| HEALTH PROMOTION AND DISEASE PREVENTION<br>**A Handbook for Teachers, Researchers, Health Professionals and Decision Makers** | |
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| **Title** | **Skin Cancer Prevention and Screening in the Republic of Macedonia** |
| **Module: 5.13** | **ECTS: 0.25** |
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| **Key words** | Skin cancer, melanoma, dermatoscopy, early diagnosis |
| **Learning objectives** | After completing this module, students and public health professionals should :<br>• assess the epidemiological situation of skin cancer or other type of cancer in their own country;<br>• be able to understand the essentials, methods and techniques of prevention programs in cancer control;<br>• estimate the economic and social impact of the disease;<br>• be familiar with new technologies used in the process of early diagnosis and creation of electronic patient record;<br>• be aware of importance of national strategies for prevention and cancer control. |

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| **Abstract** | Skin cancer is among the most common types of cancer. The incidence of skin cancer is very high and raising worldwide, especially its most serious and aggressive form, melanoma. Severe childhood sunburn and long term sun exposure over many years are the leading risk factors for skin cancer. Macedonia is situated in the region with high UV index of radiation and has an average annual incidence of skin cancer, compared with other countries in Europe and in the world. Almost all skin cancers are preventable and they are highly curable if detected and treated early. Even malignant melanoma is almost 100 percent curable if detected early, before the cancer has invaded into the deeper layers of the skin.<br><br>Since the year 2005 a new technology, dermatoscopy, has been introduced in the routine practice at the Clinic of Dermatology at the Clinical Center in Skopje. This new method of skin cancer detection makes possible diagnosis of melanoma in *in situ* stadium. It was the starting point for multiple activities and programs, which the Clinic has undertaken within the last two years, for prevention, screening and early detection of the skin cancer, as well as managing further appropriate cure. A new dermato-oncology unit was founded within the Clinic of Dermatology. Currently it is engaged in: clinical protocols of diagnosis and prevention, educational activities and informative campaigns, education of medical staff for working with this category of patients, selection of patients into groups (patients with low and high risk for developing skin cancer) and their follow-up in regular intervals, creating medical records in electronic form for each patient, promotion of dermatoscopy as a method, use of modern information and communication technologies (telemedicine, teledermatology) and active participation in the international activities for skin cancer control. |
| **Teaching methods** | • lectures<br>• seminars<br>• presentations<br>• group discussions |
| **Specific recommendations for teachers** | This module should be organised within 0.25 ECTS credit. Students can make, a practical work assignment, a review of literature/databases and prepare a report on cancer/specific disease prevention programs in their own organisation /region/country. |
| **Assessment of Students** | The final mark should be based on oral exam and structured essay. |

# SKIN CANCER PREVENTION AND SCREENING IN THE REPUBLIC OF MACEDONIA

## Suzana Kamberova, Marija V'lckova-Laskoska, Nebojsha Pesic

### Introduction

Skin cancer is one of the most frequent malignancies. It is conventionally divided into two major groups: non-melanoma (NMSC) and melanoma (MSC) skin cancer. Basal cell carcinoma and squamous cell carcinoma constitute the NMSCs. NMSCs are frequent diseases which acount for 90-96% of all skin carcinomas, and melanoma participates with only 1-4% in all cases of skin carcinomas (SCs), but 70-80% of the mortality rates contribute to this most aggressive form.

Skin cancer is predominantly, but not exclusively, a disease of white skinned globe population. Blacks, Asian, Hispanic and Native American population seem to have lower incidence of melanoma, no significant rise in incidence rate, acral body region distribution and no apparent evidence of the role of UV radiation in the etiology of this carcinoma.

