

Evidence-based Guideline on Prevention of Skin Cancer

Version 1.1 - April 2014

AWMF registration number: 032/052GGPO

Guideline (Long Version)

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1. Information about this guideline

1.1. Editors

German Guideline Program in Oncology of the Association of Medical Scientific Societies (AWMF), the German Cancer Society (DKG) and German Cancer Aid (DKH).

1.2. Leading professional society

Association of Dermatological Prevention (ADP)



on behalf of the German Dermatological Society (DDG) and the Dermatological Oncology Working Group (ADO)

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1.3. Funding of the guideline

This guideline was funded by the German Cancer Aid as part of the German Guideline Program in Oncology.

1.4. Contact

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1.5. Citation

The German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, AWMF): Evidence-based guideline on prevention of skin cancer, long version 1.1.,

2014, AWMF registration number: 032/052GGPO, <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html> (accessed on DD.MM.YYYY)

1.6. Former changes of version 1

April 2014 Version 1.1.: modifications of the chapters 'Editors' and the 'Leading professional society', minor corrections to background texts, removing level of evidence '1--' (not included in the original citation and not relevant for this guideline), specification of the SAB's role in the development process.

1.7. Special notice

Medicine is subject to a constant process of evolution, so that all information can only reflect the state of knowledge at the time the prevention guidelines are printed. The greatest possible care has been taken over the recommendations given for the primary and secondary prevention of skin cancer.

In the public interest, please notify the German Guideline Program in Oncology (GGPO) editors of any dubious discrepancies.

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1.8. Objectives of the German Guideline Program in Oncology

With the German Guideline Program in Oncology (GGPO), the Association of Scientific Medical Societies (AWMF), the German Cancer Society and German Cancer Aid have set themselves the task of jointly promoting and supporting the development, revision and use of scientifically-based and practical guidelines in oncology. This programme is based on medical scientific findings of professional associations and the German Cancer Society, the consensus of medical experts, users and patients, the AWMF's regulations governing the production of guidelines and professional support and funding of the German Cancer Aid. In order to depict the current state of medical knowledge and to take account of medical progress, guidelines need to be regularly reviewed and revised. In this respect, the use of the AWMF regulations is intended to provide a basis for the development of high-quality oncological guidelines. As guidelines constitute an important quality assurance and quality management tool in oncology, they should be specifically and consistently incorporated into everyday care. Active implementation measures as well as assessment programmes therefore play an important role in promoting the German Guideline Program in Oncology. The objective of the programme is to establish professional and medium-term financially secure preconditions for the development and production of high-quality guidelines. This is because these high-quality guidelines not only serve for the structured transfer of

knowledge, but can also play a part in formulating health system structures. Examples that may be mentioned here are those of evidence-based guidelines as a basis for compiling and updating Disease Management Programmes or the use of quality indicators derived from guidelines for certifying organ tumour centres.

1.9. Other documents relating to this guideline

This document is the long version of the evidence-based guideline on prevention of skin cancer. In addition to the long version, the following documents are supplementing this guideline:

- Summary of the guideline
- Patient guideline
- Guideline report on the process of compiling the guideline
- Evidence tables

This guideline and all the supplementary documents can be accessed via the following websites. (Please note that all these websites other than that of the Guidelines International Network are in German. Parts of the German Guideline Program and German Cancer Aid websites have an English translation.)

- German Guideline Program in Oncology (<http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html>)
- AWMF (www.leitlinien.net)
- Home pages of the professional societies involved, e.g. Association of Dermatological Prevention (www.unsererahaut.de, www.hautkrebs-screening.de)
- German Cancer Society (http://www.krebsgesellschaft.de/wub_1levidenzbasiert,120884.html)
- German Cancer Aid (<http://www.krebshilfe.de/>)
- Guidelines International Network (www.g-i-n.net)

There is a specific evidence-based guideline on diagnosis, therapy and follow-up of melanoma within the German Guideline Program in Oncology [1] that can also be accessed via the websites of the German Guideline Program in Oncology and its sponsors.

1.10. Authors

1.10.1. Co-ordination and project team

Prof. Dr. med. E.W. Breitbart

Project team (in alphabetical order):

Markus Anders (January 2013 – October 2013)
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 Dr. Beate Volkmer (March 2010 – October 2013)

1.10.2. Professional societies and organisations involved

Table 1 lists the professional medical associations and other organisations, together with their appointed representatives, involved in producing the guideline.

