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Non-melanoma skin cancers in Serbia (1999–2015) – the need for national prevention and control strategy

Nemelanomski karcinomi kože u Srbiji (1999–2015) – potreba za nacionalnom strategijom za prevenciju i kontrolu

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Abstract

Background/Aim. Non-melanoma skin cancers (NMSC) are ones of the most rapidly increasing cancers worldwide. Although NMSCs have a relatively low mortality rate, they are an important public health concern and the most costly cancers in many countries. The two main objectives in this study were: first, to analyze the trend of age-standardized incidence rate of NMSCs in Serbia and second, to assess the need for national prevention and control strategy based on analyzed trend. **Methods.** From the Serbian Cancer Registry, we extracted all cases of NMSCs registered in central Serbia from January 1, 1999 to December 31, 2015. Joinpoint regression analysis was used to define trends and annual percentage change (APC). **Results.** NMSCs significantly increased for both genders with APC of +2.32% ($p < 0.001$). Significantly increasing trend of incidence rates was higher in women (APC, +2.63%; $p < 0.0001$) than in men (APC, +2.01%; $p < 0.001$). **Conclusion.** Our results show a continuously increasing incidence rate of NMCS in Serbia. Without the national preventive strategy, current sporadic activities are highly unlikely to result in reducing the growing trends.

Key words:
skin neoplasms; carcinoma, basal cell; carcinoma, squamous cell; incidence; serbia.

Apstrakt

Uvod/Cilj. Nemelanomski karcinomi kože (engl. *non-melanoma skin cancers* – NMSC) su jedni od najbrže rastućih karcinoma širom sveta. Iako imaju relativno nisku stopu smrtnosti, zbog cene koja je potrebna za njihovo lečenje, predstavljaju veliku brigu u javnom zdravlju mnogih država. Ova studija imala je dva osnovna cilja: prvi, da analizira trend standardizovane incidencije NMCS u Srbiji i drugi, da se na osnovu anliziranog trenda proceni potreba za izradu nacionalne strategije za prevenciju i kontrolu ovog karcinoma. **Metode.** Iz Registra za rak Srbije izdvojeni su svi slučajeve NMCS registrovani u centralnoj Srbiji od 1. januara 1999 do 3. decembra 2015. godine. Trend kretanja i godišnji procenat promene incidencije (engl. *annual percentage change* –APC) izračunat je regresionom analizom pomoću tačke spajanja. **Rezultati.** NMCS su se značajno povećavali kod oba pola sa APC od +2,32% ($p < 0,001$). Značajno povećanje trenda incidencije je bilo veće kod žena (APC, +2.63%; $p < 0,0001$) nego kod muškaraca (APC, +2.01%; $p < 0,001$). **Zaključak.** Rezultati pokazuju kontinuirano povećanje stope incidencije NMCS u Srbiji. Bez nacionalne preventivne strategije vrlo je malo verovatno da će sadašnje sporadične preventivne aktivnosti smanjiti ovaj rastući trend.

Ključne reči:
koža, neoplazme, karcinom, bazocelularni; karcinom, planocelularni; incidenca; srbija.

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Introduction

Non-melanoma skin cancers (NMSC) are the most common cancers in the world. Although these cancers include other rare cutaneous neoplasms, the term generally refers to basal cell carcinoma (BCC) and squamous cell skin carcinoma (SCC) [1]. NMSC are ones of the most rapidly increasing cancers worldwide [2, 3]. The world's highest incidence is among the white population of Australia and New Zealand [4] and it is very low among the black population [5]. In the United States NMSC account for over 5.4 million cases in more than 3.3 million people and more people have had skin cancer than all other cancers combined [6].

The primary risk factor for developing NMSC is exposure to ultraviolet radiation (UVR). UVR induced deoxyribonucleic acid (DNA) damage causes genetic alterations which play a crucial role in skin photoaging and the genesis of skin cancer [7, 8]. Some studies are shown that outdoors working individuals have 40% to 80% higher risk for developing BCC and SCC due to exposure to sunlight [9, 10]. Indoor tanning is also highly associated with an increased risk of both NMSC and the risk is higher with use in early life [11, 12]. Other risk factors include the phenotype of an individual characteristics such as fair skin, blue eyes and red hair [13]. Although NMSC have a relatively low mortality rate, they are an important public health concern and the most costly cancers in many country [14–17].

