SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Epidemiological studies to develop a regional melanoma prevention strategy

By Eszter Anna Janka

Supervisor: Dr. Éva Remenyik

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By Eszter Anna Janka, Expert in Public Health

Supervisor: Prof. Éva Remenyik, MD, PhD, DSc

Doctoral School of Health Sciences, University of Debrecen

Head of the **Examination Committee***:	Prof. Margit Balázs MD, PhD, DSc
Members of the Examination Committee	Orsolya Varga MD, PhD
	Beáta Somlai MD, PhD

The Examination takes place at library of Department of Dermatology, Faculty of Medicine, University of Debrecen at 11:00 AM, February 13, 2020.

Head of the **Defense Committee**:	Prof. Margit Balázs MD, PhD, DSc
Reviewers:	Prof. Csongor Kiss MD, PhD, DSc
	Veronika Tóth MD, PhD
Members of the Defense Committee:	Orsolya Varga MD, PhD
	Beáta Somlai MD, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen at 13:00 PM, February 13, 2020.

1. INTRODUCTION

Cutaneous melanoma is a malignant tumour that originates from epidermal pigment cells of the skin (melanocytes). Melanocytes of crista neural origin are located in the basal layer of the epidermis. They produce melanin pigment, which passes through the dendrites into the epithelial cells. Nevi are benign tumours of melanocytes and they can be typical and atypical. A large number of moles and atypical moles are associated with a high risk of malignant melanoma (MM). To our knowledge, about 30% of melanomas develop in nevi, but it is not possible to predict which nevi will be transformed. The malignant transformation of melanocytes results from a number of consecutive molecular events. The sequence of steps is not always similar, so the melanoma is not a unified tumour.

1.1 Environmental factors influencing the development of melanoma

In addition to the presence of atypical moles, the ultraviolet (UV) radiation is another important risk factor for melanoma. Most (about 90%) of UV-B radiation (280-315 nm) is absorbed by the ozone layer, and many factors affect the extent of UV-B exposure, such as geographical location, atmospheric pollution, season and time of day. Contrary to UV-B radiation, most of UV-A radiation (315-400 nm) reaches the earth's surface. Their biological effect is also different. The UV-B rays are largely absorbed in the upper layers of the epidermis of the skin, only 9-15% reach melanocytes, and they directly damage DNA with inducing cyclobutane pyrimidine dimers (CPD) and to a lesser extent they also cause oxidative base damage. In contrast, UV-A rays penetrate deeper into the skin and approximately 50% reach junctional melanocytes, cause mainly oxidative base damage and single-stranded DNA breakage, thus enhancing acute and chronic tissue damage.

Artificial UV devices, like the solarium, basically emit UV-A, and many people think that solarium is safe. However, the use of artificial tanning devices increases the skin cancer risk, especially when used regularly in young ages.

According to epidemiological evidence, other significant risk factors are light skin colour, increased exposure of sunlight, and the number of sunburns people experience throughout their lives, especially at young age. The presence of more than 50 moles also represent a high risk of developing melanoma.

Age and gender are prognostic factors of melanoma. The risk of developing melanoma increases with age, although its appearance seems to be shifting to younger age. In terms of gender, while in New Zealand, in Australia and in the United States the rate of melanoma is higher among males, in European countries melanoma is more prevalent among females. In terms of melanoma localization, gender differences can also be observed, with males most likely to have melanomas localized to the trunk, while among females melanomas are most likely to be localized to the lower extremities.

1.2 Epidemiology

The incidence of both skin cancer of keratinocyte origin and malignant melanoma have increased over the last 40 years, particularly in the white-skinned population. The age-standardized incidence of melanoma in Hungary (7.1) is slightly lower than the European average (8.6), but much higher than the global average (3.0).

In Hungary, the mortality rate of melanoma is relatively high (3.2).

Melanoma is a significant burden not only for the individual, but also for society, due to the health care cost, and the loss of workforce. However, early detection improves prognosis, patient survival, and quality of life and saves costs for the health care system. The ABCDE rule helps to detect early signs of melanoma and warns of the potential malignancy of skin lesions. However, recognition is complicated by the fact that moles can be very heterogeneous, with multiple variants present simultaneously on the skin of an individual.

