



Skin Cancer Screening Makes It Possible to Detect Dysplastic Lesions and Significantly Reduce the Progression to Malignant Melanoma

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

This study takes a look at cultural practices around the world in terms of how they relate to being a contributing cause of malignant melanoma due to perceptions of skin colour and accepted tanning practices. This paper examines the effects of UV radiation in great detail and reviews skin cancer as a serious health risk due to overexposure and other factors. As part of the review of this global health threat, the demographic distribution of people who suffer from melanoma is also discussed. Currently, women between 31 and 50 years old are at the highest risk of developing skin cancer and, therefore, must be screened to reduce that risk, particularly given that malignant melanoma is better managed with earlier screening practices in middle-aged adults.

Keywords: Skin cancer; dysplastic lesions; malignant melanoma.

ABBREVIATIONS

AJCC	: American Joint Committee of Cancer	CPD	: Cyclobutane pyrimidine dimers
ALM	: Acral lentiginous melanoma	DNA	: Deoxyribonucleic acid
		HE	: Haematoxylin-eosin
		Illustr.	: Illustration(s)

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LDH : Lactate dehydrogenase
LMM : Lentigo-maligna-melanoma
MIA : Melanoma-inhibiting activity
MSH : Melanocyte-stimulating hormone
NMM : Nodular malign melanoma
PMOC : Proopiomelanocortin
SPF : Sun protection factor
UV : Ultraviolet radiation
WHO : World Health Organization

1. INTRODUCTION

There are several parameters of social behaviour influenced by the society that define health, attractiveness, and social status. Because these ideas are defined diversely, there are different definitions in different parts of the world and in the various cultures regarding the perfect pigmentation or tan of the skin. Caucasians aspire to have golden tanned skin, whereas Asians prefer a light skin tone. Due to the industrialisation of the United States and Europe at the beginning of the 20th century, light skin became associated with factory work, where there was no direct sunlight, and so in those parts of the world, it tends to be associated with low socio-economic status. In Asian countries, on the other hand, tanned skin is linked with fieldwork and therefore in those countries, tanned skin is associated with a low social status. In the 1920s, Coco Chanel established a cultural norm that saw a “golden skin tone” as a chic sign of having excess time and money for leisure activities. Yet, this ideal would not be worth striving for in Asian countries, due to social conventions such as those already mentioned.

1.1 Sunbathing – Prevalence and Risks

In European countries, a great number of people expose themselves to unhealthy doses of UV light in the pursuit of tanning their skin. This focus on suntanning has led to the use of sunbeds and excessive sunbathing on vacation, resulting in burns in the form of dermatitis solaris have become a regularity. From the age of 18 up to 45, every second person uses a sunbed at least once at a certain point in their life, and every fifth person in this age group states that he/she uses sunbeds regularly [1]. In the majority of other countries, the number of excessive sunbaths is lower [2,3]. Especially for teenagers, the high levels of exposure to the sun and the lack of use of sun protecting cremes/clothes are all of high importance. An investigation from Germany and Italy showed that people with a

high socio-economic status took more sunbaths than people with a low social status [4].

Caucasians who easily get burned and tan only a very little (skin phototypes I and II) [5,6], who have a positive personal family anamnesis for skin cancer, a light eye colour (e.g. blue), ginger or blonde hair and lots of freckles [7] are considered the biggest risk factors for getting skin cancer after chronic UV exposure. Furthermore, suffering severe sunburns with blistering in childhood and early adolescence up to the age of 20 have been associated with a higher risk for getting skin cancer [8,9,10] and childhood and adolescence have been identified as key periods for getting melanoma as an adult. This may be caused by the sensitive reaction of adolescent skin to chronic high doses of UV light [11,12]. The risk of contracting melanoma is extremely high when sunburns were suffered during adolescence, between the ages of 13 and 19, where there was frequent exposure to UV radiation for long periods of time [13,14]. The risk of getting melanoma is extremely high for women under the age of 45 who exposed themselves carelessly to UV radiation in their adolescence. This has been shown in a recent study conducted by Ting et al. [14] among 1,518 dermatological patients, where 79 of those having a malignant melanoma stated having such an anamnesis [15].

1.2 Reasons for Sunbathing

Sun-seekers have been asked for their motivation in several studies. Ranking first has been having an attractive appearance, joined by a positive psychological effect and relaxation [16-18]. Furthermore, another study by Banerjee and colleagues showed that men find women with tanned skin more attractive and healthier. This, again, is a motivation for women to regularly tan their skin to improve their appearance [19]. This study significantly showed that adults who use sunbeds on a regular basis struggle to give up this habit. What's more, experiments have shown that UV light releases endorphins, which could also promote an addiction [20]. In addition, the effects of an improved mood and mental brightening through frequent sunbathing have been described, which is reflected in seasonal mental disorders [21].

1.3 Biological Effects of Ultraviolet Radiation

Ultraviolet radiation causes a great variety of biological effects in the skin, harmless as well as

pathological ones. The UV spectrum is categorised by spectra as UV-C (100-290 nm), UV-B (290-320 nm), and UV-A (320-400 nm). More than 90% of UV-B radiation is absorbed by the epidermis, especially the stratum corneum, and this spectrum is mainly responsible for carcinogenic processes. In contrast, UV-A radiation reaches the reticular and papillary dermis and has harmful effects on connective tissue (photoaging and solar elastosis) and also has a further immunosuppressive effect [22]. The pathological effects include acute sunburn and an acute inflammatory reaction caused by too much exposure. The resulting erythema is caused mainly by the UV-B part.

Cyclobutane pyrimidine dimers (CPD), which create mutations through cytosine, are relevant on a molecular basis. These changes in the genetic code constitute the risk of propagation in daughter cells and an accumulation with regard to carcinogenesis. Further, UV-B has immunosuppressive effects that reduce antigen detection and antigen processing potency on, for example, Langerhans cells [22,23]. Physiologically, there are DNA repair mechanisms whereby mutations are detected by enzymes that block the DNA replication and cut out the mutations in order to incorporate the wild type sequence again. These complex processes are supervised by the phosphor protein53 (p53) that serves as a tumour suppressor gene and enables the repair of DNA [24,25]. In this case, p53 serves as an arrester of the G1 phase in order to allow the DNA sufficient repair time. The cell is subjected to apoptotic cell death if a repair is not possible [24]. Under the microscope, these apoptotic keratinocytes can be recognised in the epidermis as so-called sunburn cells, eosinophil rounded cells. The p53-protein also gets damaged more and more by the UV radiation, and the occurring mutations allow for, after appropriate accumulation, aberrant growth and, finally, the development of tumours [25]. Furthermore, the protein p53, as an effector/sensor, is linked to tanning [26]. It has been proven that the pigmentation is significantly stimulated by p53 through increased synthesis of melanin after UV exposure via direct activation of proopiomelanocortin (PMOC) [26]. Tanned skin has an effective sun protection factor (SPF) of only 2 to 3 [27]. The melanin pigment absorbs UV radiation, and it also absorbs free oxygen radicals that occur through the inflammation of the skin. The PMOC gene encodes the melanocyte-stimulating hormone (MSH), the adrenocorticotrophic hormone (ACTH) and beta

