

Nonmelanoma Skin Cancer in the Population of the City of Belgrade in the Period 1999–2011

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SUMMARY

Introduction Nonmelanoma skin cancers in the literature are mainly related to basal cell and squamous cell skin carcinoma.

Objective The aim of the study was to determine the trend in the incidence of histological types of nonmelanoma skin cancers in the population of the city of Belgrade from 1999 to 2011.

Methods From the Serbian National Cancer Registry we extracted all recorded cases of skin cancer in Belgrade from January 1st 1999 to December 31st 2011. Incidence rates were standardized by the method of direct standardization with the world population as the standard population. Trends and annual percentage change (APC) of incidence rate were calculated by performing joinpoint regression analyses.

Results Incidence rate of nonmelanoma skin cancer showed significantly increasing trend between 1999 and 2006 with APC of 8.6% (95% CI: 5.6–11.7), basal cell carcinoma increased with APC of 8.4% (95% CI: 5.2–11.6) and squamous cell skin carcinoma with APC of 9.33% (95% CI: 5.7–13.1). The incidence increased with age for both men and women, especially after the age of 60.

Conclusion Our results showed a continuously increasing incidence trend of both basal cell and squamous cell skin carcinomas in the population of the city of Belgrade between 1999 and 2011. Adequate primary and secondary prevention would certainly be successful in reducing this type of cancer in the future.

Keywords: nonmelanoma skin cancer; basal cell carcinoma; squamous cell skin carcinoma

INTRODUCTION

Malignant skin tumors are often classified as nonmelanoma skin cancers (NMSC) and melanoma. Although the term NMSC includes skin lymphoma, skin adnexal tumors and other rare primary skin cancers, in the literature the term is mainly related to basal cell (BCC) and squamous cell skin carcinoma (SCC). NMSCs are the most common malignant skin tumor in white population and incidence varies around the world – it is very low in black population [1], higher in European countries [2, 3], and the highest in white population in Australia [4] and Arizona, U. S. [5]. There is a general agreement that the main aetiological factor in the development of NMSC is exposure to ultraviolet (UV) B radiation [6, 7]. Cumulative exposure to sunlight is probably the most important risk factor for SCC, while BCC is more associated with intensive short-term exposure [8]. Although the mortality rate of NMSCs is low, they represent a significant economic burden to a health system and can cause significant morbidity, especially as most BCC and SCC occur on highly visible areas such as the head, neck and face [3].

Studies on the incidence of skin cancer, based on national cancer registers, are important because they provide information for

planning health policies in this growing health problem. According to our knowledge, this is the first register-based study of NMSC in Serbia, which gives the rate of incidence of both histological types – BCC and SCC.

OBJECTIVE

The aim of the study was to determine the trend in the incidence of histological types of NMSC in the population of the city of Belgrade from 1999 to 2011.

METHODS

Data sources

Information about patients diagnosed with BCC and SCC was obtained from the Serbian National Cancer Registry (the Registry), which covers the entire population of Serbia. The Registry was founded in 1970 and after a successful reorganization and improvement of data quality in 1998 it was admitted into the International Agency for Research on Cancer (IACR) and European Network of Cancer Registries (ENCR). Cancer reporting in Serbia is mandated by law and information on

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all potential new cases must be reported to the Registry. Sources of data collection for the Registry are hospitals and outpatient health institutions, oncology institutes, oncology dispensaries, oncology clinics, pathology laboratories, death reports and health insurance funds. Information on the size and migratory patterns of Belgrade's population in the past was obtained from the Statistical Office of the Republic of Serbia.

