HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2026; 13(2):1839-1862

UDC: 616-006.04-036(497.11)"2005-2024"

doi:10.5937/hpimj2602839B

Original Study

Trends in Malignant Diseases in Central Serbia and Factors Influencing Them

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SUMMARY

Introduction: In Serbia and other countries of Central and Eastern Europe, malignant disease incidence and mortality rates have risen continuously over recent decades. Despite progress in understanding cancer epidemiology, comprehensive analyses covering all tumor localizations across both sexes using modern statistical methods remain lacking for the full 2005–2024 period. Furthermore, the impact of socioeconomic factors, healthcare availability, and events such as the COVID-19 pandemic on cancer trends has not been sufficiently investigated.

Aim: To determine the time trends of incidence and mortality rates of malignant diseases in central Serbia over the period 2005–2024, identify trend breakpoints and characteristic changes, and analyze risk factors and prevention strategies for each cancer localization.

Material and Method: Incidence and mortality data for malignant diseases (both sexes, 2005–2024) were obtained from the official reports of the Institute for Public Health „Dr. Milan Jovanović Batut" Belgrade. Age-standardized rates per 100,000 inhabitants were calculated separately for women and men for each cancer type, including stomach (C16), colorectal (C18-C20), liver (C22), pancreas (C25), lung and bronchus (C34), bladder (C67), brain (C71), leukemias (C91-C95), all sites (C00-C97), and all sites except skin (C44), as well as sex-specific cancers (breast, cervix uteri, corpus uteri, ovary for women; mouth/pharynx, larynx, prostate, kidney for men). Trend analysis was performed using Joinpoint Regression Program version 5.4.0, calculating Annual Percent Change (APC), Average Annual Percent Change (AAPC), 95% confidence intervals, and p-values via t-test. The permutation test was used to determine the optimal number of breakpoints (0–3), with significance set at $p < 0.05$.

Results: Overall cancer incidence increased significantly for both sexes: AAPC = 3.20% (95% CI 0.38–6.10; p = 0.028) for women and AAPC = 6.79% (95% CI 2.37–11.41; p = 0.004) for men. Mortality also rose significantly: AAPC = 3.93% (95% CI 2.87–5.00; $p < 0.001$) for women and AAPC = 5.34% (95% CI 1.01–9.84; p = 0.017) for men. In common cancers for both sexes, two trend breakpoints were identified around 2017 and 2020, with a sharp increase in incidence (APC for men = 19.05% in 2017–2020) and mortality (APC for women = 14.15% in 2017–2020), followed by a post-2020 decline.

Among women, statistically significant increases in incidence were observed for liver (AAPC = 4.94%), pancreas (AAPC = 5.46%), bladder (AAPC = 6.55%), leukemias (AAPC = 5.75%), brain (AAPC = 2.03%), and ovary (AAPC = 0.81%) cancers. Significant declines were

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recorded for cervical (AAPC = −2.73%), stomach (AAPC = −2.72%), and corpus uteri (AAPC = −1.75%) cancers.
Among men, significant incidence increases were found for kidney (AAPC = 5.21%), pancreas (AAPC = 8.08%), colon and rectum (AAPC = 2.40%), prostate (AAPC = 2.65%), mouth and pharynx (AAPC = 3.25%), and all sites (AAPC = 1.84%-2.27%). Mortality trends in men showed significant declines for stomach (AAPC = −3.07%), larynx (AAPC = −2.47%), lung (AAPC = −0.87%), liver (AAPC = −0.94%), and all sites combined (AAPC = −0.86% to −1.23%).
Conclusion: Cancer incidence and mortality in central Serbia rose significantly from 2005 to 2024, with men showing approximately twice the rate of increase compared to women. A sharp spike in trends during 2017–2020 likely reflects a combination of improved diagnostics, changes in healthcare organization, and indirect effects of the COVID-19 pandemic including delayed diagnoses and misattribution of mortality causes. Pancreatic, liver, bladder, and kidney cancers, and leukemias represent the most dynamically increasing malignancies. Conversely, the declining trends in stomach and cervical cancers reflect clear benefits from *H. pylori* eradication, improved hygiene, screening programs. Regarding HPV vaccination, its long-term efficacy and potential delayed adverse effects require multiyear monitoring; thus it should be applied exclusively on a voluntary basis by adults with signed informed consent.
Prevention of the rising cancers requires targeted public health interventions addressing tobacco use, obesity, diabetes, alcohol consumption, and environmental exposures.

Keywords: Cancer Incidence Rate, Cancer Mortality Rate, Serbia, Risk Factors, Epidemiology, Joinpoint Regression

INTRODUCTION

Malignant diseases represent one of the most critical public health challenges of the modern world. According to the World Health Organization, cancer includes a group of diseases characterized by uncontrolled cell division which can invade surrounding tissues and metastasize to distant organs [1]. Epidemiological data indicate that malignant diseases are the second leading cause of death globally, surpassed only by cardiovascular diseases. It is estimated that around 19 million people fall ill globally every year, and almost 10 million dies from malignant diseases. In Serbia, as well as in many countries of Central and Eastern Europe, malignancies place a heavy burden on the health system, with incidence and mortality rates increasing continuously over recent decades.

Previous studies of trends in malignant diseases in Serbia have provided valuable insights into the epidemiological characteristics of these diseases. Analyzes conducted on the data of the Institute for Public Health „Dr. Milan Jovanović Batut" showed that the incidence and mortality from malignant tumors recorded a statistically significant increase in the period from 2005 to 2024, with the rate of increase in men being twice as high as in women [2].

Previous studies have documented specific trends in certain tumor localizations - such as a decrease in the incidence of stomach and cervical cancer, as well as an increase in the incidence of liver, pancreas and bladder cancer. In addition, research has indicated that the COVID-19 pandemic during 2017–2020. did not directly cause it, but it probably indirectly contributed to emphasizing the trends due to the delay in diagnosis and treatment. Key risk factors such as smoking, obesity, diabetes and alcohol consumption were also identified, which are largely responsible for the high prevalence of malignancy in the Serbian population [3,4].

Despite progress in understanding the epidemiology of malignant diseases in Serbia, there are still significant gaps in knowledge. First of all, there is a lack of comprehensive analyzes covering the entire period from 2005 to 2024 for all tumor localizations in both sexes together with the application of modern statistical methods for detecting breaking points in trends. The impact of socioeconomic factors, availability of health care and regional differences within central Serbia on malignancy trends has been insufficiently investigated.

Also, the mechanisms by which periods such as the COVID-19 pandemic [5,6] affected incidence and mortality trends have not been fully elucidated, nor is it clear whether any delays in screening and diagnostics had lasting consequences on the epidemiological picture.

AIM

The aim of this study was to determine the chronological trends of incidence and mortality rates from malignant diseases in central Serbia over the 2005-2024 period, identify trend breakingpoints and characteristic shifts, and analyze risk factors and prevention possibilities for each analyzed cancer localizations.

MATERIAL AND METHODS

This paper presents results from an academic, IV phase, retrospective, epidemiological investigation. The analysis of the trends of malignant tumors in Serbia (excluding the Autonomous Province of Kosovo and Metohija) covers the period 2005 - 2024 and was done in the Joinpoint Regression Program version 5.4.0. Incidence and mortality rates, as well as the database for malignant diseases of both sexes, were taken from the official reports from the website of the Institute for Public Health „Dr Milan Jovanović" Batut Belgrade [2,7].

Individual analysis for each disease was performed using MIcrosoft Excel. For a given year incidence rate was calculated by adding up the number of newly diagnosed women for each type of cancer recorded in that year, and then dividing that sum by the number of female residents in Serbia for that year, and multiplying the result by one hundred thousand. Mortality rates were calculated using the same formula, substituting new cases with recorded deaths. The procedure is the same for men. In this way, we obtained annual incidence and mortality rates of both sexes per 100,000 inhabitants. The processed data were then analyzed in Joinpoint Regression software.

In the Joinpoint Regression software, using a parametric method based on the t-distribution, it is possible to calculate the estimate of the statistical annual percentage change (Annual Percent Change - APC), calculate the confidence interval (95% CI), and calculate the average annual percentage change (Average Annual Percent Change - AAPC), detecting statistically significant changes in the trend over time. The statistical significance of the obtained trends was confirmed by t-test with the significance level set at $p < 0.05$.

The permutation test was employed to identify the optimal number of breakpoints, restricted to a minimum of 0 and a maximum of 3., where the significance level is set at $p < 0.05$. APC and AAPC values were calculated separately for women and men. The independent variable was calendar year and the dependent variable was the corresponding rate.

A secondary analysis was conducted to evaluate mortality and incidence trends for all cancer types combined, as well as individually by sex. For one disease, we collected data on new cases and deaths for both sexes for each year, calculated incidence and mortality rates from the same source. Where no data were available, the disease was excluded from the analysis.

The analyzed malignancies were classified according to the International Classification of Diseases of the Tenth Revision (ICD-10) are defined by appropriate codes as ICD-10 codes [8]: Stomach (C16), Colon and rectum (C18-C20), Liver (C22), Pancreas (C25), Lung and bronchus (C34), Bladder (C67), Brain (C71), Leukemias (C91-C95), All localizations (All sites (C00-C97)), and all localizations except skin (All sites but skin (C44)) were common to both sexes, then diseases specific to women: Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56) and diseases specific to men: Mouth and pharynx (C00-C10), Larynx (C32), Prostate (C61), and Kidney (C64).

The resulting trends were presented using both graphical and tabular formats., The conducted analysis included statistically significant data for several diseases, while the others were excluded because they were not statistically significant. Due to data limitations, male mouth and pharyngeal cancer (C00–C10) was included in the incidence trend analysis but excluded from the mortality trend calculations.

