Necessity of the development of a melanoma prevention program in Hungary - in the light of epidemological data

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Introduction

In the last decades the incidence of melanoma has been increasing worldwide. In Hungary, after the millennium, between 2001 and 2012 the incidence of the tumor almost doubled. Though melanoma can be seen and identified without any special instrument, in Hungary the mortality due to melanoma increased more than 200% between 1975 and 2012, and in 2012 the tumor was at the 22nd place in the rank order of mortality due to malignancies. With the increase of the thickness of tumor, the potential survival time decreases, since melanomas in advanced stage are highly aggressive and spread intensively. Consequently, prevention of the disease as well as its recognition in early stage are primary tasks of health care system. From the eighties several primary and secondary melanoma prevention programs have been organized worldwide to increase the knowledge of the people about the tumor. These campaigns notably contributed to the increasing number of the thin, early-diagnosed melanomas. The earlier identification improves the survival, which depends mostly on the tumor stage.

After removal of melanoma the regular control is extremely important. The regular control makes the early recognition of the potential metastates and the early diagnosis of second primary malignancies possible. Internationally available data prove that the risk of second primary malignancies has increased after melanoma compared to the general population. The higher overall tumor risk is mostly due to the higher incidence of skin tumors (melanoma, non-melanoma skin

cancer). Additionally, the risk of several internal malignancies (non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, kidney, bladder tumor) has also increased.

Both genetic and epigenetic factors equally play a role in melanoma formation. Several studies suggest the melanoma inducing effect of UV irradiation, however data about the role of ionizing irradiation are contradictory.

Objectives

The present work shows that health care system per se is not able and insufficient to reverse the unfavourable tendency in melanoma morbidity and mortality, therefore a widespread population based melanoma prevention program is required both for the young generation and elderly people.

The aim of the present study was to demonstrate and analyse the incidence, epidemiology, some yet unrevealed features, as well as late severe consequences of melanoma in Hungary compared to international data. Three main questions were raised, which were investigated in three groups of patients:

1. What is the stage distribution of melanomas diagnosed in our Department?
The survival time after melanoma depends mainly on the tumor stage. Therefore the stage distribution of the melanomas diagnosed at the Department of Dermatology Dermatooncology and Venereology, Semmelweis University between 2004 – 2009 was analysed (1st patient group). However, the Hungarian National Cancer

Registry – similarly to other large cancer databases (GLOBOCAN 2008, Cancer in Five Continents) – does not contain the tumor stages, which gives the significance of our study.

2. Has any risk of ionizing radiation on melanoma formation in the Power Plant of Paks? The Department of Dermatology Dermatooncology and Venereology, Semmelweis University performed a dermatooncological screening among the nuclear industry workers at the Power Plant of Paks (2nd patient group) between 2008–2009. We aimed to reveal the possible correlation between the effects of ionizing radiation and melanoma formation. The results of the screening were analysed. Our results were compared with the international data.

3. What is the risk of second primary malignancies in melanoma survivors at our Department? According to international data the risk of certain second primary tumors is higher after melanoma than in the general population. Therefore we assessed the risk of second primary neoplasms among the patients diagnosed with melanoma between 2006–2010 at our Department (3rd patient population).

Methods

Patients diagnosed with melanoma at our Department were identified in our case registry program by the help of the codes of the International Classification of Diseases and were analysed according to two different aspects. First, *the stage distribution of melanomas* of 1160 patients diagnosed between 2004-2009 was determined retrospectively (1st patient group). Second,

the risk of *second primary tumors* after melanoma in 740 patients diagnosed between 2006-2010 was examined (3^{nd} patient group).

1. Stage distribution of melanomas.

The patients from the 1^{st} group were followed from January 1, 2004 till December 31 2009. Medical imaging examinations (x-ray, ultrasound, computed tomography, magnetic resonance, positron emission tomography, bone scintigraphy), internal melanoma metastases and treatments (interferon, chemotherapy, x-ray irradiation) were added to the general database. The stage of melanomas was determined according to the 7^{th} edition of the TNM (tumor, lymph node, distant metastasis) classification as follows: in situ and stage IA, IB, IIA, IIB, IIC, IIIA, IIIB, IIIC, IV tumors. The case number in the different stages were compared with the data of the international studies performed by the American Joint Committee on Cancer (AJCC; patients from Australia, the United States and Europe) and on the basis of the Surveillance, Epidemiology and End Results (SEER; patients from the United States) program.

