Clinical study

TRENDS IN INCIDENCE OF SKIN AND LIP CARCINOMAS AND MALIGNANT MELANOMA OF THE SKIN IN SLOVENIA

V. Pompe-Kirn, A. Kansky and I. Planinšič

ABSTRACT

The incidence of skin and lip carcinomas as well as malignant melanoma of skin is greatly varying in the world. Reliable cancer incidence data can be obtained only in regions where population-based cancer registries are operating. In Slovenia the Cancer Registry has been operating since 1950 at the Institute of Oncology in Ljubljana. The average annual crude incidence rate per 100 000 of skin carcinomas was during the period 1950-1952 14.4 in males, and 19.4 in females; it rose to 20.9 in males and 25.8 in females during the 1986-1988 period. The crude rate for lip carcinoma was 6.2 in males and 1.4 in females in this first period, and it was 2.2 in males and 0.8 in females in the last period of observation; for malignant melanoma it increased from 0.7 in males and 0.8 in females to 5.0 in males and 5.2 in females. Trends in crude and cumulative incidence rates in the 1974-1988 period were analysed in details. In crude rates the trend for skin carcinoma was stable (-0.1% in males and -0.4% in females), for male lip carcinoma it was decreasing (-6.1%), whereas in malignant melanoma it was increasing in males (7.5%), and in females (7.8%). When cumulative rates till the age 74 were taken into account, a decrease of skin carcinoma in females was evident (-2.1%), the decrease of male lip carcinoma was steeper (-7.3%), whereas in malignant melanoma the increase was greater in males (8.2%), and lower in females (7.1%). Cohort-analyses showed in skin carcinoma in males a tendency of higher rates in younger birth-cohorts up to the age of 70 only; in male lip cancer younger birth-cohorts were less affected in all age groups, whereas in malignant melanoma younger birth-cohorts were more affected in both sexes in almost all age groups.

KEY WORDS:
skin and lip carcinomas, malignant melanoma, incidence, Slovenia

INTRODUCTION

Accurate population studies based on incidence figures for carcinoma and malignant melanoma (MM) of the skin are relatively few, most of the studies are unreliable from an epidemiological point of view because they are based on selected series of cases observed by clinicians or by pathologists (1). Among the first adequate approaches to this problem were the studies by MacDonald and MacDonald and Bubendorf (2,3). With a larger number of population-based cancer registries data on the incidence of malignant skin tumors in various countries became more reliable.

There is an ample evidence that carcinoma of the skin and

lips are not evenly distributed in various populations. A number of reports show that the incidence is greater in geographical areas with expressed insolation and high proportion of population engaged in outdoor activities. Such observation concerns specially people of Caucasian origin. The most susceptible are the fair-skinned people with blue irises, red hair and freckles. People of Irish and Scottish descent are particularly endangered as it was observed in Australia and the USA (4). An extremely high incidence of non-melanotic skin cancer was established among the whites in Australia: an investigation covering a population sample of 30 976 people (Carlton South, Victoria) gave a standardized incidence of 823 per 100 000 inhabitants. The rate for basal carcinoma (BCC) was 657 and for squamous cell carcinoma (SCC) 166, giving a BCC to SCC ratio of about 4:1 (5). In the USA an incidence of 71.5 for men and 47.2 for women was observed in Minnesota which is a rather northern country and whose population has a relatively low actinic exposure (6). In contrary to this a much higher incidence of 379 (539 for men and 259 for women) was detected in the area of Dallas and Forth Worth which are characterized by high insolation (7). In United Kingdom an annual incidence of 100 is suggested (1).

The incidence of carcinoma of the lips differs also a great deal between different population cohorts. White farmers seem again to be most endangered (8). According to Whelan et al. (9), the highest age-standardized incidence was detected in males in Newfoundland where it reaches 15.1, and in South Ireland 11.6. In females the disease is rare, the highest incidence being reported for South Australia 1.6 per 100 000. It is worth to mention that in certain countries, e.g. in former East Germany (10) and in Polland (11) a clear tendency to decrease is expressed.

The highest age standardized incidence of MM of the skin was again observed in Australia; in Queensland it reaches 30.9 in males and 28.5 in females, whereas the figures for New South Wales are 17.1 for males and 16.1 for females (9). In the USA the incidence rate for MM rose from 4.5 in 1970 to 11.2 in 1987 (12). From Denmark too an elevated number of patients with cutaneous MM was reported between 1943 and 1982: 3509 men and 5305 women, yielding a fivefold to sixfold increase of the age standardized incidence rate (13). In Finland the incidence rose during the 1953 to 1973 period from 1.3 to 3.8 for men and from 1.5 to 3.5 for women (14).

