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TREND INCIDENCIJE I MORTALITETA OD KARCINOMA USANA, USTA, ŽDRELA I DRUGE LOKALIZACIJE U CENTRALNOJ SRBIJI U PERIODU OD 1999. DO 2020. GODINE

TREND OF INCIDENCE AND MORTALITY RATE OF OTHER AND ILL-DEFINED SITES OF LIP, ORAL CAVITY AND PHARYNX CANCER IN CENTRAL SERBIA FROM 1999 TO 2020

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Sažetak

Uvod: *Smrtnost izazvana karcinomom je visoka u razvijenim zemljama i u zemljama u razvoju, a očekuje se i da će trendoboljevanja rasti širom sveta, posebno u zemljama sa slabijim ekonomskim razvojem, gde živi oko 82% svetske populacije*
Cilj *ovog istraživanja bio je da se predstave i procene trendovi incidencije, stope mortaliteta i MIR malignih neoplazmi drugih i nedefinisanih lokalizacija karcinoma usne, usne duplje i ždrela u centralnoj Srbiji od 1999. do 2020. godine.*
Materijal i metode: *Studija zasnovana na registru rađena je na osnovu podataka iz javno dostupnog Statističkog godišnjaka Instituta za javno zdravlje Srbije – Incidencija i mortalitet u centralnoj Srbiji, od 1999. do 2020. godine. Za izračunavanje trenda i godišnje procentualne promene (APC) korišćene su stope incidencije i mortaliteta sa odgovarajućim intervalima poverenja od 95%*
Rezultati: *U centralnoj Srbiji je od 1999. do 2020. godine registrovano ukupno 558 slučajeva (436 kod muškaraca i 122 kod žena) drugih i nedefinisanih lokalizacija karcinoma usne, usne duplje i ždrela. Gruba stopa (CR) i starosno standardizovana stopa (ASR-V) incidencije kod muškaraca su porasle (p < 0,001, za oba) tokom perioda studije, sa APC od 4,8% i 9,0%, respektivno. Gruba stopa (CR) i starosno standardizovana stopa (ASR-V) mortaliteta kod muškaraca su se smanjile (p < 0,001, za oba) tokom perioda istraživanja, sa APC od -7,5%, -7,2%, respektivno. Smanjenje stope mortaliteta je praćeno padom MIR-a između 2001. i 2020. godine, sa APC od -5,6 (p < 0,001).*
Zaključak: *Naši rezultati pokazuju da je incidencija drugih i loše definisanih mesta raka usne, usne duplje i ždrela u centralnoj Srbiji porasla tokom perioda istraživanja. Stopa mortaliteta i MIR za ovaj karcinom smanjili su se tokom 22 godine.*

Ključne reči: *loše definisana mesta raka usne, usne duplje i ždrela; stopa incidencije; stopa mortaliteta; registar raka; trendovi*

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Abstract

Introduction*:Cancer is causing death in countries with more or less economic development, and it is expected that the burden will grow worldwide, especially in countries with less developed populations, where about 82% of the global population lives.*
The aim *of this study was to present and estimate trends in incidence, mortality rate and MIR of malignant neoplasm of otherand ill-defined sites of lip, oral cavity and pharynx cancer in Central Serbia from 1999 to 2020.*
Material and methods:*The registry-based study was conducted using the data from the publically accessible Yearbooks of the Institute of Public Health of Serbia: Incidence and Mortality in Central Serbia, from 1999 to 2020. Joinpoint regression was used to determine the trend and annual percentage change (APC) of the incidence and mortality rate with corresponding 95% confidence intervals.*
Results: *A total number of 558 cases (436men and 122women) of other and ill-defined lip, oral cavity and pharynx cancer sites registered in Central Serbia from 1999 to 2020.*
The crude rate (CR) and age-standardized rate (ASR-W) of incidence in males increased (p<0.001, for both) during the study period with APC of 4.8% and 9.0%, respectively. The crude rate (CR) and age-standardized rate (ASR-W) of mortality in males decreased (p<0.001, for both) during the study period with APC of -7.5%, and -7.2%, respectively. The mortality rate decrease was followed by the decline in MIR between 2001 and 2020 with anAPC of -5.6 (p<0.001).
Conclusions: *Our results reveal that the incidence of other and ill-defined lip, oral cavity and pharynx cancer sites in Central Serbia increased through the study period. The mortality rate and MIR for this cancer decreased during 22 years.*

Key words: *ill-defined sites of lip, oral cavity and pharynx cancer; incidence rate, mortality rate, cancer registry, trends*

Uvod

Smrtnost izazvana karcinomom je visoka u razvijenim zemljama i u zemljama u razvoju, a očekuje se i da će trend oboljevanja rasti širom sveta, posebno u zemljama sa slabijim ekonomskim razvojem, gde živi oko 82% svetske populacije. Usvajanje stilova života za koje se pokazalo da povećavaju rizik od karcinoma, uključujući pušenje, lošu ishranu i fizičku neaktivnost, povećalo je opterećenje oboljevanjem od karcinoma u slabije razvijenim zemljama[1]. Oboljevanje od orofacijalnih karcinoma jeste jedan od glavnih javnozdravstvenih problema na globalnom nivou. U 2012. godini karcinom usne duplje i orofarinksa bio je šesti najčešći karcinom među muškarcima u Evropi (standardizovana stopa – ASR: 18,8/100.000), dok je među ženama rangiran na 16. mestu (ASR: 4,9/100.000) (EUCAN)[2]. U 2012. godini procenjeno je 300.400 novih slučajeva oralnih karcinoma (uključujući i karcinom usne) i 144.540 smrtnih slučajeva širom sveta. Najveće stope javljaju se u Maleziji, Južnoj i Centralnoj Aziji i Centralnoj i Istočnoj Evropi, dok su najniže u Zapadnoj Africi i Istočnoj Aziji[1].