endorphins. The transcription of these three genes takes place in keratocytes exposed to sunlight, which leads to the synthesis of the according preproteins. After appropriate processing, MSH binds to the melanocortin receptor one on melanocytes, which induces melanogenesis, melanocyte differentiation, and the melanosome transfer from melanocytes to keratinocytes [28].

1.4 Pigmented Nevi

A locally sharply determined malformation of the skin that is characterised by exuberant, or in rare cases reduced, development of one or more skin components. It may derive from parts of the skin appendage, vessels, nerves, connective tissue, or the epidermis. Combined malformations that are named after the predominant tissue are called organoid nevi. Nevi can have been in existence since birth or they can arise later in life. Melanocytic nevi are a special case. In some cases, they are a malformation, but many melanocytic nevi are benign tumours of the melanocytes.

Almost everyone has pigmented nevi (colloquially called moles). These skin lesions are of great importance. There is a tremendous variety of different types of nevi, including the non-pigmented nevi, but it is the pigmented nevi that are significant. Included among these are both innate and acquired nevi. A part of these nevi may get atypical, which means that single nevus cells show characteristics of a malignant tumour. Mostly, these atypical nevi arise from the influence of exogenous toxicants, for example UV radiation, but they also arise from genetic predisposition (so-called atypical nevus families). Black skin cancer lesions (so-called melanomas) may arise from a part of the atypical nevi. Malignant melanoma is the tumour with the fastest rise in occurrence in the world, especially in western Europe, America, and Australia. It is estimated that 1 in 75 persons born in 2000 will suffer from malignant melanoma during their lifetime.

1.4.1 Melanocytic Nevi (Nevuscellnevi)

1.4.1.1 Definition

Melanocytic nevi are based on the pigment forming cells of the epidermis. Epidermal, junctional, dermal, and rarely, subcutaneous nests of nevus cells lead to the previously described increased pigmentation of the skin.

Skin changes that are skin-coloured, pigmented to different degrees, macular, papular, or papillomatous are the clinical result. A 30-year-old central European person has, on average, 20–30 melanocytic nevi on their body. The existence and number of melanocytic nevi is genetically disposed.

UV exposure is etiologically of great importance. In addition, immunosuppression and hormonal changes (during or after puberty and during pregnancy) are important for the appearance of nevi, as well. Melanocytic nevi become manifest either at birth (congenital) or they occur over the course of life until the age of approximately 40 years. After that, a regression often takes place.

1.4.1.2 Types of melanocytic nevi

Melanocytic nevi of the junction type are melanocytic cells located in the basal cell layer of the epidermis in the form of nests. They are clinically flat, light to dark brown patches.

Melanocytic nevi of the compound type are melanocytic cells in the junction zone as well as in the corium and are clinically elevated, light to dark brown nodules or knots.

Melanocytic nevi of the dermal type are melanocytic cells located almost exclusively in the corium.

Unna type are papillomatous knots with a bumpy, grooved surface and are light to dark brown, and the Miescher type are flat, elevated, less pigmented, and often skin-coloured.

It is important to differentiate the acquired nevi from congenital nevi.

Congenital melanocytic nevi are benign innate melanocytic nevi that appear on about 1% of new-borns. Congenital nevi are based on a developmental disorder of the melanoblasts from the neural crest. This type of nevi mostly imposes as a flat patch or knot with a light to dark brown colour, and a sometimes papillomatous surface or hair. Their size varies from 1 cm to 3 cm with a potential large expansion (“giant nevi”). Over time, the pigmentation and the appearance of hair increase. One with a diameter of over 20 cm is called a nevus giganteus, which can involve the multiplication of melanocytes (melanosis verticis gyrata) at the head and also possibly at the leptomeninges (neuro-cutaneous melanosis), in

which case epilepsy, neurological disorders, and hydrocephalus should be observed.

1.4.2 Atypical melanocytic nevi

1.4.2.1 Definition

Clinically and histologically atypical melanocytic melanocytes that, initially, have been described on patients from families with a familiar malignant melanoma [29]. They have subsequently been observed on patients with non-familial melanoma. Dysplastic nevi have been debated to be a marker for an increased risk for melanoma and/or as a precursor of melanomas. It has been estimated that approximately 5% of the population has one or more dysplastic nevi.

1.4.2.2 Anamnesis and symptoms

These are mostly asymptomatic and rarely itch.

Atypical nevi can be detected using the ABCDE guidelines, which are the following criteria:

- A – Asymmetrical, irregular
- B – Border is blurred
- C – Colour is variable, with patterns from light to dark
- D – Diameter is > 5 mm
- E – Evolving and palpable

The more factors that apply, the more likely the diagnosis is malignant melanoma. This easy guideline should help the dermatologist doing risk ratification as well as making the choice of excision-worthy moles [30].

In addition, classification of the phototypes according to Fitzpatrick can provide a clue as to the risk of developing a malignant tumour [5].

1.4.2.3 Histopathology

The term “dysplastic nevus” is very imprecise and is not used uniformly as there are no clearly defined criteria for making a diagnosis. Histologically, the most frequently used criteria are the following: polymorphism of the melanocytic cells, bridge building of single nests, and patchy lymphohistiocytic infiltrate.

1.4.2.4 Therapy

Close-meshed clinical and dermatoscopic controls, if possible, with cartographic photo documentation and excision of melanoma with suspicious focusses.