RESULTS

Trend in the incidence of malignant disease for both sexes

Figure 1 and Figure 2 show trends in the incidence rate of malignant diseases for women

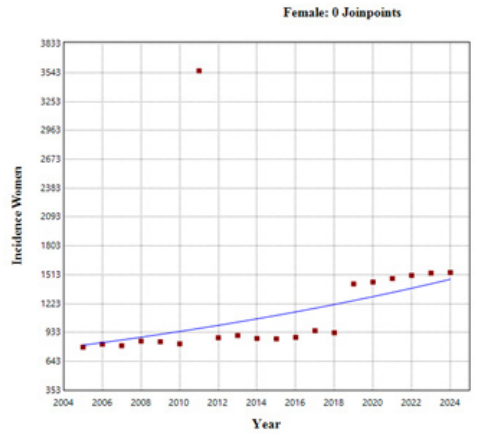

Figure 1. Trend of the incidence rate of malignant diseases for women in Serbia

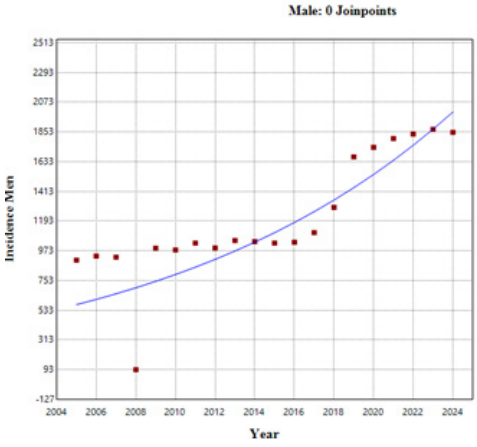

Figure 2. Trend of the incidence rate of malignant diseases for men in Serbia

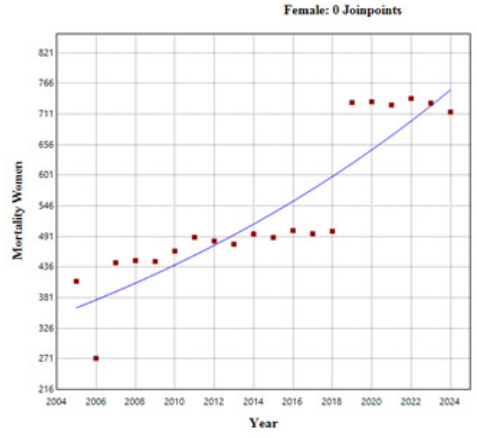

Figure 3. Trend of the mortality rate of malignant diseases for women in Serbia

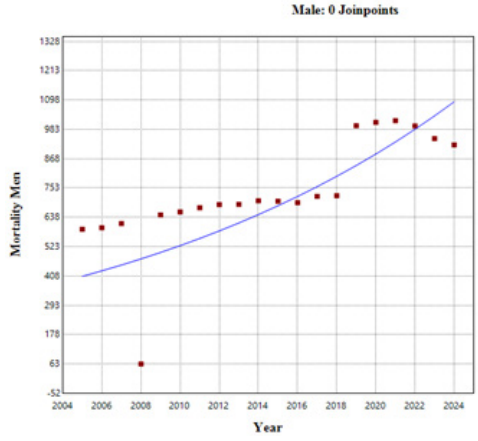

Figure 4. Trend of the mortality rate of malignant diseases for men in Serbia

and men.

Figure 1 presents the trend of the incidence rate of malignant diseases for women. Figure 2 presents the trend of the incidence rate of malignant diseases for men. The analysis revealed a statistically significant incidence trend for both sexes with the APC value for women APC = 3.20% (95% CI 0.38 - 6.10), and p value p = 0.028, while for men the APC value was APC = 6.79% (95% CI 2.36 - 11.41) with p value p = 0.004.

The AAPC value for both sexes was statistically significant with female AAPC values = 3.20 % (95% CI 0.38 - 6.00) and p value p = 0.028. For men, the AAPC value was AAPC = 6.79 % (95% CI 2.37- 11.41) with a p value of p = 0.004. The trend is in a statistically significant increase. The annual incidence rate of the trend of cancer in men is increasing at a high rate of 6.79% every year twice as fast as in women, whose incidence rate is half as low, 3.20%.

Mortality trend of malignant diseases for both sexes

Figure 3 and Figure 4 show trends in the mortality rate of malignant diseases for women and men.

Figure 3 presents the trend of the mortality rate of malignant diseases for women. The analysis revealed a statistically significant increase in the mortality trend for both sexes with the value of APC for women APC = 3.93% (95% CI 2.87 - 5.00) with p value p < 0.00. The AAPC value for women was statistically significant at AAPC = 3.93% (95% CI 2.87 - 5.00) with a p value of p < 0.00.

Figure 4 presents the trend of the mortality rate for men. The value of APC is statistically significant and was APC = 5.34% (95% CI 1.01 - 9.84) with p value p = 0.017. The AAPC value was statistically significant and amounted to AAPC = 5.34% (95% CI 1.01-9.84) with a p value of p = 0.017.

We can observe that incidence and mortality rates in women followed a similar, moderate upward trend in women, while the picture is different in the case of the opposite sex - the annual mortality rate in men increases by 5.34%, and the incidence by 6.79%, representing rates of increase nearly double those observed in women.

Trend of incidence and mortality of common malignant diseases for both sexes

Figure 5 and Figure 6 compare the trends in incidence and mortality of malignant diseases common to both sexes. In those diseases, we included the following localizations of malignant diseases: Stomach (C16), Colon and rectum (C18-C20), Liver (C22), Pancreas (C25), Lungs and bronchus (C34), Bladder (C67), Brain (C71), Leukemia (C91-C95), All localizations (C00-C97), and All sites except skin (C44).

Figure 5 represents the trend of the incidence rate, while Figure 6 represents the trend of the mortality rate of common malignant diseases for both sexes. The color of the Red line represents the female gender, and the color of the Dark Slate Blue line represents the male gender.

The analysis revealed a statistically significant incidence trend for both sexes (Figure 5) for women, the trend was continuous with zero joinpoints, yielding a steady annual increase of 3.32 % (95% CI 0.28- 6.46) with p = 0.034. The value of AAPC for women is statistically significant and was AAPC = 3.32 % (95 % CI 0.28 – 6.46) with p value p = 0.034.

For men, the result is different. Two breaking points of the incidence trend were found. The statistically significant value of APC in the period 2005 - 2017 was APC = 1.25% (95% CI 0.83-1.67), with a p value of p < 0.00, which can be confirmed on Figure 5 that until 2017 (which is the first turning point) the trend is without sudden changes, however, there is a sudden jump after 2017. For the period 2017 - 2020, the value of APC has increased sharply to 19.05 % (95% CI 11.07 - 27.61), it is statically significant with p value p < 0.00.

In the second turning point (year 2020) for the period 2020 - 2024, the value of APC dropped sharply and amounted to APC = 1.05 % (95 % CI (-1.14) – 3.29), with p value p = 0.32 without statistical significance. The AAPC value is statically significant and was 3.83% (95% CI 2.70- 4.97) with a p value of p < 0.00.

In Figure 6, we see the mortality trend of common malignant diseases for both sexes. The results show that there are two tipping points for both genders where the trends are slightly increasing until 2017. The results for women show that for the period 2005 - 2017, the value of APC was statistically significant and amounted to APC = 1.36 % (95% 1.00- 1.72) with p value p < 0.00. In the period 2017 - 2020, a sudden statistically significant increase in the value of APC was observed, APC = 14.15 % (95% CI 7.52 - 21.20) with p value p = 0.004. In the period 2020 - 2024, a sharp drop in APC value (APC = -1.10 %) (95% CI -9.96 – 0.78) was observed without statistical significance, with p value p = 0.224. The AAPC value is statistically significant and is 2.75% (95% CI 1.78-3.72) with p value p < 0.00.

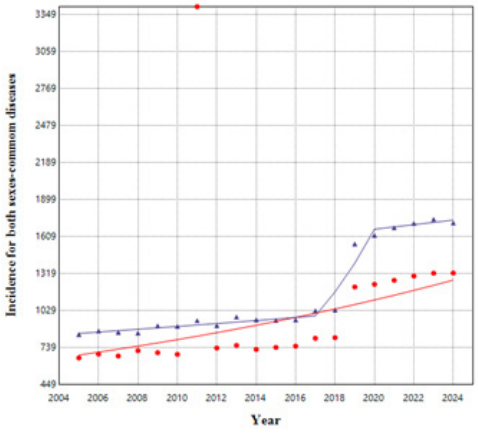

Figure 5. Incidence rates of malignant diseases for both sexes of a common disease

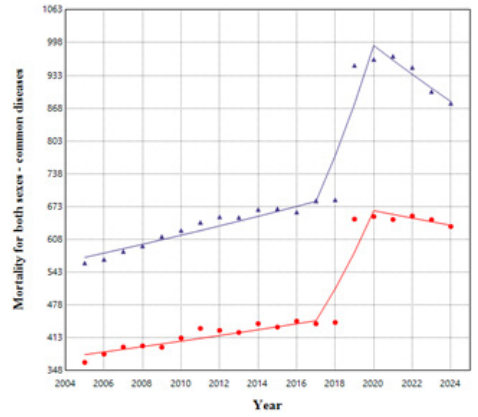

Figure 6. Trend of the mortality rate of malignant diseases for both sexes of common diseases

For men (Figure 6.) in the period 2005 - 2017, the APC value was statistically significant and amounted to APC = 1.49 % (95% CI 1.00 - 1.72), with a p value of p < 0.00. In the period 2017 - 2020, a sudden statistically significant increase in the value of APC was observed, APC = 13.22 % (95% CI 7.95 – 18.74), with p value p < 0.00. In the period 2020 - 2024, a significant decrease in the value of APC was observed, which was negative, APC= - 2.92 % (95% CI -4.37 - -1.44) and statistically significant, with p value p = 0.001. The value of AAPC is statistically significant, AAPC = 2.30 % (95% CI 1.53 - 3.06), with p value < 0.00.

Trend of incidence and mortality of specific malignant diseases for both sexes

Figure 7 and Figure 8 present trends in incidence and mortality of malignant diseases specific to both sexes. In this analysis, we included the following localizations of malignant diseases that are characteristic for women: Breast (C50), Cervix uteri (C53), Corpus uteri (C54), Ovary (C56) and men: Mouth and pharynx (C00-C10), Larynx (C32), Prostate (C61), and Kidney (C64).

The color of the Blue line represents women, and the color of the Orange Red line represents men. The calculation procedure is the same as for the previous data. The disease Mouth and pharynx (C00-C10) was excluded from the processing of the mortality trend because there were no data for it, but it was left in the processing of the incidence trend for men.

Figure 7 shows the results of the trend of the incidence of specific diseases for both sexes. There were no breakpoints in the trend for women, while there was one breakpoint for men. For women, a statistically significant increase in APC values was observed (APC = 2.81 %) (95% CI 1.62 - 4.01), with p value p < 0.00. The AAPC value is statically significant, (AAPC = 2.81 %) (95% CI 1.62 - 4.01), with a p value of p < 0.00. For men in the period from 2005 - 2017, a statistically significant increase in the incidence trend was observed with the APC value (APC = 2.27 %) (95% CI 0.63 - 3.94), with a p value of p = 0.010. In the period after 2017 (2017 - 2024), a sudden statistically significant increase in the value of APC (APC = 8.80 %) (95% CI 4.90 - 12.85) was observed, with a p value of p < 0.00. The AAPC value is statistically significant, (AAPC = 4.63 %) (95% CI 3.02 - 6.27), with a p value of p < 0.00.

