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TREND INCIDENCIJE I MORTALITETA OD KARCINOMA USNE U CENTRALNOJ SRBIJI U PERIODU OD 1999. DO 2014.

TREND OF THE INCIDENCE AND MORTALITY RATE OF LIP CANCER IN CENTRAL SERBIA FROM 1999-2014

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Sažetak

Uvod: Karcinom usne je najčešći oralni karcinom.

Cilj ovog rada bio je da se prikaže i proceni trend incidencije i mortaliteta od karcinoma usne u centralnoj Srbiji u periodu od 16 godina, od 1999. do 2014.

Materijal i metode: Epidemiološka studija zasnovana je na podacima koji su javno dostupni iz registra karcinoma "Incidencija i mortalitet od raka u centralnoj Srbiji" koji objavljuje Institut za javno zdravlje Srbije za period od 1999. do 2014. godine. Trend i godišnja procentualna promena (APC), sa odgovarajućim 95% intervalom poverenja, izračunati su pomoću joinpoint regresione analize.

Rezultati: U centralnoj Srbiji, u periodu 1999. - 2014. godine, registrovano je ukupno 1922 novoobolelih od karcinoma usne (1402 muškarca i 520 žena). Stopa incidencije i standardizovana stopa incidencije imaju statistički značajan trend pada u muškoj populaciji ($p = 0,001$, odnosno $p < 0,001$) tokom ispitivanog perioda, sa APC 4,3%, odnosno 5,2%. Kod žena, incidencija i standardizovana stopa incidencije pokazuju statistički značajan trend pada u periodu 2003.- 2011. godine, odnosno 2006. - 2011. godine, sa APC 12,3, odnosno 24,3%. Standardizovana stopa mortaliteta kod muškaraca pokazuje statistički značajan trend pada kod muškaraca sa APC, 4,5%.

Zaključak: U ispitivanom periodu trend incidencije kod muškaraca pada. Kod žena trend je divergentnog karaktera. Stopa mortaliteta karcinoma usne kod oba pola je niska i stabilna.

Ključne reči: karcinom usne, incidencija, mortalitet, registar karcinoma, trend

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Abstract

Background: Lip cancer is the most frequent oral cancer.

The aim of this study was to present and estimate trends in the incidence and mortality of lip cancer in Central Serbia during a 16-year period, from 1999 to 2014.

Material and methods: This registry-based study was carried out based on the data extracted from publicly available Yearbooks of the Institute of Public Health of Serbia – Incidence and Mortality in Central Serbia, from 1999 to 2014. The trend and the annual percentage change (APC) of the incidence and mortality rate with the corresponding 95% confidence intervals were calculated by performing joinpoint regression analyses.

Results: A total number of 1,922 cases (1,402 in men and 520 in women) of lip cancer were registered in Central Serbia from 1999 to 2014. The crude rate (CR) and age-standardized rate (ASR-W) of the incidence in males decreased ($p=0,001$, $p<0,001$, respectively) during the study period with APC of 4.3%, 5.2%, respectively. In females, CR and ASR-W of incidence showed the only significant trend between 2003-2014, 2006-2014, respectively with APC 12.3, 24.3%, respectively. ASR-W of mortality rate in males showed the decreasing trend with APC 4.5%.

Conclusions: Our results reveal that the incidence of lip cancer declines through the study period. The mortality rate is low and stable.

Key words: lip cancer, incidence rate, mortality rate, cancer registry, trends

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Uvod

Razvoj kancera nastaje usled interakcije različitih faktora rizika, kako unutrašnjih, kao što je genetska predispozicija, tako i spoljašnjih, kao što su životne navike i faktori sredine. Karcinom usta, zajedno sa drugim oralnim i faringealnim karcinomima, šesti je najčešći karcinom^{1,2}. Karcinom usta se predominantno javlja kod muškaraca³. Muška predominantnost je rezultat profesionalne i razlike u ponašanju između polova. Rad i aktivnosti na otvorenom su daleko češći kod muškaraca. Pored toga, najčešće je ovim karcinomom zahvaćana populacija starija od 60 godina. Preko 60% novoobolelih od karcinoma usta su stariji pacijenti⁴.

Skvamocelularni karcinom (SCCs) je dominantni histopatološki tip karcinoma usta⁵. SCCs je karakterističan za karcinom donje usne, dok se bazocelularni karcinomi (BCC) mnogo češće javljaju na gornjoj usni^{6,7}. Zbog svoje lokalizacije, karcinom usta deli faktore rizika sa karcinomima kože, oralnim karcinomima i karcinomima nasofarinksa. Zbog toga su glavni faktori rizika za nastanak karcinoma usne: pušenje, konzumacija alkohola, izlaganje sunčevom zračenju, posebno za spoljašnji karcinom usne⁸.

Srbija je prepoznata kao zemlja sa velikim udelom oralnih karcinoma koji se potencijalno mogu izbegnuti⁹. Zato je cilj ovog rada bio da prikaže i proceni trend incidencije i mortaliteta od karcinoma usne u centralnoj Srbiji u periodu od 1999. do 2014. godina.

Materijal i metode

Ova epidemiološka studija je sprovedena na osnovu podataka dobijenih iz javno dostupnog registra kancera – “Incidencija i mortalitet od raka u centralnoj Srbiji” koji objavljuje Institut za javno zdravlje Srbije za period od 1999. do 2014. godine, u kojima su incidencija i mortalitet prikazani prema polu i starosnoj strukturi i prema dijagnozi. Standardizovane stope incidencije i mortaliteta su izračunate na osnovu ovih podataka za oba pola. Karcinom usne je kodiran prema Međunarodnoj klasifikaciji bolesti – deseta revizija¹⁰. Odnos mortaliteta i incidencije (MIR) je dobijen deljenjem stope mortaliteta i incidencije i deljenjem standardizovane stope mortaliteta i standardizovane stope incidencije za svaku godinu.