Table 1. Skin photo types according to Fitzpatrick [5]

Photo type	Skin type	Pigmentation behaviour
I	White, very light, ginger-blond hair; blue eyes; freckles	Always burns, never gets tanned
II	White, light, ginger or blonde hair; blue, green, or light brown eyes	Often gets burned; tans rarely
III	Creamy-white, light, every skin and eye colour; frequent skin type	Occasionally mild sunburns; tans gradually
IV	Brown, typically Mediterranean; Caucasian skin	Burns seldomly; tans quickly and regularly
V	Dark brown; Middle Eastern	Burns very seldomly; tans very quickly
VI	Black	Never burns; tans very easily and quickly

1.4.2.5 Progress(ive forms) and prognosis

According to Kraemer and Greene [31], patients with dysplastic nevi occurring in their family have a higher risk for melanoma than patients with infrequent dysplastic nevi. The melanoma risk reaches up to 100% for patients with dysplastic nevi having at least two or more relatives suffering from malignant melanoma.

1.4.2 Hereditary dysplastic nevus syndrome

For the subtype with familial melanoma, BK-mole syndrome, BK-nevus syndrome and familial atypical multiple mole melanoma (FAMM) syndrome.

1.4.2.1 Definition

Hereditary syndrome with many dysplastic nevi and a high risk for melanoma.

1.4.2.2 Genetics

Possibly in the case of the subtype with familial melanoma, mutations at the p16-gene on the short arm of chromosome 9 (9p21).

1.4.2.3 Clinic

Great amount of so-called dysplastic nevi, especially on the torso, along with many normal melanocytic nevi.

Special form: dysplastic nevus syndrome with only one quadrant.

1.4.2.4 Therapy and progress

Close-meshed clinical and dermatoscopic controls every 3–6 months, if possible, with photo documentation. Excision of suspicious nevi.

Intensive sun exposure should be avoided during infancy, especially in the case of familial disposition.

1.4.2.5 Differential diagnosis

Malignant melanoma.

1.4.3 Spitz nevus

Benign juvenile melanoma, Spitz nevus.

1.4.3.1 Definition

Benign melanocytic reformation with polymorphous and cytoplasmic cells.

1.4.3.2 Epidemiology

Mostly adolescent, rarely adults.

1.4.3.3 Clinic

Hemispheric elevated, rapidly growing, reddish nodules, often on the face, and sometimes globular. Lupoid infiltrate with glass spatula pressure.

Rare entities that are not going to be considered in this work are the pigmented spindle cell Reed nevus and the nevus coeruleus. Also not considered are benign pigmented skin changes without the growth of the nevus cells and the café-au-lait patch and freckles are not going to be considered neither.

1.5 Malignant Melanoma

The malignant melanoma is a tumour of the pigment-growing cells (melanocytes and nevus cells). The manifestation de novo takes place on

clinically unremarkable skin (70%) or in the area of pre-existing nevi (30%).

1.5.1 Epidemiology

The melanoma has the most rapid increase in occurrence worldwide, where the incidence in Europe and America increases by 8-10% per year. It is the most common malignant tumour in young women in the age group of 25-29 years in the United States. The incidence per 100,000 inhabitants is lowest in Sub-Saharan Africa, and the highest is in Australia, with 60 cases per 100,000 people. The lethality could be reduced to less than 20% through intensive educational programmes and screening. The estimated risk of suffering from melanoma once in their lifetime for someone born in the year 2000 is 1:75.

1.5.2 Aetiology and risk factors

Genetic disposition of so-called melanoma-families suffering from the FAMM syndrome (see above), dysplastic nevus syndrome, or xeroderma pigmentosum. Other than genetic disposition, the disposition of the melanoma depends next on the following factors:

- Number and size of congenital nevi (lifetime risk of up to 10%)
- Light skin of phototype I or II according to Fitzpatrick [5]
- Living at geographical latitudes near the equator
- Earlier melanomas or first-degree relatives suffering from melanoma
- Exposure to UVA (number and severity of sunburns during infancy)
- CAVE: The association with UV radiation is not as strong as the association of epithelial tumours and UV exposure!

1.5.3 Clinic

The cutaneous malignant melanoma may show a great variety of manifestations. Typically, the melanoma is deep brown to blackish, but there are also reddish, blueish and even non-pigmented (so-called amelanotic) melanoma. Special forms include melanomas at the nails or non-healing, ulcerated melanoma.

1.5.4 Superficial spreading malignant melanoma (SSM)

65–70%; light brown or brownish to blackish, rarely whiteish (regression zone). In the

beginning, always flat; pigment changes of varying sizes with a change into infiltrated nodules or knots and irregular borders.

1.5.5 Nodular malignant melanoma (NMM)

15–20%; mostly small, smooth, blackish knots as a primary manifestation, but also in the form of a secondary NMM on a pre-existing SSM.

1.5.6 Lentigo-maligna-melanoma (LMM)

10%; auburn, café-au-lait, or dark brown coloured blemishes in chronically light-exposed areas or actinically damaged skin.

1.5.7 Acrolentiginous malignant melanoma (ALM)

5%; a melanoma growing at palmar, plantar, or subungual, often on pre-existing lentiginosities.

In all forms of melanoma except NMM, a horizontal growth phase occurs first, followed by a vertical growth phase that is crucial for early metastasis.

NMM and ALM often occur as amelanotic, skin-coloured primary tumours.

ALM and mucosa or uvea melanoma (missing protective melanin pigment) are nearly the only types found in Sub-Saharan Africans, Asians, and Hispanics.

1.5.8 Localizations

Melanoma can be found on every part of the body, but 90% can be found on the skin (for men, often on the torso; for women, often on the lower limbs), with 6% at the eye (mostly the choroid, so-called uvea melanoma), and 4% on the mucosa.

A metastasis mostly takes place at the lymph nodes > skin > lungs > liver > bones > brain.

1.5.9 Diagnostics

1.5.9.1 Incident light microscopy

Simple instrumental limitation to non-melanocytic diseases (e.g. hematoma, haemangioma, seborrheic keratosis).

Malignant melanomas often dermatoscopically show the following: A prominent, irregular, coarse net of pigments with inhomogeneous, irregular, and radial offshoots. Often also black spots, whiteish shrouds, and white scarred areas.

The high-resolution ultrasound is a move in the field of luxury diagnostics. Furthermore, laboratory changes can only be found in the case of advanced tumours. In this case, tumour anaemia, increased blood sedimentation rate, liver enzymes, and increased alkaline phosphatase, if the metastasis in liver and bones is increased, will take place. An increase in LDH is a seldom-seen specific indicator for remote metastasis in the following tumour markers: soluble S-100β in the case of remote metastasis and MIA (melanoma-inhibiting activity).

Imaging techniques should be realised for advanced malignant melanoma. Among these are lymph node sonographies, abdomen sonographies, and thorax X-ray.