The 5-year survival rate for malignant lesions (<1 mm tumor thickness) is 92-97%. In those with tumour thicknesses of more than or equal to 1 mm, despite of that there is no detectable

spread to regional lymph nodes or other organs at diagnosis, the 5-year survival rate is approximately 53-81%. Without distant metastasis but regional lymph node involvement at the time of diagnosis, 5-year survival rate is 40-78%. In the presence of distant metastasis, the 5-year survival rate is quite low, 15-20%. Ulcerative melanoma has a worse prognosis with the same tumour thickness. Localization of melanoma and depth of invasion (Clark level) are also associated with survival. The Clark level shows how deep the tumour cells are infiltrated into the anatomical layers of the skin. The 5-year survival in Clark level I-II is more than 90%, at level III is about 80%, for level IV is around 70%, while in level V it is already below 50%.

The most common type of melanoma is superficial spreading melanoma (SSM), occurring in about 50% of all cases. A sharply delineated, irregularly shaped, flat, multi-coloured lesion which initially shows horizontal growth but later shows vertical growth. The second most common type of melanoma is nodular melanoma (NM), which occurring in about 20-30% of melanomas. Lentigo maligna melanoma (LMM), which occurs most frequently on the skin exposed to sunlight, such as the face, is less common. Acral lentiginous melanoma (ALM) occurs in approximately 5% and is seen on the palms, soles, fingers and toes. In terms of histological types, NM has a lower survival rate.

1.3 Prevention

In order to reduce both morbidity and mortality, primary and secondary prevention should be used and improved. Primary prevention focuses primarily on reducing natural and artificial UV exposure. Numerous programs have been launched around the world to inform people about melanoma and its risks, and to raise awareness of the importance of prevention.

In addition, many organizations aim to warn of the harmful effects of the tanning bed and to regulate in an act to forbid the use of the tanning bed by persons under the age of 18. But, since melanoma is not a unified tumour type and UV exposure is responsible for melanoma development approximately in 60% of the cases, primary prevention focused on

photoprotection does not provide complete protection. In Hungary, education and screening programs were launched in the second half of the 2000s, and it is now necessary to renew or strengthen them on a new basis.

It has already been shown that population-based screening as secondary prevention is not cost-effective and is not suitable for reducing mortality. Nevertheless, effective strategies for both primary and secondary prevention may vary from country to country, depending on the composition of genetic, population, and environmental factors that contribute to the development of melanoma at a given geographical location. Epidemiological studies of melanoma incidence trends can help to improve public health efforts regarding morbidity and mortality of melanoma. These types of surveys can reveal current supply problems and allow for comparison with trends in both national and international centres.

The Department of Dermatology University of Debrecen, in Hajdú-Bihar County of Hungary, covers the Northern Great Plain area as centre that ensures care for patients diagnosed with melanoma, which provides an excellent opportunity for more detailed epidemiological analysis. The high rate of missing clinical and pathological data in cancer registries may be a limiting factor in epidemiological studies, however in our hospital records a low rate of missing data have been achieved.

2. OBJECTIVES

As the incidence of melanoma has been increased significantly in recent years, it is essential to develop appropriate prevention based on the geographical location. In Hungary, education and screening programs started in the 2000s, but nowadays they have to be renewed. In our country there was not enough surveys on the sunbathing and light protection habits of school-age children, and on the incidence trends related to melanoma, and what factors should be taken into consideration.

In our investigations we aimed to:

1. assessing the sunbathing and sun protection habits of primary and secondary school students (12-19 years old)
2. comparison of sunbathing and sun protection habits with international data
3. education and training of school physicians in order to recognize atypical nevi during physical examination and thus be involved in the development of prevention
4. to determine the incidence of malignant melanoma and to assess the current trend
5. analysing the gender and age composition of patients
6. to analyse how the type, localization, and melanoma thickness of the diagnosed tumours have been changed during the examined periods
7. identification of prevention points where improvement is possible.