Introduction

Cancer develops in the interaction of risk factors which include internal factors such as genetic susceptibility and hormonal factors and external factors such as life style and environmental factors. Lip cancer, along with other oral and pharyngeal cancer is the sixth most common cancer type worldwide^{1,2}. Lip cancer is far more common in men³. Male predominance is a result of occupational and behavioral differences among sexes. Outdoor working and outdoor activities are far more frequent in males. The population over 60 is the most affected with lip cancer. Over 60% of new cases of lip cancer occurred in older patients⁴.

Squamous cell carcinomas (SCCs) is the dominant histological type of lip cancer⁵. SCCs are typical of the lower lip, while basal cell carcinoma (BCC) is more frequent in the upper lip^{6,7}. Because of its location, lip cancer shares risk factors with skin cancers and cancers of the oral cavity and nasopharynx. Therefore, the main risk factors for lip cancer are: smoking, alcohol consumption and sun exposure, especially for external lip cancer⁸. Serbia was recognized as a country with a large proportion of potentially avoidable oral cancer⁹. The aim of this study was to present and estimate trends in the incidence and mortality of lip cancer in Central Serbia from 1999 to 2014.

Materials and Methods

This registry-based study was carried out based on the data extracted from publicly available Yearbooks of the Institute of Public Health of Serbia – Incidence and Mortality in Central Serbia, from 1999 to 2014, in which the incidence and mortality rates were aggregated and stratified by sex, 5-year age groups, and diagnosis. The age-standardized incidence and mortality rate in both sexes were calculated based on those data. Lip cancer was coded according to the tenth Revision of International Classification of Disease (codes C00-C96)¹⁰. Mortality to incidence ratio (MIR) was calculated by dividing the crude rate of mortality by crude rate of incidence for each year. The trend and the annual percentage change (APC) of the incidence and mortality rate with corresponding 95% confidence intervals (95% CI) were calculated by performing join point

Trend i godišnja procentualna promena incidencije i mortaliteta sa 95% intervalom poverenja (95%CI) izračunati su joinpoint regresionom analizom. 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 <http://surveillance.cancer.gov/joinpoint>). Promena trenda je smatrana statistički značajnom ukoliko je p-vrednost manja od 0,05.

Rezultati

U centralnoj Srbiji su u periodu 1999.-2014. registrovana ukupno 1922 novoobolela od karcinoma usne (1402 muškarca i 520 žena). Odnos muškaraca prema ženama je 2,8:1. Tabela 1 prikazuje distribuciju novo-obolelih od ovog karcinoma, stopu incidencije i mortaliteta, standardizovane stope incidencije i mortaliteta (ASR-W, standardizovane na svetsku populaciju) i MIR za prikazane stope u ispitivanom periodu kod muškaraca u centralnoj Srbiji. Najveća stopa incidencije i standardizovana stopa incidencije kod muškaraca bila je 2001. godine (5,0, odnosno 2,9), a najniža stopa incidencije i standardizovana stopa incidencije bila je 2011. godine (1,5, odnosno 0,8). Kod muškaraca, najviši mortalitet i standardizovana stopa mortaliteta bila je 2006. (0,9, odnosno 0,4), a najniža u 2012. godini (0,3, odnosno 0,2). Kod žena, najviša stopa incidencije i standardizovana stopa incidencije bila je u 2009. godini, a najniža vrednost ovih stopa bila je u 2010. i u 2011. godini (1,9, odnosno 1,0). Najviša vrednost mortaliteta i standardizovana stopa mortaliteta kod žena bile su u 1999. i 2012. godini (0,4, odnosno 0,2). Zajednička tačka regresione analize incidencije kod muškaraca pokazuje statistički značajan trend pada u periodu 1999.-2014. sa APC 4,3% (95%CI -6,5 - -2,0%, $p=0,001$). Kod žena, stopa incidencije pokazuje trend blagog porasta, koji nije statistički značajan u periodu 1999.-2003. i 2011.-2014. godine, i trend statistički značajnog pada u periodu 2003.-2011. sa APC 12,3% (95%CI -19,1 - -5,0%, $p=0,008$) (Tabela 3, Slika 1). Stopa mortaliteta kod oba pola je pokazala trend pada vrednosti koji nije statistički značajan u ispitivanom periodu (Slika 2).

regression analyses. 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 <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 number of 1,922 cases (1,402 in men and 520 in women) of lip cancer were registered in Central Serbia from 1999 to 2014. The men to women ratio was 2.8:1. Table 1 presents the distribution of new cases of lip cancer, the crude rate of incidence and mortality, the age-standardized incidence and mortality rate (ASR-W; to the world population) and mortality to incidence rate (MIR) to the specified rates according to the years of observation in males. The highest CR and ASR-W of incidence in males were in 2001 (5.0, 2.9 respectively), and the lowest values of those rates were in 2011 (1.5, 0.8 respectively). In males, the CR and ASR-W of mortality rate were highest in 2006 (0.9, 0.4, respectively), and lowest in 2012 (0.3, 0.2, respectively).

In females, the highest CR and ASR-W of incidence in 2009 (1.9, 1.0, respectively), and the lowest values of those rates were in 2010 and 2011 (0.6, 0.2, respectively). In females, the CR and ASR-W of mortality rate were highest in 1999 and 2012 (0.4, 0.2, respectively).

Joinpoint analysis of the crude rate of incidence of lip cancer in males showed a significantly decreasing trend between 1999 and 2014 with APC 4.3% (95%CI -6.5 - -2.0%, $p = 0.001$). In females, the crude rate of the incidence of lip cancer showed a non-significantly increasing trend between 1999 and 2003 and between 2011 and 2014, and a significantly decreasing trend between 2003-2011 with APC 12.3% (95%CI -19.1- -5.0%, $p=0.008$) (Table 3, Figure 1). Crude rates of mortality of lip cancer in both sexes showed a non-significant decreasing trend between 1999 and 2014 (Figure 2).