Collecting data on NMSC incidence rate based on national cancer registers is important because they provide information for planning health policies and assist in understanding needs and effectiveness of prevention for that particular region [17, 18].

Skin cancer prevention activities have been performed throughout the entire world. In Europe, Euromelanoma as a pan-European prevention programme against NMSC and melanoma started in 1999 and spread in 33 countries (Serbia included) [19–21]. However, public health significance of NMSC seems to be unrecognized in Serbia, there is no national strategy for prevention and control of these cancers and only a few studies reported incidence rate of NMSC in Serbia [18, 22].

There were two main objectives of this study: first, to analyze the trend of age standardized incidence rate of NMCS in Serbia and second, to assess the need for national prevention and control strategy based on analyzed trend.

Methods

Type of the study and data sources

In this retrospective descriptive epidemiological study, the incidence rate of NMSC in Serbia during a 17-year study period (1999–2015) was estimated. The Serbian Cancer Registry (the Registry) had been established in 1970 and became a member of the International Agency for Research on Cancer (IACR) and European Network of Cancer Registries (ENCR) in 1998. All health institutions in Serbia (private and state) are mandated by law to submit a report on all new cases of malignant tumours to The Registry. Our study was conducted in central Serbia (excluding provinces Vojvodina and Kosovo and Metohija) which had a population of 5,506,936 in 1999 and 5,203,682 in 2015. Information on the size and migration population in the past was provided by the Statistical Office of the Republic of Serbia.

Statistical analysis

From The Registry, we extracted all cases of NMSC registered in central Serbia from January 1, 1999 to December 31, 2015 based on the International Classification of Diseases, Tenth Revision (ICD-10) code C44 [23]. Age-specific incidence rates were calculated using the following age groups: below 39, 40–49, 50–59, 60–69 and over 70 years of age. To allow comparison between our data and data from other regions, age-standardized incidence rates (ASIR) were calculated using the direct standardization method to the world population [24]. Incidence rates were reported as the incidence per 100,000 persons yearly. Trends and annual percentage change (APC) of the incidence rate with corresponding 95% confidence intervals (CI) were calculated by performing joinpoint regression analyses using the Joinpoint Regression Software version 4.6.0.0 (available at https://surveillance.cancer.gov/joinpoint/download). The trend was considered as significant when the *p*-value was below 0.05 ($p < 0.05$).

Results

During the 17-years period (from January 1,1999 to December 31, 2015) a total number of 48.488 persons (25.213 men and 23.275 women) with primary non-melanoma skin cancer were reported to the National Cancer Registry of Central Serbia. Women represented 48% and men 52% of all persons. Table 1 shows age-specific incidence rates, crude rate, and age-standardized incidence rate (world standard population) per 100.000 persons for all, men and women. The age-specific incidence rates were the highest in the age group over 70 years and approximately 50% (49.9% male and 50.8% female) of all registered cases were in this age group. About 3% (2.3% male and 3.2% female) of all registered cases of NMSC belonged to a group under 39 years of age. Table 2 presents world age-standardized rate and number of patients with primary NMSC in Serbia through the entire study period.

The lowest level of ASIR of NMSC in the Republic of Serbia was in the first year of the observation period, in 1999 (19.74 per 100.000 men, 95% CI: 18.46–21.01 and 15.22 per 100.000 women). ASIR is gradually increasing and reached the highest level in 2014 (33.31 per 100.000 men, 95% CI: 31.78–34.84 and 26.12 per 100.000 women, 95% CI: 24.89–27.36). Based on the joinpoint analysis, ASIR of NMSC in Serbia significantly increased, for both gender combined, in the period 1999–2015 with APC of +2.32% (95% CI: 1.60–3.10, $p < 0.001$) (Figure 1).