Coding and analysis

From the Registry we extracted data on all cases of skin cancer recorded in Belgrade from January 1st 1999 to December 31st 2011 based on the International Classification of Diseases, Tenth Revision (ICD-10) [9] code C44. Tumors are classified according to the International Classification of Disease of Oncology, Third Edition (ICD-O-3) [10] as BCC (morphology code 8011, 8090-8110) and SCC (morphology code 8050-8080, 8120-8130). Only invasive cancers were included in the study (i.e. containing "/3" as the last digit in the morphology code). World age-standardized incidence rates (WASR) were calculated using the direct standardization method [11] to allow comparison of incidence rates with the rest of the population. Incidence rates are presented as incidence per 100,000 persons in a year. Age-specific incidence rates were calculated using the following age groups: younger than 20 years, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and 80 years and older. Trends and annual percentage change (APC) of incidence rate were calculated by performing joinpoint regression analyses to identify the year in which a significant change in incidence rates occurred. For regression analyses, we used Joinpoint Regression Program version 4.1.0 (available at <http://surveillance.cancer.gov/joinpoint>). To describe trends in incidence rate we used the term "significant increase", which signified that the slope of the trend was statistically significant ($p < 0.05$). For non-significant trends ($p > 0.05$), we used the terms "non-significant increase" or "slower rate of increase". Data analysis was performed by using SPSS version 20.0 (SPSS Statistics, IBM Corporation).

RESULTS

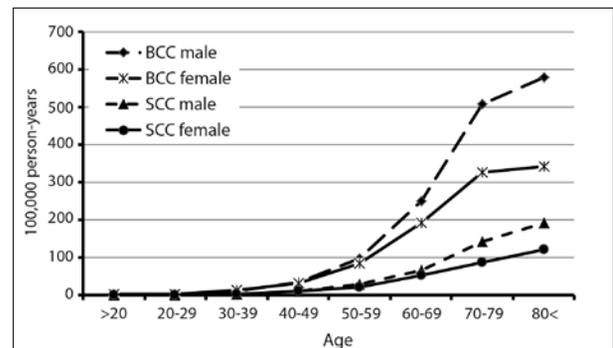
During the 13-year period (from January 1st 1999 to December 31st 2011) a total number of 11,590 persons with primary NMSC were identified in residents of the city of Belgrade. There were 9,063 persons with primary BCC (4,600 men and 4,463 women), and 2,527 with SCC (1,295 men and 1,232 women). The ratio of persons with BCC to persons with SCC was 3.6:1. Men represented 50.86% of all persons and women 49.14%. The men to women ratio was 1.03:1. The minimum and maximum age range for patients with NMSC was found to be 9 and 99, respectively. The mean age of all patients was 67.43 years (men 67.65 and women 67.20). The Belgrade population size increased from 1,568,754 in 1999 to 1,647,490 inhabitants in 2011. Table 1 presents age-specific incidence rates, crude rate,

Table 1. Age-specific, age-standardised incidence rate (per 100,000 persons), crude rate and number of patients with primary nonmelanoma skin cancer in Belgrade, 1999–2011

Age group (years)	Male		Female		Overall	
	N	I	N	I	N	I
<20	9	1.5	12	2.1	21	1.8
20–29	20	2.7	30	3.8	50	3.3
30–39	81	11.6	119	15.7	200	13.7
40–49	324	45.5	325	40.4	649	42.8
50–59	872	125.2	867	105.7	1739	114.7
60–69	1651	317.2	1560	245.8	3211	278.0
70–79	2204	648.5	2009	412.7	4213	509.3
>80	734	769.8	773	464.5	1507	575.8
Crude rate*	N/A	59.9	N/A	52.0	N/A	55.7
WASR*	N/A	33.0	N/A	25.2	N/A	28.5

* all ages

N – number; I – incidence; N/A – not applicable; WASR – world age-standardized rate



Graph 1. Age-specific incidence rate (per 100,000 person-years) of patients with primary basal cell carcinoma (BCC) and squamous cell skin carcinoma (SCC) in Belgrade, 1999–2011

and age-standardized incidence rate (WASR) per 100,000 persons for the entire study period (1999–2011) for all, men and women. The incidence of NMSC increases with age for both men and women, especially after 59 years of age, and is highest in the oldest age groups (>80 years). The increase was higher for men than for women. The incidence of BCC, throughout the study period, was noticeably higher for men than for women in age groups above 69 years; in contrast, in age groups below 59 years, the incidence of BCC was at the similar level for men and women or slightly higher for women (Graph 1). As for BCC, the incidence of SCC increased with age for both genders, and it was higher for men than for women in age groups above 69 years.