There are much more data on the incidence and epidemiology on melanoma than of the NMSC. Mortality from NMSC's is almost always from SCC (squamous cell carcinoma), a form of cancer strongly linked to cumulative lifetime sun exposure, whereas melanoma is connected with intermittent and excessive sun exposure (sun burns) especially in the early childhood. A small number of skin cancers may be from other causes, such as exposure to some chemicals, arsenic in contaminated drinking water in etiology of basal cell carcinoma, infection with human papilloma viruses, etc. There is evidence of a link between skin cancer and diet. Some authors have pointed out that people who eat a high fat diet have a few times greater risk of developing premalignant lesions and skin cancer than those eating a low fat diet. On the other side, a healthy diet rich in vegetables, fruits and grains, contains nutrients and compounds that strengthen the immune system, including its ability to fight tumors, and may help prevent skin cancer and other forms of cancer. An interesting study was published recently - the combination of exercise and caffeine increases destruction of precancerous cells that have been damaged by the sun's ultraviolet-B radiation, according to a team of researchers at Rutgers University. Some of the damaged (precancerous) skin cells die naturally through apoptosis -- the process that occurs when the body orders damaged cells to die. But the rate of cell death among the precancerous cells was the highest in the group that drank caffeine and exercised (1).

It is widely accepted that the incidence rates of melanoma are rising worldwide. Some geographic distribution differences are noted. It is estimated that there were 132 000 cases of melanoma diagnosed world-wide in the year 2000 and 37 000 deaths caused by this disease. In Europe, the same year, it is estimated, there were 35 000 new cases which resulted in 9000 deaths of melanoma. The annual worldwide burden of melanoma is unevenly split between high – resources countries, on one side, and low- and medium-resource countries, on the other. The death/ incidence ratio is strikingly different in these two groups (140 000 cases and 25 000 deaths in the first and 28 500 cases and 12 000 deaths in the second group), (2).

The highest incidence rates of melanoma are reported in Australia (Queensland) and New Zealand, especially among the European and Israel imigrant population (annual incidence is more than double the highest rates recorded in Europe) (3). The incidence of melanoma has doubled in Europe between 1960s and 1990s. In the mid 1990s melanoma incidence rates were by far the highest in northern and Western Europe, but mortality rates were higher in

males from eastern and southern Europe. Melanoma rates are still rising in all Europe, but the mortality rates seem to level off in northern and western, but not in Eastern Europe. The explanation of this trend lies in a growing public awareness of UV radiation (UVR) and early symptoms of the disease in North and less in West Europe countries and detection of melanoma in earlier stage (*thin* melanomas).

Little data are published about epidemiology features and melanoma prevention in the countries with intermediate-risk populations, like the Republic of Macedonia, which have average annual incidence rate of melanoma compared with other geographical regions in the world (4). In the neighboring countries from the same region there are also not many studies on this subject. For example, in Croatia there is an average annual increase of incidence rate of melanoma of 8%, and in Slovenia melanoma skin cancer in the last four decades has been multiplied 7 times among men and 4 times among women (5-6).

Almost all skin cancers are preventable and highly curable if detected and treated early. Even the most dangerous type of skin cancer, the malignant melanoma, is almost 100 percent curable if detected early, before the cancer has invaded into the deeper layers of the skin. Otherwise, it can easily spread to the lungs, liver and other vital organs if not properly treated. Melanoma arises in 80 to 90 percent of the cases *de novo* (on previously normal skin) and in only 20-10 percent in a preexisting nevus. It is suggested that SSM (superficial spreading melanoma) is more often seen type in a connection with a nevus and that nodular melanoma develops on a normal skin. Therefore, any new lesion, that appears after the age of twenty, should be examined by a specialist.

**ABCDE rule/ symptoms for recognition of malignant melanoma (7)**

ABCDE rule/ symptoms help patients and doctors in early recognition of malignant melanoma. If a mole or pigmented spot shows any ABCDE symptoms patient should see and consult the doctor at once. The five basic ABCDE symptoms are the following:

A = Asymmetric configuration of the pigmented lesion (one half of the mole does not match the other half);

B = Border of the lesion is irregular (edges of the mole are ragged, notched or blurred);

C = Color of the lesion is non-homogenous (the mole's pigmentation is uneven or changes, with various shades of tan; brown and black, as well as blue, white and red);

D = Diameter greater than 6 mm.