Ipak, u poslednjih nekoliko decenija incidencija oralnog karcinoma značajno je smanjena kod oba pola u Aziji, Severnoj Americi i Australiji, kao i u Južnoj i Zapadnoj Evropi[3]. Pušenje, konzumiranje alkohola i HPV infekcija glavni su faktori rizika za oralni karcinom; pritom, kombinacija konzumiranja cigareta i alkohola pokazuje sinergističke efekte[4]. Doprinos faktora rizika opterećenju od oboljevanja karcinoma razlikuje se u različitim regionima sveta[5]. Procenjuje se da pušenje ima doprinos u skoro tri četvrtine smrtnih slučajeva od karcinoma oralne regije (uključujući ždrelo) u zemljama sa visokim ekonomskim razvojem, odnosno u 37% smrtnih slučajeva u zemljama sa niskim i srednjim ekonomskim razvojem. Konzumiranje alkohola utiče približno na jednu trećinu smrtnih slučajeva u razvijenim zemljama i na jednu sedminu smrtnih slučajeva u nisko i srednje razvijenim zemljama[6]. Utvrđeno je da je učestalost novih slučajeva veća ukoliko se konzumiraju duvan i alkohol zajedno, što ukazuje na multiplikovanje efekata ova dva faktora rizika kao karcinogena oralne šupljine / ždrela[7]. Učestalost konzumiranja duvana porasla je u mnogim zemljama Istočne i Severne Evrope, kao i među ženama u Južnoj i Zapadnoj Evropi[3]. Ovi podaci su u suprotnosti sa trendom opadanja u svim uzrastima, primećenom kod muškaraca i žena u mnogim drugim razvijenim zemljama, u kojima je

Introduction

Cancer is causing death in countries with more or less economic development, and it is expected that the burden will grow worldwide, especially in countries with less developed populations, where about 82% of the global population lives. Adopting a lifestyle that has been shown to increase the risk of cancer, including smoking, eating poorly, and physical inactivity, has increased the burden of cancer in less developed economies[1]. Orofacial cancer is one of the major concerns when it comes to public health on a global scale. In 2012, cancers of the oral cavity and oropharynx were the sixth-most common cancer among men in Europe (Ages standardized rate (ASR): 18.8/100000] while in the case of women, they were ranked 16th (ASR: 4.9/100 000) (EUCAN)[2]. In 2012, there were estimated 300,400 new cases of oral cancer and 144,540 deaths worldwide (including cancer of the lip). The highest rates occur in Melanesian, South Central Asia, and Central and East Europe, while the lowest rates are in West Africa and East Asia[1].

In the past few decades, the incidence of oral cancer has significantly decreased among male and female patients in Asia, Northern America, and Australia, as well as between male and female patients in southern and Western Europe, respectively[3]. Smoking, alcohol consumption, and infection by HPV are the main risk factors for oral cancer, and the combination of cigarettes and alcohol has synergistic effects[4]. The contribution of all of these risks to burden differs in different regions of the world[5]. Smoking is estimated as contributing to almost three-quarters of deaths from oral cancer (including the pharynx) in countries with high incomes and as contributing to 37% of death in countries with low and middle incomes, while alcohol accounts for approximately one-third of deaths, and one-seventh of deaths, respectively[6]. The association between tobacco and alcohol is stronger among smokers than non-smokers, indicating an over-multiplication effect of smoking and alcohol on oral/pharynx carcinogens[7]. The rate of tobacco consumption has increased in many countries of Eastern and Northern Europe, as well as among women in Southern and Western Europe[3]. This contrasts to the decreasing trend inall ages, which has been observed in males as well as females of many other developed countries where the epidemic of tobacco began earlier and was declining.

epidemija duvana počela ranije i trenutno opada. Dodatno, stope incidencije oralnih karcinoma povezanih sa HPV infekcijom (npr. orofilaksa, krajnici i dno jezika) u nekim zemljama su povećane, što, delimično, može biti posledica promena u oralnom seksualnom ponašanju[8].

Nekoliko faktora može uticati na promenu trenda mortaliteta – promena u prevalenciji izloženosti ključnim faktorima rizika za datu bolest, dostupnost dijagnostike i rane dijagnoze i pristup ranoj dijagnozi[7,9]. U tom kontekstu, u Srbiji su uočene značajne varijacije u poslednjih trideset godina. Prethodna istraživanja analizirala su trend mortaliteta od karcinoma orofarinksa (OPC) u Srbiji[10,11]. Međutim, nedostaju ažurirana istraživanja o trendovima incidencije i mortaliteta od karcinoma usana, usta, ždrela i druge lokalizacije u centralnoj Srbiji (idLOP). U okviru analize trenda oboljevanja i smrtnosti od nekog karcinoma, preporučljivo je paralelno proceniti preživljavanje. U tu svrhu može se koristiti i analizirati odnos mortalitet–incidencija (MIR)[12]. Stoga je cilj ove studije bio da se prezentuju i procene trendovi incidencije, stope mortaliteta i MIR karcinoma usana, usta, ždrela i druge lokalizacije u centralnoj Srbiji od 1999. do 2020. godine.