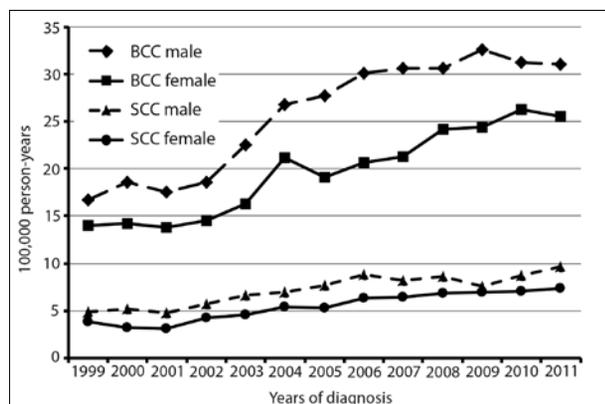
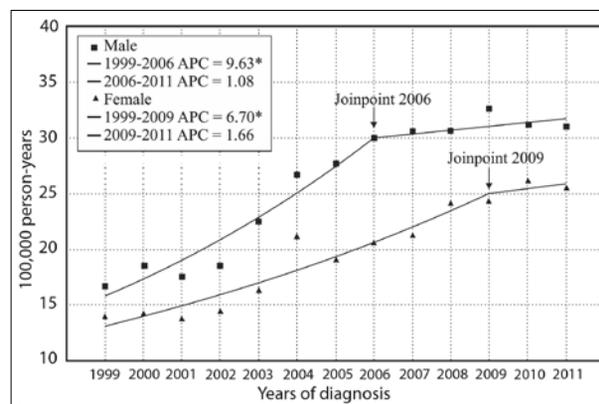
The absolute annual number of patients with NMSC increased from 543 in 1999 to 1,229 in 2011. WASR increased during the 13-year interval for both women and men, the highest being in 2011 for both men and women (40.65 per 100,000 men, 95% CI: 37.42–43.88 and 32.89 per 100,000 women, 95% CI: 30.30–35.48) (Table 2). WASR for NMSC in the period 1999–2011 was 33.02 per 100,000 men and 29.19 per 100,000 women (Table 1).

BCC was the predominant form of NMSC in Belgrade over the study period. WASR in patients with BCC in-

Table 2. Age-standardised incidence rate (per 100,000 persons) and number of patients with primary nonmelanoma skin cancer in Belgrade, 1999–2011

Year	Male			Female			Overall		
	N	WASR	95% CI	N	WASR	95% CI	N	WASR	95% CI
1999	267	21.55	18.96–24.13	276	17.87	15.76–19.98	543	19.25	17.63–20.87
2000	295	23.66	20.96–26.36	276	17.45	15.39–19.51	571	20.14	18.49–21.79
2001	282	22.35	19.74–24.96	270	16.87	14.86–18.88	552	19.16	17.56–20.76
2002	315	24.18	21.51–26.85	297	18.69	16.57–20.82	612	20.97	19.31–22.63
2003	386	29.09	26.19–31.99	357	20.91	18.74–23.08	743	24.35	22.60–26.10
2004	443	33.69	30.55–36.83	433	26.55	24.05–29.05	876	29.56	27.60–31.52
2005	483	35.37	32.22–38.53	414	24.35	22.01–26.70	897	28.93	27.03–30.82
2006	534	38.89	35.59–42.18	486	26.92	24.52–29.31	1020	31.95	29.99–33.91
2007	539	38.84	35.56–42.12	506	27.72	25.30–30.14	1045	32.52	30.55–34.50
2008	570	39.28	36.05–42.50	584	31.04	28.53–33.56	1154	34.52	32.53–36.51
2009	581	40.22	36.95–43.49	565	31.29	28.71–33.87	1146	35.07	33.04–37.10
2010	592	39.88	36.67–43.09	610	33.20	30.56–35.83	1202	35.91	33.88–37.94
2011	608	40.65	37.42–43.88	621	32.89	30.30–35.48	1229	36.13	34.11–38.15