Tabela 1. Broj novoregistrovanih pacijenata, stopa incidencije i mortaliteta i standardizovana stopa incidence i mortaliteta karcinoma usta kod muškaraca u centralnoj Srbiji od 1999. do 2014.

Table 1. The number of newly registered cases, the crude rate and the age-standardized incidence and mortality rate of lip cancer in males from Central Serbia from 1999-2014

Year	Incidence			Mortality			MIR of CR	MIR of ASR-W
	Count	CR	ASR-W	Count	CR	ASR-W		
1999	105	3.9	2.1	18	0.7	0.4	0.18	0.19
2000	107	4.0	2.3	16	0.6	0.3	0.15	0.13
2001	132	5.0	2.9	13	0.5	0.3	0.10	0.10
2002	108	4.1	2.3	17	0.6	0.3	0.15	0.13
2003	93	3.5	2.0	10	0.4	0.2	0.11	0.10
2004	115	4.3	2.5	12	0.5	0.2	0.12	0.08
2005	92	3.5	1.8	17	0.6	0.3	0.17	0.17
2006	91	3.5	1.8	23	0.9	0.4	0.26	0.22
2007	74	2.8	1.6	13	0.5	0.2	0.18	0.13
2008	75	2.9	1.5	22	0.8	0.4	0.28	0.27
2009	90	3.5	1.8	12	0.5	0.2	0.14	0.11
2010	72	2.8	1.5	10	0.4	0.2	0.14	0.13
2011	40	1.5	0.8	14	0.5	0.2	0.33	0.25
2012	77	3.0	1.6	8	0.3	0.1	0.10	0.06
2013	58	2.3	1.1	10	0.4	0.2	0.17	0.18
2014	73	2.9	1.4	15	0.6	0.2	0.21	0.14

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

Tabela 2. Broj novoregistrovanih pacijenata, stopa incidencije i mortaliteta i standardizovana stopa incidencije i mortaliteta karcinoma usta kod žena u centralnoj Srbiji od 1999. do 2014.

Table 2. The number of new cases, the crude rate and the age-standardized incidence and mortality rate of lip cancer in females from Central Serbia from 1999-2014

Year	Incidence			Mortality			MIR of CR	MIR of ASR-W
	Count	CR	ASR-W	Count	CR	ASR-W		
1999	25	0.9	0.5	10	0.4	0.2	0.44	0.40
2000	27	1.0	0.5	4	0.1	0.1	0.10	0.20
2001	43	1.5	0.7	9	0.3	0.1	0.20	0.14
2002	48	1.7	0.8	7	0.2	0.1	0.12	0.13
2003	53	1.9	1.0	3	0.1	0.0	0.05	0.00
2004	33	1.2	0.5	9	0.3	0.1	0.25	0.20
2005	43	1.5	0.8	8	0.3	0.1	0.20	0.13
2006	36	1.3	0.7	4	0.1	0.0	0.08	0.00
2007	39	1.4	0.6	5	0.2	0.0	0.14	0.00
2008	33	1.2	0.5	3	0.1	0.0	0.08	0.00
2009	28	1.0	0.4	5	0.2	0.0	0.20	0.00
2010	17	0.6	0.2	6	0.2	0.1	0.33	0.50
2011	17	0.6	0.2	7	0.3	0.1	0.50	0.50
2012	21	0.8	0.3	10	0.4	0.1	0.50	0.33
2013	28	1.0	0.3	3	0.1	0.0	0.10	0.00
2014	29	1.1	0.4	3	0.1	0.0	0.09	0.00

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

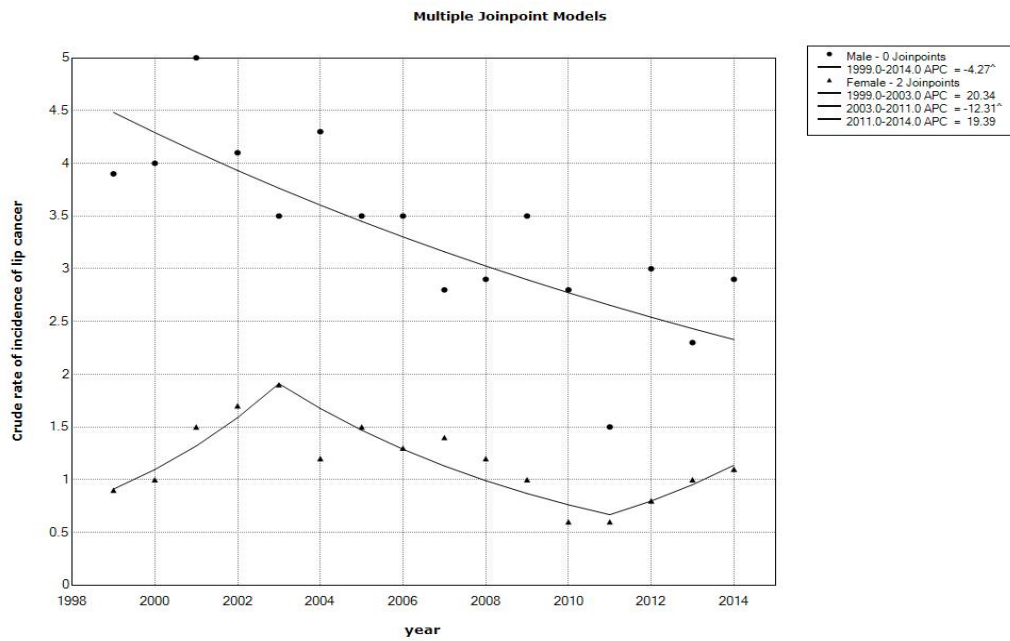
Tabela 3. Analiza trenda incidencije i mortaliteta karcinoma usta u centralnoj Srbiji u periodu od 1999. do 2014.**Table 3.** Joinpoint analysis of the trend in the crude rate of incidence and mortality rate of lip cancer in Central Serbia from 1999-2014