The main factors contributing to the development of cutaneous carcinomas may be listed as follows: 1) exposure to UV light, 2) exposure to other carcinogens, 3)genetic disposition, 4)viruses, 5)old age etc. Various mechanisms may induce cancer, e.g. physical and chemical damages to DNA, liberation of deoxyribonucleases from lysosomes, impaired or exhausted DNA repair in keratinocytes, suppression of cellular immunity, the presence of oncogens. It is highly probable that similar contributing factors are operational in MM, but this remains to be proved.

Reliable cancer incidence data can be obtained only in regions where population-based cancer registry is operating. In Slovenia the Cancer Registry has been operating since 1950 at the Institute of Oncology in Ljubljana. In the present article detailed data on the incidence of skin and lip carcinomas as well as skin MM in Slovenia are presented. In addition, the recent knowledge in carcinogenesis for these three cancers is shortly reviewed.

Carcinogenesis

In man UV radiation, specially the so-called UV B range, including 290 to 320 nm wave lengths, is believed to be the most important skin carcinogen. A dose which provokes a given tumor end point represents a cumulative figure derived from many exposures. Blum demonstrated the quantitative nature of tumor response in the ears of haired mice and Forbes in hairless mice (15). Data from animal studies indicate that both fractionation and attenuated delivery of UV increase the carcinogenic effectiveness of given dose.

On molecular level the process of photocarcinogenesis is characterized by absorption of UV light by a molecule, so-called chromophore: DNA, RNA, proteins (keratin, collagen, elastin), porphyrin and other substances. During this process photoproducts, e.g. thymine dimers, other pyrimidine adducts, free radicals, DNA crosslinks with proteins and other substances are being formed .The enzymatic DNA repair which normally follows the UV-induced damage is often deficient in photocarcinogenesis (16). Histological changes may be divided in acute and chronic. The acute damage includes spongiosis of the epidermis, cell edema, vacuolisation and eosinophilia of cytoplasm, pyknosis of nuclei in the keratinocytes (sunburn cells). The main chronic damage is represented by elastosis of the dermis, parakeratosis and atrophy of the epidermis, dilatation of superficial capillaries, followed by atypia of keratinocytes. Immediately after a single exposure to the UV B radiation, a dose-dependent arrest of mitotic activity for 6-24 hours, followed by a reactive proliferation on days 2-7, can be observed (17). Besides keratinocytes, melanocytes and fibroblasts too are important targets of the UV carcinogenesis.

Further factors which may contribute to the development of skin carcinomas are methylcholantrene, benzpyrene, certain tars, ionizing radiation and others. Many hereditary traits are potentially relevant in skin carcinogenesis, e.g. the amount of pigment in the skin, enzymatic DNA repair system, the number of melanocytic nevi and others. The role of human papilloma viruses in skin carcinogenesis, specially the HPV 16 and 18 has still not been unequivocally proven for non-immunosuppressed individuals. Inherited or acquired immunosuppression is also an important contributing factor. The increased incidence of skin carcinomas in elderly people

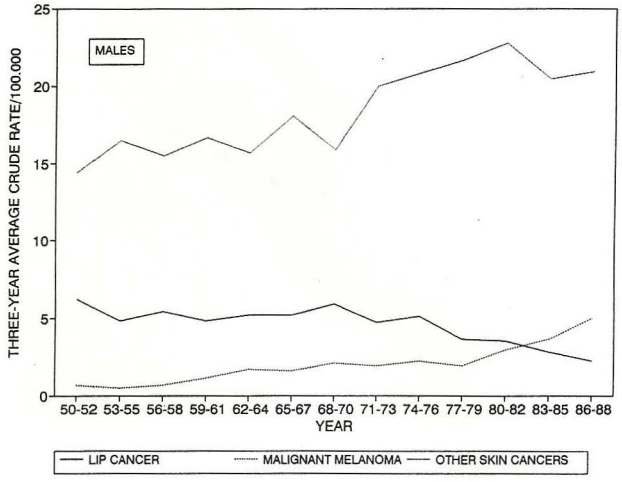

Figure 1:
Incidence of lip cancer, malignant melanoma, and other skin cancers in males; Slovenia, 1950-1988