A sentinel-lymph-nodes-diagnostic of the regional draining lymph node should be used for melanomas with a skin depth > 1 mm. A method that is gaining more and more importance, especially for the survival of the patient, is the selective resection of lymph nodes.

For metastasising melanomas: bone scintigraphy, full-body CTs, skull NMR, and if necessary, positron emission tomography (method for recognising an increased tumour metabolism with a resolution capacity of at least 5 mm, to be indicated in the case of unclear CT results).

1.5.10 Histology

Criteria for malignancy:

- Asymmetric tumour structure, flattening of the reticular structure
- Papagote ascent of light cells in the whole epithelial unit (“full sickness atypia”)
- Missing differentiation of cells towards the skin depth
- Invasion of the tumour cells into the corium
- Core-plasma relationship with prominent nucleus; nuclear polymorphisms; increased mitoses
- Ulceration, regression, and sclerotic areas on pre-existing nevus cell

- Lymphohistiocytic infiltrate
- Important data are the Clark level and the Index according to Breslow.

The so-called Breslow index provides information about the depth of the invasion in millimetres. This depth is determined with the help of an ocular micrometre and describes the invasion route that has been taken by the tumour cells. It covers the way from the granular cell layer until the deepest invasion of the tumour cells. It is easier to reproduce than the Clark Level.

The Clark Level, introduced by Dr. Wallace H. Clark Jr., has been defined as follows:

- Level I Tumour cells exclusively in the epidermis (melanoma in situ)
- Level II Reaching up to the stratum papillary
- Level III Filling the entire stratum papillary
- Level IV Reaching up to the stratum reticular
- Level V Reaching up to the subcutis

The Clark classification correlates with the five-year survival rate. Special forms include melanoma in situ, intraepidermal melanocytic hyperplasia with cell atypia, polypoid dysplastic desmoplastic neurotropic balloon cell-like or myoxid malignant melanoma.

1.5.11 Immunohistology

The antigens S-100, HMB-45, Melan A/MART-1 and the proliferation marker Ki-67/MIIB-1 associated with melanoma are used to differentiate melanomas from undifferentiated pleomorphic spindle cell tumours of other entities or to determine high levels of proliferation activity. They are also used in sentinel lymph node examinations to detect **micro metastases**. Essentially, immunohistology is used to exactly determine the skin depth. A high mitosis index, ulceration, and regression zones are linked to a worse prognosis.

Table 2. Correlation of primary tumour thickness and survival rate

	5-year survival rate	Clark level		Breslow index	
		Depth (in mm)	5-year survival rate	Depth (in mm)	5-year survival rate
II	99%	>0,85	99%	>0,75	95-99%
III	95%	0,86-1,69	94%	0,76-1,49	90-95%
IV	75%	1,70-3,64	78%	1,50-4,00	60-75%
V	39%	>3,64	42%	>4,00	<50%

1.5.12 Classification/prognosis

EORTC stadia classification:

- I : Primary tumour without metastases on the lymph nodes or remote metastases or satellite metastases (up to 3 cm around the primary tumour). Five-year survival rate, 80%
- Na : In-transit metastases (< 3 cm distance to the primary tumour) and not beyond the regional lymph nodes. Five-year survival rate, 40%,
- Mh : Regional metastases on the lymph nodes. Five-year survival rate, 20%.
- II : Remote metastases
- non-visceral : Five-year survival rate, 5%.
- visceral : Five-year survival rate, 0%.

1.6 Special Forms of Malignant Melanoma

1.6.1 Melanomas during pregnancy

Melanocytic nevi get activated during pregnancy quite often. But it is not assured that it influences the progress of a malignant melanoma.

1.6.2 Malignant melanoma during infancy and adolescence (up to 18 years)

Children often get melanomas on the base of neuro-cutaneous melanosis. In this case, metastasising melanomas may occur during early infancy.

1.6.3 Congenital melanomas

They grow from transplacental metastasis of a motherly melanoma or from the area of congenital melanocytic giant nevi. Very poor prognosis.

1.6.4 Metastasising melanoma without known primaries (about 5% of all patients)

A detailed anamnesis (earlier excisions, excisions of skin changes) is crucial in this case. During the inspection of the whole body and the mucosa, scars should also be taken into account. Signs of regression of earlier melanomas should be observed as well.

1.6.5 Familiar melanomas

Different candidate-genes (e.g. p16INK4a) on chromosome 9. The risk for melanomas is higher the more family members suffer from melanomas. Dermatological check-ups every 6 months.

Table 3. The new American Joint Committee of Cancer (AJCC) classification

Stage	Characteristics
IA	Tumour < 1.0 mm without ulceration and Clark Level II/III tumour; participation of the nodes; no remote metastases
IB	Tumour < 1.0 mm with ulceration or Clark Level IV/V tumour; tumour 1.0–2.0 mm without ulceration; no participation of LN; no remote metastases
IIA	Tumour 1.0–2.0 mm with ulceration; tumour 2.0–4 mm without ulceration; no participation of the LN, no remote metastases
IIB	Tumour 2.0–4.0 mm with ulceration; tumour > 4.0 mm without ulceration; no participation of the LN, no remote metastases
IIC	Tumour > 4.0 mm with ulceration; no participation of the LN, no remote metastases
IIIA	Tumour of every size without ulceration with 1–3 positive lymph nodes and micro metastases
IIIB	Tumours of every size without ulceration with 1–3 positive lymph nodes and micro metastases; tumours of every size with ulceration with 1–3 positive lymph nodes and micro metastases; tumours of every size with 2–3 positive lymph nodes and intransitive/satellite metastases without metastasising lymph nodes
IIIC	Tumours of every size with ulceration with 1–3 positive lymph nodes and metastases; tumours of every size with four or more metastasising lymph nodes or intransitive/satellite metastases with metastasising lymph nodes
IV	Tumours of every size with infection of all lymph nodes and remote metastases

1.6.6 Multiple melanomas

Five percent of all melanoma patients get second or even more malignant melanomas from a primary tumour. Potential risk group is co-existence of xeroderma pigmentosum.

1.6.7 Neuro-cutaneous melanosis

Epidermal melanocytes on skin and meninges, sometimes on the galea (cutis verticis gyrata). Early malignant degeneration possible. This clinical picture often only gets discovered through neurological failures (e.g. attack of sudden cramps). Regular MRT-controls of the brain and further dermatological check-ups.