Crude rate - Incidence	Segment	Period	APC	95%	p-value
Male - 0 Joinpoints	1	1999-2014	-4.3 [^]	-6.5 - -2.0	0.001
Female - 2 Joinpoints	1	1999-2003	20.3	-0.5 -45.6	0.055
Female - 2 Joinpoints	2	2003-2011	-12.3 [^]	-19.1 - -5.0	0.008
Female - 2 Joinpoints	3	2011-2014	19.4	-11.7 -61.4	0.052
Crude rate -mortality					
Male - 0 Joinpoints	1	1999-2014	-2.1	-5.1-1.0	0.163
Female - 0 Joinpoints	1	1999-2014	-2.0	-8.1-4.5	0.511
ASR-W Incidence rate					
Male - 0 Joinpoints	1	1999-2014	-5.2 [^]	-7.4 - -2.9	<0.001
Female - 2 Joinpoints	1	1999-2006	5.2	-5.2 – 16.7	0.296
Female - 2 Joinpoints	2	2006-2011	-24.3 [^]	-40.9 - -3.1	0.031
Female - 2 Joinpoints	3	2011-2014	26.9	-14.1 – 87.4	0.197
ASR-W Mortality rate					
Male – 0 Joinpoints	1	1999-2014	-4.5 [^]	-7.8 – -2.8	0.015
Female -	Not calculated				

[^] 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 ASR-W mortality rate for females was not calculated

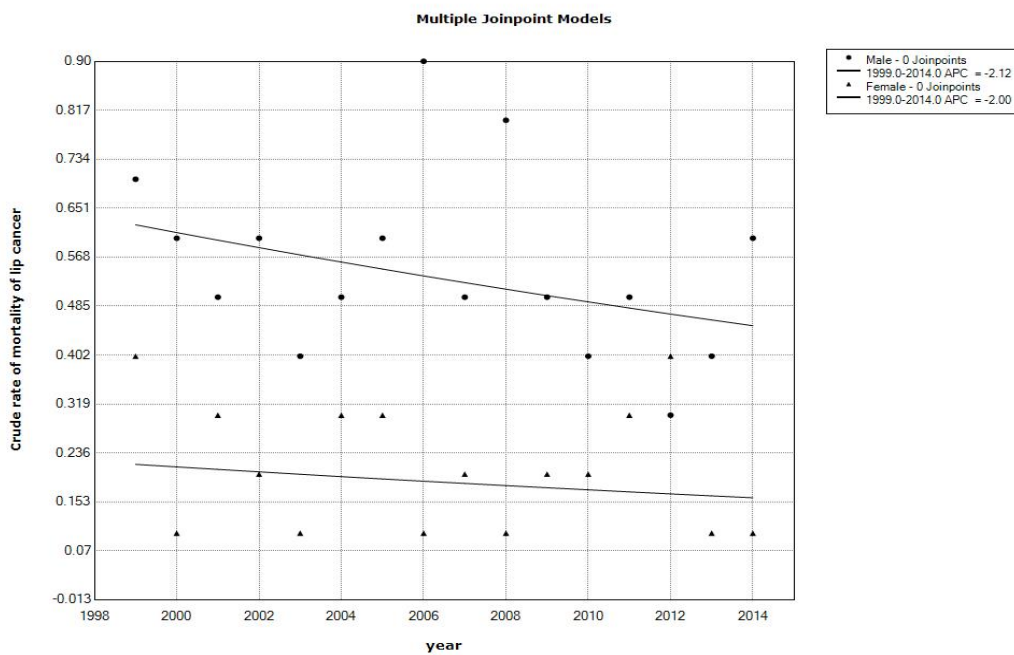
Standardizovana stopa incidencije kod muškaraca je pokazala statistički značajan trend pada vrednosti u periodu 1999.-2014. sa APC 5,2% (95%CI -7,4 - - 2,9%, p < 0,001). Kod žena je standardizovana stopa incidencije pokazala statistički značajan trend pada u periodu 2006.-2011. godine, sa APC -24,3% (95%CI -40.9 - - 3.1, p = 0,031) (Slika 3). Standardizovana stopa mortaliteta od karcinoma usne kod muškaraca je pokazala statistički značajan trend pada u ispitivanom periodu sa APC 4,5% (95%CI -7.8 - -2,8, p = 0,015) (Slika 4).

The age-standardized incidence rate in males showed a significantly decreasing trend between 1999 and 2014 with APC 5.2% (95%CI -7.4 - -2.9%, p < 0.001). In females, the age-standardized incidence rate of lip cancer showed the only significant trend between 2006 and 2011 with APC -24.3% (-95%CI -40.9 - -3.1, p=0.031)(Figure 3). The age-standardized mortality rate of lip cancer in males showed a significantly decreasing trend during the period from 1999-2014 with APC -4.5% (95%CI -7.8 - -2.8, p = 0.015)(Figure 4).