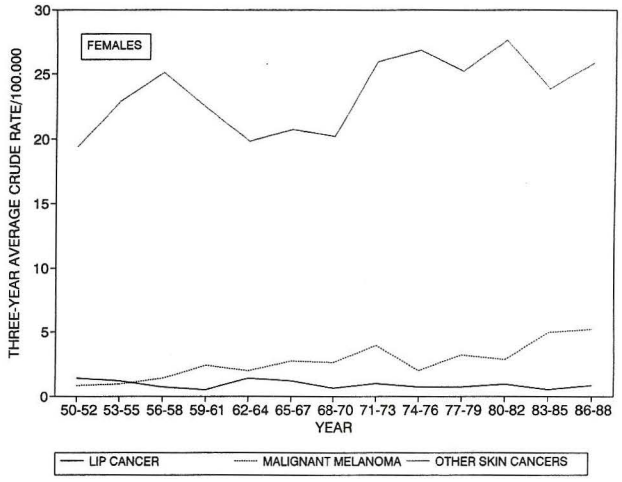

Figure 2:
Incidence of lip cancer, malignant melanoma, and other skin cancers in females; Slovenia, 1950-1988

is most probably due to an exhausted DNA repair mechanism and an impaired cellular immunity.

There is convincing evidence that UV light and heredity play an important role in the genesis of MM. A number of investigations in experimental animals has shown that after exposure to UV light precursor melanocytes become activated and start to proliferate (18,19). Certain clinical studies make the information available of convincing trends towards increasing risk of MM with increased exposure to the sun (20, 21,22). Heredity seems to be also a contributory factor: blue eyes, fair or red hair, pale complexion. Since the report by Cowly (23) more cases of familial occurrence of MM were observed; it is believed that the inheritance is polygenic (24). The presence of benign melanocytic nevi has been documented in 16 epidemiological studies on MM. The risk with increasing number of nevi has generally been higher in the category with the greatest number of nevi, the relative risk being higher than 10. Other factors such as occupational exposure to chemicals, ionizing radiation, use of steroid hormones, diet and others from present evidence have only week effects if any (25).

MATERIAL AND METHODS

Data from the Cancer Registry of Slovenia concerning non-melanoma skin cancer, lip cancer and malignant melanoma of the skin were analysed. Time trends for the 1950-1988 period were studied, birth cohort analysis for the 1964-1988 period, and an analysis of histologic types in non-melanoma skin cancer for the 1984-1988 period was done. The Cancer Registry covers a two million population of Republic Slovenia. Registration is compulsory, strict data protection measures are respected when analysing the data.

Non-melanoma skin cancer (other skin cancers) were registered since 1950 as all other cancer sites. They were classified according to the 8th revision of the International Classification of diseases under the number 173. According to the data of the Cancer Registry 98% of non-melanoma skin cancer cases were carcinomas. Registration of these carcinomas was certainly not as complete as for breast or lung cancer, but in Slovenia there were no private facilities to treat skin cancer, and at least all irradiated cases were notified to the Registry because there were only three institutions in Slovenia with radiation treatment facilities. Some surgically treated lesions with favorable prognosis escaped the registration, however. In figures non-melanoma skin cancer is marked as "other skin" cancers.

For data analysis, standard descriptive epidemiological methodology was used (18).

In birth-cohort analysis age-specific incidence rates are plotted according to the year of birth. This analysis shows whether persons born in certain year carry with them throughout their life a relatively higher or lower rate of the disease studied.

RESULTS

Time trends of crude incidence rates are shown on figures 1 and 2. Three year averages were used to overcome the annual chance peaks. The crude rate of carcinomas was 14.4 in the 1950-1952 period and rose to 20.9 in 1986-1988. Corresponding values for females changed from 19.4 to 25.8.

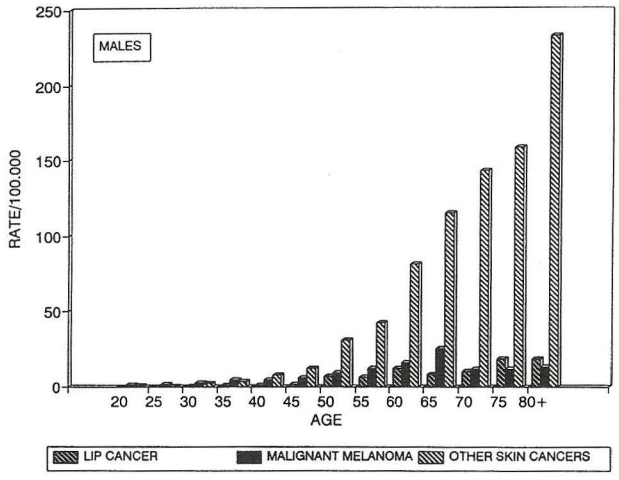

Figure 3:
Average annual incidence of lip cancer, malignant melanoma, and other skin cancers in males by age; Slovenia, 1984-1988