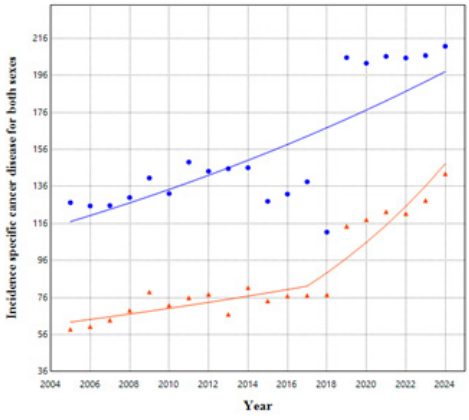

Figure 7. Incidence rates of specific malignant diseases for both sexes in Serbia 2005-2024

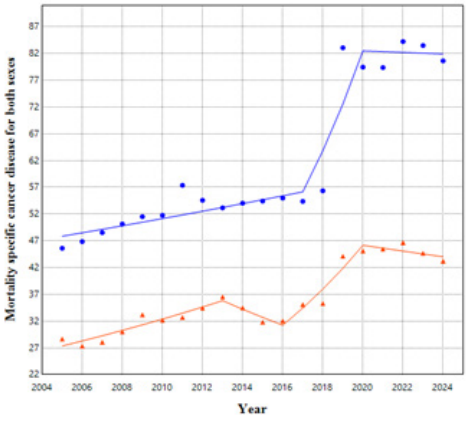

Figure 8. Mortality rates of specific malignant diseases for both sexes, Serbia 2005-2024

Figure 8 shows the results of the mortality trend of specific diseases for both sexes. For women in the period 2005 - 2017, a statistically significant value of APC was observed (APC = 1.34 %) (95% CI 0.66-2.03), with p value p = 0.001.

In the period 2017 - 2020, there was a sharp statistically significant increase in APC values for women (APC = 13.68 %) (95% CI 1.39 - 27.46), with a p value of p = 0.031. After 2020, (2020 - 2024) a sharp decline in trend was observed with a negative value of APC (APC = - 0.17%) (95% CI (-3.72) – 3.51), without statistical significance, and a p value of p = 0.920. The AAPC value for women is statistically significant, (AAPC = 2.87%) (95% CI 1.03 – 4.74), with a p value of p = 0.002.

For men in the period 2005 - 2013, the value of APC is statistically significant, (APC = 3.43 %) (95% CI 1.81 - 5.07), with p value p = 0.001. And after 2013 (2013 - 2016), there was a sharp decline in the trend with the APC value being negative (APC = - 4.46 %), (95% CI -17.30 – 10.37), with p value p = 0.492 without statistical significance. After 2016 (2016 - 2020) there was a sharp increase in APC whose value was statistically significant (APC = 10.26%), (95% CI 2.59-18.51), with p value p = 0.014, while in the period after 2020 there is a downward trend with a negative value of APC (APC = - 1.18%) (95% CI (-5.59) – 3.43), and p value p = 0.570 without statistical significance. For men, the AAPC value was without statistical significance (AAPC = 2.54 %) (95% CI -0.07 – 5.22), with a p value of p = 0.057.

Trends in incidence and mortality rates of all malignant diseases for women

From the previous data and figures for the female gender, we can see that there were changes only in 2017. Using the database from

Table 1. Trend of incidence of malignant diseases for women with tabular results

Disease - Female	Period	APC	Lower CI	Upper CI	Prob > |t|	Trend
Liver (C22)	2013-2024	11.0352*	6.9889	15.2345	0.000024	Statistically significant growth
Leukemias (C91-C95)	2005-2024	5.7464*	3.4623	8.0809	0.000041	Statistically significant growth
Bladder (C67)	2012-2022	5.8259*	3.6087	8.0906	0.000081	Statistically significant growth
Bladder (C67)	2022-2024	44.6414*	14.6983	82.4013	0.004657	A sudden statistically significant jump
Brain (C71)	2005-2024	2.0275*	0.3098	3.7747	0.023075	Statistically significant slight increase
Pancreas (C25)	2005-2024	5.4634*	3.5571	7.4048	0.000009	Statistically significant growth
Cervix uteri (C53)	2005-2024	-2.7270*	-3.6829	-1.7616	0.000014	Statistically significant decline
Lung and bronchus (C34)	2005-2016	1.5459*	0.1111	3.0012	0.036790	Slight statistically significant growth
Corpus uteri (C54)	2018-2024	-6.5767*	-8.5642	-4.5460	0.000007	Statistically significant decline
Ovary (C56)	2005-2024	0.8140*	0.3264	1.3040	0.002485	Slight statistically significant growth
Stomach (C16)	2005-2024	-2.7235*	-5.3406	-0.0340	0.047491	Statistically significant decline
All sites but skin (C44)	2016-2020	6.3438*	0.8138	12.1772	0.028481	Statistically significant growth
Disease - Female	**Period**	**AAPC**	**Lower CI**	**Upper CI**	**P-Value**	**Trend**
All sites but skin (C44)	2005-2024	1.1247	-0.7874	3.0736	0.250848	No statistical significance
Liver (C22)	2005-2024	4.9393*	1.7847	8.1917	0.001962	Statistically significant growth
Leukemias (C91-C95)	2005-2024	5.7464*	3.4623	8.0809	0.000041	Statistically significant growth
Bladder (C67)	2005-2024	6.5500*	3.7908	9.3827	0.000002	Statistically significant growth
Brain (C71)	2005-2024	2.0275*	0.3098	3.7747	0.023075	Statistically significant growth
Pancreas (C25)	2005-2024	5.4634*	3.5571	7.4048	0.000009	Statistically significant growth
Cervix uteri (C53)	2005-2024	-2.7270*	-3.6829	-1.7616	0.000014	Statistically significant decline
Lung and bronchus (C34)	2005-2024	2.7649	-0.5551	6.1957	0.103581	No statistical significance
Corpus uteri (C54)	2005-2024	-1.7511*	-2.4874	-1.0092	0.000004	Statistically significant decline
Ovary (C56)	2005-2024	0.8140*	0.3264	1.3040	0.002485	Statistically significant growth
Stomach (C16)	2005-2024	-2.7235*	-5.3406	-0.0340	0.047491	Statistically significant decline

the official website of the Batut Belgrade Institute, we conducted a new analysis where we included all diseases for both sexes. We used the mortality rates and incidence rates that we collected for each disease for the time period 2005 - 2024 for the previously analyzed diseases. Of the previously mentioned diseases, after a detailed analysis in the program, those that are not statistically significant were excluded from the final analysis. The results of the trend of the incidence of malignant diseases for the female gender are shown in tabular form (Table 1 and Table 2) and graphically (Figure 9 and Figure 10).

Trend of malignancy incidence rates for women

Figure 9 is divided into four parts, where we

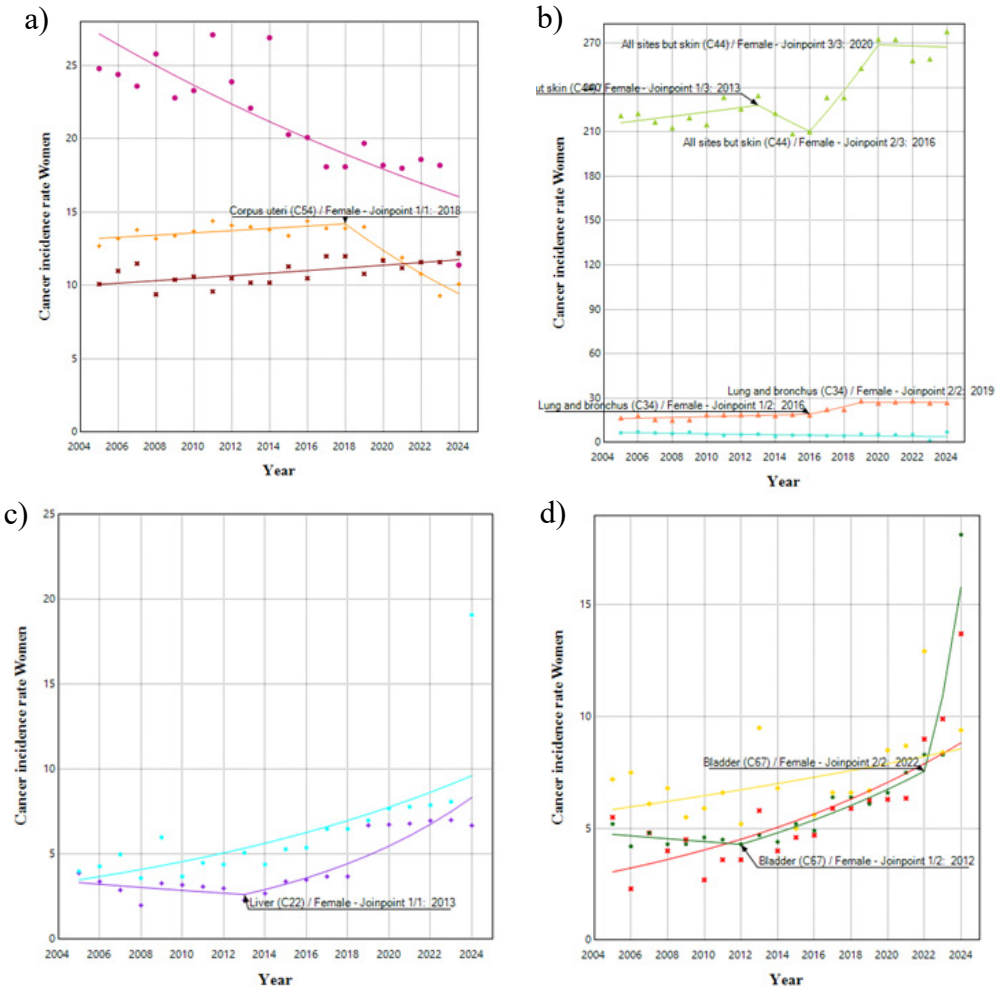

Figure 9. Trend of the incidence rate of selected diseases for women in Serbia 2005-2024

a) Medium Violet Red - *Cervix uteri (C53)*, Dark Orange - *Corpus uteri (C54)*, Maroon - *Ovary (C56)*

b) Yellow Green - *All sites but skin (C44)*, Coral - *Lung and bronchus (C34)*, Turquise - *Stomach (C16)*

c) Aqua - *Pancreas (C25)*, Blue Violet - *Liver (C22)*

d) Gold - *Brain (C71)*, Red- *Leukemias (C91-C95)*, Dark Green - *Bladder (C67)*

presented the following diseases in different colors: a) Medium Violet Red - Cervix uteri (C53), Dark Orange - Corpus uteri (C54) and Maroon - Ovary (C56), while b): Yellow Green - All sites but skin (C44), Coral - Lung and bronchus (C34) and Turquoise - Stomach (C16), c): Aqua - Pancreas (C25), Blue Violet - Liver (C22), and d): Gold - Brain (C71), Red - Leukemias (C91-C95), Dark Green - Bladder (C67).

By analyzing the trend of the incidence of these diseases, which we have shown in Figure 9 and Table 1, we obtained the results for malignant diseases:

We observed a statistically significant APC value for Liver disease (C22), in the period 2013 - 2024, (APC = 11.04 %) (95% CI 6.99-15.23) with p value p < 0.00. The value of AAPC for the period 2005-2024 was statistically significant and amounted to AAPC = 4.94 % (95% CI 1.78-8.19) with p value p = 0.002.

Then, in the period 2012 - 2022 for Bladder disease (C67), a statistically significant value of APC was observed (APC= 5.83 %) (95% CI 3.61 - 8.09) with p value p < 0.00. In the period 2022 - 2024, the value of APC is high and statically significant (APC = 44.64 %) (95% CI 14.70 – 82.40) with p value p = 0.005. The value of AAPC for the period 2005-2024 was statistically significant and amounted to AAPC = 6.55% (95% CI 3.79 - 9.38) with p value p < 0.00 increasing.