Table 1: Overview of the associations, professional societies, organisations and patient representative groups involved and their appointed representatives

Professional societies and organisations involved	Representative
Association to Promote Dialogue in the Health System	Dr. Carsten Schwarz
Buxtehude Skin Cancer Self-Help Group	Annegret Meyer, Martina Kiehl
Centre for Media and Health Communication	Dr. Bettina Fromm (retired)
Dermatological Histology Working Group (ADH)	Prof. Dr. Christian Sander
Dermatological Oncology Working Group (ADO)	Prof. Dr. Axel Hauschild (retired), Prof. Dr. Carola Berking
European Society for Skin Cancer Prevention (EUROSKIN)	Dr. Rüdiger Greinert
Federal Association of German Pathologists (BDP)	Prof. Dr. Erhard Bierhoff*

Professional societies and organisations involved	Representative
Federal Office for Radiation Protection (BfS)	Dr. Monika Asmuß
German Association of Occupational Physicians (VDBW)	Dr. Uwe Gerecke
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German Ophthalmological Society (DOG)	Prof. Dr. Rudolf F. Guthoff
German Psoriasis Association	Hans-Detlev Kunz, Christiane Rose (retired)
German Society for Dermatosurgery (DGDC)	Dr. Christoph Löser
German Society for Epidemiology (DGEpi)	Prof. Dr. Andreas Stang
German Society for Journalism and Communication Science (DGpuK)	Dr. Eva Baumann
German Society for Occupational and Environmental Medicine (DGAUM)	Prof. Dr. Hans Drexler
German Society for Oral and Maxillofacial Surgery (DGMKG)	Prof. Dr. Dr. Bernhard Frerich, Dr. Dr. Heidrun Schaaf (representative)
German Society for Social Medicine and Prevention (DGSMP)	Prof. Dr. Alexander Katalinic, Dr. Annika Waldmann (representative)
German Society of Obstetrics and Gynaecology (DGGG)	Dr. Grit Mehlhorn
German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (HNO)	Prof. Dr. Friedrich Bootz (retired), PD Dr. Andreas Gerstner

Professional societies and organisations involved	Representative
German Society of Pathology (DGP)	PD Dr. Christian Rose*
German Society of Paediatric and Adolescent Medicine (DGKJ)	Prof. Dr. Peter Höger
German Society of Urology (DGU)	Prof. Dr. Jürgen Gschwend
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Professional Association of German Ophthalmologists (BVA)	Prof. Dr. Holger Mietz
Professional Association of German Urologists (BDU)	Dr. Bernt Göckel-Beining
Professional Association of Gynaecologists (BVF)	Dr. Wolfgang Cremer
Professional Association of Paediatric and Adolescent Physicians (BVKJ)	Dr. Herbert Grundhewer
Psycho-Oncology Working Group of the German Cancer Society (PSO)	Prof. Dr. Susanne Singer
Society of Epidemiological Cancer Registries in Germany (GEKID)	Dr. Annika Waldmann
* = joint representative of the professional association and the professional society	

The distribution of authors between the working groups responsible for the different chapters is presented in Table 2.

Table 2: Working groups and their members

Working groups for chapter	Working group members (Working Group leader in bold)
Chapter 3: Status quo skin cancer	A. Waldmann , K. Beifus, E.W. Breitbart, R. Greinert, A. Katalinic, J. Köberlein-Neu, B. Volkmer
Chapter 4: Primary prevention	M. Diensberg , M. Asmuß, H. Drexler, R. Greinert, H.