N – number; WASR – world age-standardized rate; CI – confidence interval

**Graph 2.** Age-standardised incidence rate (World Standard Population) per 100,000 person-years of patients with primary basal cell carcinoma (BCC) and squamous cell skin carcinoma (SCC) in Belgrade, 1999–2011**Graph 3.** Joingpoint analyses of age-standardized incidence rates (World Standard Population) of basal cell carcinoma (BCC) in Belgrade, 1999–2011, with annual percentage change (APC)

* significant increase

creased from 15.02 (16.69 men, 14.00 women) per 100,000 persons in 1999 to 27.78 (31.03 men, 27.78 women) per 100,000 persons in 2011 (Graph 2). The overall age-standardized incidence rate for persons with SCC increased during the study period from 4.23 (4.86 men, 3.87 women) per 100,000 persons in 1999 to 8.35 (9.62 men, 7.35 women) per 100,000 persons in 2011 (Graph 2).

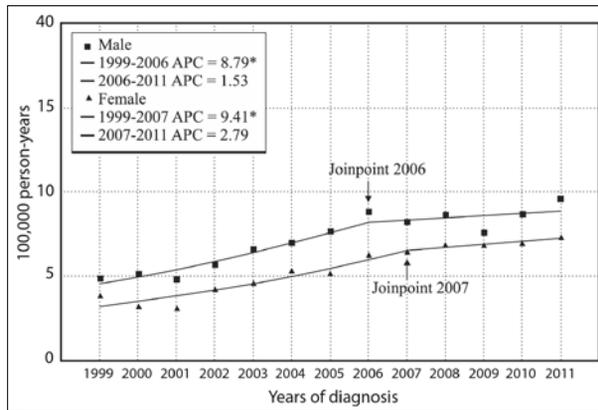
Joingpoint analysis of the incidence rate (WASR) of NMSC cancer showed significantly increasing trend between 1999 and 2006 with APC of 8.6% (95% CI: 5.6–11.7, $p < 0.001$) and non-significant increase between 2006 and 2011 (APC 3%, 95% CI: -1.8–7.9, $p = 0.19$). BCC increased sharply from 1999 to 2006 with APC of 8.4% (95% CI:

5.2–11.6, $p < 0.001$), and then showed slower rate of increase in the second part of the study period (APC 2.9%, 95% CI: -2–8.2). The increase for SCC was significantly higher between 1999 and 2006 (APC 9.33%, 95% CI: 5.7–13.1, $p < 0.001$) than from 2006 to 2011 (APC 2.8%, 95% CI: -2.8–8.8, $p = 0.3$) (Table 3). Similar pattern was observed between sexes. Age-standardized rates for men with BCC increased from 1999 to 2006 at an APC of 9.6% (95% CI: 6.5–12.8, $p < 0.001$) and for women 1999–2009 at an APC of 6.7 (95% CI: 4.6–8.8, $p < 0.001$) (Graph 3). Age-standardized rates for men with SCC increased at an APC of 9.4% between 1999 and 2006 (95% CI: 5.2–13.8, $p < 0.001$) (Graph 4).

Table 3. Annual percentage change (APC) and 95% confidence intervals (CI) in incidence of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and nonmelanoma skin cancer (NMSC) in Belgrade, 1999–2011

Calendar period	BCC			SCC			NMSC		
	APC	95% CI	p	APC	95% CI	p	APC	95% CI	p
1999–2006	8.4*	5.2–11.6	0.001	9.3*	5.7–13.1	0.001	8.6*	5.6–11.7	0.001
2006–2011	3	-2.0–8.2	0.2	2.8	-2.8–8.8	0.3	2.9	-1.8–7.9	0.2
1999–2011	6.1*	3.7–8.5	0.001	6.6*	3.8–9.4	0.001	6.2*	3.9–8.5	0.001

* statistically significant increase



Graph 4. Joinpoint analyses of age-standardized incidence rates (World Standard Population) of squamous cell skin carcinoma (SCC) in Belgrade, 1999–2001, with annual percentage change (APC)

* significant increase

DISCUSSION

To our knowledge, this is the first registry-based study that analyzed trends of NMSC in Belgrade. In the last 13 years, numbers of patients with NMSC in the capital of Serbia increased more than twofold in both men and women. Potential problem in direct comparisons of our results to results from other regions are different standard populations used for age-standardized rate in different countries. Study conducted in the USA generally used the U.S. standard population [5, 12], some studies used the Canadian [13], Australian [14], European [15–18] or world standard population [2, 19, 20, 21].