In the period 2005 - 2016 for the disease Lung and bronchus (C34), statistically significant value of APC (APC = 1.55 %) (95% CI 0.11- 3.00), with p value p = 0.037. The AAPC value was without statistical significance and amounted to AAPC = 2.76 % (95% CI (-0.56)- 6.20) with p value p = 0.104.

In the period 2016 - 2020, for the disease All sites but skin (C44), a statistically significant value of APC (APC= 6.34 %) (95% CI 0.81 – 12.16) was observed with p value p = 0.028. The AAPC value was statistically significant, and was AAPC = 1.12 % (95% CI (-0.79)- 3.07) with p value p = 0.251.

In the period 2005 - 2024, for the

disease Brain (C71), a statistically significant value of APC was observed (APC = 2.03 %) (95% CI 0.31 - 3.78) with p value p = 0.023. The AAPC value was statistically significant and amounted to AAPC = 2.03 % (95% CI 0.31 - 3.78) with a p value of p = 0.023.

Statistically significant APC value in the period 2005 - 2024 for Pancreas disease (C25) (APC = 5.46 %) (95% CI 3.56 – 7.40), with p value p < 0.00. The AAPC value was statistically significant and amounted to AAPC = 5.46% (95% CI 3.56 – 7.40) with a p value of p < 0.00.

Also, for the disease Leukemias (C91 - C95), in the period 2005 - 2024, a statistically significant value of APC (APC = 5.75 %) (95% CI 3.46 - 8.08) was observed with p value p < 0.00. The AAPC value is statistically significant, and was AAPC = 5.75% (95% CI 3.46 - 8.08) with p value p < 0.00.

In the period 2005 - 2024 Ovary (C56), a statistically significant value of APC was observed (APC = 0.81 %) (95% CI 0.33 – 1.30) with p value p = 0.002. The value of AAPC in the same period for this disease is also statistically significant and amounted to

Table 2. Mortality trend of malignant diseases for women with tabulated results

Disease	Period	APC	Lower CI	Upper CI	Prob > |t|	Trend
Cervix uteri (C53)	2005-2024	-1.4435*	-1.9765	-0.9076	0.000024	Statistically significant decline
Breast (C50)	2005-2008	-6.4140*	-10.7378	-1.8807	0.009214	Statistically significant decline
Colon and rectum (C18-C20)	2005-2024	-0.8068*	-1.1746	-0.4377	0.000231	Statistically significant decline
Leukemias (C91-C95)	2005-2022	6.0618*	4.5580	7.5872	< 0.000001	Statistically significant growth
Leukemias (C91-C95)	2022-2024	-89.1551*	-92.7877	-83.6929	< 0.000001	A sudden statistically significant drop
Corpus uteri (C54)	2005-2024	2.2306*	0.4875	4.0038	0.014805	Statistically significant growth
Bladder (C67)	2005-2024	4.2158*	0.8299	7.7155	0.017113	Statistically significant growth
Brain (C71)	2005-2024	-0.9602*	-1.7834	-0.1301	0.025867	Statistically significant decline
Pancreas (C25)	2005-2024	0.7758*	0.4176	1.1352	0.000243	Slight statistically significant growth
Lung and bronchus (C34)	2007-2021	2.9729*	2.3030	3.6472	< 0.000001	Statistically significant growth
Stomach (C16)	2005-2024	-3.4489*	-4.4232	-2.4647	0.000001	Statistically significant decline
Disease	**Period**	**AAPC**	**Lower CI**	**Upper CI**	**P- Value**	**Trend**
Cervix uteri (C53)	2005-2024	-1.4435*	-1.9765	-0.9076	0.000024	Statistically significant decline
Breast (C50)	2005-2024	-1.0703*	-1.8017	-0.3335	0.004478	Statistically significant decline
Colon and rectum (C18-C20)	2005-2024	-0.8068*	-1.1746	-0.4377	0.000231	Statistically significant decline
Leukemias (C91-C95)	2005-2024	-16.5717*	-19.9387	-13.0632	< 0.000001	Statistically significant decline
Corpus uteri (C54)	2005-2024	2.2306*	0.4875	4.0038	0.014805	Statistically significant growth
Bladder (C67)	2005-2024	4.2158*	0.8299	7.7155	0.017113	Statistically significant growth
Brain (C71)	2005-2024	-0.9602*	-1.7834	-0.1301	0.025867	Statistically significant decline
Pancreas (C25)	2005-2024	0.7758*	0.4176	1.1352	0.000243	Statistically significant growth
Stomach (C16)	2005-2024	-3.4489*	-4.4232	-2.4647	0.000001	Statistically significant decline
Lung and bronchus (C34)	2005-2024	0.7592	-0.7767	2.3189	0.334513	No statistical significance

AAPC = 0.81% (95% CI 0.33 - 1.30) with p value p = 0.002.

For these mentioned diseases, the trend of incidence was increasing and statistically significant, however, for the following diseases, the trend is in a significant decrease with statistical significance:

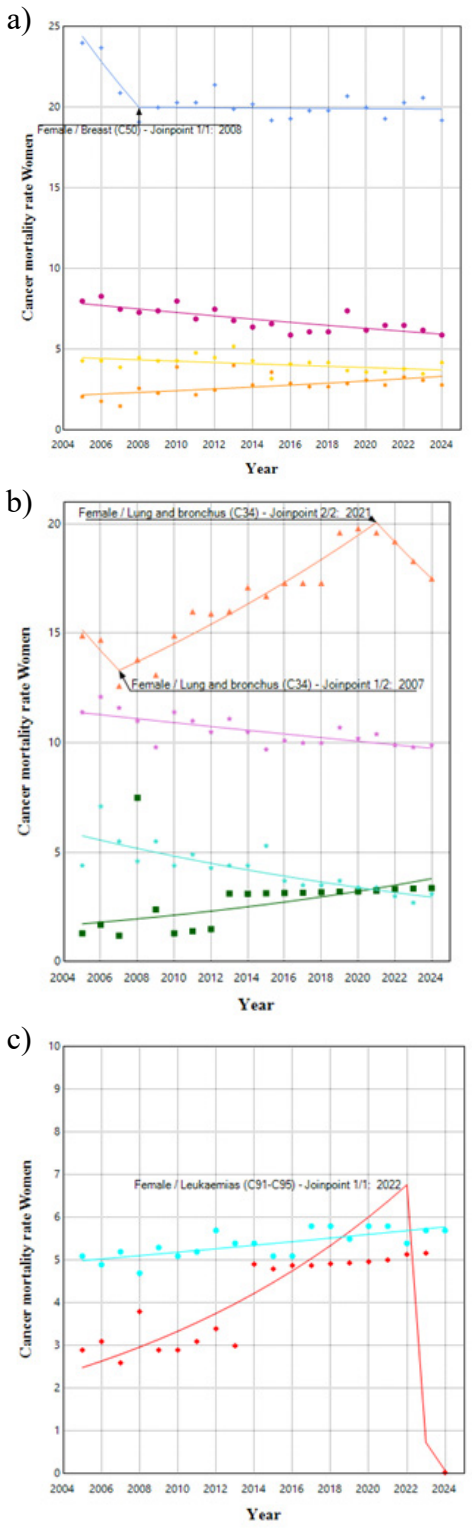

Figure 10. Mortality trend of malignant diseases for women in Serbia 2005-2024

a) Medium Violet Red - *Cervix uteri (C53)*, Comflower Blue - *Breast (C50)*, Dark Orange - *Corpus uteri (C54)*, Gold - *Brain (C71)*

b) Orchid - *Colon and rectum (C18-C20)*, Dark Green - *Bladder (C67)*, Coral - *Lung and bronchus (C34)*, Turquise - *Stomach (C16)*

c) Aqua - *Pancreas (C25)*, Red - *Leukemias (C91-C95)*

A statistically significant negative APC value was observed for Cervix uteri (C53), in the period 2005 - 2024, (APC= - 2.73%) (95% CI (- 3.68) – (- 1.76)) with p value p < 0.00. The AAPC value was negative and statistically significant, and amounted to AAPC = - 2.73% (95% CI (-3.68)- (-1.76)) with p value p < 0.00.

Then Stomach (C16), in the period 2005 - 2024, a statistically significant value of APC was recorded, which is negative (APC = - 2.72%) (95% CI (-5.34) – (-0.03)) with p value p = 0.047. The AAPC value for the mentioned period was negative and statistically significant and amounted to AAPC = -2.72% (95% CI (-5.34) - (-0.03)) with p value p = 0.047.

In the period 2018 - 2024, with a statistically significant negative value of APC was the disease Corpus uteri (C54), (APC = - 6.58 %) (95% CI (-8.569 - (-4.55)), with p value p < 0.00. The value of AAPC was statically significant in the period 2005 - 2024 with a negative value of AAPC and amounted to AAPC = - 1.75 % (95% CI -2.49 – (- 1.01)), and p value p < 0.00.

Trends in malignancy mortality rates for women

We collected mortality rates for each disease for the time period 2005 - 2024 for the same diseases from the same source. Of the previously mentioned diseases, after a detailed analysis in the program, those that are not statistically significant were excluded from the final analysis. The results of the mortality trend of malignant diseases for the female gender are presented tabularly (Table 2) and graphically (Figure 10).

Figure 10 is divided into three parts where we have presented the mortality trend for the following diseases in different colors: a) Medium Violet Red - Cervix uteri (C53), Comflower Blue - Breast (C50), Dark Orange - Corpus uteri (C54), and Gold - Brain (C71), b): Orchid - Colon and rectum (C18-C20), Dark Green - Bladder (C67), Coral - Lung and bronchus (C34) and Turquoise - Stomach (C16) and c): Aqua - Pancreas (C25), and Red - Leukemias (C91-C95).

By analyzing the mortality trend of these diseases, which we have shown in Figure 10 and Table 2, we obtained the results for malignant diseases:

In the period 2005 - 2024 for the

disease Corpus uteri (C54), a statistically significant value of APC (APC = 2.23 %) (95% CI 0.49 – 4.00) was observed with p value p = 0.015. The value of AAPC for the period 2005 - 2024 is statistically significant, and was AAPC = 2.23 % (95% CI 0.49 – 4.00) with p value p =0.015.

In the period 2005 - 2024 for Bladder disease (C67), a statistically significant value of APC was observed (APC = 4.22%) (95% CI 0.83 - 7.72) with p value p = 0.017. The value of AAPC for the period 2005 - 2024 is statistically significant, and was AAPC = 4.22 % (95% CI 0.83-7.72) with p value p = 0.017.

In the period 2007 - 2021 for the disease Lung and bronchus (C34), a statistically significant value of APC was observed (APC = 2.97%) (95% CI 2.30 - 3.65) with p value p < 0.00. The value of AAPC for the period 2005 - 2024 is without statistical significance, and was AAPC = 0.76 % (95% CI (-0.78) - 2.32) with p value p = 0.335.