Table 1

Age-specific, age-standardized incidence rate (per 100.000 persons), crude rate and number of patients with primary non-melanoma skin cancer in Serbia, 1999–2015

Parameters	Male		Female		Overall	
	n	I	n	I	n	I
Age group (years)						
≥ 39	578	19.16	739	24.56	1317	21.85
40–49	1280	40.20	1212	37.14	2492	38.65
50–59	3636	116.18	3208	96.62	6844	106.10
60–69	7148	286.82	6060	210.45	13208	245.84
≤ 70	12571	549.32	12056	373.25	24627	446.46
Crude rate*	N/A	56.70	N/A	49.64	N/A	53.08
WASR*	N/A	29.53	N/A	22.76	N/A	25.74

n – number of patients; I – incidence; N/A – not applicable; WASR – World age-standardized rate; *all ages.

Table 2

Age-standardized incidence rate (per 100.000 persons) and number of patients with primary non-melanoma skin cancer in Serbia, 1999–2015

Year	Males			Females			Overall		
	n	WASR	95% CI	n	WASR	95 % CI	n	WASR	95 % CI
1999	916	19.74	18.46–21.01	843	15.22	14.20–16.25	1759	17.21	16.40–18.01
2000	1227	26.62	25.13–28.10	1066	19.46	18.29–20.63	2293	22.62	21.70–23.55
2001	1203	25.67	24.22–27.12	991	17.36	16.28–18.44	2194	21.11	20.23–22.00
2002	1258	26.63	25.16–28.10	1052	18.52	17.41–19.64	2310	22.16	21.25–23.06
2003	1316	27.22	25.75–28.69	1138	19.75	18.61–20.90	2454	23.05	22.14–23.96
2004	1408	29.76	28.21–31.32	1365	24.13	22.85–25.41	2773	26.62	25.63–27.61
2005	1370	27.56	26.10–29.02	1269	21.88	20.67–23.08	2639	24.31	23.38–25.24
2006	1731	35.33	33.66–36.99	1633	27.73	26.39–29.08	3364	31.07	30.02–32.12
2007	1472	29.53	28.02–31.03	1356	22.70	21.49–23.91	2828	25.72	24.78–26.67
2008	1644	32.33	30.76–33.89	1577	25.40	24.14–26.65	3221	28.44	27.46–29.43
2009	1679	33.53	31.93–35.14	1506	25.21	23.94–26.49	3185	28.91	27.91–29.92
2010	1569	30.83	29.31–32.36	1531	25.25	23.99–26.52	3100	27.69	26.72–28.67
2011	1593	30.90	29.38–32.42	1506	24.72	23.47–25.96	3099	27.41	26.45–28.38
2012	1622	30.73	29.24–32.23	1507	24.15	22.93–25.37	3129	27.06	26.11–28.00
2013	1681	30.69	29.23–32.16	1689	26.04	24.80–27.29	3370	28.00	27.06–28.95
2014	1830	33.31	31.78–34.84	1717	26.12	24.89–27.36	3547	29.27	28.31–30.23
2015	1694	31.44	29.94–32.94	1529	23.40	22.23–24.58	3223	26.98	26.04–27.91

n – number of patients; WASR – world age-standardized rate; CI – confidence interval.

ASIR was higher in women Significantly increasing trend of (APC, +2.63%; 95% CI: 1.50–3.80; $p < 0.0001$) (Figure 2) than in men (+APC, 2.01%; 95% CI: 1.01–3.10; $p < 0.001$) (Figure 3).