In contrast to the results from Australia [4] or Arizona (U.S.) [5], we found a remarkably lower age-standardized incidence rate for patients in our study. This is understandable because both mentioned regions are with the highest level of UV radiation in the world [3]. Exposure to UV radiation, especially UVB but also UVA, seems to be the most important risk factor that leads to the development of NMSC [6, 7]. South West England is also associated with the high UV radiation exposure. Study from South Wales reported incidence rate of 128/100,000 person-years for men with BCC and 105/100,000 person-years for women with BCC which is a higher incidence rate than in any other European country [22]. Switzerland and Italy have the highest average altitude in mainland Europe and as such have higher UV radiation levels. Switzerland and Italy reported incidence rates of NMSC of around 70/100,000 person-years in 1995 [23, 24]. Incidence rates of NMSC in our finding are also lower than that in Denmark [2], Germany [25], Slovakia [26] and Croatia [21].

The most likely explanation for this difference is the fact that the Serbian Cancer Registry does not have reliable data on multiple NMSC, and only records first NMSC in an individual. If a person has more than one skin cancer, it is recorded as a single case. It has been estimated that 25% [25] to 40% [27] of patients diagnosed with BCC carcinoma present a new skin carcinoma in the following 5 years or one-third of patients with BCC developed

multiple BCCs during an average follow-up period of 10 years. An additional reason for lower incidence rate in our study compared to those of others could be a predominantly urban community from which our data originates. Theoretically, numbers of individuals who have outdoor occupations should be lower in urban community than in rural. It is well known that outdoor workers have increased risk of skin cancer compared to indoor workers [16, 28]. Data from other regions, with which we compared our results, are generally related to the whole community (urban and rural).

Our study showed that skin cancer is most common among the elderly and that the age-specific incidence rates increase more in the age groups 60–70 and ≥ 80 years. Most studies have reported increased incidence of skin cancer in older age groups [2, 4, 13, 18]. Cumulative sun exposure, during lifetime, is a well known risk factor for skin cancer [8]. Ageing of the population could also be a part of the explanation for the observed increases of age-specific incidence rate.

BCC is a dominant type of NMSC in our study. The BCC to SCC ratio was 3.6:1 in both men and women, which is within the range of observations made in other areas: 3.8:1 in Croatia [21], 4.9:1 in Slovakia [26] and 5.8:1 in Denmark [2].

The age-standardized incidence rates of NMSC in our study increased in both men and women during the whole study period (1999–2011). Joinpoint analyses showed a significantly higher increase of BCC and SCC in the first seven years of the study period (1999–2006) than in the second part (2006–2011). Studies from other countries suggested an increasing trend, although the rate of increase varied from one study to another. A study in Scotland, U.K., reported rates of BCC increasing from 35.6/100,000 person-years in 1978 to 97.5/100,000 person-years in 2004 for male population and 25.7 to 67.4/100,000 person-years for female population in the same period (standardized to the European population) [18]. In the same study, SCC increased from 16.1/100,000 person-years in 1978 to 36.9/100,000 person-years in 2004 for male and 6.3 to 13.8/100,000 person-years for female population. Data from the Eindhoven Cancer Registry, Netherlands, published by Flohil et al. [20] described an increase of histologically confirmed BCC of about 7-fold in the last 25 years in both men and women. Among Asians who lived in Singapore BCC incidence rates increased from 1.3/100,000 person-years from 1968 until 1972 to 5.7/100,000 person-years from 1998 until 2002 [29]. The increased incidence rate is related to greater exposure to UV radiation and increased number of people who spend more time on outdoor activities (sports, sunbathing, walking, gardening etc.) compared to prior generations. It is a known fact that the risk of BCC is increased by recreational exposure to the sun during childhood and adolescence, especially intense intermittent sun exposure [8]. Also, depletion of the ozone layer over the past decades allows UVB radiation to reach the Earth's surface easier [30].