1.7 Skin Cancer as a Health Risk of UV Exposure

Freckles, mole formation, and scars are direct results of the acute erythematic consequences of inadequate UVB radiation. Chronical submaximal repeated doses of UVB (sunburn) include photoaging, the growth of actinic keratoses of non-melanocytic skin cancer (white skin cancer), as well as the risk of growing a melanoma [32,33]. It is estimated that about 65% of all skin cancer cases (melanoma and non-melanocytic tumours) are caused by inadequate sunlight exposure [33]. The special significance of UV exposure with regard to the growth of cutaneous malignant melanomas has been investigated narrowly by a Danish case study [34].

Basal cell carcinoma is by far the most common tumour induced by UV exposure (about one-quarter of all tumours). But the malignant melanoma, with about 4,000 new incidences in England, has a special importance as 75% of all skin cancer cases are melanomas [35].

Acute sunburns, photo-induced drug response, polymorphous light eruption, and atypical melanocytic lesions, as well as blistering and the suppression of DNA repair or suppression of immune functions, have been observed as dermatological consequences of using sunbeds [36]. Furthermore, these uses increase the risk for melanomas and plate-cell carcinoma [33].

1.8 Worldwide Incidence of Skin Cancer

Skin cancer is the most common tumour disease in Australia, with a significant mortality and morbidity [37] and a clear increase in incidences.

In addition, the increasing mortality rate due to melanoma is of high importance [8,38]. The increase in UV exposure is striking in Europe in the last half of the century as well. Sweden observed a yearly incidence of malignant melanoma of 8.2 cases in 1970 and an incidence of 27.3 cases in 100 inhabitants in 2006. In Greece, the incidence of skin cancer is increasing but not as dramatically as in northern European countries [39,40]. Partly, these campaigns should also be linked to the pursuit of a healthy lifestyle and organic nutrition, as many people can be reached through these channels. Furthermore, the significance of checking up on yourself or having regular dermatological check-ups should be imparted so that changes in moles can be detected. Skin screening programmes covered by public insurance should be especially emphasised. In addition, it would be desirable to change the ideal in the media of beautifully tanned skin to an elegant paleness to limit the incidences of photoaging and the growth of melanoma.

1.9 Early Detection of Skin Cancer with the Help of Screening Programmes

The German Dermatological Association, as well as associations of other countries, initiated intensive educational programmes because of the increasing incidence of melanoma (and non-melanocytic skin tumours). They made it, together with the German professional association of dermatologists, to initiate a skin cancer screening programme covered by the public and private insurances. Patients starting at the age of 25 or 35 are being checked for pigmented skin changes over the entire body. The number of insurances offering these screening programmes could be increased during the period of only a few years caused by the population accepting them. Dermatologists, having done a special formation, have biopsied the skin changes that showed clinical signs of an atypia. They used the ABCDE guidelines (see Section 1.4.2.2).

2. STUDY OBJECTIVES

In the present work, the biopsies of pigmented lesions received in a large skin centre were examined with regard to significant demographic populations. For that, samples from all over Germany were examined. However, a claim to a representative sample in statistical terms cannot be made.

With the help of this investigated collective, the following questions were to be answered:

- How often do pigmented skin changes occur in the whole collective of a histological sending laboratory?
- What is the age distribution of patients with pigmented nevi?
- What percentage of the pigmented lesions are histologically atypical?
- Is there a special frequency for the sending of pigmented samples according to the season (summer or winter)?

3. MATERIALS AND METHODS

The results were analysed with the help of descriptive statistics (average and standard deviation). The statistical evaluation was made with the programme SPSS version 06.0.1 (IBM Corp., Armonk, NY, USA). Every non-parametric test (Wilcoxon test) has been considered statistically significant with an error probability of $P < 0.05$.

The histological diagnoses of the submitted histological material from the dermatological centre of Prof. Hengge were evaluated. The formal infected biopsies and excises were reprocessed histologically and analysed by fixation, paraffin embedding, and preparation of 4 nm slices as well as colourings (especially HE). As a standard, special colourings by immunohistochemistry (antibody against S100, HMB45, Melan A, and Ki-67) were used as proliferation markers for pigmented lesions, and they then were analysed by an expert. The expert, U.H., has professional experience of 17 years in the field of dermatohistopathology and was certified by the medical association Nordrhein in 2006. In the case of pigmented lesions that were hard to determine, the samples were presented to the special clinic Hornheide (Münster) in the course of their dermatohistopathological quality circle or they were resent to other special institutions (Prof. Kerl, Universitätsklinik Graz).

The histological diagnoses were populated to a Windows Access database and were browsed in the course of the doctoral thesis for the corresponding diagnoses (dermal nevus, compound nevus, junctional nevus, atypical compound nevus, atypical junctional nevus, lentigo maligna, and malignant melanoma).

In total, all data sets from the 3rd quarter of 2009 (summer quarter) and the 3rd quarter of 2011

(summer quarter) or in the 1st quarter of 2010 (winter quarter) and the 1st quarter of 2011 (winter quarter) were analysed. A response to the question of whether there was any correlation between the season and the excision of moles or the probability of atypia was possible by choosing these specific periods.

4. RESULTS

4.1 Patient Characteristics

4.1.1 Demographical data

The number of excised pigmented lesions was determined for the different quarters (Table 4). The total number of histological investigations in the corresponding quarter is also shown in Table 4. This reveals that the percentage of investigated pigmented skin changes increased steadily from the 3rd quarter of 2009, starting with 13.3% (3/2009) and rising to 19.1% (1/2010), and in the year 2011, it rose to 24.0% (1/2011) and 24.5% in the 3rd quarter of 2011.

In the first quarter of 2011, for example, 2,205 pigmented skin changes were investigated, whereas there were only 2,010 investigations in the 3rd quarter of 2010. A part of the rising numbers can be explained by a general rise in sending to the laboratory; nonetheless, the relative changes of the individual forms of pigmented nevi have a significant importance.

In these model quarters (1/2011 and 3/2011), it is striking that 43.3% (1st quarter 2011) or 45.7% (3rd quarter of 2011) of the samples were taken from male patients. In total, the age distribution ($P < 0.05$) shows that pigmented skin changes were removed from more women than men in all four model quarters; only the first quarter of 2011 shows a slightly higher rate of men (321) than women (303) regarding the analysed pigmented skin lesions.