Working groups for chapter	Working group members (Working Group leader in bold)
	Grundhewer, S.M. John, J. Reichrath, H. Siekmann, S. Singer, B. Volkmer
Chapter 5.1: Secondary prevention – early detection of skin cancer	B. Göckel-Beining , J.-F. Chenot, W. Cremer, R. Greinert, A. Stang, B. Volkmer (with scientific advice from the international experts of the Scientific Advisory Board: J. Aitken, M. Boniol, J.-F. Doré, M. Elwood, S.W. Fletcher, R. Gallagher, S. Gandini, A. Geller, A.C. Halpern, R. Lucas, A.A. Marghoob, J. Schüz, C. Sinclair, M.A. Tucker, M. Weinstock)
Chapter 5.2: Secondary prevention – screening test / presumptive diagnostic procedures	C. Berking , E.W. Breitbart, T. Eigentler, G. Mehlhorn, P. Mohr, D. Sturm
Chapter 5.3: Secondary prevention – confirmatory diagnostic procedures	C. Rose , E.W. Breitbart, T. Eigentler, A. Gerstner, C. Löser, C. Sander
Chapter 5.4: Secondary prevention – doctor-patient communication	C. Schwarz , M. Anders, M. Diensberg, G. Egidi, M. Kiehl, A. Meyer, H.-D. Kunz, A. Rogge, D. Sturm
Chapter 5.5: Secondary prevention – implementation and quality assurance of skin cancer screening	A. Katalinic , M. Anders, E.W. Breitbart, M. Diensberg, H. Drexler, S.M. John, B. Löpker, H. Siekmann, D. Sturm
Chapter 6: Information of the population / public	E.W. Breitbart , M. Anders, E. Baumann, G. Egidi, M. Kiehl, A. Meyer, H.-D. Kunz, C. Schwarz, S. Singer
Chapter 7: Quality indicators	S. Wesselmann , M. Anders, E. Baumann, E.W. Breitbart, J.-F. Chenot, W. Cremer, M. Diensberg, M. Follmann, B. Göckel-Beining, H. Grundhewer, A. Katalinic, M. Klinkhammer-Schalke, D. Kunz, M. Nothacker, A. Rogge, R. Stadler

1.10.3. Patient involvement

The guideline was drawn up with the direct participation of several patient representatives. Annegret Meyer and Martina Kiehl from the Buxtehude Skin Cancer Self-Help Group and Hans-Detlev Kunz from the German Psoriasis Association were invited as patient representatives. Christiane Regensburger represented the German Working Party for the Assistance of Persons with Disabilities and Chronic Diseases and their Relatives (BAG). These representatives were included as voting members on the working groups compiling the guideline.

1.10.4. Methodological support

By the German Guideline Program in Oncology:

- Dr. med. Markus Follmann, MPH MSc, Office of the German Guideline Program in Oncology – German Cancer Society
- Prof. Hans-Konrad Selbmann, Association of Medical Scientific Societies (AWMF).
- Dipl.-Soz.Wiss Thomas Langer, Office of the German Guideline Program in Oncology – German Cancer Society

By external contractors:

- Dr. med. Michaela Eikermann, Monika Becker, Thomas Jaschinski, Christoph Mosch; Institute for Research in Operative Medicine (IFOM), University of Witten/Herdecke
- Dr. Barbara Buchberger, MPH, Dr. Romy Heymann, Chair of Medical Management, University of Duisburg-Essen.

1.10.5. Translation

The document was translated by mt-g medical translation GmbH & Co. KG, Ulm, reviewed by the Association of Dermatological Prevention (ADP).

1.11. General remarks on the terminology used

Gender

In the interest of greater legibility, the use of the masculine and feminine forms at the same time will be avoided. All references to persons will apply equally to members of both sexes.

Patient

Similarly, for reasons of greater legibility, the term patient will frequently be used, even though the target group of this guideline is the general population. As a rule, the members of this group are not ill (with skin cancer), so that strictly speaking they are not patients.

Skin cancer

The term *skin cancer* is often understood to mean malignant melanoma only. When reference is made to skin cancer in this guideline, all skin cancer entities are intended, in particular the three most common forms mentioned below:

- Malignant melanoma (MM),
- Basal cell carcinoma (BCC),
- Squamous cell carcinoma (SCC).

2. Introduction

2.1. Scope and objective

2.1.1. Aim and problem statement

The aim of developing the *evidence-based guideline on prevention of skin cancer* is to adapt the primary and secondary prevention of skin cancer to the current state of international scientific knowledge. In so doing, the guideline is intended to contribute both to improvements in the health status and to a higher quality of life of the population. These aims are to be achieved primarily by reducing the incidence, morbidity and mortality of skin cancer.