For statistical analysis chi-squared test was used, $p<0.05$ was considered as statistically significant.

2. Risk of second primary tumors.

The patients from the 3^{rd} group were followed from January 1, 2006 till December 31, 2010. Data about additional internal diseases, tumors in the family medical history, the patients' profession were collected in their case. Additionally, we identified the patients with multiple primary melanomas.

Statistical analysis of the risk of second primary tumors among melanoma survivors was performed by

indirect standardization. Data obtained from our department (sample) were compared with that of the Hungarian National Cancer Registry (population). We estimated the difference between observed (O) and expected (E) values dividing them into two age groups (-49 years, 50- years) according to their age at the time of the primary melanoma diagnosis. Standardized incidence rate (SIR) was then established as the ratio of O and E values (SIR=O/E). The confidence intervals were evaluated by Rothman and Boice. We accepted a significant difference between O and E values at the 0.05% level, if the 95% confidence limits excluded unity. Excess absolute risk (EAR[1]) was calculated on the basis of person years (PYR) data obtained in the sample and in the population ($EAR=10^5(O-E)/PYR$). PYR values were accumulated from the time point of the diagnosis of the first melanoma until the last control examination, death, or December 31, 2010. We also tested there was significant difference between genders and/or age groups. This estimation was based on a Pearson-Yates test.

The collected data of the two patient groups (1st and 3rd group) resulted in a database containing 72 480 elements, that can be a basis of further studies

3. The risk of melanoma at the Nuclear Power Plant of Paks

The patients from the second group involved the employees of the Nuclear Power Plant of Paks (n=556) who had undergone a dermatooncological screening between 2008–2009 organized by the Department of Dermatology Dermatooncology and Venereology,

[1] EAR: expressing the difference of the absolute risk between sample and control population

Semmelweis University. The examination was voluntary, held on every other week at the power plant with the contribution of 2 or 3 physicians/occasion. We collected the data about the patients and the examinations in questionnaires. The first part of the questionnaires (questions 1-11.) was filled out by the workers (name, date of birth, duration of the work in the power plant). The type of the work was characterized as hazardous or non-hazardous one dependent on the environment of the work with or without the possibility of ionizing radiation exposure. In addition, everybody was asked for sun exposure habits (sunny hours/day outdoor), the number of bullous sunburns in the past, the frequency of possible tanning bed use. Skin tumors in the medical history were also registered. The second part of the questionnaire was filled out by the examiner dermatologist (questions 12-16.). Pigmented and dysplastic nevi, cutaneous signs of the chronic UV damage and tumor suspicious lesions were analysed by dermatoscopy and registered in the questionnaire. The lesions clinically suspicious for malignant tumors were removed and examined histologically.

Statistical analysis: a chi-squared test was used, $p<0.05$ was considered as statistically significant. Data were compared with the results of the 6th Hungarian Euromelanoma screening campaign in 2009, the year of the study. Yates's correction was applied because of the low case number.

Results

1. The stage distribution of melanomas at the Department of Dermatology, Dermatooncology and Venereology, Semmelweis University

1160 melanomas were diagnosed at our Department between 2004 and 2009. 48% of the patients were males (n=558), 52% were females (n=602). In situ (17.8%) and stage II melanomas (21.9%) contributed equally, representing about fifth of all cases. Half of all cases (49.7%) were stage I, one tenth of them (10.3%) were stage III melanomas. In situ and stage I tumors were in excess among females, while stage II and III tumors among males. Late melanomas (stage IV) were experienced only by few patients (*Figure 1).*