In both model quarters of the year 2011, the proportion of female patients with pigmented skin lesions removed for diagnostic purposes was highest in the age distribution of 31–50 years. In the 1st quarter of 2011 (winter quarter) 50.7% of the pigmented skin lesions were removed from patients between the ages of 31 and 50. In the 3rd quarter of 2011 (summer quarter), 48.8% were removed in the same age distribution. This is the largest group for women as well as men (1st place). The next group is the age distribution of over 51 years (2nd place) (Fig. 1 and Fig. 2). In the 1st quarter of 2011 (winter quarter), the age distribution of 19 to 30 years was a small

group of 16.9%, with 372 samples (3rd place). But in the 3rd quarter of 2011 (summer quarter), they resulted in being an important group with 21.0% and 423 samples. The different histological entities in the corresponding gender and age distributions for both model quarters (1st and 3rd quarters of 2011) are shown in total numbers as well (Fig. 1 and Fig. 2). The fact that there were more dermal nevi being removed from women in all age distributions than from men (< 0.01) is striking. This may be caused by a higher aesthetical demand of women, who may be more affected by dermal nevi than men (Fig. 1 and Fig. 2).

4.2 Types of Extracted Nevi

The next step was analysing the extracted pigmented moles. For that, the moment (quarter of extraction) was put into relation to the histological type of mole (Fig. 3). Next to the earlier described trend of dermal nevi being the most commonly extracted entity, the junctional

nevi along with the compound nevi are the second most commonly extracted types of skin changes. The junctional nevi dominated in the 3rd quarter of 2009 and in the 1st quarter of 2010 with 25.98% and 23.97%, respectively, whereas the compound nevi were dominant in the 1st quarter of 2011 and the 3rd quarter of 2011 with 29.8% and 23.9%, respectively. The rate of atypical nevi or pigmented malign biopsies is described in the next section.

4.3 Dignity of the Extracted Pigmented Skin Changes

The percentage of atypical lesions in the total number of pigmented lesions were analysed for the earlier chosen quarters (Fig. 4). The percentage of atypical pigmented skin changes was between 12.57% and 33.43% (average: 22.5%) in the chosen quarters. The atypical junctional nevi, atypical compound nevi, and Lentigo malign and malignant melanoma shown in Fig. 3 were subsumed.

Table 4. List of histological investigation

Quarter	Number of histologically investigated pigmented skin changes	Total number of histological investigations
3/2009	485 (13.3%)	3,640
1/2010	851 (19.1%)	4,455
1/2011	2,205 (24.0%)	8,480
3/2011	2,010 (24.5%)	8,201

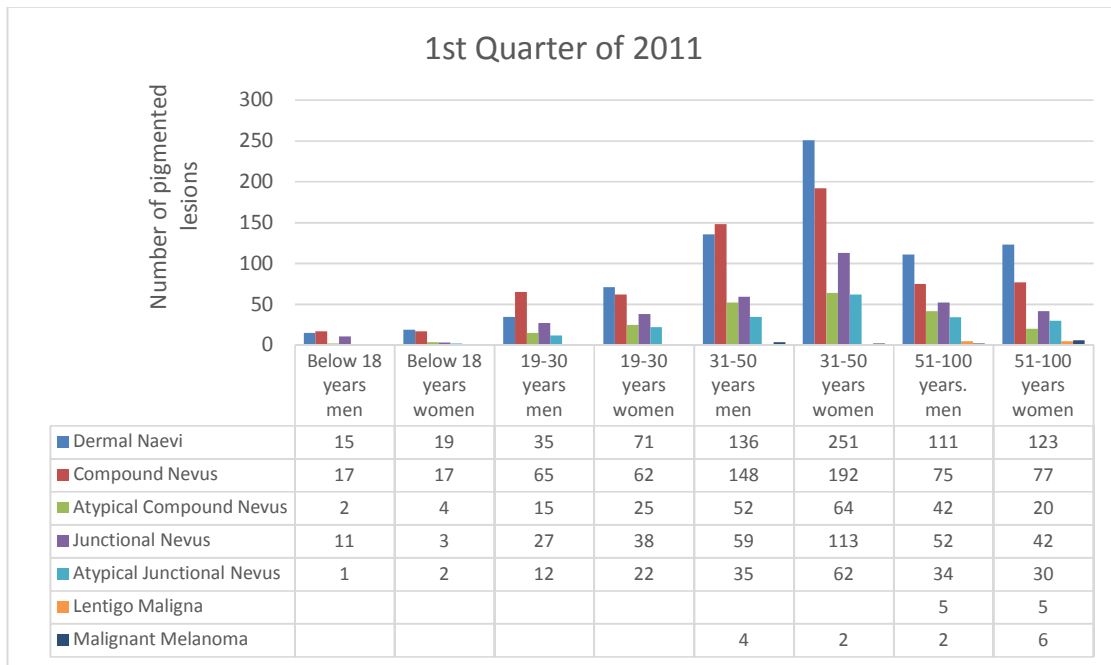


Fig. 1. Graphical representation showing pigmented lesions in 1st quarter of 2011

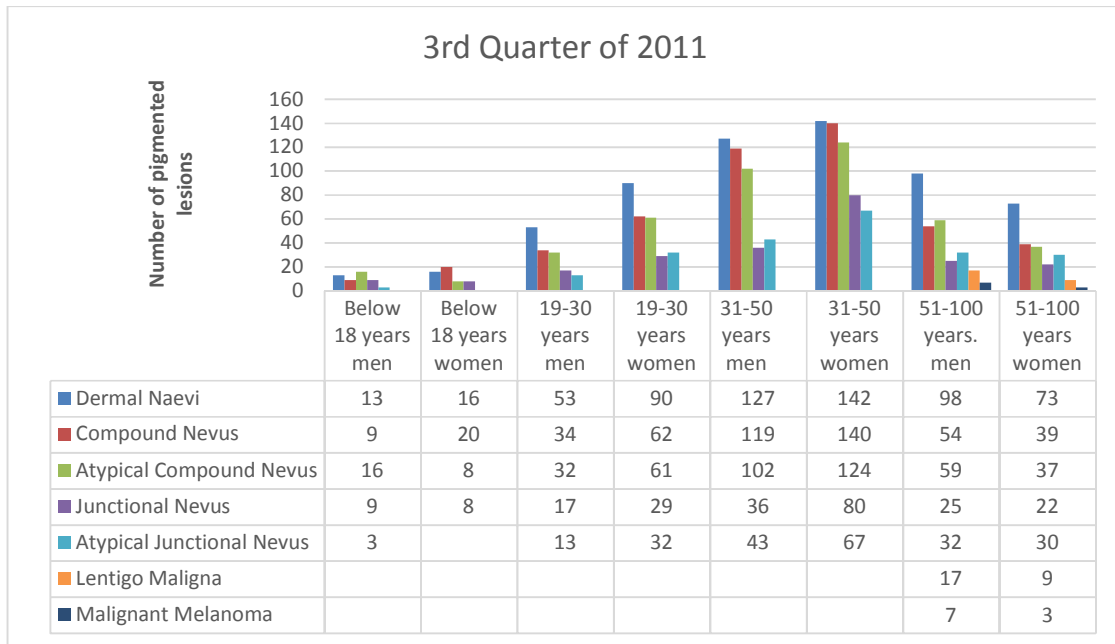


Fig. 2. Graphical representation showing pigmented lesions in 3rd quarter of 2011