Carcinoma of the lips in males showed a steady decline of crude rates from 6.2 in 1950-1952 to 2.2 in 1986-1988. In females the corresponding values were 1.4 and 0.8. The crude rate of malignant melanoma rose from 0.7 during 1950-1952 to 5.0 in 1986-1988 in males, and from 0.8 to 5.2 in females.

Taking into account the possibility that in the first years of cancer registration in Slovenia,the underreporting of cases

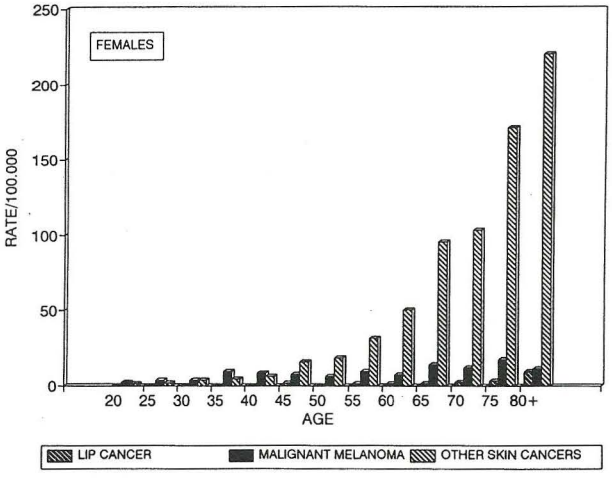

Figure 4:
Average annual incidence of lip cancer, malignant melanoma, and other skin cancers in females by age; Slovenia, 1984-1988

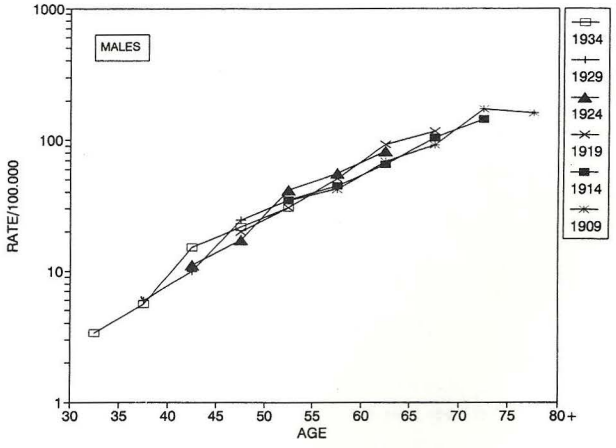

Figure 5:
Age-specific incidence of other skin cancers in males by birth cohorts; Slovenia, 1964-1988

was greater then later-on, a closer look to the 1974-1988 time period was given. During this 15-year period the crude rates of skin cancer remained more or less stable in both sexes with an average annual percentage change of -0.1% for males and of -0.4% for females; the rates of lip cancer in males were decreasing with an average annual percentage change of -6.1%, whereas the rates of malignant melanoma were increasing in both sexes with an average annual percentage change of 7.5% and 7.8%.

Crude rates do not take into account the eldering of Slovene population during the analysed time period. As all studied cancer sites are more common in older age groups (figures 3

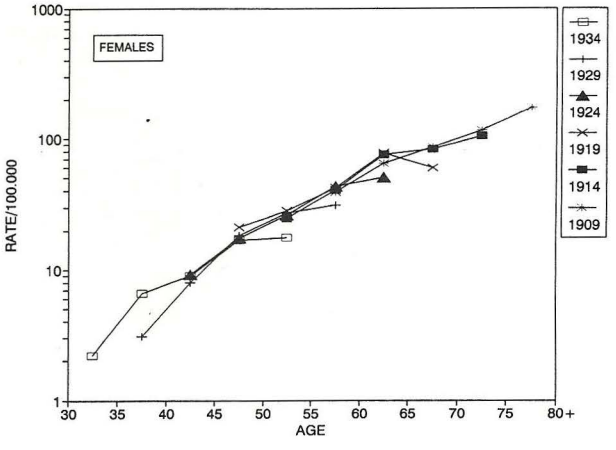

Figure 6:
Age-specific incidence of other skin cancers in females by birth cohorts; Slovenia, 1964-1988