In the period 2005 - 2022, for the disease Leukemias (C91-C95), a statistically significant value of APC (APC = 6.06 %) (95% CI 4.56 – 7.59) was observed with p value p < 0.00. In the period 2022 - 2024, a negative and statistically significant value of APC was observed, (APC = -89.16 %) (95% CI (- 92.79) - (-83.69)) with p value p < 0.00. The AAPC value was negative and statistically significant, and amounted to AAPC = - 16.57% (95% CI (-19.94) - (-13.06)) with p value p <0.00.

In the period 2005 - 2024, for Pancreas disease (C25), a statistically significant value of APC (APC = 0.78 %) (95% CI 0.42 – 1.14) was observed with p value p < 0.00. The AAPC value for the period 2005 - 2024 is statistically significant, and was AAPC = 0.78 % (95% CI 0.42 – 1.14) with p value p < 0.00.

For these mentioned diseases, the trend of mortality was increasing and statistically significant, however, for the following diseases, the trend is significantly decreasing with statistical significance:

In the period 2005 - 2008 for Breast (C50), a sharp decline was observed with a statistically significant value of APC (APC = - 6.41%) (95% CI (-10.74) – (-1.88)) and p value p = 0.009. The value of AAPC in the period 2005-2024 was negative and statistically significant, and amounted to AAPC = - 1.07 % (95% CI (-1.80) – (-033)) with p value p = 0.004.

In the period 2005 - 2024 for the disease Colon and rectum (C18-C20), the value of APC was negative and statistically significant (APC = - 0.81 %) (95% CI (-1.17) - (-0.44)) with p value p < 0.00. The AAPC value for the same period was negative and statistically significant, and amounted to AAPC = - 0.81 % (95% CI (-1.17) – (-0.44)) with p value p < 0.00.

In the period 2005 - 2024 for the disease Cervix uteri (C53), a negative statistically significant APC value was observed (APC = - 1.44 %) (95% CI (-1.98) - (- 0.91)) with p value p < 0.00. The AAPC value for the period 2005 - 2024 is negative and statistically significant, and amounted to AAPC = -1.44 % (95% CI - 1.97 – (-0.91)) with p value p < 0.00.

In the period 2005 - 2024 for Stomach disease (C16), a negative statistically significant value of APC was observed (APC = - 3.45 %) (95% CI (- 4.42) - (- 2.46) with p value p < 0.00. The value of AAPC for the period 2005 - 2024 was negative and statistically significant, and amounted to AAPC = -3.44 % (95% CI (- 4.42) - (- 2.46)) with p value p < 0.00.

Trends in incidence and mortality rates of all malignant diseases for men

From the previous data and figures for the male gender, we can see that changes in the trend occurred only in 2017. Using the database from the official website of the Batut Belgrade Institute, we conducted a new analysis where we included all diseases for the male sex. We used the mortality rates and incidence rates we collected for each disease for the time period 2005 - 2024 for the previously mentioned diseases. Of the previously mentioned diseases, after a detailed analysis in the program, those that are not statistically significant were excluded from the final analysis. The results of the trend of incidence and mortality of malignant diseases for the male gender are shown in tabular form (Table 3 and Table 4) and graphically (Figure 11 and Figure 12).

Trend in incidence rates of malignancy for men

Figure 11. is divided into three parts where we have presented the incidence trend for the following malignant diseases in different colors: a) Royal Blue - Kidney (C64), Cyan - Colon and rectum (C18-C20), Plum - Prostate (C61), and Chartreuse - Pancreas (C25). While b): Dark Salmon- All sites (C00-C97), and Yellow

Table 3. Trend of incidence of malignant diseases for men with tabular results

Disease Man	Period	APC	Lower CI	Upper CI	Prob > |t|	Trend
Kidney (C64)	2005-2024	5.2060*	1.3281	9.2324	0.010887	Statistically significant growth
Colon and rectum	2005-2024	2.4030*	0.7419	4.0916	0.006886	Statistically significant growth
Leukemias (C91-95)	2017-2024	13.5807*	6.4886	21.1451	0.001026	Statistically significant growth
Pancreas (C25)	2005-2021	3.3096*	1.5740	5.0748	0.000954	Statistically significant growth
Pancreas (C25)	2021-2024	37.5205*	10.2627	71.5166	0.007715	Statistically significant growth
Prostate (C61)	2005-2024	2.6539*	0.9763	4.3594	0.003646	Statistically significant growth
All sites (C00-C97)	2005-2024	1.8446*	0.2086	3.5073	0.029089	Statistically significant growth
All sites but skin (C44)	2005-2024	2.2675*	0.8730	3.6813	0.002980	Statistically significant growth
Mouth and pharynx (C00-C10)	2005-2024	3.2518*	1.1260	5.4223	0.004629	Statistically significant growth
Disease Man	**Period**	**AAPC**	**Lower CI**	**Upper CI**	**P-Value**	**Trend**
Kidney (C64)	2005-2024	5.2060*	1.3281	9.2324	0.010887	Statistically significant growth
Colon and rectum (C18-C20)	2005-2024	2.4030*	0.7419	4.0916	0.006886	Statistically significant growth
Pancreas (C25)	2005-2024	8.0825*	4.4012	11.8935	0.000011	Statistically significant growth
Prostate (C61)	2005-2024	2.6539*	0.9763	4.3594	0.003646	Statistically significant growth
All sites (C00-C97)	2005-2024	1.8446*	0.2086	3.5073	0.029089	Statistically significant growth
All sites but skin (C44)	2005-2024	2.2675*	0.8730	3.6813	0.002980	Statistically significant growth
Mouth and pharynx (C00-C10)	2005-2024	3.2518*	1.1260	5.4223	0.004629	Statistically significant growth
Leukemias (C91-C95)	2005-2024	1.7640	-3.6412	7.4724	0.530041	No statistical significance

Green - All sites but skin (C44) and c): Tan - Mouth and Pharynx (C00-C10), Red - Leukemias (C91-C95).

By analyzing the trend of the incidence of these diseases, which we have shown in Figure 11 and Table 3, we obtained the following results for malignant diseases:

In the period 2005 - 2024, for disease Kidney (64), a statistically significant APC value was observed (APC = 5.21 %) (95% CI 1.33 - 9.23) with a p value of p = 0.011. Value of AAPC for the period 2005-2024. year is statistically significant, and was AAPC = 5.21 % (95% CI 1.33 - 9.23) with p value p =0.011.

In the period 2005 - 2024, for the disease Colon and rectum (C18-C20), a statistically significant value of APC (APC = 2.40 %) (95% CI 0.74 - 4.09) was observed with p value p = 0.007. Value of AAPC for the period 2005-2024. year is statistically significant, and was AAPC = 2.40 % (95% CI 0.74 - 4.09) with p value p =0.007.

In the period 2005 - 2021, for the disease Pancreas (C25), a statistically significant value of APC (APC = 3.31 %) (95% CI 1.57 - 5.07) was observed with p value p < 0.00. In the period 2021-2024. year, a statistically significant APC value was observed (APC = 37.52 %) (95% CI 10.26 - 71.52), with a p value of p = 0.008. The AAPC value for the period 2005 - 2024 is statistically significant, and was AAPC = 8.08 % (95% CI 4.40 - 11.89) with a p value of p < 0.00.

In the period 2005 - 2024, for prostate disease (C53), a statistically significant value of APC (APC = 2.65 %) (95% CI 0.98 – 4.36) was observed with p value p = 0.004. The value of AAPC for the period 2005 - 2024 is statistically significant, and was AAPC = 2.65 % (95% CI 0.98 - 4.36) with p value p = 0.004.

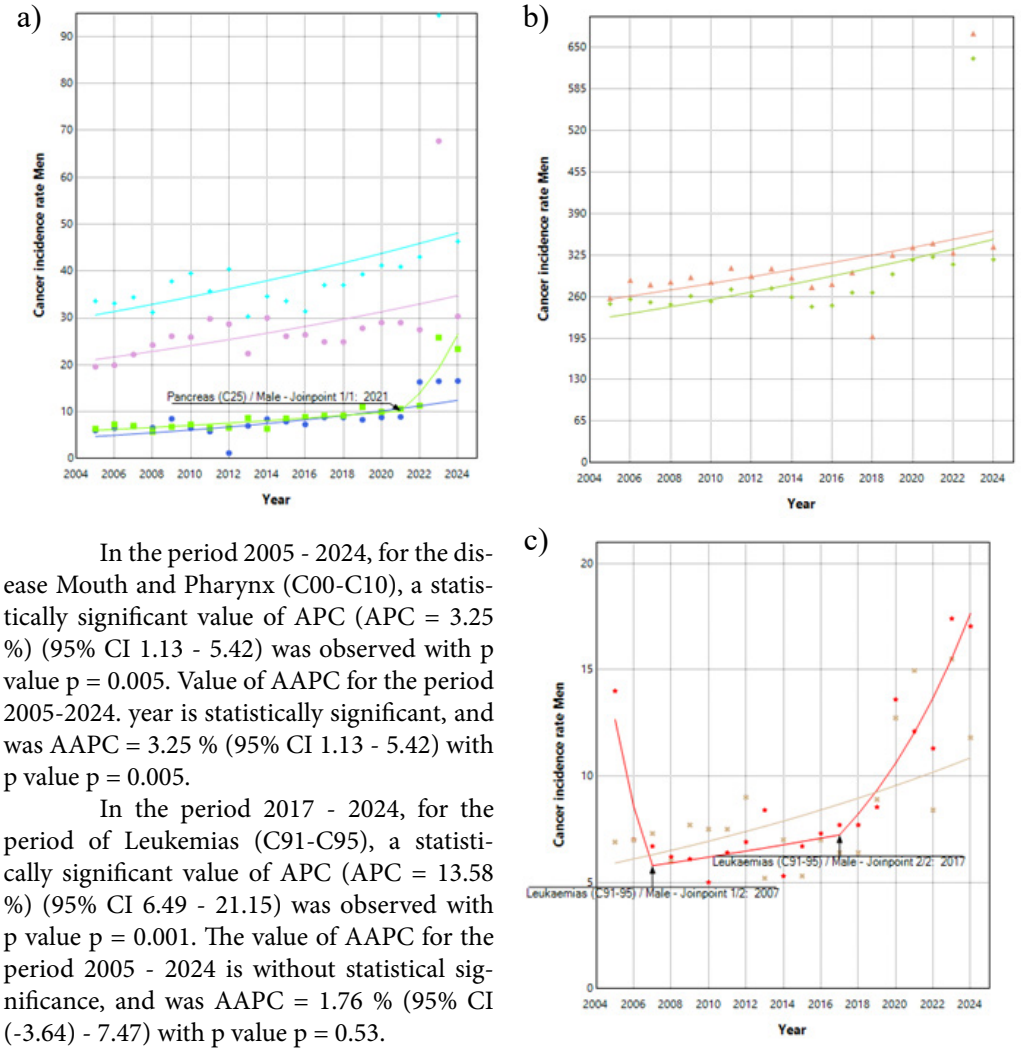

Figure 11. Trend of the incidence rate of malignant diseases for men in Serbia 2005-2024

a) Royal Blue - *Kidney (C64)*, Cyan - *Colon and rectum (C18-C20)*, Plum - *Prostate (C61)*, Chartreuse - *Pancreas (C25)*

b) Dark Salmon - *All sites (C00-C97)*, Yellow Green - *All sites but skin (C44)*

c) Tan - *Mouth and Pharynx (C00-C10)*, Red - *Leukemias (C91-C95)*

In the period 2005 - 2024, for the disease Mouth and Pharynx (C00-C10), a statistically significant value of APC (APC = 3.25 %) (95% CI 1.13 - 5.42) was observed with p value p = 0.005. Value of AAPC for the period 2005-2024. year is statistically significant, and was AAPC = 3.25 % (95% CI 1.13 - 5.42) with p value p = 0.005.