To enable the evidence-based guideline on prevention of skin cancer to attain this aim, the current international scientific and medical status quo of skin cancer necessary for this purpose is described in Chapter 3. These statements form the basis for establishing the questions and recommendations listed below. Specifically, the authors and editors of the evidence-based guideline on prevention of skin cancer hope for a wide-ranging consideration of the recommendations on the following points:

- Primary prevention,
- Secondary prevention,
- Screening / screening test,
- Presumptive diagnostic procedures,
- Confirmatory diagnostic procedures,
- Doctor-patient communication,
- Information of the population,
- Implementation of screening and quality assurance.

At the same time, the guideline will express a view on the following questions, among others:

- What lifestyles reduce the risk of developing skin cancer?
- What lifestyles should be recommended for certain groups of people (e.g. persons at risk, children/ adolescents and adults)?
- What preventive behavioural measures are suitable for communicating knowledge and permanently changing the public's behaviour?
- Are there effective population-based and individual measures for early detection of skin cancer?
- How should screening be carried out?
- What recommendations can be given for screening persons at risk?
- What diagnostic measures are there?
- What diagnostic measure (or what combination of measures) is suitable for screening?
- What confirmatory diagnostic procedures are there?
- How should a histopathological diagnostic procedure be carried out?
- How should a patient-doctor discussion be constructed (structure) and what information should be communicated in what form?

- What information is necessary for citizens to be able to take an informed decision for or against participating in an early detection examination?
- What professional prerequisites do doctors and assistants need to have or to provide in order to be able to undertake screening?

The subsequent diagnostic procedure as well as the treatment and follow-up of skin cancer are not discussed in this guideline. In the case of malignant melanoma, reference is made here to the evidence-based guideline diagnosis, therapy and follow-up of melanoma [1].

2.1.2. Target audience

The recommendations of the evidence-based guideline prevention of skin cancer are directed at all doctors and members of professional groups involved in the prevention and early detection of skin cancer. These include resident physicians with a preventive role (dermatologists, general practitioners, medical practitioners, non-specialist physicians, internal specialists in primary care, gynaecologists, urologists, surgeons, paediatricians, ENT specialists, oral and maxillofacial surgeons, histopathologists, dentists) as well as nursing staff and health assistants. Further audiences include medical scientific professional societies and professional associations, patient representatives and skin cancer self-help groups as well as quality assurance bodies and Federal and State Institutions, such as the Federal Office for Radiation Prevention (BfS), the Central Institute for Outpatient Care Provision in Germany (ZI), the Joint Federal Committee (G-BA) and the Society of Epidemiological Cancer Registries in Germany (GEKID).

Lastly, the guideline is directed at the population. A separate evidence-based patient guideline / lay version has been produced to provide a direct approach to the population.

2.2. Interface with the evidence-based guideline on diagnosis, therapy and follow-up of melanoma

(AWMF No 032/024GGPO)

The original plan was for a “skin cancer” guideline that was intended to cover the areas from prevention to palliative care. However, for pragmatic reasons such as scope and feasibility, it was instead decided in the preparatory and harmonisation phase to produce two guidelines linked via an interface group.

The interface group consisted of Prof. Dr. Breitbart (evidence-based guideline on prevention of skin cancer, co-ordinator) and Prof. Dr. Garbe and Prof. Dr. Schadendorf (evidence-based guideline on diagnosis, therapy and follow-up of melanoma, co-ordinators). The respective representatives of the other interface group or their deputies were always present in the harmonisation processes of the two guidelines.