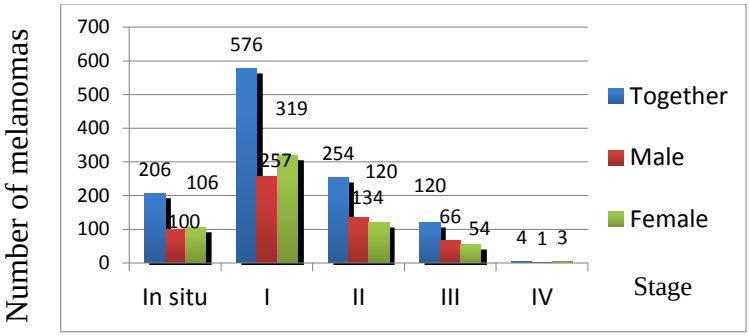

Figure 1. The stage distribution of the melanomas diagnosed at theDepartment of Dermatology, Dermatooncology and Venereology, Semmelweis University between 2004-2009

We compared the stage distribution of our patients with the results of the AJCC and SEER cohort studies. It was shown that 57.7% of the patients from the SEER and 25.6% from the AJCC cohort belonged to the stage IA. 43.8% of our patients proved to be stage IA, which is between the values of the two big cohorts. In the early stages (IB-IIA) our patients occured in the lowest per cent. From the stage IIC the percentage of our patients exceeded the rate of both the SEER and AJCC cohort, respectively. In the stages IIIA and IIIB – which present already with regional lymph node metastases – again our patients occurred in the highest rate. In the last stages the distribution became more favourable; in stage IIIC our patients occurred in lower rate than the patients of the AJCC cohort. In stage IV the rate of our patients was lower either than that it in the SEER or in the AJCC cohort *(Figure 2.).*

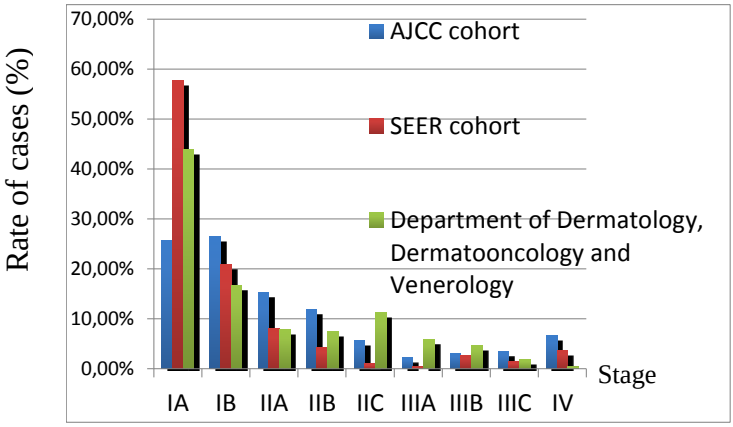

Figure 2. The stage distribution of the melanomas at our Department, in the AJCC and SEER cohort

2. The risk of melanoma among the nuclear industry workers

We screened 556 workers – 281 males and 275 females – in the Nuclear Power Plant of Paks. 80% of the screened males had been working in the power plant in average for 18 years with ionizing sources in strictly controlled environment. In contrast, the work of females was mostly devoided of direct contact with ionizing radiation, they worked in the power plant for 19 years in average.

Most of the screened workers had skin type II, and spent in average 2 hours/day on the sun. We registered the cutaneous signs of chronic UV damage (actinic keratosis, solar lentigo and/or elastosis) by 34% of the males and 41% of the females. Very low per cent of the screened population had more than 10 dysplastic nevi (2% of males, 0.4% of females).

During the one year screening period we identified three histologically verified malignant skin tumors; one in situ melanoma and two basal cell carcinomas.

The melanoma was detected in a 53-year-old female patient. Her skin was type I and had four bullous sunburns, hence we noticed the signs of chronic sun damage (solar lentigos, elastoses) on her skin. The melanoma was on her left arm, in the area exposed to sunshine. She had been working for 26 years in the power plant in ionizing radiation free environment.

Basal cell carcinomas were verified in two male patients. Both of them were working with ionizing

sources at least for 20 years, none of them had malignant skin tumor in the medical history. The younger male was 37-year-old, had type I skin and had had 3 bullous sunburns. The older male was 53-year-old with type II skin and had never bullous sunburn.