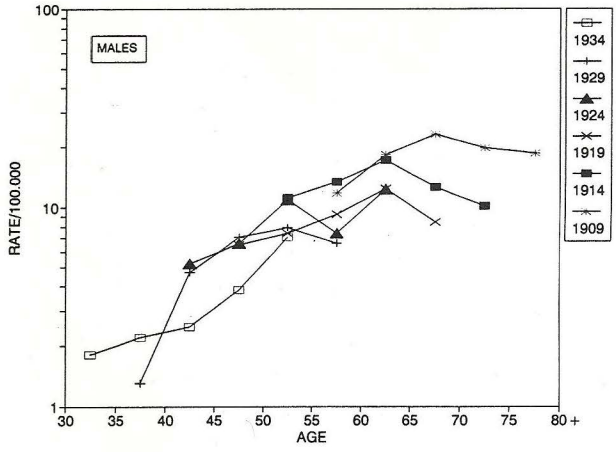

Figure 7:
Age-specific incidence of lip cancer in males by birth cohorts; Slovenia, 1964-1988

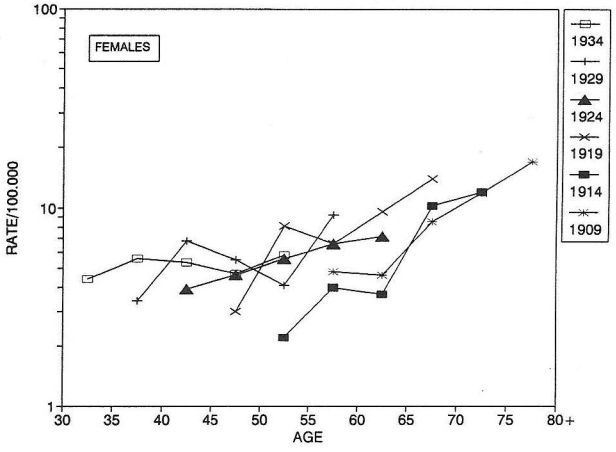

Figure 9:
Age-specific incidence of malignant melanoma in females by birth cohorts; Slovenia, 1964-1988

and 4), this eldering of Slovene population influenced the crude rates and their trend. So, when cumulative rates till the age 74 only were taken into account, the calculated average annual percentage changes were slightly different. In other skin cancers in females the decrease was more evident (-2.1%), and so it was in male lip cancer (-7.3%); in malignant melanoma in males the increase was greater (8.2%), whereas in females it was lower (7.1%).

These results provoked us to analyse the data for the three cancer sites by birth cohorts for six five-years periods. In other skin cancers in males in younger birth-cohorts a tendency of higher rates was expressed up to the age of 70 years, whereas in females a tendency of lower rates in these cohorts was indicated up to the age of 80 years (Figures 5 and 6). In male lip cancer younger birth-cohorts were less affected than the older ones in all age groups (Figures 7), whereas in malignant melanoma younger birth-cohorts were more affected in both sexes (Figures 8 and 9).

In the period 1984-1988, 26% of non-melanoma skin cancers were squamous cell carcinomas, 69% basal cell carcinomas, 1% adenocarcinomas , 2% non specified carcinomas, and 2% were other malignancies, e.g. some

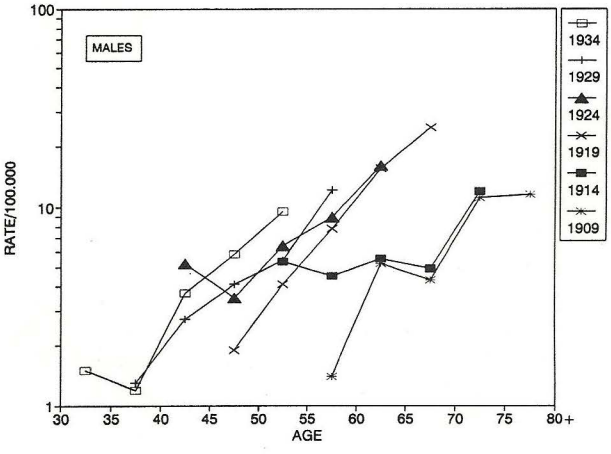

Figure 8:
Age-specific incidence of malignant melanoma in males by birth cohorts; Slovenia, 1964-1988