E = Elevation /infiltration of the lesion.

There is also a dermatoscopic ABCD algorithm that means: A for asymmetry, B for abrupt cut off of the edge of the lesion, C for evaluation/presence of the six colors and D for different dermatoscopic structures.

Although the ABCDE rules are very helpful for early distinction of suspicious lesions there is some percent of malignant pigmentary changes that lack these features. In addition, any new lesion which is up to 3 mm in diameter simply cannot be diagnosed as suspicious only by unaided clinical inspection.

**Basal and squamous cell cancers**

*Basal cell cancer* is seen as nodule (pale, wax-like, pearly nodule) or ulcer (irritated patch or sore that won't heal), which has a long evolution over many years. It is the most common skin cancer (8).

*Squamous cell cancer* is a keratotic skin lesion with underlying infiltration. It grows more quickly than basal cell cancer and appears as red or pink patch that may have a scaly or crusted surface and an open sore in the center or persistent open sore that gradually enlarges and may bleed (8).

## Early detection saves lives

People have a greater risk for skin cancer if they have a genetic inheritance predisposing them towards the disease and/or live in an environment that is "rich" in risk factors. The type of the skin seems to be of crucial significance (white population) in combination with exposure to UV radiation during life. Most of the cases of skin carcinoma (of any kind) appear on open parts of the body (face, neck, lower extremities). *Risk factors* for melanoma skin cancer are:

- Excessive exposure to sunlight (UV radiation), sun damage (burns);
- Fair skin, freckles, skin photo type 1 or 2, blond or red hair;
- multiple or more than 2 atypical moles on the skin;
- familial or personal history of melanoma / NMSC;
- compromised immune system; age (older people are at higher risk although melanoma also appear in the young, even children);
- gender (male predominance);
- some inherited skin diseases (Xeroderma pigmentosum).

Early detection is very important because almost all skin cancers can be completely cured if detected early enough. Each individual is recommended to attend the doctor for examining of the skin at least once a year, especially high risk persons for skin cancer. They also have to perform monthly skin self-examinations of all skin surfaces and mucous membranes, and to protect themselves from UVR (7).

## Melanoma prevention and early detection in the Republic of Macedonia

In our country, there was no adequate management of the patients with melanoma, in the last decades of the 20-th century. Patients were diagnosed often in the late stadium of the disease, with distant metastasis already present, and sometimes without previous consultation with a dermatologist at all. The detection of melanoma was confined to clinical inspection and excision biopsy in suspicious cases (almost always when it was too late).

There were only few efforts for public education campaigns, detection of the risk factors and target population groups or for early diagnosis. Most of the population, even a great percentage of the highly educated, believed that it is dangerous to excise a pigment lesion (nevus). Even the local traditional healers took their part in this process, performing an act of healing by "natural ointments".

Bearing in mind that skin carcinoma, even melanoma, has its chance to be healed completely, if detected in an early stage (*in situ*), we were looking for the best method to achieve this goal.

The facts promoted by WHO state that 40% of carcinomas can be prevented and 1/3 can be cured if early detected. All we need is to find the way and means to do that. The outbreak of new technologies helped us in our quest (9).

During screening examinations, some melanomas may remain unnoticed by the clinician. Some simply lack clinical features suggestive of melanoma. Performing total-body skin

examination and comparing the findings to baseline photographs is the only technique that can aid in identifying new or changed lesions. The suspect lesion can then be evaluated further with the new technologies to determine whether biopsy or excision is warranted. One of these new techniques for early diagnosis is dermatoscopy. With the aid of a dermatoscope clinicians can make the diagnosis of melanoma even if they lack classic "ABCD" features (10-11).