Compared to other regions, annual percent change of NMSC incidence rate in Belgrade for the period 1999–2006

is higher. In Manitoba, Canada, annual rates for BCC and SCC increased 2.4% per year [8], in Sweden for SCC it was 4.0% per year [31], in Singapore 2.8% for BCC and 0.9% for SCC (from 1968 to 1997) [32], in New Hampshire, U.S., increase was 4.4% per year for BCC [33]. A recent study from Denmark [2] showed an increase in BCC incidence rate during the study period (1978–2007) of around 4.0% per year. Observation that the annual increased incidence rate in our study was less rapid during the last 6 years than in the first 7 years could be explained by the improvement in the completeness of the skin cancer registration records in the Serbian Cancer Registry. Before the reorganization of the Serbian Cancer Registry, carried out in 1998, the reporting to the Registry had lacked the appropriate data quality. The number of cases with malignant tumors reported to the Registry was approximately the same or even lower compared to the number of cases deceased from cancer. The reorganization of the data collection was achieved and improved by a more active approach including training health workers on registering malignant tumors and training IT support for data entry. Several years were necessary to stabilize the data quality and avoid underreporting. We believe that observed in-

creases in incidence rates of BCC and SCC in the last 6 years are more likely to present the true incidence trends in Belgrade. Support to this claim is provided by similar annual increases of incidence rates published for other abovementioned regions.

CONCLUSION

Our results showed a continuously increasing incidence of both BCC and SCC in the population of the city of Belgrade between 1999 and 2011. An increase of incidence was lower during the last 6 than in the first 7 years of the study period, probably because of improvement in the completeness of the skin cancer registration records in the Serbian Cancer Registry. We believe that incidence rates in the second half of the study period present the true incidence trend of skin cancer in Belgrade. By presenting these findings we would like to emphasize the problem of continuously increasing incidence of skin cancer in the future for the health policy makers. Adequate primary and secondary prevention would certainly be successful in reducing this type of cancer in the future.

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Немеланомски карциноми коже код становника Београда у периоду 1999–2011. године

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КРАТАК САДРЖАЈ

Увод Немеланомски карциноми коже се у литератури најчешће односе на базоцелуларне и планоцелуларне карциноме коже.

Циљ рада Циљ истраживања је био да се одреди тренд промене инциденције хистолошких типова немеланомских карцинома коже код становника Београда од 1999. до 2011. године.

Методе рада Из Регистра за малигне болести Републике Србије издвојили смо све регистроване случајеве карцинома коже у Београду од 1. јануара 1999. до 31. децембра 2011. године. Стопе инциденције су стандардизоване методом директне стандардизације, а као стандардна популација коришћена је популација света. Тренд кретања и годишњи проценат промене инциденције (енгл. *APC*) израчунат је регресионом анализом помоћу тачака спајања (енгл. *joinpoint regression analysis*).

Резултати Стопа инциденције за немеланомске карциноме коже показала је значајни тренд пораста између 1999. и 2006. године са *APC* од 8,6% (95% *CI* 5,6–11,7). Стопа инциденције базоцелуларног карцинома се повећала са *APC* од 8,4% (95% *CI* 5,6–11,7), а планоцелуларног карцинома коже са *APC* од 9,33% (95% *CI* 5,7–13,1). Инциденција се повећавала са старашћу пацијената код оба пола, посебно после 60. године.

Закључак Наши резултати су показали непрестано повећање тренда инциденције базоцелуларног и планоцелуларног карцинома коже код становника Београда између 1999. и 2011. године. Правилна примарна и секундарна превенција би свакако имала успеха у смањењу овог типа карцинома у будућности.

Кључне речи: немеланомски карциноми коже; базоцелуларни карцином; планоцелуларни карцином коже

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