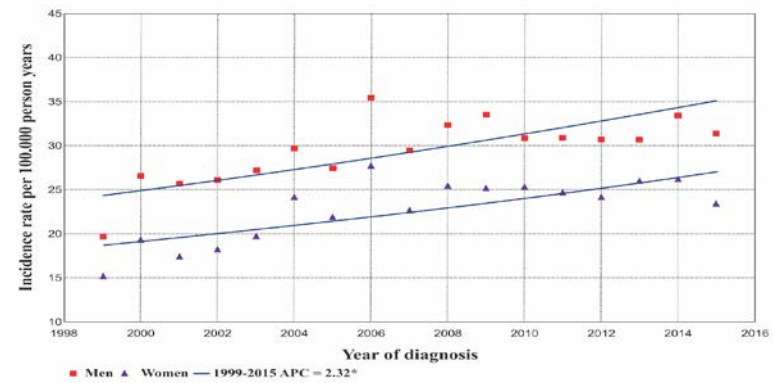

Fig. 1 – Joinpoint analyses of age standardized incidence rates (world standard population) of non-melanoma skin cancer in Serbia, 1999–2015, men and women combined, with annual percentage change (APC).

***significant increase.**

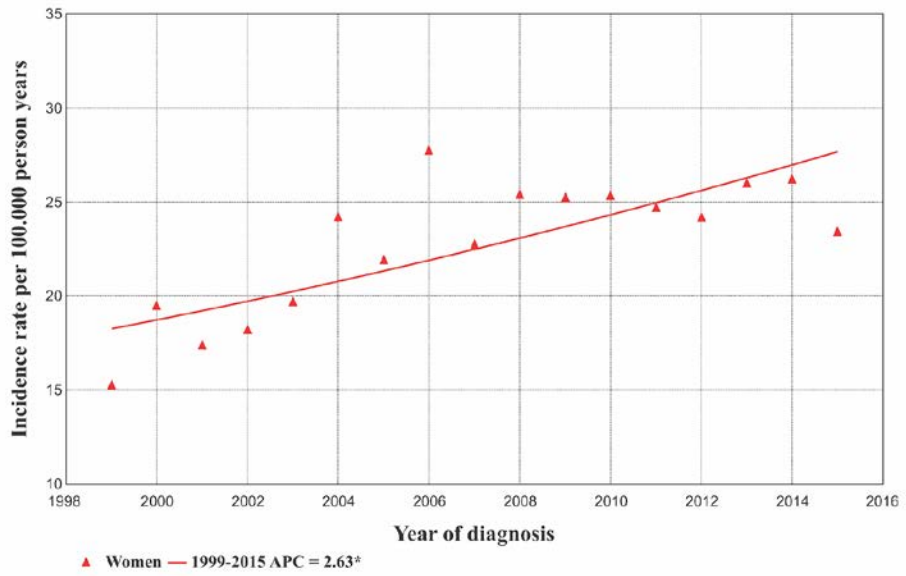

Fig. 2 – Joinpoint analyses of age standardized incidence rates (world standard population) of non-melanoma skin cancer in Serbia, 1999–2015, with annual percentage change (APC) for women. *significant increase.

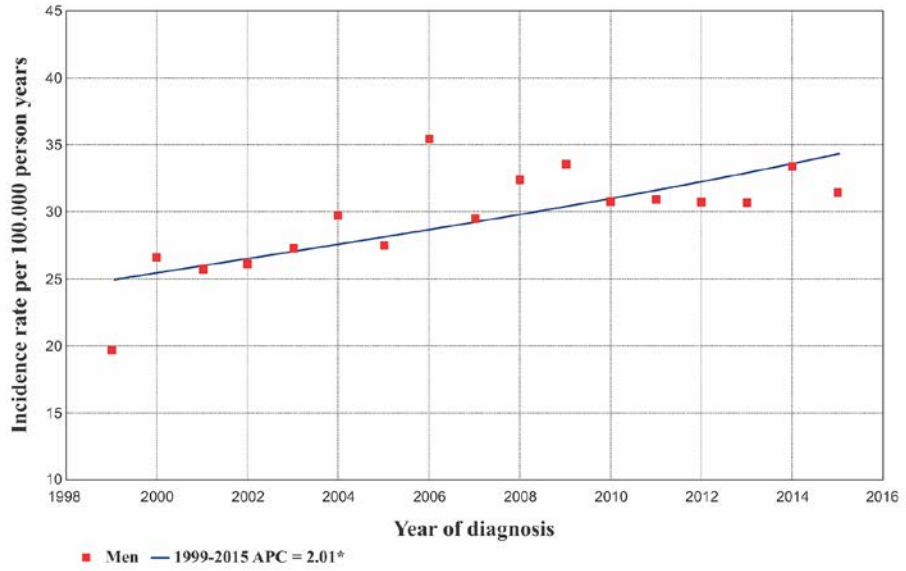

Fig. 3 – Joinpoint analyses of age standardized incidence rates (world standard population) of non-melanoma skin cancer in Serbia, 1999–2015,with annual percentage change (APC), for men. *significant increase.