Cilj ovog istraživanja bio je da se predstave i procene trendovi incidencije, stope morta-liteta i MIR malignih neoplazmi drugih i nedefinisanih lokalizacija karcinoma usne, usne duplje i ždrela u centralnoj Srbiji od 1999. do 2020. godine.

Materijal i metode

U ovom istraživanju korišćeni su podaci dobijeni iz javno dostupnog registra kancera, Incidencija i mortalitet od raka u centralnoj Srbiji, koji je Institut za javno zdravlje Srbije objavio za period od 1999. do 2020. godine; tu su incidencija i mortalitet prikazani prema polu i starosnoj strukturi i prema dijagnozi. Standardizovane stope incidencije i mortaliteta izračunate su na osnovu ovih podataka za oba pola. Karcinom usana, usta, ždrela i druge (idLOP) lokalizacije kodiran je prema Međunarodnoj klasifikaciji bolesti – deseta revizija (MKB-10) – kao C14. Odnos mortaliteta i incidecnije (MIR) dobijen je deljenjem stope mortaliteta i incidencije i deljenjem standardizovane stope mortaliteta i standardizovane stope incidencije za svaku godinu. Za analizu trenda korišćena je Joinpoint regresiona analiza, pri čemu se izračunavala godišnja procentualna promena (APC) incidencije, mortaliteta i MIR-a sa 95% intervalom poverenja (95% CI).

However, in some countries, the incidence rates of oral cancers related to the HPV infection (e.g., orophylaxis, tonsils, and the base of tongue) have increased, which may be partly due to the changes in the oral sexual behaviour[8]. Several factors may affect the trend in mortality rates such as the change in prevalence of the exposure to key risk factors for the disease, availability of diagnostics and early diagnosis, and the access to early diagnosis[7;9]. In the context of Serbia, significant variations have been observed in the context of the last decade of the twenty-first century.

Previous literature has reported trends in oropharyngeal cancer (OPC) mortality in Serbia[10,11]. However, there is a lack of updated research on the incidence and mortality trends of other and ill-defined sites in the lip, oral cavity and pharynx in Central Serbia (idLOP). It is recommendable to estimate survival together with incidence and mortality. For that purpose, it can be used and analyzed mortality-incidence ratio (MIR)[12]. Therefore, the aim of this study was to present and estimate trends in incidence, mortality rate and MIR of malignant neoplasm of other and ill-defined sites in the lip, oral in Central Serbia from 1999 to 2020.

The aim of this study was to present and estimate trends in incidence, mortality rate and MIR of malignant neoplasm of othe rand ill-defined sites of lip, oral cavity and pharynx cancerin Central Serbia from 1999 to 2020.

Material and methods

Publicly available Yearbooks of the Institute of Public Health of Serbia: Incidence and Mortality in Central Serbia, from 1999 to 2020, were used to extract data for the registry-based study. Extracted data consisted of the incidence and mortality rates aggregated and stratified by gender, 5-year age groups, and diagnosis. Malignant neoplasm of other and ill-defined sites in the lip, oral cavity, and pharynx(idLOP) was coded according to the tenth Revision of the International Classification of Disease (code C14)[13]. Mortality to incidence ratio (MIR) was calculated as a ratio of the crude mortality rate and crude incidence rate for each year. Joinpoint regression analysis calculated the trend and the annual percentage change (APC) of the incidence and mortality rate with corresponding 95% confidence intervals (95%CI). The optimal number of joinpoints was identified using the Monte Carlo permutation method. For trend analyses, the Joinpoint Regression Program version 4.1.0 was used (available at

Optimalan broj prelomnih tačaka dobijen je metodom Monte Karlo permutacije. Za analizu trenda korišćen je programski paket Joinpoint Regression Program, verzija 4.1.0 (dostupan na linku: http://surveil- lance. cancer.gov/joinpoint). Nulta hipoteza testirana je sa pragom značajnosti $p < 0,05$.

Rezultati

U centralnoj Srbiji je u periodu od 1999. do 2020. godine registrovano ukupno 558 novooboleli slučajeva karcinoma usana, usta, ždrela i druge lokalizacije (436 muškarca i 122 žene) (Tabela 1). Odnos muškaraca prema ženama je 3,6 : 1. Najviše novooboleli bilo je starosti od 40 do 65 godina – 53,2% kod muškaraca i 46,7% kod žena. Ukupan broj umrlih u periodu obuhvaćenom ispitivanjem iznosio je 480 slučajeva (391 umrli muškarac i 89 umrlih žena) od idLOP-a registrovanih u centralnoj Srbiji od 1999. do 2020. godine (Tabela 2). Najviše umrlih bilo je starosti od 40 do 65 godina – 83,4% kod muškaraca, odnosno 42,7% kod žena.

U Tabeli 3 predstavljena je opšta (CR) i standardizovana stopa incidencije i mortaliteta (ASR-W, prema svetskoj populaciji) od idLOP-a. Najveće CR i ASR-W incidencije kod muškaraca bile su 1999. i 2017. godine (1,4, 0,9, odnosno 0,8), a najniže vrednosti tih stopa bile su 2005. godine (0,3, odnosno 0,1). Kod muškaraca, CR i ASR-W stope mortaliteta bile su najveće 2001. godine (1,2, odnosno 0,7), a najniže 2011. godine (0,3, odnosno 0,2). Kod žena, najveće vrednosti CR i ASR-W incidencije bile su 2012. godine (0,5, odnosno 0,2), a najniže vrednosti tih stopa bile su 2010. i 2011. godine (0,0, odnosno 0,0). Kod žena, vrednosti CR i ASR-W stope mortaliteta bile su veoma niske između 1999. i 2020. godine – u rasponu od 0,0 do 0,3.