3. MATERIALS AND METHODS

3.1 Population of school-age children

A cross-sectional study was performed in 2007 to determine skin type, number of pigmented lesions, and sun protection and sunbathing habits. A total of 20 schools in Debrecen, 12 primary schools and 8 secondary schools (1157 students) were involved. Primary school students were 12 to 15 years old, while secondary school students were 15 to 19 years old. 18 school doctors attended dermatologic training. Their involvement was also advisable because all students are required to undergo an annual physical examination at the school. School physicians recorded the number and location of the typical and atypical nevi, and the skin type on the Fitzpatrick scale. The nevi number has been categorized as: less than 5; 5-20; and more than 20 nevi.

In addition to the physical examination, the students completed a questionnaire on their sunbathing and sun protection habits at home with the help of their parents. The 44-item questionnaire was compiled by dermatologists at the Department of Dermatology, which included details on sun protection and sunbathing habits, solarium use and number of sunburns. A total of 612 evaluable questionnaires were processed.

Both parents and students gave their consent to the study (ethical approval number 2592/2007).

3.2 Melanoma population

The retrospective study was based on the melanoma database of the Department of Dermatology at the University of Debrecen, supplemented with histological and clinical data recorded in the MedSolution hospital information system. (Study Ethics Approval Number: 9555-2 / 2017 / EKU). As the Department of Dermatology was the melanoma centre of Hajdú-Bihar county during the examined period (2000-2014), our data are representative of the population living in this county. The study period was divided into five three-year periods (2000-2002; 2003-2005; 2006-2008; 2009-2011; 2012-2014). Data from 1509 histologically verified melanoma from a total of 1464 individuals were analysed.

In order to calculate the standardized incidence, the population of Hajdú-Bihar County for each year was provided by the Central Statistical Office (CSO) (population determination on January 1 of each year). Data from the Central Statistical Office and the National Cancer Registry were used to determine the reference population. For the year 2000, the incidence value was not calculated because we do not have reliable data for this year in the National Cancer Registry database. We used age standardized data from the world standard population to determine the incidence trend.

3.3 Statistical analysis

For categorical variables, chi^2 or Fisher exact test was used. Two groups were compared using an independent t-test or Mann-Whitney U test. When comparing three or more groups, we performed an ANOVA test supplemented with a Tukey post hoc test. Binomial logistic regression was used to analyse the determinants of sunburn. Furthermore, the factors influencing high nevus numbers and high melanoma tumour thickness were investigated by multinomial logistic regression.

National standardized melanoma incidence rates were calculated using direct standardization. We used the age distribution of world standard population as the standard population. In Hajdú-Bihar County, the age-standardized melanoma incidence rate (per 100,000) was calculated by indirect standardization relative to national data. The melanoma incidence trend was analysed using a joinpoint regression test, which determined the annual percent change (APC) and average annual percent change (AAPC) and identified the breakpoints in the trend.

Significance level was $p < 0.05$ in all cases. Statistical analysis was performed using SPSS 19 and Joinpoint Regression Program.

4. RESULTS

4.1 Study on school-age children

A total of 1157 students (704 primary school students, 453 secondary school students) from 20 schools were involved. The 18 school doctors examined the students' skin, determined which skin type they belong to, and determined the number of typical and atypical nevi. The average age was 13.11±0.50 years for primary school students and 17.06±0.55 years for secondary school students. In case of gender there was a significant difference between the two groups, the proportion of girls was being higher at primary school, while the rate of boys was higher at secondary school ($p=0.027$).

The self-reported questionnaire was completed in evaluable way by 612 people, of whom 393 were primary school students and 219 were secondary school students. The mean age of those completing the questionnaire was 13.16±0.55 years for primary school students and 17.09±0.55 years for secondary school students. No significant difference was found in terms of gender frequency ($p=0.070$).

4.1.1 Survey by school physicians

School physicians determined the number of typical and atypical nevi on the skin of the students (N=1157). In both age groups, moles were significantly more frequently localized on the trunk ($p<0.001$). 22.6% of primary school students and 11.9% of secondary school students had less than 5 nevi. Approximately 55.1% of the younger age group and 54.8% of the older age group had 5 to 20 nevi. 20.7% of primary school students and 27.2% of secondary school students had more than 20 nevi. Very few percent of the students had no moles on their skin (primary school students: 1.6% and secondary school students: 6.0%).