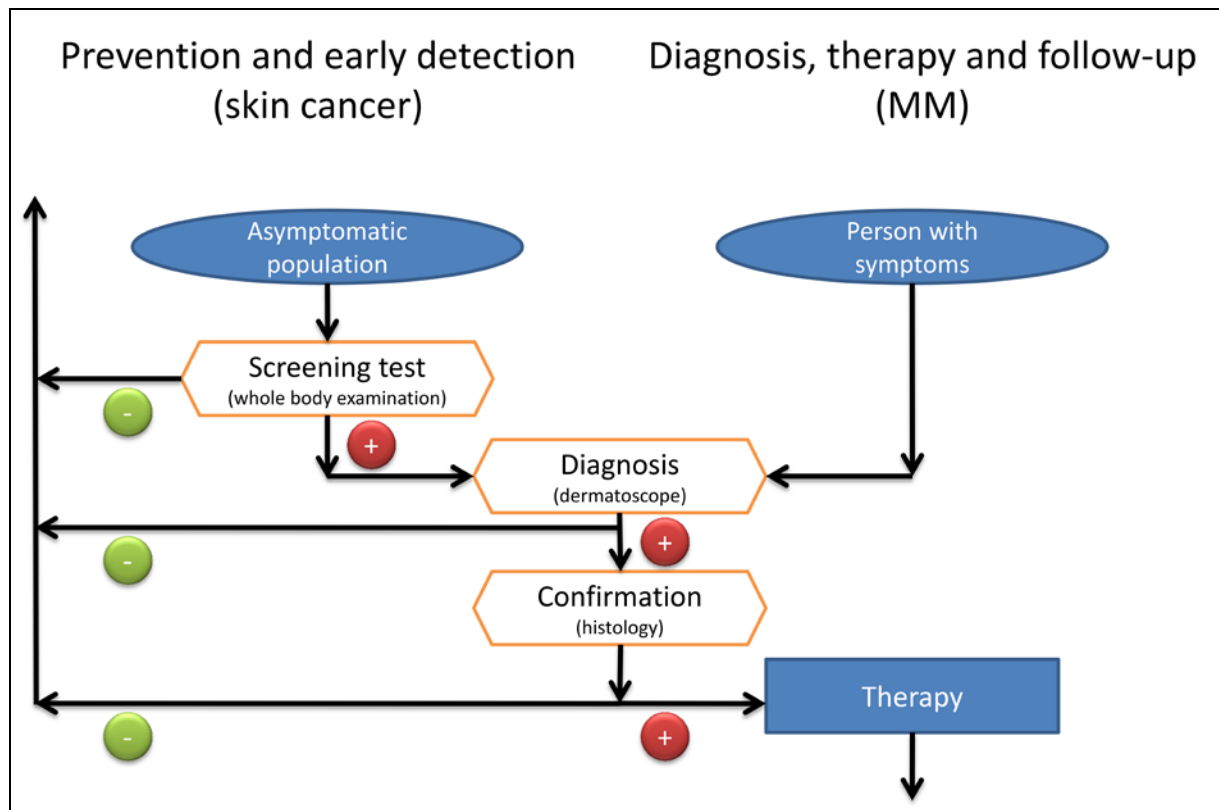


Figure 1: Overview of the interface with the evidence-based guideline on malignant melanoma

2.3. Period of validity and update process

The estimated period of validity of the guideline on the prevention of skin cancer is 5 years.

To be able to convey the latest state of knowledge in the field of skin cancer prevention, updates of the guideline will be necessary. A revision will be undertaken five years after completion of the follow-up research, i.e. June 2017.

Comments and advice on the update process are expressly requested and should be addressed to the guideline office:

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2.4. Methodology

A detailed description of the methodological process can be found in the guideline report (www.leitlinienprogramm-onkologie.de/OL/leitlinien.html)

2.4.1. Modified SIGN evidence grading system

In order to classify the risk of bias of the studies identified, a modified system (see Table 3) has been used in this guideline based on that of the Scottish Intercollegiate Guidelines Network (SIGN, see <http://www.sign.ac.uk/pdf/sign50.pdf>). In the system presented here, cross-sectional studies on diagnostic questions and pre-post comparisons have been included in level 2, as these have not previously been explicitly listed there.

Table 3: Modified SIGN classification of evidence table

Evidence class	Description (modifications in italics)
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of systematic errors (bias)
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of systematic errors (bias)
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of systematic errors (bias)
2++	High-quality systematic reviews of case-control or cohort studies (<i>including pre-post comparisons</i>) or High-quality case-control or cohort studies (<i>including pre-post comparisons</i>) with a very low risk of systemic distortions (confounding, bias or chance) and a high probability that the relationship is causal or <i>High-quality studies with a cross-sectional design to investigate diagnostic quality with a very low risk of systematic bias.</i>
2+	Well conducted case-control or cohort studies (<i>including pre-post comparisons</i>) with a low risk of systemic distortions (confounding, bias or chance) and a moderate probability that the relationship is causal or <i>Studies with a cross-sectional design to investigate diagnostic quality with a moderate risk of systematic bias.</i>
2-	Case-control or cohort studies (<i>including pre-post comparisons</i>) with a high risk of systematic distortions (confounding, bias, chance) and a significant risk that the relationship is not causal or <i>Studies with a cross-sectional design to investigate diagnostic quality with a high risk of systematic bias.</i>
3	Non-analytic studies, e.g. case reports, case series, <i>studies with a cross-sectional design without investigations for diagnostic quality.</i>

Evidence class	Description (modifications in italics)
4	Expert opinion.