Discussion

This national register-based study analyzed trends of NMSC over a period of 17 years. It it is one of the few studies [18, 22] describing the incidence of NMSC in the Republic of Serbia. The study showed that NMSC are the most common among the elderly; the age-specific incidence rates is the highest in the age group over 70 years (50%) and very low in the younger age (3%). The age distribution of NMSC cases was similar to other reports [4, 25–28]. Many studies have confirmed that cumulative exposure to UVR, especially in the first two decades of life, plays the key role in carcinogenic process of skin cancers [7, 8]. The reason for the highest age-specific incidence rates in elderly in our study is probably the ageing of the population in Serbia. Another reason for prevalence of skin cancers in the age group over 70 years could be a lack of information regarding the importance of harmfulness of excessive exposure to UVR among the elderly population at the time in their youth. Although the incidence rate is very low in younger age this is the right time to start with preventive activities. NMSC generally take many years to appear but are usually caused during young age. The most of the damage resulting in skin cancers occurs in the adolescent and childhood and therefore prevention strategies need to focus on sun protection

education especially towards these age groups [29, 17]. Thus, schools are the most important institution where awareness of NMSC and education of sun protection should start. In Australia, the country with the highest incidence rate of NMSC in the world, SunSmart Schools Program is the main skin cancer control strategy for more than 20 years. This program includes promoting the use of sun-protective clothing and shade-seeking behavior [30]. Many Australian schools have already improved sun-protective behaviors [31]. In Serbia, there are no national educational school programs focused on sun protection so far. In fact, only one published educational program was implemented for some high school students in Belgrade from 2007 to 2008. The goal of this program was to increase awareness among students of harmfulness of excessive exposure to UVR and to educate them on sun protection measures [32].

After analyzing ASIR of NMSC in our study, noticeable differences between gender were found: they were much higher in men than in women during the whole study period (1999–2015). Our results are compatible with findings from studies in other countries [4, 33–35]. Incidence rates tend to be higher in men than in women most likely because in Serbia, men are more likely to have an outdoor occupation. Another reason could be different way of dressing and hairstyle between the genders.

Age-standardized incidence rates of NMSC in Serbia have increased more than 1.5-fold from 1999 to 2015 and our results showed a continuously increasing incidence rate. The continuously increasing incidence rates of NMSC were also recorded in Australia [4], New Zeland [36], the United States [6], Canada [37], Asia [38, 39] and in European countries: Netherlands [40], Denmark [41], Italy [42] and Switzerland [43]. Explanations for this increasing incidence rates could be several factors. First, and the most likely factor is the increased number of people who are expose to greater UVR compared to prior generations. Spending the holiday at sunny destinations and outdoor sport activities has become more popular and more achievable than in the past, which prolonged exposure to sunshine and increased cumulative ultraviolet exposure consequently. Cumulative ultraviolet exposure is well known risk in photoaging of the skin and genesis of skin cancer [7, 8]. The increasing incidence rate of NMSC in our research may also suggest that people in Serbia are not fully aware of the dangers of the excessive exposure to UVR and that little attention has been paid to raise awareness of the harmful effects of the sun in the past. Euromelanom Serbia, a part of the pan-European association of Euromelanoma Europe, has been implementing significant awareness-raising activities and changing the public's behavior regarding sun protection in recent years. Media campaign of Euromelanoma Serbia under the slogan "Serbia has a skin cancer problem" informs the public about adequate protection against UVR, both from sun and from artificial sources of UVR. This campaign uses various means of public communication to promote skin awareness (brochures, pamphlets, posters, mass media advertising) and benefits from an Internet platform for Serbia (https://www.euromelanoma.org/serbia). Another possible reason for growing skin cancer incidence is depletion of the ozone layer in the atmosphere and the increased air pollution in the past. Depletion of the ozone layer facilitated UVR to reach the Earth's surface and increased the intensity of ultraviolet light exposure [44].