Atypical moles were seen by 62.8% of students, according to school physicians. 54.7% of primary and 35.1% of secondary school students had one or two atypical moles. Atypical nevi above ten were present in 3.0% of the younger age group and 1.1% of the older age group.

4.1.2 Self-Reporting Questionnaire

A questionnaire was used to assess the sunbathing habits of students (N=612) by age and sex. In primary school, 70.1% of girls and 29.9% of boys had sunbathing ($p<0.001$). The same trend was observed among secondary school students, with significantly more girls sunbathing (61.5%) than boys (38.5%) ($p<0.001$). 39.2% of primary school students and 23.3% of secondary school students sunbathed only during holidays, while the proportion of those who sunbathe on a daily or weekly basis during the summer was 15.0% for the former group and for the latter group 23.7%. On average, students spent approximately 6 hours per day during the summer season (primary school: 5.82±2.84 hours/day; secondary school students: 6.16±3.02 hours/day); most of them avoided the period when UV radiation is highest.

Investigating the number of sunburns, we found that about 73.7% (N=451) of students had experienced severe sunburn in their lifetime, 43.3% of primary school students and 52.5% of secondary school students reported 3 or more sunburns. The number of sunburns was significantly higher among secondary school students (4.83±4.23) than among primary school students (3.80±2.93) ($p=0.007$).

In addition, the survey showed that about 10.1% of students had no protection against the sun. The use of sunscreen ($p=0.002$) and the use of hat as a sun protection were significantly more common among primary school students ($p<0.001$) than among secondary school students. Considering all ages, girls preferred to use sunscreen, while boys preferred clothing as sun protection.

Most students (primary school girls: 58.1%; secondary school girls: 40.2%; primary school boys: 49.0%; secondary school boys: 44.2%) applied sunscreen with sun protection factor (SPF) 15-30. Only 15.9% of primary school boys, 6.3% of high school boys, 12.0% of younger girls, and 10.3% of older girls used sunscreen with SPF >30.

6.9% of students have already used solarium and significantly more secondary school students (15.1%) applied than primary school students (2.3%) ($p<0.001$). The majority of students (57.1%) stated that they used an artificial tanning machine to achieve a trendy brown skin colour, while 23.8% reported that they used to prevent sunburn.

4.1.3 Physical examination of the students completing the self-reported questionnaires by school physicians

The skin of the students (N=612) who completed the self-report questionnaire correctly was categorized by school physicians on the Fitzpatrick skin type scale. 21.4% of the students belonged to skin type I, 60.8% to skin type II, 16.5% to skin type III, and only 1.3% belonged to skin type IV. The majority of students (primary school: 55.5%; secondary school: 51.6%) had nevi number between 5 and 20. 23.7% of the young age group and 27.9% of the older age group had more than 20 moles. Furthermore, 18.3% of primary school students had less than 5 moles, while 2.6% had no nevi at all. For secondary school students, the former parameter was found to be 15.1%, while the latter was 5.5%.

We examined the factors influencing juvenile sunburn in primary and secondary school students using binomial logistic regression. Among primary school students were more likely to have sunburns, those have light hair ($p=0.049$), those with type I ($p=0.012$) or type II skin type ($p=0.003$), those who prefer direct sunbathing ($p=0.035$).), and who do not wear any sun protection clothes while outdoors ($p=0.037$). In the case of secondary school students, only the gender was a significant influencing factor, boys were more likely to burn than girls ($p=0.035$). In addition, we examined the variables associated with the higher nevi number using multinomial logistic regression. The analysis showed that there is a greater chance of having more than 20 moles of those with Fitzpatrick skin type I ($p=0.001$) or type II ($p=0.001$) or those who use a solarium ($p=0.040$).

4.2 Analysis of melanoma data

The basis of our study was the database of 1509 cases of malignant melanoma (1464 patients). The study period (2000-2014) was divided into five three-year periods (2000-2002; 2003-2005; 2006-2008; 2009-2011; 2012-2014). 231 tumours (229 people) in the 2000-2002 period, 271 melanomas (266 patients) in the 2003-2005 period, 338 melanomas (320 people) in the 2006-2008 period and 351 tumours (342 patients) between 2009 and 2011, while data from 318 melanomas (307 persons) were analysed in the 2012-2014 period.