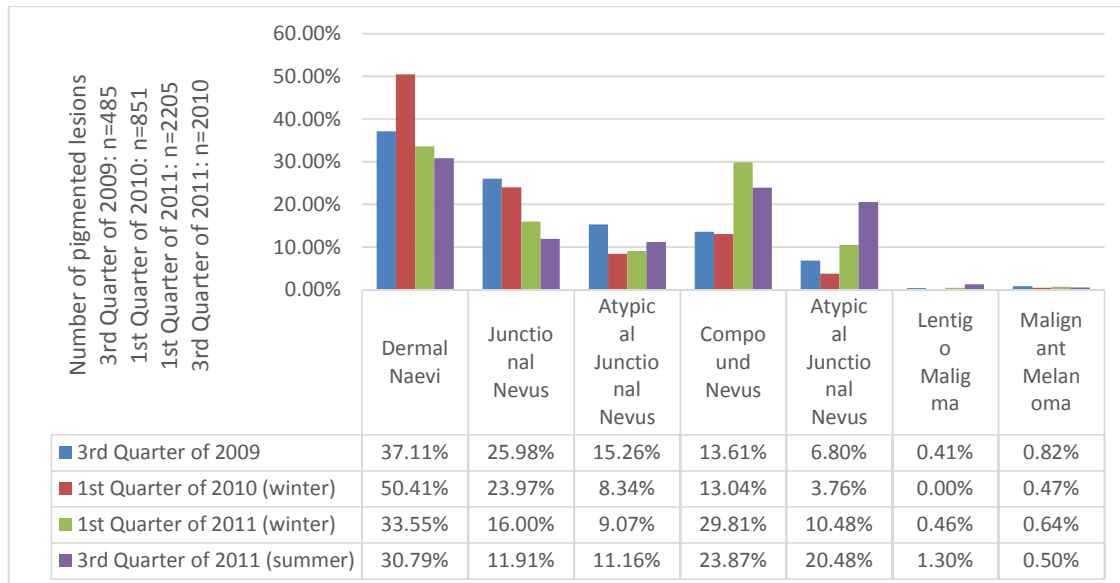


Fig. 3. Graphical representation showing pigmented lesions in all quarters

An important result of my work is the striking fact that the number of extracted atypical pigmented moles is higher in the summer months (July, August, September) than in the corresponding winter months (January, February, March; $P < 0.05\%$). The percentage of the Lentigo maligna and the malignant melanomas were on the low side and did not show any significant fluctuation.

5. DISCUSSION

5.1 Discussion of the Method

From the retrospective analysis of the histological evaluation of submissions to a medium-sized histological laboratory, with senders from all over Germany, a trend in the behaviour of dermatologists with regards to the

removal of pigmented skin lesions over the periods of the different quarters could be obtained. Of course, an investigation of that statistical power is not suitable for making generally valid statements. This is what the large-scale skin cancer screening programmes that are being analysed by the public health insurance and the associations for established dermatologists aim for. However, such a random sample shows that the number of samples of pigmented skin lesions have significantly increased over the last years. Therefore, it is up to the large-scale investigations by the health insurers to maybe quantify these trends on a large scale with the help of their billing data. At this time, it is uncertain at what point we will get such results. An obligation to report a tumour disease only exists in a small number of federal states. The register for cancer of the Saarland as well as the register for cancer of Schleswig-Holstein are to be mentioned. The register for cancer of dermatologists in North Rhine-Westphalia has collected the data for skin tumours for only a few years now, and atypical moles are not registered by the currently available registers for reporting cancer. This would be the only opportunity to make a comprehensive statement about the increase in reported atypical nevi in comparison to the total number of skin samples of all dermatohistopathologies. Unfortunately, an evaluation like this will not take place in the near future.

5.2 Reasons for the Rise in Dermato-histopathological Examinations of Pigmented Skin Lesions

There are two reasons, based on my work, that could possibly explain the observed increase in histological investigations of pigmented skin changes. On the one hand, the increased sensitivity of the affected patients should be mentioned here, which enables a dermatological examination of the entire intuition due to the skin cancer screening that is available nationwide and paid for from the 25th through the 35th year of life. Better education and more sensible treatment of patients with UV radiation has already had a positive effect—similar to smoking campaigns. However, a further improvement of this still relatively young area of medical education is necessary in order to reach as much of the population as possible.

On the other hand, the extra-budgetary remuneration of medical services within the framework of skin cancer screening, including the services of the dermatohistopathologist, is to be mentioned. This financial incentive also particularly motivates the treating physician to carry out such a skin cancer screening for all eligible patients because it represents a statutory insurance benefit every two years. This can—depending on the federal state—generate an