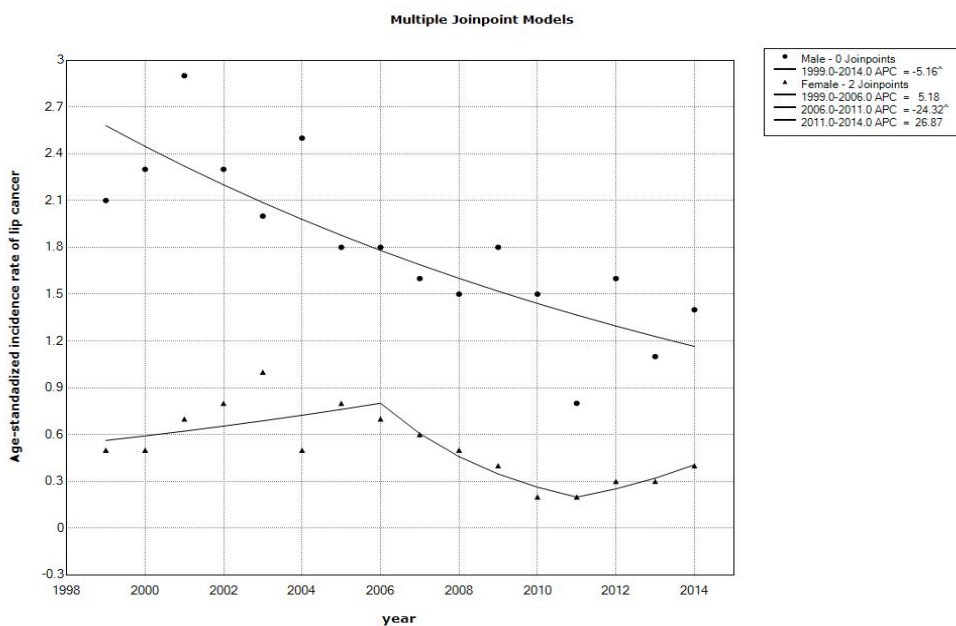
Slika 1. Trend stope incidencije karcinoma usta u centralnoj Srbiji u periodu od 1999. do 2014.

Figure 1. The trend of crude rate of incidence of lip cancer in Central Serbia from 1999-2014



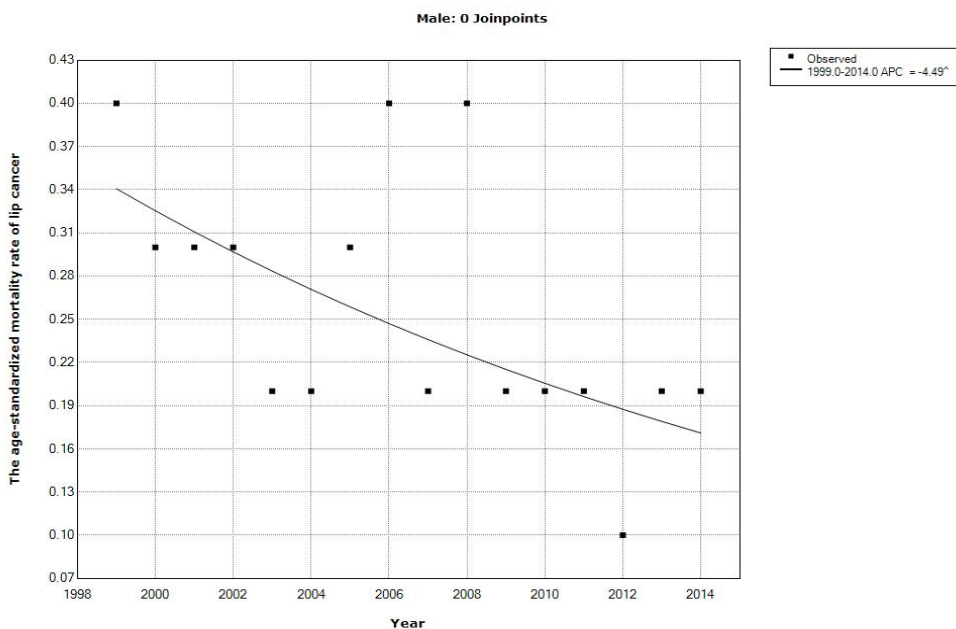
Slika 2. Trend mortaliteta karcinoma usta u centralnoj Srbiji u periodu od 1999. do 2014.

Figure 2. The trend of crude rate of mortality of lip cancer in Central Serbia from 1999-2014



Slika 3. Trend stanadardizovane stope incidencije karcinoma usta u centralnoj Srbiji u periodu od 1999. do 2014.

Figure 3. The trend of ASR-W of incidence of lip cancer in Central Serbia from 1999-2014



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 0 Joinpoints.

Slika 4. Trend stanadardizovane stope mortaliteta karcinoma usta u centralnoj Srbiji u periodu od 1999. do 2014.

Figure 4. The trend of ASR-W of mortality of lip cancer in Central Serbia from 1999-2014

Diskusija

Glavni nalaz ove studije je trend pada incidencije karcinoma usne kod muškaraca i niska, bez promena, vrednost mortaliteta kod oba pola. U ispitivanom periodu kod žena postoji divergentni trend, nakon statistički značajnog pada incidencije u periodu 2006.-2011, postoji trend blagog porasta koji nije statistički značajan sve do kraja ispitivanog perioda. Rezultati pada trenda incidencije karcinoma usne su u skladu sa podacima koji su objavljeni za grad Beograd za period 1999.-2011¹¹. Profil karcinoma usne u Beogradu se gotovo kompletno poklapa sa profilom za centralnu Srbiju koji je dobijen u ovom istraživanju. Globalno gledano, smanjenje incidencije u centralnoj Srbiji se poklapa sa podacima publikovanim za Evropu (3) i Sjedinjene Američke Države¹². Odnos muškarac/žena (2,8) približan je vrednostima koje su dobijene na globalnom nivou (2,5)⁴. Generalno, smanjenje ovog odnosa je registrovano delom zbog smanjenja incidencije kod muškaraca, a delom i zbog povećanja incidencije kod žena, posebno zbog porasta incidencije karcinoma gornje usne^{3,13}.

Nedavno publikovana studija³ je utvrdila da je 60% oralnih karcinoma, karcinoma jednjaka, larinksa, grlića materice i mokraćne bešike moguće izbeći, odnosno prevenirati. Stoga, fokus javnog zdravlja treba da bude na merama prevencije i smanjenja učestalosti faktora rizika. Glavni faktori rizika za karcinom usne su: pušenje^{3,14}, konzumiranje alkohola^{15,16} i izlaganje sunčevom zračenju. Prvi korak u smanjenju faktora rizika za nastanak ovog karcinoma na nacionalnom nivou je postignut donošenjem zakona o zaštiti stanovništva od izloženosti duvanskom dimu¹⁷.