Zbog male učestalosti karcinoma kod žena, regresiona analiza urađena je samo za pripadnike muškog pola. Analiza trenda incidencije idLOP-a kod muškaraca pokazala je značajno povećanje trenda između 2001. i 2017. godine, sa APC od 4,8% (95% CI 1,1% – 8,7%; $p < 0,001$). Standardizovana stopa incidencije kod muškaraca pokazala je značajno povećanje trenda između 2005. i 2015. godine, sa APC od 9,0% (95% CI 1,3% – 17,2%; $p < 0,001$) (Grafikon 1). Opšta stopa mortaliteta od idLOP-a kod muškaraca pokazala je statistički značajan trend opadanja vrednosti između 1999. i 2010. godine, sa APC -7,5 (95% CI od -14,3 do -0,2; $p < 0,001$). Standardizovana stopa mortaliteta od idLOP-a kod muškaraca pokazala je značajan trend smanjenja tokom

http: //surveillance.cancer.gov/joinpoint). The trend was considered to be significantly changing when the p-value was below 0.05 ($p < 0.05$).

Results

A total of 558 cases (436 males and 122 females) of other and ill-defined lip, oral cavity and pharynx sites were registered in Central Serbia from 1999 to 2020 (Table 1). The men to women ratio was 3.6:1. Most new cases were aged 40–65 years in males (53.2%) and females (46.7%). The total number of deaths in a specific period was 480 cases (391 deaths in males and 89 deaths in females) of other ill-defined lip, oral cavity and pharynx sites registered in Central Serbia from 1999 to 2020 (Table 2). Most deaths were aged 40-65 in males (83.4%) and in females (42.7%).

Table 3 presents the distribution of idLOPby age and the crude rate of incidence and mortality, the age-standardized incidence and mortality rate (ASR-W; to the world population) and mortality to an incidence rate (MIR) to the specified rates according to the years of observation. The highest CR and ASR-W of incidence in males were in 1999 and 2017 (1.4, 0.9 and 0.8, respectively), and the lowest values of those rates were in 2005 (0.3, 0.1, respectively). In males, the CR and ASR-W of the mortality rate were highest in 2001 (1.2, 0.7, respectively) and lowest in 2011 (0.3, 0.2, respectively). In females, the highest CR and ASR-W of incidence were in 2012 (0.5, 0.2, respectively), and the lowest values of those rates were in 2010 and 2011 (0.0, 0.0, respectively). In females, the CR and ASR-W of mortality rate were very low between 1999–2020, in the range of 0.0–0.3.

Joinpoint regression analysis was performed only in males due to small rates in females. Joinpoint analysis of the crude incidence rate of idLOPin males showed a significantly increasing trend between 2001 and 2017 with APC4.8% (95%CI 1.1–8.7%, $p<0.001$). The age-standardized incidence rate in males showed a significantly increasing trend between 2005 and 2015, with APC 9.0% (95%CI 1.3 – 17.2%, $p<0.001$) (Figure 1). Crude mortality ratesof LOPnsin males showed asignificantly decreasing trend between 1999 and 2010with APC -7.5 (95%CI -14.3 - -0.2, $p<0.001$). The age-standardized mortality rate of idLOP in males showed a significantly decreasing trend during the period from 1999 to 2010 with APC -7.2% (95%CI -13.7 - -0.1, $p<0.001$) (Figure 2).

perioda od 1999. do 2010. godine, sa APC -7,2% (95% CI od -13,7 do -0,1; p < 0,001) (Grafikon 2). MIR je kod muškaraca pokazao značajan trend opadanja u periodu između 2001. i 2020. godine (APC -5,6, 95% CI od -9,2 do -1,8; p < 0,001) (Grafikon 3)

The MIR in males showed a significantly downward trend between 2001 and 2020 (APC -5.6, 95%CI -9.2 – -1.8, p<0.001) (Figure 3).

Tabela 1. Broj novoregistovanih pacijenata obolelih od nespecifičnog karcinoma usana, usta i farinksa podeljen na osnovu pola i starosti i odnos obolelih muškaraca i žena u centralnoj Srbiji od 1999. do 2020. godine

Table 1. Total number of new cases of other ill-defined sites of lip, oral cavity and pharynx cancer by age and gender, and M/F ratio in Central Serbia, between 1999-2020.

Period	Males				Females				M/F ratio
	Total	< 40	40-65	65+	Total	< 40	40-65	65+	
2020	31	0	9	22	11	1	2	8	2.8
2019	22	1	7	14	6	0	0	6	3.7
2018	16	0	7	9	7	0	2	5	2.3
2017	49	0	27	22	11	0	8	3	4.5
2016	32	0	19	13	6	0	3	3	5.3
2015	31	2	15	14	4	2	2	0	7.8
2014	15	0	8	7	7	0	4	3	2.1
2013	17	0	10	7	4	0	1	3	4.3
2012	18	0	9	9	13	0	7	6	1.4
2011	10	1	6	3	4	0	1	3	2.5
2010	13	0	6	7	1	0	1	0	13.0
2009	17	0	10	7	9	0	7	2	1.9
2008	12	0	4	8	6	0	3	3	2.0
2007	14	0	8	6	2	0	1	1	7.0
2006	18	0	11	7	2	1	0	1	9.0
2005	7	0	1	6	1	0	1	0	7.0
2004	18	1	15	2	5	0	3	2	3.6
2003	10	0	4	6	5	2	3	0	2.0
2002	12	0	8	4	2	1	1	0	6.0
2001	10	1	7	2	9	0	4	5	1.1
2000	27	0	15	12	2	0	1	1	13.5
1999	37	0	26	11	5	0	2	3	7.4
Total	436	6	232	198	122	7	57	58	3.6