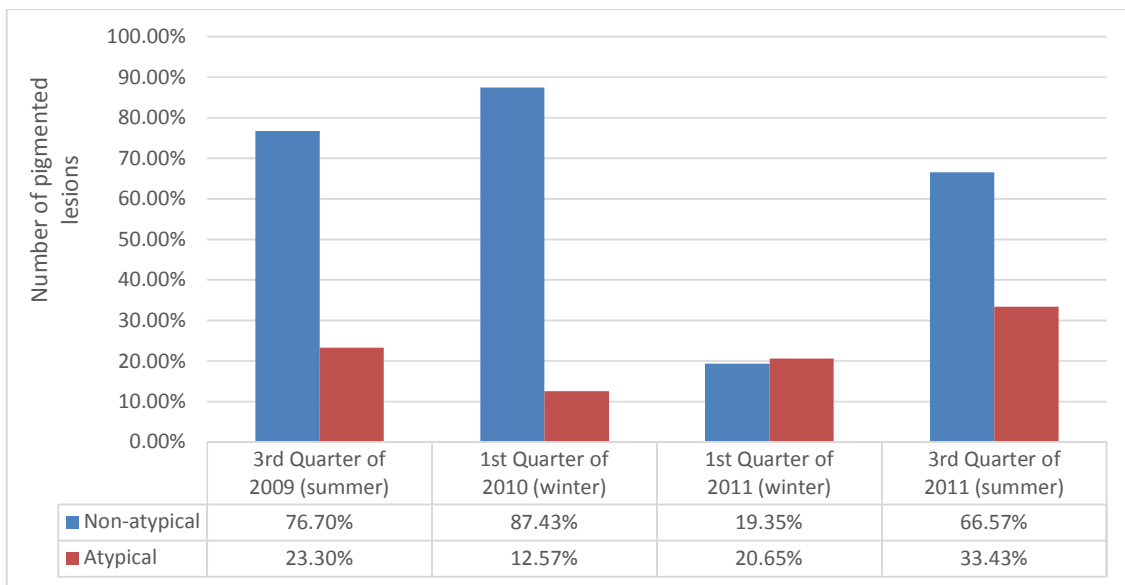


Fig. 4. Overall scenario of pigmented lesions

additional income of between 12 and 18 euros per insured person. However, these relatively manageable additional costs are also economically advantageous for the health insurance carriers in the context of early detection/prevention, since white skin tumours (plate epithelial carcinoma and basal cell carcinoma) as well as malignant melanomas are increasingly diagnosed in earlier stages, with less penetration depth. This is shown nicely in the publicly available cancer registers of Saarland and Schleswig-Holstein. Both changes are due to the fact that more and more patients are having a dermatological screening examination. The dermatologist also gives valuable advice on how to deal sensibly with the sun in the context of skin cancer screening and provides individual advice, which should increase the motivation to improve sun protection even further.

5.3 Rise in Histologically Examined Pigmented Skin Changes

Over the four different model quarters, it was shown that the proportion of pigmented lesions in the total test material of a medium-sized dermatohistopathological laboratory increased constantly over the two years tested. This share ultimately amounted to 25%.

5.4 Number of Pigmented Skin Changes in the Overall Collective of a Histological Laboratory Centre

The relative proportion of pigmented skin changes increased constantly over the analysed two years, amounting to 13.3% in the third quarter of 2009 and rising to just under 25% in the other two quarters (1st and 3rd quarters of 2011). This underlines the importance of skin cancer screening and its use by the insured.

5.5 Gender and Age Distribution of the Removed Pigmented Skin Lesions

As in other screening programmes, the proportion of women in such programmes is higher in skin cancer screening. The most frequently studied age groups were the middle-aged patients (31–50), followed by those over 50. There is a clear need for improvement in the age group of 19- to 30-year-old patients, whose percentage was between 16.9% and 21%.

5.6 Types of Extracted Pigmented Nevi

From the frequency of distribution of removed nevi, it became clear that many dermal nevi were removed. These skin changes, which can usually be classified clinically flawless, possibly represent a consequence of the relatively generous skin cancer screening, in which up to five moles may be taken within the framework of the programme. It is now up to the physician or the patient to strictly orient the number of removed moles according to the ABCDE criteria (suspicious pigmented skin changes) or whether aesthetically/cosmetically disturbing moles such as dermal nevi (between 30% and 50% of all removed pigmented lesions) were removed. This thesis may be stated according to the data from my work.

5.7 Dignity of the Extracted Pigmented Skin Lesions

The fact of whether more atypical moles are removed and whether this is reflected in a reasonable cost–benefit ratio with the expenditure incurred is essential for the success of an effective early detection programme. It can be seen from my work that in the hands of dermatologists the “hit rate” of atypical pigment lesions after histological processing lies between 12.6% and 33.4%. This is a significant proportion, which almost always allows a cure at this stage and thus improves the morbidity of the investigated patient collectives. This happens against the background that about 30% of the atypical nevi are precursors for malignant melanoma.

5.8 Seasonal Distribution of the Excision of Moles

An important result of the present work is also the higher frequency of atypical pigment changes that were subjected to histological examination in the summer months (July, August, September). This may be most likely due to the fact that patients are made aware of moles by themselves or by their surroundings after UV exposure (outdoor exposure or holidays). The subsequent visits to the dermatologist thus lead to the higher excision rate of screened moles. The hit rate of atypical nevi was also higher in each of the summer quarters. The prevalence of atypical moles in the 3rd quarter 2011 is high with about one-third of the excised pigment changes. This may be a result of the consistent Euro melanoma

screening week and the increasingly internalised early diagnosis by patients. Ultimately, the earlier detection of atypical moles that was described in the present study coincides with the prevalence data of malignant melanoma, according to which more and more melanomas are detected, but which, fortunately, show a decreasing depth of invasion (Breslow index) when diagnosed (cancer registries of Saarland and Schleswig-Holstein).

A similar study from 2007 is available for the federal state of North Rhine–Westphalia [41]. In this study, a network of physicians evaluated data from a population of about 75,000 individuals, 796 of whom were identified with a newly diagnosed skin cancer in a period from July 1998 to June 2006 (five-year period). In this study, 13.6 cases of melanoma were found in 75,000 individuals who were men and 18.5 who were women. This results in an incidence of malignant melanoma in North Rhine–Westphalia comparable to other incidence rates. For the Schleswig-Holstein cancer registry, age-related incidence rates of 12.3 for men and 14.8 per 100,000 women were each found in the observation period from 1998 to 2001 (three years) [42]. This earlier detection goes hand-in-hand with a significantly improved prognosis and may be regarded as a success of the educational and screening investigations. The fact that the lentigo maligna and melanoma entities had no seasonal frequency fluctuations may be due to the too small collective for this question.

6. CONCLUSION

Causes of skin cancer studied insufficiently. Some factors increase skin cancer risk; knowing them is possible to reduce the likelihood of this disease.

These results document clearly for the first time that after the end of the summer, when many patients expose themselves to the sun with their naked skin, conspicuous moles are recognized, and accordingly, after the end of the holiday, in autumn, the patients go to the dermatologist, who then excises suspicious moles. The project showed as well that large-scale systematic skin cancer screening is feasible and has the potential to reduce skin cancer burden, including mortality. Based on the results of SCREEN, a national statutory skin cancer early detection program was implemented in Germany in 2008.

Skin cancer screening made it possible to detect dysplastic lesions at an early stage and thus significantly reduce the progression to malignant melanoma.

In general, there are better survival prognoses through skin cancer screening for women and men with malignant melanoma.

There is a need for educational work with information about the early signs of malignant melanoma, about the dangers of intensive and long-term tanning, the identification of high-risk groups subject to regular medical examinations.

CONSENT AND ETHICAL APPROVAL

As per university standard guidelines, participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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