In 2005, at the Clinic of Dermatology, University "Ss. Cyril and Methodius" Faculty of Medicine, Clinical Center in Skopje, dermatoscopy was introduced for the first time into clinical practice. It is a world-wide used method for detection and differential diagnosis of melanoma and other melanocytic and non-melanocytic pigmented skin lesions. The method is almost a century old but it entered in routine medical praxis in the late 1980s when more cheaper and hand-held dermatoscopes were made. Today, it is in vivo method which combines optical instruments and digital cameras imaging techniques. It visualizes skin epidermal structures not seen with naked eye. These structures have generated new terminology and clinical criteria for assessing pigmentary lesions. The technique is sensitive, specific, non-invasive and comfortable for the patient.

The introduction of the method in the public health institutions in Macedonia was a starting point for the Department of Dermato-oncology within the Clinic of Dermatology to initialize a series of activities related to prevention and early detection of skin cancer, particularly of melanoma.

**Primary prevention – our objectives**

There are four basic components of cancer control:
- Prevention
- Early detection
- Diagnosis and therapy
- Palliative care

Our aim was to start both primary prevention program, which is a long term task, and a wide campaign in the whole country for early detection. Also we want to create better conditions for proper diagnosis and treatment of these patients.

Primary prevention means prevention of the development of the malignancy itself, and secondary prevention is prevention of death in patients with already existing malignancy (early detection).

To have a functional primary prevention it is necessary at first to identify the risk factors inducing skin carcinoma and to present them to the public. We have used most frequently a form of a media-aided regular distribution of information. We started a number of medical guided campaigns (newspaper interviews, TV educational programs, open contact programs, printed materials/booklets for patient's use) for understanding and avoiding the risk factors and for promoting the self-inspection/examination practice.

The accent was put on a well established relation of melanoma /NMSC to a sun exposure, especially excessive sun exposure.

The Republic of Macedonia is a country situated in the Mediterranean Region, in Southern Europe with very high UV index during summer months, with average rate of 7 to 9. The predominant photo type of the skin in our population is 2, rarely 1 and 3 (highly susceptible to sun damage).

To attract more patients, who might be unaware of health risks we started (in addition to our regular patients) weekly screening and consultant examinations of the skin of subjects, who responded to our call for preventive care and early cancer detection. Part of the consultations were payment - free, in order to examine subjects who are in a difficult socioeconomic situation (and only seek medical care when they have to) or simply those who needed additional motive to see a specialist. Our aim was to select subjects that belong to the risk population groups. The public response to our initiatives and campaigns was excellent and far above our expectation.

We divided the healthy group of patients into two major categories:

- patients with high risk for developing a skin carcinoma (one or more risk factors present); and
- patients with low or minimal risk for melanoma.

A regular short or long term follow up (on 3 and on 6 months intervals) in our Department was suggested to the patients from the first group. Skin protective measures (Box. 1) and regular self skin examination (SSE) once a month was recommended to the patients from the second group.

Special attention was given to children prevention and work with parents on the issues of best sun protection for this target group.

Creating conditions for international cooperation with people/organizations who work in this field of interest was our next priority. We made contacts and begun activities and exchange of experiences and data. The first Basic Seminar for Dermatoscopy was organized in June 2007 in Skopje, at the Clinical Center, for the medical professionals (mostly dermatologists) from our country. Our team of experts performed the lectures, with an invited lecturer, Primarius Dr. J. Bandic, ORS Hospital (Oncology Research Surgery), Belgrade, R. Serbia.

We were also, for the first time, a part of an international initiative regarding skin cancer prevention, as representatives of our country. In May 2007, we joined other European countries in a project called *Euromelanoma day* in organization of the European Academy of Dermatology and Venerology (EADV). The idea was to do a free of charge skin examination of volunteers in all dermatology centers from the participating countries on the same day of the month of May every year in order to raise the public awareness for early detection and recognition of melanoma.

Currently we carry on a study for assessment of our population's behavior regarding sun protective habits (old and newly formed) and knowledge of the early signs and symptoms of the skin carcinomas. According to the information gathered we shall find out the weak spots of our educational programs and in the future we can focus on their correction.

