a lower survival rate (53, 54). Further research is needed to analyze the absolute effect of risk factors, PSA screening, and treatment (2). It is suggested that surveillance over this cancer should focus on the most vulnerable categories (38).

Such analyses should be a reference for policy makers and other decision-makers for the development of effective prevention and treatment strategies (3).

Conclusion

Older men should be the focus of preventive activities for prostate cancer. Further research is needed to determine the impact of recognized risk factors on the mortality of this cancer in Montenegro. The lack of data on PSA testing in Montenegro prevents us from commenting on its impact on mortality. Prostate cancer is the second cause of cancer death among men, and rising trend in prostate cancer mortality indicates the need for more effective prevention, screening, early diagnosis, and treatment measures in Montenegro. Our study suggests that more attention should be paid to this malignancy in the future, with strategies created to monitor the effect of carried-out preventive activities on mortality, especially pronounced among older men.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interests.

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