The screening's results were compared with the data of the 6th Hungarian Euromelanoma day by chi-squared analysis. Yates's correction was applied because of the low case number. The Euromelanoma day's and the power plant's screening data did not show significant difference (p=1; 95% confidence interval). According to our result the melanoma incidence doesn't differ significantly between the employees of the Nuclear Power Plant of Paks and the general Hungarian population, that correlates with the international literature.

3. The risk of second primary tumors in melanoma survivors at the Department of Dermatology, Dermatooncology and Venereology, Semmelweis University

We assessed the risk of subsequent primary malignancies among 740 (males: n=366; 49.5%, females: n=374; 50.5%) patients who were diagnosed with melanoma between 2006-2010 at our Department. During the 1499 person-years follow-up period 115 second malignant tumors were diagnosed (males: 64, females: 51). 70 (9.5%) patients had one, 16 (2%) patients had two, while 1 (0.1%) patient had three subsequent cancers. 81% of the subsequent tumors (n=93) was skin tumor (38% melanoma, 62% non-melanoma skin cancer).

Additionally to the second skin tumors the patients had different second primary internal malignancies (kidney, prostate, bladder, colon, rectum, tongue, lung, laryngeal, uterus, cervix, breast tumors, chronic lymphocytic leukemia, non-Hodgkin's lymphoma). 44 patients had multiple melanomas, 7 of them (16%) had additional non-melanoma primary cancer (non-melanoma skin cancer: n=5, kidney tumor: n=1, colon tumor: n=1).

We analysed the risk of second primary tumors after melanoma; according to our calculation the overall risk of subsequent primary tumors increased 15-fold in male, 11-fold in female melanoma survivors compared to the general Hungarian population (males: SIR:15.42, O:61, 95% CI, 15.34-15.51, EAR: 0.32; females: SIR:10.55, O:51, 95% CI, 10.49-10.60, EAR:2.81). The elevated tumor risk was primarily due to additional cutaneous malignancy development, including primary melanomas. Non-melanoma skin cancers occurred also with elevated incidence, the SIRs showed significantly higher risk in both genders compared to the general population (males: 17.12, females: 17.55). Additionally, some non-cutaneous second primary cancers also occurred with higher risk after melanoma: chronic lymphocytic leukemia, colon-sigma and kidney cancer had significantly increased risk in both genders. We experienced higher risk for cervical cancer and non-Hodgkin's lymphoma only in females, while bladder tumor in males. On the other hand, the risk of lung and prostate cancer in males, breast cancer in females was found significantly lower compared to the general population.

Conclusions

The incidence of melanoma is increasing as much as in Hungary as worldwide. The significance of the tumor is growing, since its aggressive spreading results in internal metastases even in case of only few millimeter thick tumors.

Since the survival time depends mostly on the tumor stage the stage distribution of the melanomas diagnosed at our Department (1st patients group) was assessed and our results were compared with the data of AJCC (patients from Australia, the United States, Europe) and SEER (patients from the United States) cohort. According to the analysis 43.8% of our patients belonged to the stage IA, which is between the value of the AJCC and SEER cohort. Only 0.4% of our patients proved to be in stage IV that is lower than the rate either of AJCC or of SEER group. Comparing our results with international data it may be concluded that the incidence of the very early stage of melanoma with good prognosis was very high, while the incidence of the latest (IV) stage, neglected melanoma was very low in our department.

Our results are highly favourable compared to some East-Central European countries. These data suggest the highly qualified expertness of the Dermatological centers in the region of our department.

The results of the oncodermatological screening among the nuclear industry workers (2nd patient group) of the power plant at Paks show that the melanoma incidence at the special workplace doesn't differ significantly from the Hungarian and international data.

We diagnosed one melanoma in very early, in situ stage. In the tumor's development rather the UV than the ionizing radiation (ionizing radiation free work circumstances, skin type I, four bullous sunburns in the medical history, signs of UV damage on the skin, melanoma in sunshine localization) could have played a role. Most of the studies focusing on the skin effects of ionizing radiation failed to analyse the potential role of UV irradiation which may modify the results of the examinations. It can be concluded that documentation of UV irradiation is absolutely necessary when the role of epigenetic factors is examined.