In the period 2017 - 2024, for the period of Leukemias (C91-C95), a statistically significant value of APC (APC = 13.58 %) (95% CI 6.49 - 21.15) was observed with p value p = 0.001. The value of AAPC for the period 2005 - 2024 is without statistical significance, and was AAPC = 1.76 % (95% CI (-3.64) - 7.47) with p value p = 0.53.

In the period 2005 - 2024, for the disease All sites (C00-C97), a statistically significant value of APC was observed (APC = 1.84%) (95% CI 0.21 - 3.51) with p value p = 0.029. The value of AAPC for the period 2005 - 2024 is statistically significant, and was AAPC = 1.84 % (95% CI 0.21 - 3.51) with p value p = 0.029.

In the period 2005 - 2024, for the disease All sites but skin (C44), a statistically significant value of APC was observed (APC = 2.27 %) (95% CI 0.87 - 3.68) with p value p = 0.003. The value of AAPC for the period 2005 - 2024 is statistically significant, and was AAPC = 2.27 % (95% CI 0.87 - 3.68) with p value p = 0.003.

Trend in Malignancy Mortality Rates for men

We collected mortality rates for each disease for the time period 2005 - 2024 from the same source. Of the previously mentioned diseases, after a detailed analysis in the program, those that are not statistically significant were excluded from the final analysis. The results of the mortality trend of malignant diseases for the male gender are shown in tabular form (Table 4) and graphically (Figure 12).

Figure 12 is divided into four parts where we presented the trend of mortality for the following malignant diseases in different colors: a) Royal Blue - Kidney (C64), Dark Goldenrod - Lung and bronchus (C32), Gold - Brain (C71), b): Cyan - Colon and rectum (C18-C20), Medium Turquoise - Stomach (C16), Chartreuse - Pancreas (C25) and Dim Gray - Liver (C22). While c): Dark Salmon - All sites (C00-C97), Yellow Green - All sites but skin (C44) and d): Medium Orchid - Larynx (C32), Dark Magenta - Prostate (C61).

By analyzing the mortality trend of these diseases, which we have shown in Figure 12 and Table 4, we obtained the following results for malignant diseases:

In the period 2005 - 2024, for Pan-

Table 4. Trend of the mortality rate of malignant diseases for men

Disease	Period	APC	Lower CI	Upper CI	Prob > |t|	Trend
Lung and bronchus (C34)	2005-2008	4.5811*	1.5247	7.7295	0.006455	Statistically significant growth
Lung and bronchus (C34)	2021-2024	-8.2338*	-10.9157	-5.4711	0.000039	Statistically significant decline
Colon and rectum (C18-C20)	2005-2024	0.5886*	0.2117	0.9670	0.004125	Statistically significant growth
Stomach (C16)	2005-2024	-3.0683*	-3.5895	-2.5443	< 0.000001	Statistically significant decline
Larynx (C32)	2005-2024	-2.4745*	-3.0911	-1.8540	< 0.000001	Statistically significant decline
Brain (C71)	2016-2024	-3.7472*	-6.6308	-0.7746	0.017492	Statistically significant decline
Pancreas (C25)	2005-2024	0.7670*	0.1486	1.3893	0.017814	Statistically significant growth
Liver (C22)	2005-2024	-0.9370*	-1.6376	-0.2314	0.012176	Statistically significant decline
Kidney (C64)	2005-2015	6.3677*	4.0224	8.7659	0.000029	Statistically significant growth
All sites (C00-C97)	2005-2024	-0.8566*	-1.6548	-0.0520	0.038248	Statistically significant decline
All sites but skin (C44)	2005-2024	-1.2305*	-2.0833	-0.3703	0.007691	Statistically significant decline
Disease	**Period**	**AAPC**	**Lower CI**	**Upper CI**	**P-Value**	**Trend**
Lung and bronchus (C34)	2005-2024	-0.8658*	-1.4920	-0.2355	0.007160	Statistically significant decline
Colon and rectum (C18-C20)	2005-2024	0.5886*	0.2117	0.9670	0.004125	Statistically significant growth
Stomach (C16)	2005-2024	-3.0683*	-3.5895	-2.5443	< 0.000001	Statistically significant decline
Larynx (C32)	2005-2024	-2.4745*	-3.0911	-1.8540	< 0.000001	Statistically significant decline
Brain (C71)	2005-2024	-1.3693	-2.7642	0.0457	0.057808	Without significance
Pancreas (C25)	2005-2024	0.7670*	0.1486	1.3893	0.017814	Statistically significant growth
Liver (C22)	2005-2024	-0.9370*	-1.6376	-0.2314	0.012176	Statistically significant decline
Kidney (C64)	2005-2024	3.3719*	1.7629	5.0064	0.000034	Statistically significant growth
All sites (C00-C97)	2005-2024	-0.8566*	-1.6548	-0.0520	0.038248	Statistically significant decline
All sites but skin (C44)	2005-2024	-1.2305*	-2.0833	-0.3703	0.007691	Statistically significant decline

creas disease (C25), a statistically significant value of APC (APC = 0.77 %) (95% CI 0.15 - 1.39) was observed with p value p = 0.018. The AAPC value for the period 2005 - 2024 was statistically significant, and amounted to AAPC = 0.77 % (95% CI 0.15 - 1.39) with a p value of p = 0.018.

In the period 2005 - 2015, for disease Kidney (C64), a statistically significant value of APC (APC = 6.37 %) (95% CI 4.02 - 8.77) was observed with p value p < 0.00. The AAPC value for the period 2005 - 2024 was statistically significant, and amounted to AAPC = 3.37 % (95% CI 1.76 - 5.01) with p value p < 0.00.

In the period 2005 - 2024, for the disease colon and rectum (C18-C20), a statistically significant value of APC (APC = 0.59 %) (95% CI 0.21 - 0.97) was observed with p value p = 0.004. The AAPC value for the period 2005 - 2024 is statistically significant, and was AAPC = 0.59 % (95% CI 0.21 - 0.97) with p value p = 0.004.

In the period 2005 - 2008, for Lung and bronchus disease (34), a statically significant value of APC (APC = 4.58 %) (95%CI 1.52

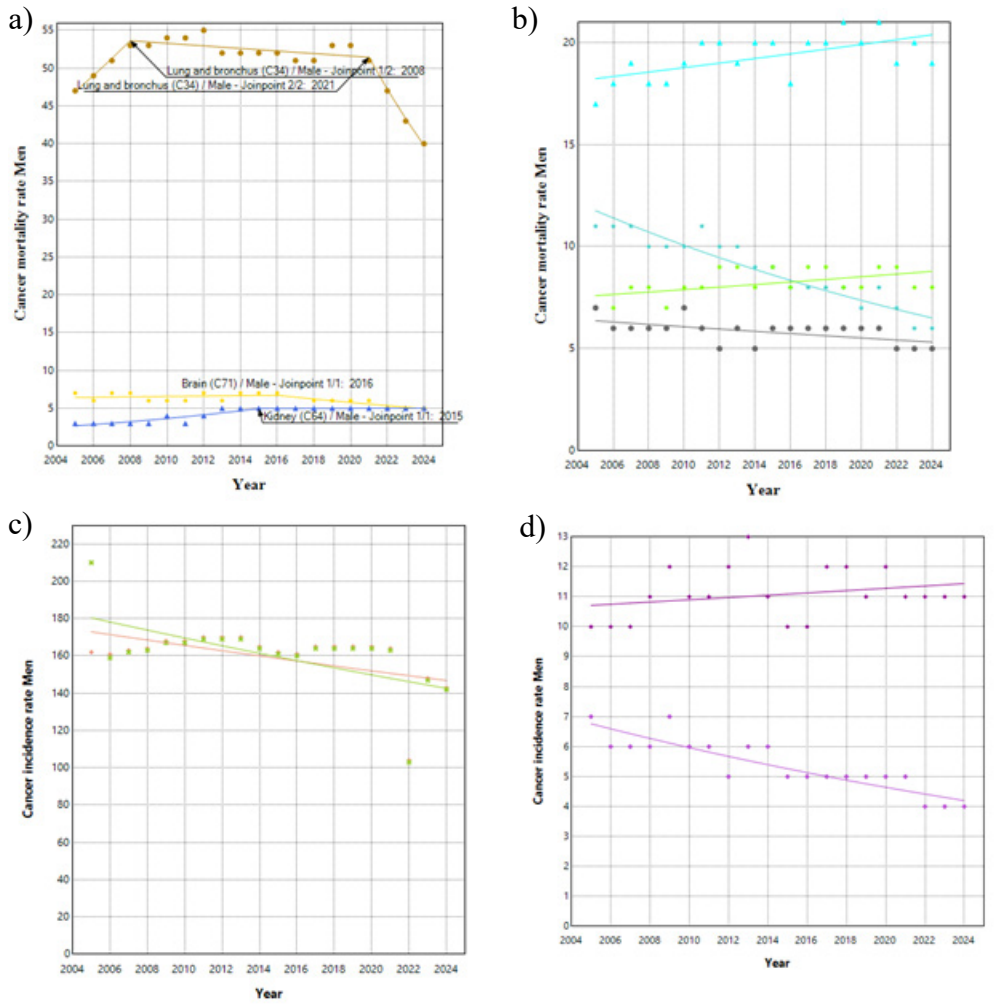

Figure 12. Trend of the mortality rate of malignant diseases for men in Serbia 2005-2024

a) Royal Blue - *Kidney (C64)*, Dark Goldenrod - *Lung and bronchus (C32)*, Gold - *Brain (C71)*

b) Cyan - *Colon and rectum (C18-C20)*, Medium Turquoise - *Stomach (C16)*, Chartreuse - *Pancreas (C25)*, Dim Gray - *Liver (C22)*

c) Dark Salmon - *All sites (C00-C97)*, Yellow Green - *All sites but skin (C44)*

d) Medium Orchid - *Larynx (C32)*, Dark Magenta - *Prostate (C61)*

- 7.73) was observed with p value p = 0.006. For the period 2021-2024. year, a negative statistically significant APC value was observed (APC = - 8.23 %) (95% CI (-10.92) - (-5.47)) with p value p < 0.00. The AAPC value for the period 2005 - 2024 is statistically significant, and it was AAPC = - 0.87 % (95% CI (-1.49) - (-0.24)) with p value p = 0.007.