Tabela 2. Broj pacijenata umrlih od nespecifičnog karcinoma usana, usta i farinksa podeljen na osnovu pola i starosti i odnos obolelih muškaraca i žena u centralnoj Srbiji od 1999. do 2020. Godine

Table 2. Total number of deaths of other ill-defined sites of lip, oral cavity and pharynx cancer by age and gender, and M/F ratio in Central Serbia, between 1999-2020

Period	Males				Females				M/F ratio
	Total	< 40	40–65	65+	Total	< 40	40–65	65+	
2020	19	0	11	8	5	0	1	4	3.8
2019	12	0	6	6	0	0	0	0	-
2018	13	0	4	9	4	0	1	3	3.3
2017	26	0	14	12	3	0	1	2	8.7
2016	31	0	18	13	4	0	2	2	7.8
2015	21	0	14	7	2	0	3	0	10.5
2014	14	0	10	4	2	0	2	0	7.0
2013	9	0	8	1	3	0	1	2	3.0
2012	11	0	3	8	5	0	2	3	2.2
2011	9	0	4	5	6	0	1	5	1.5

2010	9	0	6	3	3	0	1	2	3.0
2009	9	0	5	4	0	0	0	0	-
2008	14	0	5	9	6	0	2	4	2.3
2007	19	0	9	10	6	1	0	5	3.2
2006	28	0	15	13	7	0	3	4	4.0
2005	16	0	12	4	2	1	1	0	8.0
2004	22	3	11	8	6	0	4	2	3.7
2003	18	0	10	8	3	0	1	2	6.0
2002	16	0	7	9	4	0	3	1	4.0
2001	31	0	17	14	9	1	3	5	3.4
2000	30	0	13	17	2	0	1	1	15.0
1999	14	1	9	4	7	1	5	1	2.0
Total	391	4	211	176	89	4	38	48	4.4

Tabela 3. Broj novoregistovanih pacijenata, stopa incidencije i mortaliteta i standardizovana stopa incidecnije i mortaliteta nespecifičnog karcinoma usana, usta i farinksa u Centralnoj Srbiji od 1999 do 2020.godine

Table 3. Crude rate, ASR-W of incidence and mortality and mortality to incidence ratio of other ill-defined sites of lip, oral cavity and pharynx cancer, by gender in Central Serbia from 1999-2020

	Males						**Females**					
Period	Incidence		Mortality		MIR of CR	MIR of ASR	Incidence		Mortality		MIR of CR	MIR of ASR
	CR	ASR-W	CR	ASR-W			CR	ASR-W	CR	ASR-W		
2020	0.9	0.4	0.6	0.3	0.67	0.75	0.3	0.1	0.1	0.0	0.33	0.00
2019	0.7	0.3	0.4	0.2	0.57	0.67	0.2	0.0	0.0	0.0	0.00	
2018	0.5	0.2	0.4	0.2	0.80	1.00	0.2	0.1	0.1	0.0	0.50	0.00
2017	1.4	0.8	0.8	0.4	0.57	0.50	0.3	0.2	0.1	0.0	0.33	0.00
2016	0.9	0.5	0.9	0.5	1.00	1.00	0.2	0.1	0.1	0.0	0.50	0.00
2015	1.2	0.7	0.8	0.5	0.67	0.71	0.1	0.1	0.1	0.0	1.00	0.00
2014	0.6	0.3	0.5	0.3	0.83	1.00	0.3	0.1	0.1	0.1	0.33	1.00
2013	0.7	0.4	0.4	0.2	0.57	0.50	0.1	0.1	0.1	0.0	1.00	0.00
2012	0.7	0.4	0.4	0.3	0.57	0.75	0.5	0.2	0.2	0.1	0.40	0.50
2011	0.4	0.3	0.3	0.2	0.75	0.67	0.1	0.1	0.2	0.1	2.00	1.00
2010	0.5	0.3	0.3	0.2	0.60	0.67	0.0	0.0	0.1	0		
2009	0.7	0.4	0.3	0.2	0.43	0.50	0.3	0.2	0.0	0.0	0.00	0.00
2008	0.5	0.3	0.5	0.3	1.00	1.00	0.2	0.1	0.2	0.1	1.00	1.00
2007	0.5	0.3	0.7	0.4	1.40	1.33	0.1	0.0	0.2	0.1	2.00	
2006	0.7	0.4	1.1	0.6	1.57	1.50	0.1	0.0	0.3	0.1	3.00	
2005	0.3	0.1	0.6	0.4	2.00	4.00	0.0	0.0	0.1	0.1		
2004	0.7	0.5	0.8	0.5	1.14	1.00	0.2	0.1	0.2	0.1	1.00	1.00
2003	0.4	0.2	0.7	0.4	1.75	2.00	0.2	0.2	0.2	0.0	1.00	0.00
2002	0.5	0.3	0.6	0.3	1.20	1.00	0.1	0.1	0.1	0.1	1.00	1.00
2001	0.4	0.3	1.2	0.7	3.00	2.33	0.3	0.2	0.3	0.2	1.00	1.00
2000	1	0.6	1.1	0.7	1.10	1.17	0.1	0.0	0.1	0.0	1.00	
1999	1.4	0.9	0.5	0.4	0.36	0.44	0.2	0.1	0.2	0.2	1.00	2.00