To assess the second primary tumor risk among the melanoma survivors (3rd patient group) we studied subsequent primary malignancies following melanoma. Our results clearly show that the risk of second primary cancers elevated after melanoma compared to that found in the general population. Our findings suggest that the elevated risk is primarily resulted from the increased melanoma and non-melanoma skin cancer risk (standardized incidence rate: 17). Additionally, we experienced significantly elevated risk after melanoma in case of some internal tumors (chronic lymphocytic leukemia, colon, kidney tumor). The risk of non-Hodgkin's lymphoma and cervical carcinoma was higher among females, while bladder carcinoma occurred with higher risk among males.

The excessive increase of melanoma incidence and the elevating mortality during the last decades in Hungary indicates that the efforts to prevent melanoma are inadequate up to now. It is an urgent need to establish

population based primary and secondary prevention programs.

The detailed informations about UV protection and skin cancers could reach the majority of the population via school education, family doctors and media prevention programs. In addition, to prevent subsequent skin and internal malignancies among melanoma survivors, patient education, self-examination and frequent medical, particularly dermato-ocnological control would play a basic role. The permanent information and postgraduate education of the physicians has outstanding importance. Examination of the skin should be a part of general medical examination.

The campaign would result in growing awareness about the UV protection and skin tumors. Consequently, the number of new skin malignancies would decrease and patients would visit dermatologists with earlier tumors. The higher rate of melanomas removed in early stage would clearly increase the survival time. In consequence, the number of patients with late melanoma would radically decrease that would simultaneously result in lower examination/diagnostic and therapeutic costs.

The main results of the study:

a) Analysis of the data of 1309 patients with melanoma according to two different aspects resulted in two separate databases consisting of 72 480 elements which may serve as a basis for further studies.
b) We examined 1160 patients with newly diagnosed melanoma according to new prognostic

factors (TNM stages) compared to the National Cancer Register; consequently, our study resulted in novel, additional information and database on melanoma prognosis. We concluded that among the newly diagnosed melanomas in Semmelweis University the proportion of the earliest, IA stage tumors (43.8%) was high compared to the international data (AJCC patient group). Similarly, it was also favourable that the ratio of the latest stage melanomas (IV) with the worst prognosis was very low (0.4% of melanomas).

c) We concluded that the frequency of melanoma was not higher among nuclear industrial workers than in the general Hungarian population. Moreover, our study suggests taking into consideration the skin effects of UV irradiation when the role of epigenetic factors in melanoma formation is analysed.

d) In Hungary the risk of second primary cancers among melanoma survivors was first estimated in our Department. The findings suggest that the risk of all second primary tumors - in accordance with international data - is significantly (11-15-times) higher compared to the general population. The higher risk was mostly caused by the elevated incidence of second primary melanoma and non-melanoma skin cancers. Beside the skin tumors the risk of some second internal malignancies was also significantly higher after melanoma.

e) Our results emphasize that the regular oncological control is basically important after melanoma to

diagnose the possible second skin or internal malignancies in time. The histological analysis of any tumor propagation is also essential in these patients to differentiate the metastases from second malignancies, since the life expectance of the patients depends on the early started specific anti-cancer therapy.

Publications

Thesis-related publications

1. Tóth V, Somlai B, Hatvani Z, Szakonyi J, Gaudi I, Kárpáti S. (2013) Melanoma Screening in a Hungarian Nuclear Power Plant. Pathol Oncol Res, 19(2):323-8

2. Tóth V, Hatvani Zs, Somlai B, Hársing J, László JF, Kárpáti S. (2013) Risk of subsequent primary tumor development in melanoma patients. Pathol Oncol Res, 19(4): 805-10.

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7. Tóth V. A bőrfüggelékek betegségei. In: Pónyai K, Kárpáti S. (szerk.), Bőrgyógyászat és Venerológia. Asszisztensi jegyzet. Digitalbooks, Budapest, 2011: 251-63.

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Asszisztensi jegyzet. Digitalbooks, Budapest, 2011: 264-91.

9. Tábi T, Szökő E, Mérey A, Tóth V, Mátyus P, Gyires K. (2013) Study on SSAO enzyme activity and anti-inflammatory effect of SSAO inhibitors in animal model of inflammation. J Neur Transm, 120(6):963-7.