Ipak, Srbija i dalje ima reputaciju zemlje sa vrlo visokom prevalencijom pušenja, smatra se delom jer je pušenje povezano sa brojnim socio-ekonomskim faktorima. Studija sprovedena u našoj zemlji je pokazala da su najveći zavisnici od pušenja bile najsiromašnije žene¹⁸. Pušenje i konzumiranje alkohola su dobro utvrđeni faktori rizika^{1,19}. Pušenje i konzumiranje alkohola imaju i individualno i sinergističko dejstvo. Kombinacije pušenja i teškog alkoholizma stvara 38 puta veću šansu za razvoj karcinoma usne u odnosu na one koji ne upražnjavaju nijednu od ovih navika²⁰. Osim toga, visoka stopa incidencije ovog karcinoma se poklapa teritorijalno sa velikom konzumacijom alkohola u centralnoj i istočnoj Evropi⁴.

Discussion

The main finding of the study is a decreasing trend of the incidence of lip cancer in men and low and stable mortality in both sexes. In the study period, the incidence rate in females showed divergent trends, and after a significant decrease in the incidence between 2006 and 2011, there was the trend of a non-significant increase until the end of the study period. The results of significantly decreased rates are also coherent with the data published for lip cancer in Belgrade from 1999-2010¹¹. Lip cancer profile in Belgrade almost matches Central Serbia profile. In global terms, a declining incidence trend of lip cancer in Central Serbia parallels observations from Europe (3) and the United States¹². The male:female ratio (2.8) is similar to the global M/F ratio (2.5)⁴. Generally, a declining trend of M/F ratio was noticed partly due to decreasing of incidence in males, and partly due to rising of incidence in females, especially the incidence of the upper lip cancer^{3,13}.

A recently published study⁹ established that 60% of cancers of the oral cavity, the oesophagus, the larynx, the corpus uteri and the bladder are considered to be avoidable which indicates great opportunities for prevention. Therefore, the focus of public health activities should be on measures of prevention and reduction of lip cancer risk factors. The main modifiable risk factors for lip cancers are smoking^{3,14} and alcohol consumption^{15,16} and sun exposure. The first step in risk factors reduction at the national level was done with the creation of a legislation framework for tobacco control¹⁷.

Yet, Serbia still has a reputation of a country with a very high prevalence of smoking. The smoking cessation is also related to socio-economic factors. It was established that the most addicted people were the poorest women¹⁸. Smoking and alcohol consumption are well established risk factors^{1,19}. Smoking and drinking alcohol have an individual and synergistic effect. The combination of smoking and heavy drinking creates 38 times higher risk for lip cancer compared to the risk of abstainers from both habits²⁰. The high lip cancer incidence matched the great alcohol consumption in Central and Eastern Europe⁴. The above-mentioned findings suggest that high prevalence of risk factors for lip cancer was registered in Serbia only in a few studies, which implies that improved and expanded surveillance of risk factors at the national level is needed.

Gore pomenuti nalazi ukazuju da je visoka prevalencija faktora rizika za nastanak ovog karcinoma registrovana u Srbiji u samo nekoliko studija i da je potreban poboljšani i prošireni nadzor ovih faktora rizika na nacionalnom nivou.

Trend pada incidencije karcinoma usne kod muškaraca može biti prvi rezultat kontrole pušenja u našoj zemlji. Osim toga, može biti i posledica manje izloženosti sunčevom zračenju usled smanjenja populacije u ruralnim oblastima²¹. Sličan efekat se može dobiti i smanjenjem aktivnosti na otvorenom. Sunčeva svetlost i zračenje se ubrajaju u snažne sugestivne faktore rizika¹⁹. Efekat izlaganja sunčevom zračenju na sam mehanizam nastanka karcinoma usne zavisi od vremena izlaganja i tipa aktivnosti. Dugoročno izlaganje suncu na poslu je prediktor za nastanak karcinoma usne, a izlaganje tokom odmora i slobodnog vremena izgleda da ima zaštitni efekat²². U grupu potencijalnih faktora rizika posebnu pažnju privlači HPV infekcija²³. Nedavno objavljeni podaci pokazuju da je ukupna HPV prevalencija i 16/18 HPV prevalencija u Srbiji kod žena zdravog izgleda i normalnog citološkog nalaza na grliću materice vrlo visoka²⁴. Time se zaokružuje slika o Srbiji kao zemlji sa visokom prevalencijom faktora rizika za karcinom usne.

Gotovo ceo ispitivani period karakteriše nizak MIR, što ukazuje na pravovremenu dijagnozu ovog karcinoma u centralnoj Srbiji. Svakako da su rana detekcija i lečenje povezani sa boljim ishodom, zato je razvoj skrining programa neophodan, posebno u mlađoj populaciji²⁵.

Globalna standardizovana stopa incidencije za karcinom usne u 2012. godini je procenjena na 0,3/100000, sa vrlo izraženim regionalnim razlikama. Prema GLOBOCAN-ovim procenama, incidencija ovog karcinoma kod muškaraca u Srbiji je u 2012. godini rangirana na 12. mestu, a na 21. kod žena. Razmatrajući stopu mortaliteta, prema GLOBOCAN-ovim procenama, Srbija se nalazi na 15. mestu po smrtnosti u muškoj populaciji i na 14. po smrtnosti u ženskoj populaciji. Centralna i istočna Evropa se smatraju regionom sa visokom stopom prevalencije karcinoma usne^{19, 26}. Gotovo petina novih slučajeva (19,2%) se javlja na prostoru centralne i istočne Evrope⁴. Dakle, Srbija je okružena zemljama sa vrlo visokom učestalošću ovog karcinoma. Najveće stope karcinoma usne su posebno karakteristične za sledeće zemlje istočne Evrope, posebno u muškoj populaciji: u Bugarskoj, Češkoj, Mađarskoj, Poljskoj, Rumuniji i Slovačkoj²⁷. Izrazito visoke stope smrtnosti su registrovane u Mađarskoj devedesetih godina prošlog veka.