4.2.1 Incidence of melanoma and trend analysis

Using data from the Central Statistical Office and the National Cancer Registry, we calculated the national standardized incidence rates (standard population: world standard population distribution) for each year. While in 2001 the standardized incidence of melanoma in Hungary was 8.99, in 2014 it was 15.64. Observing the national incidence trend, we found a significant increase between 2001 and 2014 (AAPC: 4.55 [3.62; 5.50]; $p<0.001$).

We also determined the incidence of melanoma in Hajdú-Bihar County between 2001 and 2014. Similar to the national trend, there was also an increase, however more moderate (AAPC: 3.04 [0.07; 6.11]; $p=0.045$). Investigating further the trend, a breaking point was seen in 2007. In the first period, between 2001 and 2007, a significant increase in the incidence was observed (APC: 9.84 [3.52; 16.55]; $p=0.006$), which however stopped in 2007. There was a slight decrease after 2007, but this decrease was not significant (APC: -2.45 [-5.99; 1.23]; $p=0.164$).

Except in 2007, 2009, 2013 and 2014, the standardized incidences in our region did not differ significantly from the national incidence.

In terms of gender, standardized incidence rates were higher in females in the Northeast region, but this difference was not significant in any of the years.

However, in case of age groups there were significant differences, with the highest incidence rates observed in the age group over 60 years. The incidence was significantly higher in the

older age groups (40-59; 60-79; 80x) than in the under 40s. Only between the two older age groups (60-79 vs. 80x) was found no significant difference in incidence.

4.2.2 Characteristics of melanomas

Although the incidence was higher in 2007 and 2009 in Hajdú-Bihar County than the national one, the average tumour thickness was relatively low and the majority of patients were diagnosed with thin melanoma in these years.

Observing the 3-year periods also shows that in each period (2003-2005: $p<0.001$; 2006-2008: $p<0.001$; 2009-2011: $p<0.001$; 2012-2014: $p=0.041$) the Breslow tumour thickness was significantly lower than in the period 2000-2002, but the average tumour thickness increased again in 2012-2014 to a level significantly higher than in the 2006-2008 period ($p=0.018$). Furthermore, in the AJCC classification, the proportion of stage IA melanomas increased after the 2000-2002 period, but decreased in the 2012-2014 period and the presence of lymph node metastasis (stage III) and the rate of diagnosed tumours with distant metastasis (stage IV) increased during this period.

Further analysis of the data showed that although the incidence of tumours greater than 4 mm increased in patients between 40 and 79 years, it was highest in patients over 80 years of age, showing a further increase in the last 3 years of the study period. The incidence of tumours of 2.01 to 4.00 mm increased in patients under 60 years of age and in the population over 80 years of age in 2012-2014. The proportion of tumours of 1 mm or less increased in all age groups between 2000 and 2011; however, in subsequent periods, their incidence decreased in all age groups.

In our analysis, we found no significant difference between age ($p=0.887$) and gender ($p=0.570$) comparing the five periods. In the melanoma type, the superficial form was the most common ($p<0.001$), while the highest prevalence rate was the Clark III level ($p<0.001$). Regarding localization, we found significant differences between the gender. Overall, in all five periods,

males had significantly higher incidence of melanoma in the trunk, whereas females had a higher incidence of lower extremities ($p<0.001$).

4.2.3 Investigation of factors associated with worse disease prognosis

Multinomial logistic regression was used to examine the determinants of thicker tumours. We found that thicker tumours were less likely to occur in the 2003-2011 period than in the 2000-2002 period, but this trend was no longer apparent in the 2012-2014 period. Age proved to be the most important influencing factor, and the incidence of tumours larger than 2 mm increased with age. Male gender and melanoma location were also important influencing factors. There was a greater chance of having thicker melanomas on the trunk or lower extremities.

5. DISCUSSION

Childhood sunburn is a major risk factor for the development of skin cancer, so it is important to start sun protection education programs early in school. In order to be effective in education programs, it is important to assess sun protection and sunbathing habits of students.