CR – crude rate ASR-W – the age-standardized rate

Tabela 3. Analiza trenda incidencije i mortaliteta nespecifičnog karcinoma usana, usta i farinksa u Centralnoj Srbiji u periodu od 1999 do 2020.godine
Table 3. Joinpoint analysis of the trend in the crude rate, ASR-W of incidence and mortality rate and MIR of other and ill-defined sites of lip, oral cavity and pharynx cancer, by gender in Central Serbia from 1999-2020

	Period	APC	95%CI	p
Incidence - Crude rate	1999-2001	-49.0	-78.2-19.7	0.100
	2001-2017	4.8*	1.1-8.7	<0.001
	2017-2020	-5.9	-38.6-44.1	0.800
Incidence - ASR -W	1999-2001	-41.3	-73.5-30.1	0.200
	2001-2005	-8.6	-38.6-36	0.600
	2005-2015	9.0*	1.3-17.2	<0.001
	2015-2018	-15.8	-61.9-86.5	0.600
	2018-2020	8.2	-51.1-139.6	0.800
Mortality - Crude rate	1999-2010	-7.5*	-14.3--0.2	<0.001
	2010-2020	4.3	-4.5-13.9	0.300
Mortality - ASR -W	1999-2010	-7.2*	-13.7--0.1	<0.001
	2010-2020	1.7	-6.6-10.6	0.700
MIR male	1999-2001	84.1	-51-591.8	0.300
	2001-2020	-5.6*	-9.2--1.8	<0.001

* indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha =0.05 level, 95%CI – 95% confidence interval, trend for incidence, and mortality rate for females wasn't calculated

Diskusija

Naša studija utvrdila je da je stopa incidencije idLOP-a kod muškaraca u Srbiji povećana u periodu od 2005. do 2015. godine. Smrtnost od LOPns-a kod muškaraca pokazala je opadajući trend između 1999. i 2010. godine. Pored toga, ovaj trend prati i pad MIR-a kod muškaraca između 2001. i 2020. godine. U periodu obuhvaćenom istraživanjem, incidencija i stope mortaliteta kod žena bile su veoma niske i stabilne. Rezultati povećanja stope incidencije koherentni su i sa podacima zbirno objavljenim za karcinome ždrela (C09–C10, C12–C14) u Beogradu od 1999. do 2010. godine[11]. Ako se trend incidencije uporedi sa svetskim trendom incidencije orofaringealnog karcinoma, mogu se uočiti slični obrasci[14]. U ovoj studiji[14] oktriveno je da su slučajevi orofaringealnig karcinoma česti u razvijenim zemljama, među pripadnicima oba pola i među mlađom populacijom (starost manja od 60 godina). Literatura iz većine zemalja širom sveta pokazuje da je stopa oralnog karcinoma najmanje dva puta veća kod muškaraca nego kod žena starosti od 15 do 19 godina[15-19], što je i našom studijom za idLOP potvrđeno. Naši rezultati pokazuju da je ovaj karcinom bio čest kod muškaraca starijih od 40 godina, kao i da je, u proseku, polovina pacijenata imala između 40 i 65 godina.

Discussion

The temporal trend of incidence rates of idLOP in males in Serbia increased during the period of 2005–2015. The mortality of LOPns in males showed a decreasing trend between 1999 and 2010. In addition, this trend is followed by the decline of MIR in males between 2001 and 2020. In the study period, the incidence and mortality rates in females were very low and stable. The significantly increased incidence rate results are also coherent with the data published for pharyngeal cancers (C09-C10, C12-C14) in Belgrade from 1999 to 2010[11]. If we compare the incidence trend with the worldwide trend in the incidence of oropharyngeal cancer similar patterns can be noticed[14]. This study [14] revealed that OPC cases are common in developed countries, among both genders and in younger populations (age < 60 years). The literature from most countries worldwide demonstrates that the rate of oral cancer is at least twice as high in males than in females[15-19], as we confirmed in our study for the idLOP. This cancer was common in males over 40 years, and on average half of the patients were between 40-65 years. This observation suggests that sex and age should be taken into consideration as factors increasing the risk of developing idLOP.

Ovakvi nalazi treba da ukažu na to da se pol i starost razmatraju kao faktori koji povećavaju rizik od razvoja idLOP-a.

Nedavno istraživanje u Srbiji pokazalo je da je stopa mortaliteta od orofacijalnih karcinoma u našoj zemlji u sedamnaestogodišnjoj analizi trenda stabilna[10]. Naši ažurirani podaci za idLOP pokazuju da su stope mortaliteta u opadanju između 1999. i 2010. godine. Slični rezultati prijavljeni su za istu MKB-10 dijagnozu u Brazilu za slični period praćenja, između 2002. i 2013. godine[20], i u SAD-u, za period između 1999. i 2020. godine[18]. Na smanjenje mortaliteta od karcinoma delom bi moglo uticati poboljšanje u definisanju specifičnih lokalizacija karcinoma ove regije. Smanjenje stope smrtnosti od idLOP-a, karcinoma koje je, kako se smatra, teško klinički ispitati, može biti posledica poboljšanog pristupa zdravstvenim ustanoyama i naprednim hirurškim metodama.