A few activities of this kind are going on at the moment, and include a particular target groups. Multiple - choice questionnaires were made and distributed randomly with topics that are related to a specific aspect of the issue in focus, affecting that particular group. For example, a material was distributed among parents of the children in low grade classes in elementary schools and kindergartens in the region of Skopje regarding the children's sun protection and sun damage. Similar questionnaire will be given to all dermatologists in the Republic to evaluate their skill and willingness to do a regularly total body examination of the skin of patients, who would come for another skin disease. American Academy of Dermatology previously reported that only a few (30%) respondent dermatologists customarily perform this examination, and that 49% reported screening of patients thought to be at higher

risk. Performing of this screening is highly recommended because, as the recent studies have shown, higher skill of dermatologists compared with other professionals in diagnosing of pigmented skin lesions is followed by detection of an earlier stage melanoma(12,13).

To achieve a change in a population behavior 3 to 5 years at least are needed. This is a continuous process and we are still working on that.

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**Box 1.** Skin protective measures against cancer

- Limit sun/ UV exposure time;
- Protect the skin with clothing, long sleeve shirt and long pants;
- Seek shade, especially between 10am and 5pm;
- Use sunscreen with sun protective factor (SPF) of 15 and higher;
- Wear sunglasses and broad brim hat to protect face, ears and neck;
- Protect children;
- Avoid other sources of UVR (tanning beds and sun lamps).

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**Secondary prevention**

In the field of early detection of skin carcinoma, especially a fatal melanoma, we are investing much more effort. Prior to the introduction of dematoscopy method we registered between 5 to 7 melanoma cases at our Department per year. Since then the number of seen and diagnosed patients with melanoma as well as with NMSCs has multiplied several times

Between December 2005 and July 2007 (approximately a twenty-month-period) we have diagnosed 32 new cases of melanoma, which were confirmed by histopathology later. A case study of this material indicates the following:

Women predominate, 19 cases (59,4%), compared to men, 13 cases (or 40, 6%), which is opposite from the European and world statistics. Average age for females was 50,7 years, the youngest patient being 21 years old, the oldest 74. The average age in males was 57, 4 years, the youngest was 29 years old, and the oldest 80.

Majority of the cases were from the big city centers, most of them from the capital, town Skopje (43,7 %). Only 3 patients were from the countryside. Surprisingly, one third of the patients were highly educated (34%), among them even four medical doctors (12,5%). The average delay from the first sign of the suspicious lesion to the visit of our Department was 2 years (two patients reported a slowly growing dark maculae in a period of 20 years). The main reasons for the delay were fear of carcinoma diagnosis, lack of time, as well as dogma that it might be more dangerous and one should never excise a skin carcinoma.

In two male patients there was a positive family history of melanoma (father died of melanoma in both cases). There was only one case with multiple melanocytic nevi on the skin, and all other cases had predominantly very clear skin with 0-20 nevi on their whole body. One patient (80-years-old) had removed 15 basaliomas in the last decade and during the follow up period (post operationem pro melanoma) he developed another two new pigmented basal cell carcinomas.

Skin cancer was most frequently found on the extremities, 28,1% on the upper, and 25% on the lower limbs (Tab. 1). There was a slight predominance of the lesions on the right half of the body (60%).

**Table 1.** Site (location) of the skin cancer detected in patients at the Clinic of Dermatology, Medical Faculty in Skopje, in the period from December 2005 to July 2007.

| Site/ location | Patients with a diagnosed skin cancer | |
|---|---|---|
| | Number | % |
| Upper limbs | 9 | 28.1 |
| Lower limbs | 8 | 25.2 |
| Back trunk | 6 | 18.7 |
| Stomach | 3 | 9.3 |
| Chest | 2 | 6.2 |
| Face | 4 | 12.5 |
| T o t a l | 32 | 100.0 |

The leading symptom was itching, followed by bleeding of the lesion. In the majority of the cases a member of the family noticed the lesion (a wife or daughter, usually) and reported it as slowly enlarging. Only two patients were detected during routine examination for other skin disease. Almost all patients were with skin photo type 2 or 1 and with history of sunburn in the past, frequent excessive sun exposure during weekends and holidays in the previous years. Freckles on the skin of the open parts of the body, light brown hair and blue or green eyes were found in 80% of the cases.