According to our 2007 survey, most students used sunscreen or some of sun protection methods, but 74.0% had at least one severe sunburn. The use of sun protection methods and the prevalence of sunburn vary considerably between countries and age groups. In Greece, 72.1% of coastal elementary school students report always wearing sunscreen, while 40.6% of students wear hats and 46.3% prefer to stay in the shade. Correspondingly, 66.9% of the students said that they did not burn at all last summer. Even among Italian children aged 11-14, few students reported sunburn (24.0%), although 38.0% of these students spent 4 to 8 hours a day out in the sunlight in the summer and 30.0% stayed out in the midday, but 80.0% of the children applied sunscreen. In contrast, a study in southern Brazil with a high incidence of fair-skinned people found that while 74.3% of students used sunscreen, about 73.0% had at least one sunburn. Several other surveys, like ours, have shown that although the percentage of people who use sunscreen, wear a hat and stay in the shade is relatively high, the number of sunburns is still high.

Examining the factors with influence on sunburn, we found that secondary school boys were more likely to burn, while among primary school students a positive correlation was shown between sunburn and direct sunbathing, light hair colour and skin colour, and avoiding protective clothing during exposure to sunlight.

School physicians who identified a large number of typical and atypical nevi on students' skin were involved in our study. Most students had nevi between five and twenty. In the older age group, the number of the detected moles was higher. The majority of moles in both groups were localized to the trunk. In addition, school physicians detected at least one clinically atypical

nevus on 67.0% of the students. It is likely that in our study, despite their dermatological training, doctors overestimated the number of atypical nevi. One study showed that doctors with inadequate experience were more likely to overestimate the number of atypical nevi during initial evaluations. Routine application of dermatoscope improves the skills of primary care physicians in recognizing and evaluating clinically atypical nevi, and may reduce the number of unnecessary excisions and interventions, but this would require continuous practice and self-monitoring training.

The presence of multiple nevi may indicate genetic susceptibility and/or skin damage due to UV light, which are individual predisposing factors to melanoma. Our study showed that students of Fitzpatrick skin type I or II and those using sunbeds were more likely to have more than 20 nevi. The proportion of solarium users among older students was relatively high (15.1%), but the result was surprising among primary school students because 2.3% had already tried an artificial tanning appliance. Our investigation took place in 2007, at that time there was no provision restricting the use of solarium in Hungary. In 2010, the law came into force prohibiting the use of indoor tanning appliances under 18 years in Hungary. In 2009, IARC ranked UV equipment as one of the most powerful carcinogens. The use of solarium equipment is prohibited in more European Union countries and in Australia under the age of 18. Several studies have confirmed that the use of sunbeds in adolescence not only increases the risk of developing melanoma, but can also result that a tumour developing at an early age.

It can be stated that in order to develop proper sunbathing habits and to reduce the incidence of skin cancers, it is essential to educate Hungarian students on proper sunbathing and sun protection behaviour. In addition, informing the parents is also essential as parents are the largest source of information alongside the media. Educational programs would be most effective if they were implemented with intensive collaboration of dermatologists and school physicians. School physicians need to be much more involved in education and thus in the

primary prevention of malignant melanoma. There is a need for child health education to begin as early as possible, and political support is also needed to achieve effective protection structures. The factors increasing the risk of developing melanoma can be reduced by developing these primary prevention strategies.

In Hungary, we have limited data not only on the risk factors for malignant melanoma, but also few data has been provided on the incidence of the disease itself in Central and Eastern Europe. According to our calculations, the melanoma incidence values in Hungary show greater similarity between Hungary and Slovenia than Hungary and Slovakia, or Hungary and Austria, which may be surprising, and suggesting that Hungary and Slovenia may be more similar regarding environmental UV radiation and/or demographics. Furthermore, the average annual increase in melanoma in Hungary was also similar to the estimated AAPC in Slovenia over similar periods.

In the north-eastern region of Hungary, the incidence of melanoma from 2001 to 2012 was generally equal to or slightly higher than the national average. Despite of the high incidence, the median thickness of tumours showed a declining trend in Northeast Hungary between 2000 and 2009, suggesting an increase in the proportion of patients diagnosed with early-stage melanoma. We hypothesize that this may at least partly be the result of the high participation and activity of physicians and patients in melanoma screening campaigns (e.g. Euro-Melanoma Day) that has been started in this period in Hungary.