The decreasing trend of lip cancer incidence in males might be the first result of controlling tobacco use. Additionally, the downward trend of lip cancer incidence in males may also be caused by less sunlight exposure due to a reduction in the population living in rural areas²¹. A similar effect could be achieved with a reduction of outdoor occupancy. Sunlight and radiation were established as strongly suggestive risk factors for lip cancer¹⁹. The effect of sunlight exposure on the carcinoma mechanism depends on the time of exposure and different activities. Long-term and constant exposure to sunlight during work is a predictor of lip cancer, but exposure during holidays and leisure seems to have a protective effect²². In the group of possible risk factors of lip cancer, special attention was drawn to the HPV infection²³. Recent data showed that the prevalence of the overall and 16/18 HPV infections in Serbian women was high in women with a healthy appearance and a cytologically normal cervix²⁴. The above-mentioned facts complete the image of Serbia as a region with the high prevalence of lip cancer risk factors.

Almost the whole of the study period is characterized by low mortality/incidence ratio, which implies that lip cancer was timely diagnosed in Central Serbia. The early detection and treatment of lip cancer are related to better prognosis. Therefore, the development of screening program is needed, especially in younger population that is affected²⁵.

The global ASR-W of lip cancer in 2012 was estimated at 0.3/100,000 with pronounced regional differences. Regarding the GLOBOCAN estimates in 2012, Serbia was ranked at the 12th place by the incidence rate of lip cancer in males and at the 21st place by the incidence of lip cancer in females. Considering the mortality rate, this comparison with GLOBOCAN 2012 estimates showed that Serbia was placed at the 15th place in males and at the 14th place in females. Central and Eastern Europe is considered as a region with a relatively high incidence rate of lip cancer^{19, 26}. Almost one fifth of new cases (19,2%) occurred in Central and Eastern Europe⁴. Serbia is surrounded with countries with the high prevalence of this cancer. The highest rates of lip cancer mortality are typical for Eastern Europe²⁷, particularly for males from Bulgaria, the Czech Republic, Hungary, Poland, Romania and Slovakia. An extremely high rate of mortality was observed in Hungary in the mid-1990's.

Nedostaci studije

Potrebno je napomenuti nekoliko mogućih nedostataka ove studije. Strategije u kontroli kancera su vezane za epidemiološke podatke. Zato je kvalitet podataka u registrima karcinoma vrlo značajan. Potencijalni problemi u klasifikaciji karcinoma usne javljaju se zbog same lokalizacije promene³. Ovaj karcinom je tip oralnog karcinoma koji je lokalizovan na spoju usne šupljine i kože, što može dovesti do toga da bude dijagnostikovano kao karcinom kože²⁸. Ipak, Svetska zdravstvena organizacija je kvalitet podataka koji se odnose na uzork smrti u Srbiji ocenila kao umeren²⁹. Takođe, procenat nepoznatih i nedefinisanih uzroka smrti kod obolelih od karcinoma pokazuje da su podaci o uzrocima smrti u Srbiji umerenog kvaliteta³⁰. Osim toga, GLOBOCAN 2012 je kategorisao podatke iz Srbije kao B2, što podrazumeva visoko kvalitetne regionalne podatke za stope incidencije i srednjeg kvaliteta podatke vezane za smrtnost.

Zaključak

Rezultati naše studije ukazuju da je profil karcinoma usne u centralnoj Srbiji stabilan i ima trend pada u ispitivanom periodu. Nakon 2011. godine, pokazuje se blagi trend porasta incidencije u ženskoj populaciji. Smrtnost od karcinoma usne u istom periodu prati trend incidencije. Na osnovu ovoga može se zaključiti da epidemiološka slika ovog karcinoma na ovoj teritoriji nije dramatična. Ali, GLOBOCAN predikcije ukazuju na porast incidencije ovog karcinoma usled porasta i starenja populacije. Pored toga, zemlje u razvoju su bile pogođene tranzicijom od zaraznih ka nezaraznim bolestima³¹, što ukazuje na mogući trend rasta u narednom periodu. Stoga, visoka prevalencija faktora rizika, naročito pušenje i konzumiranje alkohola, ukazuju da postoji prostor za javnozdravstvene aktivnosti na nacionalnom nivou. Ove aktivnosti treba da budu usmerene na ekonomski efikasne mere u redukciji pušenja i smanjenju konzumiranja alkohola, kao i na uporno širenje svesti o rizicima preteranog izlaganja suncu.

Limitations of the study

Several possible limitations of this study should be considered. Strategies for cancer control are based on the epidemiology data. Therefore, the quality of cancer registers is crucial. The potential classification problem arises from the position of lip cancer³. This cancer is a form of oral cancer located at the junction between the oral cavity and the skin which could be misdiagnosed as skin cancer²⁸. The quality of data related to the cause of death in Serbia was assessed as moderate by the World Health Organization²⁹. The percentage of unknown and ill-defined cancer deaths for the most recent year indicated that cause-of-death data in Serbia were of moderate quality³⁰. Furthermore, GLOBOCAN 2012 categorized data from Serbia as B2 which means high quality regional data (coverage between 10% and 50%) for the incidence rates and medium quality for complete vital registration for the mortality rates.

Conclusion

Pooled evidence implies that the profile of lip cancer in Central Serbia is stable and declines in the study period. After 2011, there are indications of a slight increase in female incidence. The mortality for the same period follows the pattern of incidence. Based on that, it can be concluded that the epidemiological picture of lip cancer is not dramatic. However, predictions for this cancer indicate its increase based on population growth and aging. Additionally, developing countries were affected by transition from infectious diseases to noncommunicable diseases³¹, which implicates further possible increasing trend. Therefore, the high prevalence of risk factors, especially smoking habits, alcohol consumption, indicates that there is a place for public health activities at the national level. Those activities should be focused on cost-effective policies to reduce alcohol and tobacco use and persistent dissemination of information about the risks of sun over-exposure.