To our deepest regret the majority of cases that we detected, at the time of the diagnosis were nodular (thick) melanomas (67%). Only 21% were SSMs (superficial spreading melanomas) or thin melanomas (<4 mm), and 12% had Lentigo maligna melanoma (without a nodus formation) on the face. We did not find any acrolentiginous melanoma. We compared our results with the study carried out in the nearby region in BIH, at the Cantonal Hospital in Zenica where 99 melanomas were detected during the period 1996-2006. The nodular melanoma was the most frequent type (72,72%), which is similar with our findings (67%). They had less of Lentigo maligna melanoma (only 2,02%) compared to our melanoma patients. BIH study also indicates that there is a need of active prevention and educational programs in that population (14).

We have created a specific database (a kind of a clinical skin cancer register) for all the patients at our Department with their personal history and disease related facts. The advent of digital imaging equipment has made it easy to store, retrieve and compare images of melanocytic lesions over time. This includes dermatoscopic images. All data are saved in a digital form and are easily reproducible at the patient's next visit. This is crucial for early detection in patients who are on a follow up protocol (early notice of a changing pigment lesion). From these records we can also gather many epidemiologic facts for a further research and statistical and other use.

**Future goals and perspectives**
There are many open questions to be answered in the time to come. We are at the beginning of a long road. Some practical issues that have to be pointed out as our further goals consist of tasks, such as:
- Promoting our Department of Dermato-oncology within the Clinic of Dermatology at the Medical Faculty in Skopje as a referent center for prevention and early detection of skin carcinoma on the territory of the whole country. There will be the main database

with all the relevant information about screening and early detection, follow-up and further treatment of patients with skin cancer in Macedonia and a center for planning and coordination of all future activities;

- Establishing a new Society for Dermatoscopy and Early Detection of Skin Carcinoma that will include highly specialized medical professionals working in all bigger centers in the Republic. They will spread and promote cancer prevention programs and will be specialized in early detection of carcinoma of the skin;
- Forming of a multidisciplinary team of specialists in the Clinical Center, Medical Faculty in Skopje and in other countries in the SEE Region and broader, with dermatologists, surgeons, pediatricians, oncologists, histopathologists, epidemiologists, psychologists and others, which will work together on managing of this group of patients with melanoma/other skin carcinoma;
- Connecting with an on–line consultation forums and working groups (teledermatology, teledermatoscopy), for exchange of information, experiences and knowledge. Our databases are specific, containing clinical and dermatoscopic images, which makes this e-health form of collaboration an option highly convenient and necessary for our practice.

The strategies for early prevention are divided into two groups of activities:
- Rising population awareness for the early symptoms and signs of skin carcinoma which would lead them to seek advice from a doctor or a specialist dermatologist as soon as a suspicious mole or other change on the skin is noticed; and
- Creating national and regional screening programs for asymptomatic population enhances the chances of a patient for a complete cure.

This second issue will be of special interest for us in the future, to strengthen the collaboration with the relevant institutions in the government and health departments, as well as with international organizations which offer financial and other kind of support for cancer control programs in the developing countries. We wish the results of our work to influence on better health policy, which will promote more efficient cancer prevention and control programs in the Republic of Macedonia and other countries in SEE Region, Europe and the world.

**Exercise**
**Task 1:**
Students are required to create a sample questionnaire for gathering data to asses people's behavior related to risk factors for development of skin carcinoma, and their knowledge of adequate sun protection.

**Task 2:**
Students are required to collect available information on cancer
(melanoma and other types of cancer) screening programs from one high developed country in northern or western Europe, or in the world, and to compare them with the same programs in a developing country. They are asked to compare the incidence and mortality rates.

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