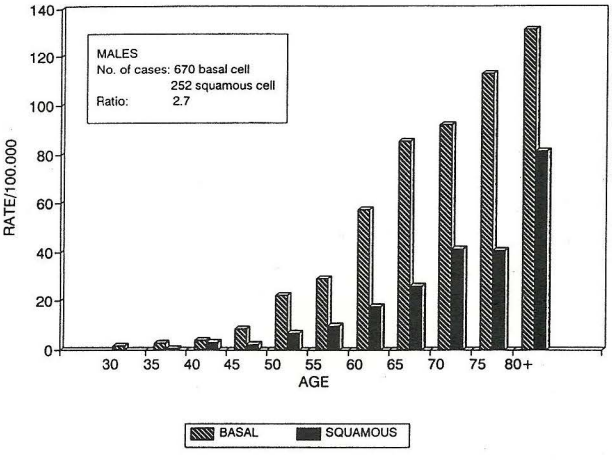

Figure 10:
Average annual incidence of basal-cell and squamous-cell skin carcinoma by age in males; Slovenia, 1984-1988

angiosarcomas, non-Hodgkin's lymphomas, etc.. On Figures 10 and 11 the age-specific incidence rates for squamous-cell and basal-cell carcinomas are given. Despite higher absolute numbers in females, the rates were higher in males. The reason is that there are more women older than 50 years in the Slovene population.

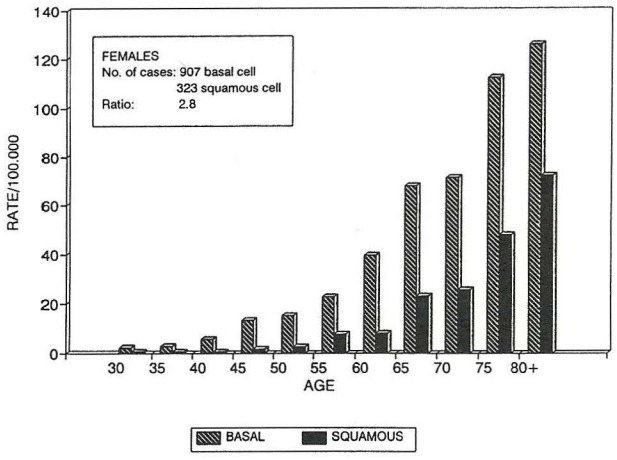

Figure 11:
Average annual incidence of basal-cell and squamous-cell skin carcinoma by age in females; Slovenia, 1984-1988

DISCUSSION

The incidence of skin carcinoma in Slovenia is lower than in Minnesota (6) or Iowa (7) and essentially lower than in Australia (5). The age-specific rates disclose that the highest values were in the age group over 80 years which corresponds to the data in the Minnesota study.Interesting is that in Slovenia birth-cohorts show opposite tendencies in males and females. In contrast to the relatively steady trend of BCC and SCC in Slovenia, in British Columbia, which is relatively low sunlight area, the age standardized incidence rate rose during the 1973-1987 period for BCC from 70.7 to 120.4 in males and from 61.5 to 92.2 in females. The increase for SCC was from 16.6 to 31.2 in males and from 9.4 to 16.9 in females (19). The ratio BCC to SCC was in our study 2.7 for males and 2.8 for females which seems to be in the normal range. However, higher ratios are mentioned in the literature: 4:1 in Queensland, 6:1 in Minneapolis and San Francisco and even 9:1 in certain areas of USA (20).

The steady decline of carcinoma of lips in Slovenia my be explained by the fact that the number of people engaged in outdoor activities was constantly dwindling. Birth-cohort analysis support this statement.

There was a steep increase in malignant melanoma incidence in the studied period in crude and cumulative rates in Slovenia too; birth-cohort analysis indicate that more recent birth-cohorts experienced higher incidence rates in each age. This fact is possibly related to a marked increase in sunbathing habits. Despite this increase Slovenia is in comparison with other countries in the world still on the lower side.

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AUTHORS' ADDRESSES

Vera Pompe-Kirn M. D., Ph. D., professor of cancer epidemiology,
Head Cancer Registry, Institute of Oncology, Zaloška 2, 61000 Ljubljana, Slovenia
Aleksej Kansky M. D., Ph. D., professor of dermatology,
Štihova 26, 61000 Ljubljana, Slovenia
Ivan Planišič M. D., Ph. D., professor of dermatology, Dpt. of Dermatology,
University Clinical Center, Zaloška 2, 61000 Ljubljana, Slovenia