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LITERATURA /REFERENCES

1. Maruccia M, Onesti M, Parisi P, Cigna E, Troccola A, Scuderi N. Lip cancer: a 10-year retrospective epidemiological study. *Anticancer research*. 2012;32(4):1543-6.
2. Warnakulasuriya S. Causes of oral cancer-an appraisal of controversies. *British dental journal*. 2009;207(10):471.
3. Moore S, Johnson N, Pierce A, Wilson D. The epidemiology of lip cancer: a review of global incidence and aetiology. *Oral diseases*. 1999 Jul;5(3):185-95. PubMed PMID: 10483063.
4. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA: a cancer journal for clinicians*. 2017;67(1):51-64.
5. Casal D, Carmo L, Melancia T, Zagalo C, Cid O, Rosa-Santos J. Lip cancer: a 5-year review in a tertiary referral centre. *Journal of Plastic, Reconstructive & Aesthetic Surgery*. 2010;63(12):2040-5.
6. Zitsch RP, Lee BW, Smith RB. Cervical lymph node metastases and squamous cell carcinoma of the lip. *Head & neck*. 1999;21(5):447-53.
7. Khuder SA. Etiologic clues to lip cancer from epidemiologic studies on farmers. *Scandinavian journal of work, environment & health*. 1999;125-30.
8. Lopez EP-M, Minarro-Del Moral R, Martinez-Garcia C, Zanetti R, Rosso S, Serrano S, et al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. *British journal of cancer*. 2003;88(11):1702.
9. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in Europe: a study of eleven major cancers amenable to lifestyle change. *International journal of cancer*. 2007 Mar 15;120(6):1336-43.
10. World Health Organization. International classification of diseases and related health problems, 10th revision. Volume 1st edition. <http://www.who.int/classifications/icd/en/>.
11. Videnović G, Ilić D, Miljuš D, Krasić D, Vlahović Z, Živković S, et al. Lip, oral cavity and pharyngeal cancers in the population of the city of Belgrade in the period 1999-2010. *Vojnosanitetski pregled*. 2016;73(1):53-8.
12. Shiboski CH, Shiboski SC, Silverman S. Trends in oral cancer rates in the United States, 1973-1996. *Community dentistry and oral epidemiology*. 2000;28(4):249-56.
13. Czerninski R, Zini A, Sgan Cohen H. Lip cancer: incidence, trends, histology and survival: 1970-2006. *British Journal of Dermatology*. 2010;162(5):1103-9.
14. Çankaya H, Garça MF, Bozan N, Isik D, Kiroglu AF. Epidemiological features of the lip cancers and it's relation with smoking. *Eastern Journal of Medicine*. 2013;18(2):64.
15. Maruccia M, Onesti MG, Parisi P, Cigna E, Troccola A, Scuderi N. Lip cancer: a 10-year retrospective epidemiological study. *Anticancer research*. 2012 Apr;32(4):1543-6.
16. Radoi L, Paget-Bailly S, Cyr D, Papadopoulos A, Guida F, Schmaus A, et al. Tobacco smoking, alcohol drinking and risk of oral cavity cancer by subsite: results of a French population-based case-control study, the ICARE study. *European Journal of Cancer Prevention*. 2013;22(3):268-76.
17. O'Rourke M, Djukic J. Welcome to Serbia: feel free to smoke. *Tobacco control*. 2008 Dec;17(6):428-30. PubMed PMID: 18827037.
18. Djikanovic B, Marinkovic J, Jankovic J, Vujanac V, Simic S. Gender differences in smoking experience and cessation: do wealth and education matter equally for women and men in Serbia? *Journal of Public Health*. 2011;33(1):31-8.
19. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral oncology*. 2009 Apr-May;45(4-5):309-16.
20. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer research*. 1988;48(11):3282-7.

21. Blomberg M, Nielsen A, Munk C, Kjaer SK. Trends in head and neck cancer incidence in Denmark, 1978–2007: focus on human papillomavirus associated sites. *International journal of cancer*. 2011;129(3):733-41.
22. Perea-Milla Lopez E, Minarro-Del Moral RM, Martinez-Garcia C, Zanetti R, Rosso S, Serrano S, et al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. *British journal of cancer*. 2003 Jun 02;88(11):1702-7.
23. Galyon SW, Frodel JL. Lip and perioral defects. *Otolaryngologic clinics of North America*. 2001;34(3):647-66.
24. Malisic E, Brotto K, Krivokuca A, Cavic M, Jankovic R. Overall human papilloma virus and types 16/18 prevalence in women with normal cervical cytology in Serbia: is it time for human papillomavirus testing and/or vaccination. *Journal of BUON : official journal of the Balkan Union of Oncology*. 2014;19(4):973-9.
25. Llewellyn CD, Johnson NW, Warnakulasuriya S. Factors associated with delay in presentation among younger patients with oral cancer. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2004;97(6):707-13.
26. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer*. 2015;136(5).
27. La Vecchia C, Lucchini F, Negri E, Levi F. Trends in oral cancer mortality in Europe. *Oral oncology*. 2004;40(4):433-9.
28. Macfarlane GJ, Boyle P, Evstifeeva T, Scully C. Epidemiological aspects of lip cancer in Scotland. *Community dentistry and oral epidemiology*. 1993;21(5):279-82.
29. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bulletin of the World Health Organization*. 2005 Mar;83(3):171-7.
30. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *European journal of cancer*. 2013 Apr;49(6):1374-403.
31. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *The lancet oncology*. 2012;13(8):790-801.