Životni stilovi su društveno strukturirani, a procene sugerišu na to da bi se gotovo 70% slučajeva karcinoma moglo izbeći zahvaljujući promenama u načinu života, koje se tiču pušenja, alkohola, ishrane i seksualnog ponašanja[21]. Nacionalni profil faktora rizika za orofacijalne karcinome, kojima pripada i idLOP, uključuje prekomerno pušenje, konzumaciju alkohola i visoku prevalenciju HPV infekcija. Srbija se još uvek smatra državom sa veoma visokom stopom pušenja[22], a efekti u smanjenju pušenja još nisu procenjeni[23]. Takođe, studije su pokazale da našu zemlju karakteriše prekomerna konzumacija alkohola u različitim populacijama[24-26].

Među mogućim faktorima rizika za nastanak karcinoma orofacijalne regije nalaze se HPV infekcije[27], kojima se poslednjih godina posvećuje posebna pažnja. Sa HPV infekcijom[28] se takođe povezuje predilekciona mesta na usni, usnoj duplji i ždrelu. Podaci iz novijih istraživanja pokazuju da u Srbiji postoji generalno visoka prevalencija HPV infekcije, kao i visoka prevalencija HPV-a, 16/18 kod žena sa zdravom kožom i normalnom citologijom u cervikalnoj šupljini[29,30], što ukazuje na to da bi HPV vakcinacija mogla biti primarna preventivna strategija u smanjenju karcinoma ove regije. Međutim, ona u našoj zemlji za sada nije deo obaveznog nacionalnog programa imunizacije[31]. Sve navedeno vezano za faktore rizika upotpunjuje sliku Srbije kao zemlje sa visokom učestalosti faktora rizika od pojave orofacijalnog karcinoma. Primena preventivnih mera sa ciljem smanjenja faktora rizika svakako može dati kumulativni efekat; ipak, efekti ovih mera ispoljavaju se tek nakon dugotrajnog perioda primene.

A recent analysis in Serbia showed that the mortality rate of orofacial cancers in our country in the 17-year trend analysis is stable [10]. Our study shows that mortality rates have been declining between 1999 and 2010. Similar results were reported for the same ICD-10 code in Brazil for a similar period, between 2002–2013[20] and in the US between 1999–2020[18]. The decline in this cancer group could also be affected by the improvement in defining the specific location of the death cause. The reduction in mortality rate in these cases, which are considered difficult to examine clinically, may be due to the increased access to healthcare facilities and advanced surgical methods.

Lifestyles are socially structured, and estimates suggest that nearly 70% of cases could be avoided through lifestyle changes such as smoking, alcohol, diet, and sexual behaviour[21]. National risk factors profilefor OPC cancers include excessive smoking, alcohol consumption and high HPV prevalence. Serbia is still considered to have an exceptionally high smoking rate[22], and the effects of tobacco control[23] haven't been estimated yet. Studies reported that our country is characterized by excessive alcohol consumption in different populations[24-26].

In the group of possible risk factors forOPC cancers, special attention was drawn to HPV infection[27]. Other and ill-defined sites in the lip, oral cavity,and pharynx[28] cancers are associated with HPV infection. Recent data show that, in Serbia, there is a high prevalence of HPV infection in general and 16/18 women with healthy skin and normal cytology in the cervical cavity[29]. These findings are consistent with the latest research[30]. Therefore, HPV vaccination can be a primary prevention strategy in reducing OPC generally, but in our country, this vaccine is not part of the mandatory national immunization program[31]. The facts mentioned above complete Serbia's image of a country with high levels of risk factors for OPC generally. However, these preventive measures may be able to alter or reduce the rates only for a long time since carcinogen factors have cumulative effects and a long-time delay. Also, considering the association between the impact of HPV immunization and the reduction of oropharyngeal cancer, estimation of lung cancer trends should be included.

The idLOP cancer is specific because the ICD-10 code C14 can be classified as oropharyngeal cancer (C14.0 and C14.2), but also includes overlapping lesions of lip, oral cavity, and pharynx.

Efekte imunizacije HPV vakcinom treba dodatno analizirati uz procenu trenda karcinoma pluća.

Ovaj tip karcinoma, označen prema MKB-10 kao C14, može se klasfikovati dvojako, kao karcinom orofaringsa (C14.0 i C14.2), ali takođe uključuje uznapredovale lezije usne, usne duplje i ždrela. Prijavljene stope incidencije za ovaj karcinom do 2007. godine bile su manje od stopa mortaliteta, što može ukazati na nedostatke u Nacionalnom registru karcinoma, jer je MIR za idLOP bio veći od 1. Ovaj pokazatelj može se višestruko analizirati. MIR se najpre može koristiti za procenu preživljavanja kod pacijenata sa idLOP-om[12]. Prema našim podacima, MIR za idLOP se kontinuirano smanjivao sa 2,33 u 2001. godini na 0,67 i 0,75 u 2019. i 2020. godini, s vrhuncem vrednosti od 4,00 u 2005. godini. Moguće je da je smanjenje od 5,6% u MIR-u idLOP-a pokazatelj boljeg preživljavanja ovog raka tokom dvadesetak godina. Glavni razlozi povećanja stope preživljavanja verovatno su opsežniji programi preventivnih pregleda i rano otkrivanje bolesti, kao i unapređenje znanja i stavova o strategijama u smanjenju preventibilnih faktora rizika i povećanje kvaliteta zdravstvene zaštite, koja se pruža pacijentima sa orofacijalnim karcinomima. Drugo, ukoliko sagledavamo vrednosti MIR-a u odnosu na vrednosti incidencije ovog tipa karcinoma[32], može se očekivati da je porast incidencije delom posledica poboljšanja kvaliteta Nacionalnog registra karcinoma. Konkretno, analiza nedovoljno definisanih lokalizacija karcinoma jedan je od značajnih pokazatelja kompletnosti Nacionalnog registra karcinoma[33]. Treće, pomenuta MKB-10 šifra klasifikovana je kao garbage dijagnoza sa umerenim uticajem na donošenje odluka javnozdravstvene politike[34]. Preterana upotreba garbage dijagnoza maskira pravi obrazac smrtnosti u jednoj populaciji. Stoga, na osnovu naših nalaza o povećanju stope incidencije idLOP-a i padu mortaliteta i MIR-a moglo bi se zaključiti da je prevalencija faktora rizika za orofacijalne karcinome visoka u našoj zemlji, da postoje određenja poboljšanja u kompletnosti registra karcinoma, kao i u popunjavanju potvrda o smrti tokom 22 godine.