For these mentioned diseases, the trend of mortality was increasing and statistically significant, however, for the following diseases, the trend is significantly decreasing with statistical significance:

In the period 2016 - 2024, for Brain disease (C71), a negative statistically significant value of APC (APC = -3.75 %) (95% CI (-6.63) - (-0.77)) was observed with p value p = 0.017. The value of AAPC for the period 2005 - 2024 is negative, and was AAPC = -1.37 % (95% CI (-2.76) - (-0.04)) with p value p = 0.056 without statistical significance.

In the period 2005 - 2024, for Stomach disease (C16), a negative statistically significant value of APC (APC = -3.07 %) (95% CI (-3.59) – (-2.54)) was observed with p value p < 0.00. The AAPC value for the period 2005 - 2024 is negative and statistically significant, and was AAPC = -3.07 % (95% CI (-3.59) – (-2.54)) with p value p < 0.00.

In the period 2005 - 2024, for the disease Larynx (C32), a negative statistically significant value of APC (APC = -2.47 %) (95% CI (-3.09) - (-1.85)) was observed with p value p < 0.00. Value of AAPC for the period 2005-2024. is negative and statistically significant, and amounted to AAPC = -2.47 % (95% CI (-3.09) - (-1.85)) with p value p < 0.00.

In the period 2005 - 2024, for Liver disease (C53), a negative statistically significant value of APC (APC = -0.94 %) (95% CI (-1.64) - (-0.23)) was observed with p value p = 0.012. The AAPC value for the period 2005 - 2024 is negative and statistically significant, and was AAPC = -0.94 % (95% CI (-1.64) - (-0.23)) with p value p = 0.012.

In the period 2005-2024. year, for

the disease All sites (C00-C97), a negative statistically significant APC value was observed (APC = -0.86 %) (95% CI (-1.65) - (-0.05)) with p value p = 0.038. The AAPC value for the period 2005 - 2024 is negative and statistically significant, and amounted to AAPC = -0.86 % (95% CI (-1.65) - (-0.05)) with p value p = 0.038.

In the period 2005 - 2024, for the disease All sites but skin (C44), a negative statistically significant APC value was observed (APC = - 1.23 %) (95% CI (-2.08) - (-0.37)) with p value p = 0.008. The AAPC value for the period 2005 - 2024 is negative and statistically significant, and amounted to AAPC = -1.23 % (95% CI (-2.08) - (-0.37)) with p value p = 0.008.

DISCUSSION

The results of this study demonstrate a statistically significant increase in both incidence and mortality rates from malignant diseases in central Serbia in the 2005-2024 for both sexes. The annual incidence rate in men (AAPC = 6.79%) was twice the rate in women (AAPC = 3.20%), while mortality in men also increased at faster rate (AAPC = 5.34%) than in women (AAPC = 3.93%). In both genders, a sharp change in trends was recorded in the period 2017–2020. year, with a sharp increase in incidence and mortality during that period, followed by a decline after 2020. These changes likely reflect the combined effect of improved diagnostics, increased disease awareness, and the indirect impact of the COVID-19 pandemic. Cancer of the pancreas, liver, bladder and leukemia stand out among the increasing diseases, while the incidence and mortality from cancer of the stomach and cervix are in statistically significant declined. Disease etiology, early detection [9], and subsequent clinical outcomes remain critical clinical determinants; earlier detection dramatically improves long-term survival rates [10]. Table 5 outlines these primary risk factors and corresponding preventive strategies.

The analysis of risk and prevention factors shown in Table 5 reveals that most malignant diseases with increasing incidence in Serbia have common modified risk factors. Tobacco consumption has been identified as a key risk factor for lung and bronchial, bladder, kidney, larynx, oral cavity and stomach cancer [11–13]. However, the declining mortality rates forlung cancer in men (AAPC = −0.87%) and larynx (AAPC = −2.47%) suggest a positive public health impact from local smoking cessation campaigns and tobacco control measures implemented in Serbia. Conversely, obesity and diabetes mellitus type 2 are particularly significant risk factors for cancer of the pancreas (AAPC women = 5.46%; men = 8.08%), liver (AAPC women = 4.94%) and bladder cancer (AAPC women = 6.55%), whose trends record the most dynamic growth in the analyzed period [14,15]. Prevention of these diseases requires comprehensive public health measures aimed at weight control, physical activity and nutritional education. The decline in the incidence of cervical cancer (AAPC = −2.73%) and gastric cancer (AAPC = −2.72%) are likely associated with improved sanitary standards, H. pylori eradication, the progress of screening programs and vaccination [4,11,16]. These results confirm that targeted preventive interventions can produce measurable reduction in the burden of malignant disease. For kidney cancer (AAPC men = 3.37%), in the etiology of which environmental chemicals and herbal preparations with nephrotoxic effects play a significant role, prevention involves improving water quality, raising awareness of harmful substances and promoting a healthy lifestyle [17–19]. The growing incidence of leukemia in women and men points to the importance of preventing exposure to ionizing radiation, air pollution and certain chemicals, with mandatory regular monitoring of the blood count for early detection of the disease [20–22].

Based on these findings, several characteristic patterns can be observed that deserve a more detailed interpretation.

The general upward trajectory of cancer incidence and mortality in central Serbia aligns with trends observed across Central and Eastern Europe. In these regions, the epidemiological transition towards chronic non-communicable diseases takes place in the conditions of a specific socioeconomic and demographic context. A particularly worrying finding is the significantly higher rate of increase in incidence in men (AAPC = 6.79%) compared to women (AAPC = 3.20%), which can be explained by the combination of a higher prevalence of risk factors such as smoking, alcohol consumption and physical inactivity, but also by a potentially lower rate of use of preventive health services in the male popula-

Table 5. Presentation of risk factors for malignant diseases

Disease	Risk factors	Prevention
Mouth and pharynx (C00-C10)	Tobacco, alcohol, nutrition, genetics, infection (HPV) [24].	The presence of certain biomarkers in saliva [23], as much information as possible about this disease, regular visits to the dentist, vaccination [24].
Stomach (C16)	Genetics, age, some congenital medical conditions and mutations. Tobacco, alcohol, diet, H. pylori bacteria (induces chronic inflammation, which causes disorders in the body), coffee, high salt intake, canned foods that are high in salt, foods high in sodium (dumplings, noodles), fried foods [11].	If the risk factors were modified (stopping the use of tobacco and alcohol, changing the diet), the progression of the disease would be prevented [11].
Colon and rectum (C18-C20)	Age, sex, family history of colorectal cancer, high-calorie diet, animal fat, alcohol, genetics, obesity, [25] anatomical location, diabetes mellitus, tobacco [26].	Change in diet, cessation of alcohol and cigarette consumption, education on risk factors [3].
Liver (C22)	Chronic inflammation [9, 27] reduced exposure to aflatoxins, obesity, diabetes, alcohol and tobacco consumption, poor food and water hygiene, poor nutrition, vitamin deficiency [28].	Prevention of risk factors, better diagnostics, improvement in diagnosis in the treatment of cirrhosis, introduction and vaccination against hepatitis B [28].
Pancreas (C25)	Positive family history, tobacco, alcohol consumption, diet, physical inactivity and diabetes mellitus [14], obesity [15].	Prevention of risk factors (ceasing alcohol and cigarette consumption, taking care of diet) [15].
Larynx (C32)	Tobacco, alcohol, HPV infection, herbicides. of course, genetics also plays a big role[12].	You should take care of the oral microbiome because certain types of bacteria can be the cause of cancer and the main marker of the disease[12].
Lung and bronchus (C34)	Tobacco, airborne particles (air pollution) [13].	Prevention of risk factors (ceasing the use of cigarettes), healthy and antioxidant diet [13].
Breast (C50)	Chronic inflammation [9, 29]	Women's education, regular check-ups, healthy antioxidant diet [4], early detection [30].
Cervix uteri (C53)	Poor hygiene, changing multiple partners, HPV, early intercourse [16].	By improving screening and vaccination, education [4, 31, 32].
Corpus uteri (C54)	High consumption of meat, animal fats and sugar, along with a lack of raw vegetables in the diet, affects the risk of invasive uterine cancer [33].	By improving screening and vaccination against the HPV, women's education [4,31,32].
Ovary (C56)	Age, genetics, infertility treatment, obesity, substitution in menopause, genetics, women who have not given birth are at greater risk. Talc and asbestos. High intake of animal fats, alcohol and tobacco [34].	Tubal ligation, hysterectomy, physical activity, women's education [34].
Prostate (C61)	Age (person's age) and genetics in case this disease existed in the family [35].	Screening, greater awareness of men [35, 36].
Kidney (C64)	Tobacco, overweight. Special attention should be paid when using certain plant species that cause problems with the kidneys due to their chemical components, then hypertension, chemicals, genetics [17,18,37].	Change of habits (ceasing the use of cigarettes and stopping the consumption of alcohol). Fruit and vegetable consumption, physical activity. Maintaining a healthy weight. Raising public awareness about a healthy lifestyle [19].
Bladder(C67)	Tobacco, poor diet, excessive supplementation, processed meat, higher levels of vitamin D, pay special attention to the chemical composition of the water (water chlorination, arsenic contamination) [38].	Fruits, vegetables, antioxidants, take care of the dose of vitamin A because it is harmful in larger quantities. Using vitamin E reduces the risk of urinary bladder disease, fluid intake, physical activity [38].

Disease	Risk factors	Prevention
Brain (C71)	Diabetes, obesity, inadequate nutrition, stress, tobacco, alcohol, exposure to chemicals (pesticides, industrial solvents), anthropometric indicators (height, weight, waist circumference and arm circumference) [39].	Dietary balance, antioxidants, stress control, anti-inflammatory diet, vitamin C and vitamin E, consumption of coffee and tea in optimal quantities, Mediterranean diet, consumption of fish, herbs with antioxidant and anticancer properties, turmeric [39].
Leukemias (C91-C95)	Age, reduced access to effective treatment, genetics, immune functions, infections (hepatitis C) [22], ionizing radiation, tobacco, air pollution, obesity, physical inactivity, hypercholesterolemia [20,21]	Immunization, avoidance of ionizing radiation and certain chemicals, identification of the disease in time, regular skinning, blood tests, in case the disease is inherited, it is necessary to monitor the development of the disease in a person due to early signs and symptoms of the disease, prevention of comorbidities, use of appropriate drugs, chemotherapy, lifestyle changes [21]

tion. Analogously, the higher mortality in men (AAPC = 5.34%) compared to women (AAPC = 3.93%) indicates that men not only get sick more often, but also that the disease at the time of diagnosis is more often in an advanced stage.

The sharp increase in incidence and mortality between 2017 and 2020, which was registered in common malignant diseases for both sexes (APC incidence for men = 19.05%; APC mortality for women = 14.15%), is a phenomenon that requires careful interpretation. This period precedes the COVID-19 pandemic, but coincides with changes in the organization of the Serbian health system, a possible improvement in case registration and a potential increase in the availability of diagnostic capacities. The sharp decline that follows after 2020, especially pronounced in mortality (APC for men = -2.92%), probably reflects the distortion caused by the pandemic - due to delays in diagnosis and limited access to oncology services, some cases remained unregistered during that period or mortality was directly attributed to the COVID-19 infection instead of the underlying malignancy. This artifact in the data should be kept in mind when interpreting the trends that include 2020-2022. a year.