A more significant incidence rate increase of NMSC for women (APC = +2.63%; $p < 0.0001$) compared to men (APC = +2.01%; $p < 0.001$), in our study, is similar to that of the Leiter et al. [34] study from two federal states in Germany. They reported a more significant increase for women than for men between 1999 and 2012 in Schleswig-Holstein federal state (women APC = +3.3%; men APC = +2.3%) and between 1970 and 2012 in Saarland federal state (women APC = +6.3%; men APC = +6.0%). Higher increase in ASIR of NMSC in women was observed also in The Netherlands [45] and Denmark [41]. Gender difference in increasing standardized incidence rate of NMSC can be caused by the use of tanning beds, because women are more prone to use sun tanning or indoor tanning than men. Use of tanning beds started in 1970s for cosmetic use [46] and more than 30 years later Bataille et al. [47], in an epidemiological study on sunbed use in Europe, reported that more than half of Northern European population between 18 and 50 years were using tanning beds. Some other studies have shown that indoor tanning increases the risk of NMSC by 40% to 102% [11], doubling the risk of SCC and increasing risk of BBC by 50% [48]. Since indoor tanning had been identified as carcinogenic, many European countries (France, Spain, Portugal, Germany, Austria, Belgium, England, Wales, Northern Ireland and Scotland) made age restrictions and demanded parental permission for tanning beds use [46]. Brazil outlawed indoor tanning for all age groups since 2011 [46]. There is still no law in Serbia limiting the use of salon tanning and it seems that people are not aware of the dangers of it – in fact many people still believe that tanned skin is more attractive and "looks healthy". Restrictions on the use of salon tanning in Serbia could certainly prevent the growth of incidence rate of NMSC in the future.

At first glance, low mortality rate of NMSC along with the lower age-standardized incidence rates in Serbia (Table 2) than in other countries [4, 6, 42, 43] may not qualify NMSC prevention as the national financial resource's optimal candidate. This attitude is, of course, understandable due to the fact that Serbia is among the poorer countries in the world and already has very high mortality rates in other malignant diseases. However, the growing trend in NMSC incidence rates, shown in our research (Figures 1–3) suggests that this type of carcinoma will undoubtedly become a significant health problem unless prevention measures are timely taken. Without the national preventive strategy, current sporadic preventive activities in Serbia are highly unlikely to result in reducing the growing trends.

Furthermore, we believe that shown NMSC incidence rate in Serbia is lower than the actual one. The reason is that the Serbian Cancer Register, following the recommendations of the IARC and ENCR, records only one NMSC per person, the first one. If a patient has multiple or a reccurent skin cancer – this is recorded as a single case. This method of

recording data could result in underestimation of the true incidence of NMSC in Serbia. In Australia, Keim et al. [49] found that 16% to 56% of patients with primary NMSC developed additional SCC or BCC. A similar underestimation of the true incidence of NMSC has been reported in the United Kingdom [50] and Germany [51].

We strongly hope that our results prove the need to form the national prevention strategy to promote NMSC awareness, provide sun protection education and restrict indoor tanning.

Conclusion

Our results showed a continuously increasing incidence rate of non-melanoma skin cancer in Serbia between 1999 and 2015. We observed much higher age-standardized incidence rates in men than in women but the increase was more significant for women compared to men. Increasing incidence rate of non-melanoma skin cancer could suggest that people in Serbia are not fully aware of the dangers of exposure to ultraviolet radiation and that little attention has been paid in the past to raise awareness of the harmful effects of both sun and indoor tanning. The development of a national prevention strategy that would include raising public awareness of non-melanoma skin cancer, education on sun protection and limitation of the use of sunbed tanning by the law could certainly reduce the morbidity of these cancer in Serbia.

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