Ograničenja studije

Postoji nekoliko mogućih ograničenja ove studije. Strategije prevencije raka proizlaze iz epidemioloških podataka; zato je vrlo važna procena kvaliteta registra raka.

Until 2007, the reported incidence rates were less than the mortality rates, meaning there were many gaps in the cancer registry, and diagnosis was delayed. The period before 2007 was characterized by the MIR of idLOP higher than 1. This indicator can be analyzed manifold. Firstly, the MIR can be used to indicate survival in idLOP patients[12]. According to our findings, the overall trend of idLOP MIR continuously decreased from 2.33 in 2001 to 0.67 and 0.75 in 2019 and 2020, with a peak in 2005 (4.00). Hopefully, the 5.6% reduction in MIR of idLOPis an indicator of improved survival from this cancerover 20 years. The main reasons for the increase in survival rates are probably more extensive screening programs and early detection of diseases, as well as the promotion of knowledge and attitudes about strategies in the reduction of modifiable risk factors and the promotion of improved care for patients with oral cancers. Secondly, if the incidence is related to the MIR of idLOP[32], we might expect a rise in incidence to be a consequence of improving cancer registry completeness. Particularly, the analysis of the ill-defined cancer site is a significant indicator of the completeness of the cancer registry[33]. Thirdly, this ICD-10 code is classified as garbage code with a medium impact on policy-making[34]. Excessive use of garbage codes masks the true mortality pattern. Therefore, according toour findings of an increase in the incidence rate of idLOP and a decline in mortality and MIR, it might be summarized that risk factors for orofacial cancers persist, but the completeness of the cancer registry and quality of death certificates improved over 22 years.

Limitations of the study

There are several possible limitations to this study. Strategies for cancer prevention are derived from the epidemiological data. Therefore, the level of quality of the cancer register is important. The quality of the cause of death data in Serbia has been rated moderately by the World Health Organization [35]. Also, moderate quality of death data can be assumed based on the percentage of unknown and ill-defined cancer deaths in our country[36]. The anatomical definition of cancer in this sector is usually not the same among studies, which makes comparisons of incidence, mortality, or survival challenging.

Svetska zdravstvena organizacija procenila je kvalitet podataka o uzrocima smrti u Srbiji kao umeren[35]. Takođe, umeren kvalitet naših mortalitetnih podataka može se potvrditi na osnovu udela nedovoljno definisanih stanja u ukupnom mortalitetu[36], te podatke dobijene iz registra treba analizirati sa određenom rezervom. Sem toga, anatomska klasifikacija karcinoma ove regije je heterogena u studijama, pa je poređenje rezultata vrlo izazovno.

Zaključak

Orofaringealni karcinomi mogu se u velikoj meri sprečiti kontrolom faktora rizika povezanih sa zdravim stilovima života. Analiza trenda stopa incidencije i mortaliteta od karcinoma od ključnog je značaja za epidemiološki nadzor karcinoma. Stope incidencije idLOP-a pokazale su porast, koji prate smanjena stopa smrtnosti i MIR-a u Srbiji između 1999. i 2020. godine. Ovi nalazi ukazuju na moguće poboljšanje kompletnosti i kvaliteta registra karcinoma. S druge strane, zemlje u razvoju prolaze transformaciju od zaraznih bolesti ka nezaraznim bolestima, što potencijalno upućuje na to da se deo porasta incidencije ovih karcinoma može pripisati i ovoj transformaciji[37]. Posledično, povećanje stope incidencije ukazuje na visoku prevalenciju faktora rizika, uglavnom pušenja i konzumiranja alkohola, što sugeriše na to da postoji potreba za kreiranjem nacionalne javnozdravstvene strategije sa ciljem smanjenja upotrebe alkohola i duvana.

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Conclusion

OPC cancers can be highly prevented by controlling the risk factors associated with a healthy lifestyle. Examining cancer incidence and mortality rates is critical for cancer epidemiology and surveillance. The cancer incidence rates for other and ill-defined sites in the lip, oral cavity, and pharynx showed a rise, followed by a decline in mortality rates and MIR in Serbia between 1999 and 2020. These findings imply possible improvement in completeness of cancer registry. On the other hand, developing countries underwent a transformation from infectious illnesses to noncommunicable diseases, potentially indicating that this rise can be attributable to the transition [37]. Subsequently, the high presence of risk factors, mostly smoking and drinking, suggests that public health initiatives should be taken at the national level. Those initiatives should be focused on cost-effective procedures to reduce alcohol and tobacco use.

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