The downward trend in gastric cancer incidence and mortality in both sexes (AAPC for women = -2.72%; for men -3.07%) is in line with the global trend related to the improvement of hygienic conditions, the reduction of the prevalence of *Helicobacter pylori*, changes in dietary habits and reduced dietary sodium intake. This represents a highly encouraging epidemiological signal, confirming that lifestyle and environmental modifications can successfully lower cancer burdensat the population level. Similarly, the statistically significant decline in cervical cancer incidence (AAPC = -2.73%) and the decline in breast cancer mortality (AAPC = -1.07%) can be partially attributed to improved screening and the increasing use of vaccination, although the pace of decline remains modest and indicates room for further strengthening of prevention programs.

In contrast, the raid growth in pancreatic (AAPC women = 5.46%; men = 8.08%), liver (AAPC women = 4.94%) and female bladder cancer (AAPC women = 6.55%) presents a worrisome outlook. Pancreatic cancer has an extremely poor prognosis and an almost parallel trend in incidence and mortality, which means that the increase in morbidity directly correlates with the increase in mortality. The increase in the incidence of liver cancer may be related to chronic hepatitis B and C, the increasing prevalence of obesity and nonalcoholic fatty liver disease, as well as previous exposure to aflatoxins. In parallel, the growth of the incidence of bladder cancer in women (AAPC = 6.55%), which is characteristically faster than the growth in men, may be a consequence of changes in exposure to risk factors, but also of improved diagnostics in the female population, where this disease has traditionally been undiagnosed for longer due to its more atypical clinical presentation.

Finally, the upward trends in prostate cancer (AAPC = 2.65%) and kidney cancer in

men (AAPC = 5.21%), as well as the increase in the incidence of tumors of the mouth and pharynx (AAPC = 3.25%), are consistent with the trends described in the literature for the region. Increased prostate cancer detection is likely driven by wider adoption of opportunistic prostate-specific antigen (PSA) screening., while the rise in kidney and oral cavity cancers point to persistent exposure to tobacco smoke and alcohol. Vaccination against HPV, which presents one of the risk factors (Table 5), serves as a primary preventive measure; however, it remains a debatable measure, and its effects and delayed side effects must be monitored for several years.

Overall, the epidemiological picture of malignant diseases in central Serbia in the analyzed period reflects insufficiently controlled risk factors related to lifestyle, with partially positive effects of certain preventive interventions, and clearly indicates the need for more comprehensive and coordinated oncological prevention at the national level.

This study has several limitations that should be considered when interpreting the results. First, our analysis includes aggregated data at the level of central Serbia, without the possibility of insight into regional differences within the territory itself, which can mask local epidemiological specificities. Additionally, data from the Autonomous Province of Kosovo and Metohija were unavailable, limiting the generalizability of these conclusions to the entire territory of Serbia. In addition, official registry data were used as a source, which may be subject to underreporting, especially in the earlier years of the analyzed period or during periods of health system disruption such as the COVID-19 pandemic. Third, while Joinpoint regression analysis enables the detection of changes in trends over time, but cannot establish a cause-and-effect relationship between identified risk factors and observed changes in trends. Finally, this study lacked access to individual-level data regarding socioeconomic status, healthcare access, or personal risk exposures, which would otherwise provide a more granular understanding of cancer determinants in Serbia.

CONCLUSION

Timely recognition of oncology symptoms, together with raising health literacy and public awareness, represents a critical cornerstone for improving treatment outcomes. The etiology of malignant diseases is multifactorial involving a complex web of health determinants. These include chronic conditions such as type 2 diabetes mellitus obesity, socioeconomic status, lifestyle, environmental factors such as water chlorination, arsenic contamination, air pollution, ionizing radiation, chemicals (like pesticides, industrial solvents), talc, asbestos, and toxic plant components. Furthermore, dietary habits, chronic psychological stress, sanitary conditions, genetic predispositions, and immune system status all contribute to individual oncogenic risk to varying degrees. It is important to note that favorable living conditions reduce, but do not eliminate, the risk of disease, since exposure to certain exogenous factors can trigger oncogenesis in populations that do not exhibit classic risk factors. This complexity requires an individualized approach to risk assessment and preventive interventions.

Organized screening programs enable the detection of malignant diseases in an early, potentially curable stage and represent an indispensable element of organized oncological care. However, the effectiveness of screening largely depends on the availability and quality of the diagnostic infrastructure, as well as on the trust that patients have in the health system. Cavic et al emphasize that improving the availability of radiological diagnostics, both invasive and non-invasive techniques, is essential for Serbia, and that specialized personnel trained for the systematic management of screening programs and appropriate institutional infrastructure are necessary. Currently, a shortage ofqualified clinical experts and bioinformaticians, along with the limited availability of clinical studies, represents a structural deficit that slows down progress in the diagnosis and treatment of malignant diseases at the national level.

Ultimately, prevention remains the most effective and cost-effective tool in the fight against malignant diseases. Cessation of tobacco and alcohol consumption, reduction of exposure to aflatoxins, control of drinking water quality and adoption of healthy lifestyle habits can statistically significantly reduce the incidence of numerous malignancies. Taking into account that many of the mentioned risk factors are modified and subject to individual and collective intervention, improving the health behavior of the population through

education, systemic public health measures and the availability of preventive services is a priority of exceptional social and medical importance.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Trendovi malignih bolesti u centralnoj Srbiji i faktori koji na njih utiču

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KRATAK SADRŽAJ

Uvod: U Srbiji i drugim zemljama Centralne i Istočne Evrope, stope incidencije i mortaliteta od malignih bolesti kontinuirano rastu poslednjih decenija. Uprkos napretku u razumevanju njihove epidemiologije, nedostaju sveobuhvatne analize koje obuhvataju ceo period od 2005. do 2024. godine, na svim lokalizacijama tumora za oba pola, koristeći savremene statističke metode. Uticaj socioekonomskih faktora, dostupnosti zdravstvene zaštite i događaja poput pandemije COVID-19 na trendove raka takođe nije dovoljno istražen.

Cilj: Utvrditi vremenske trendove incidencije i mortaliteta od malignih bolesti u centralnoj Srbiji u periodu 2005–2024, identifikovati prelomne tačke trenda i karakteristične promene, kao i analizirati faktore rizika i mogućnosti prevencije za svaku analiziranu lokalizaciju raka.

Materijal i metode: Podaci o stopama incidencije i mortaliteta od malignih bolesti (za oba pola, 2005–2024) dobijeni su iz zvaničnih izveštaja Instituta za javno zdravlje „Dr Milan Jovanović Batut" Beograd. Stope standardizovane po starosti na 100.000 stanovnika izračunate su odvojeno za žene i muškarce za svaku vrstu raka, uključujući rak želuca (C16), kolorektalnog (C18-C20), jetre (C22), pankreasa (C25), pluća i bronhija (C34), bešike (C67), mozga (C71), leukemije (C91-C95), sve lokalizacije (C00-C97) i sve lokalizacije osim kože (C44), kao i polno-specifične karcinome (dojke, grlića materice, materice, jajnika za žene; usne šupljine/ždrela, larinksa, prostate, bubrega za muškarce). Analiza trenda je sprovedena korišćenjem Joinpoint Regression Programa verzije 5.4.0, izračunavajući godišnju procentualnu promenu (APC), prosečnu godišnju procentualnu promenu (AAPC), 95% intervale poverenja i p-vrednosti putem t-testa. Test permutacije je korišćen za određivanje optimalnog broja prelomnih tačaka (0–3), sa značajnošću postavljenom na $p < 0,05$.

Rezultati: Ukupna incidencija raka značajno se povećala kod oba pola: AAPC = 3,20% (95% CI 0,38–6,10; p = 0,028) za žene i AAPC = 6,79% (95% CI 2,37–11,41; p = 0,004) za muškarce. Mortalitet je takođe značajno porastao: AAPC = 3,93% (95% CI 2,87–5,00; $p < 0,001$) za žene i AAPC = 5,34% (95% CI 1,01–9,84; p = 0,017) za muškarce. Kod čestih karcinoma za oba pola, identifikovane su dve prelomne tačke trenda oko 2017. i 2020. godine, sa naglim porastom incidencije (APC za muškarce = 19,05% u periodu 2017–2020) i mortaliteta (APC za žene = 14,15% u periodu 2017–2020), nakon čega je usledio pad posle 2020. godine.

Među ženama, statistički značajan porast incidencije primećen je za karcinom jetre (AAPC = 4,94%), pankreasa (AAPC = 5,46%), bešike (AAPC = 6,55%), leukemije (AAPC = 5,75%), mozga (AAPC = 2,03%) i jajnika (AAPC = 0,81%). Značajan pad je zabeležen za karcinom grlića materice (AAPC = −2,73%), želuca (AAPC = −2,72%) i materice (AAPC = −1,75%).

Među muškarcima, značajno povećanje incidencije je utvrđeno za bubrege (AAPC = 5,21%), pankreas (AAPC = 8,08%), kolon i rektum (AAPC = 2,40%), prostatu (AAPC = 2,65%), usnu šupljinu i ždrelo (AAPC = 3,25%) i sve lokalizacije (AAPC = 1,84%–2,27%). Trendovi mortaliteta kod muškaraca pokazali su značajan pad za želudac (AAPC = -3,07%), larinks (AAPC = -2,47%), pluća (AAPC = -0,87%), jetru (AAPC = -0,94%) i sve lokalizacije zajedno (AAPC = -0,86% do -1,23%).

Zaključak: Učestalost i mortalitet od raka u centralnoj Srbiji značajno su porasli od 2005. do 2024. godine, pri čemu su muškarci pokazali približno dvostruko veću

stopu rasta u poređenju sa ženama. Nagli skok trendova tokom 2017–2020. verovatno odražava kombinaciju poboljšane dijagnostike, promena u organizaciji zdravstvene zaštite i indirektnih efekata pandemije COVID-19, uključujući odložene dijagnoze i pogrešno pripisivanje mortaliteta. Rak pankreasa, jetre, bešike, leukemije i bubrega predstavljaju najdinamičnije rastuće maligne bolesti. Opadajući trendovi raka želuca i grlića materice odražavaju jasne koristi od eradikacije H. pylori, poboljšane higijene, programa skrininga i diskutabilno vakcinacije protiv HPV-a čiji se efekti i odloženi neželjeni efekti moraju pratiti više godina, zbog čega treba da bude samo na dobrovoljnoj bazi. Prevencija porasta broja karcinoma zahteva ciljane intervencije javnog zdravlja koje se bave upotrebom duvana, gojaznošću, dijabetesom, konzumiranjem alkohola i izloženošću faktorima iz životne sredine.

Ključne reči: stopa incidencije raka, stopa mortaliteta raka, Srbija, faktori rizika, epidemiologija, joinpoint regresiona analiza

Received: **May** 27, 2026
Accepted: **June** 4, 2026