Several international studies have looked at gender differences in the incidence of melanoma in geographically diverse countries. While in Australia, New Zealand and the United States a higher incidence was observed in men, in many European countries a higher incidence was observed for women, we have the same conclusion although this difference was not significant in our study.

Regarding the localization of melanoma in our study, there was a difference between the gender, by males most likely to localize to the trunk and by females to the lower extremity. A Finnish and a German study came also to this observation.

It is worrying that the incidence of thicker melanomas increased in 2012-2014. Multinomial logistic regression analysis was used to determine the risk population for the worse prognosis melanoma. We know that Breslow tumour thickness is an independent predictor of survival. Our regression analyses showed that in the case of higher age, the presence of melanoma on the trunk or on lower limbs, and the male gender, the chance of being diagnosed with a thicker tumour is higher. According to our study, the increase in the incidence of thicker melanomas may be due at least partly to the high and increasing incidence of melanoma in people over 60 years of age. A recent report highlighted the increasing prevalence of thick melanomas in some European countries, which may lead to an unfavourable trend in melanoma mortality in the coming years, but detailed statistical analysis was not possible due to the relatively high rate of missing clinical and pathological data in several cancer registries.

In the absence of actual evidence regarding reducing the mortality of melanoma, to the best of our knowledge, population-level skin screening cannot be recommended. The results of a study in Schleswig-Holstein, Germany, also showed that there is no evidence that screening for skin cancer is an effective prevention of melanoma death. However, by identifying a high-risk population, screening would be more cost-effective and efficient for the target population. Our results have highlighted a high-risk population over the age of 60 where regular melanoma screening could be rewarding. For optimal utilization of health capacities and the availability of this population, it could be considered that these people are the target group of general practitioner care for chronic cardiovascular, metabolic and musculoskeletal disorders, thus further training of general practitioners on melanoma would be useful.

For younger generations, greater emphasis should be placed on education for primary prevention and self-monitoring, for example as part of pregnancy care, and through ongoing school awareness programs, which may be more cost-effective than screening and more effective in the long term.

6. SUMMARY

A study among primary and secondary school students found that although many people use sunscreen, a high percentage of students reported sunburn, and the use of solarium was also relatively high in both age groups. Multinomial regression analysis showed that those with light skin types and those using sunbeds were more likely to have high nevi numbers. Examining the trend in the incidence of melanoma, we found that both the national and Hajdú-Bihar County standardized incidence increased between 2001 and 2014. The proportion of melanomas diagnosed with higher tumour thickness and those diagnosed in Stage III and Stage IV increased in 2012-2014.

Our results showed the need to improve prevention strategies in Hungary. On the one hand, it would be important to involve school physicians to improve primary prevention in order to make students and their parents more aware of the risk factors, and, on the other hand after dermatological training they will be able to appropriately and regularly check students' skin. For melanoma, targeted population-level screening would be necessary and cost-effective. General practitioners could effectively participate in screening the target population, i.e. those over the age of 60.

7. PUBLICATION LIST

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Candidate: Eszter Janka
Neptun ID: KI9M0Z
Doctoral School: Doctoral School of Health Sciences
MTMT ID: 10053301

List of publications related to the dissertation

1. **Janka, E.**, Kékedi, K., Várvölgyi, T., Gellén, E., Kiss, B. K., Remenyik, É., Emri, G.: Increasing melanoma incidence in the elderly in North-East Hungary: is this a more serious problem than we thought?
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2. Gellén, E., **Janka, E.**, Tamás, I., Ádám, B., Horkay, I., Emri, G., Remenyik, É.: Pigmented naevi and sun protection behaviour among primary and secondary school students in an Eastern Hungarian city.
   Photodermatol. Photoimmunol. Photomed. 32 (2), 98-106, 2016.
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   IF: 2.662

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3. Gellén, E., Fidrus, E., **Janka, E.**, Kollár, S., Paragh, G. J., Emri, G., Remenyik, É.: 5-Aminolevulinic acid photodynamic therapy with and without Er:YAG laser for actinic keratosis: changes in immune infiltration.
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