2.4.2. System of grading recommendations

The methodology of the German Guideline Program in Oncology (GGPO) allows for grades of recommendation to be allocated by the guideline authors as part of a formal consensus procedure. Accordingly, a multi-step, nominal group process moderated by the Association of Scientific Medical Societies (AWMF) was undertaken.

In the guideline, all evidence-based statements (see 0) and recommendations are assigned the level of evidence (see 2.4.1) of the studies on which they are based, while recommendations are also assigned a degree of strengths a strength (grade of recommendation). In terms of the strength of recommendation, three grades of recommendation are distinguished in this guideline (see Table 4), each of which is also reflected in the way in which the recommendations are worded.

Table 4: Grades of recommendation used

Grade of recommendation	Description	Wording
A	Strongly recommended	must
B	Recommended	should
0	Neither recommended nor not recommended	can

2.4.3. Statements

Apart from the recommendations, the guideline also contains evidence- or consensus-based statements. Statements are defined as expositions or explanations of specific facts or issues with no direct need for action. They are approved in a similar procedure to that used for recommendations in a formal consensus process. Evidence-based statements are also graded in accordance with the previously mentioned modified SIGN evidence grading (see 2.4.1).

2.4.4. Expert Consensus (EC)

Recommendations decided upon on the basis of a consensus of experts, and not on the basis of a systematic search or an adaptation of the guidelines, are identified as such by the grade "EC". Symbols representing the strength of recommendation are not given for ECs. The strength of recommendation is implicit in the wording of the sentence (must/should/can), in accordance with the grading in Table 4.

2.4.5. Independence and disclosure of possible conflicts of interest

German Cancer Aid provided financial resources through the German Guideline Program in Oncology (GGPO). These resources were used for staffing costs, office materials, literature procurement and consensus conferences (room hire, technology, catering, moderator's fees, travelling expenses of participants). The compilation of the guideline was editorially independent of the funding organisation. All members provided a written disclosure of possible conflicts of interest during the guideline process. The conflicts of interest disclosed are included in the guideline report to this guideline (<http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>). The disclosures of conflicts of interest were inspected and assessed by the co-ordinator. Following review by the guideline co-ordinator, none of the reported conflicts of interest was classed as sufficiently critical to have an impact on the remit.

As the Association of Dermatological Prevention (ADP) and with it in particular the guideline co-ordinator Prof Dr Breitbart has been active since the 1980s in the area of both primary and secondary prevention of skin cancer and in particular has designed, implemented and analysed the SCREEN project (SCREEN: Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) [2], which was the basis for the introduction of national skin cancer screening in Germany, a potential conflict of interests was envisaged by the GGPO. In order to address this point the promotion of the guideline project was subjected to a neutral appraisal of the guideline by international experts.

Thus, it was intended to ensure that the evidence on secondary prevention was assessed independently. In order to meet this precondition already in the creation process, international experts in the field of skin cancer prevention have been included in the development of the guideline's chapter on the early detection of skin cancer. These experts are members of the Scientific Advisory Board (SAB) for the Prevention of Skin Cancer (see guideline report) that was founded in 2009 [3]. Furthermore the neutrality of the assessment regarding scientific evidence was ensured through the commission of external institutions (see chapter 5.2. in the guideline report).

2.5. Abbreviations used

Abbreviation	Explanation
ADP	Association of Dermatological Prevention
AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
ALM	Acral-lentiginous melanoma
ArbSchG	Law on the Implementation of Protective Measures to Improve the Safety and Health of Employees at Work
AUVA	Austrian General Accident Insurance Institute
AWMF	Association of Medical Scientific Societies
BCC	Basal cell carcinoma
BER	Base-excision repair
BfS	Federal Office for Radiation Protection
BG ETEM	Professional Association of the Energy Textile Electrical and Media Products Sector
BKK	Company health insurance funds
CG	Control group
CI	Confidence interval
CLSM	Confocal laser scanning microscopy
CMN	Congenital melanocytic naevi
CPD	cis-syn-cyclobutane-pyrimidine dimers
CRBC	CPD-retaining basal cells
CT	Computer-assisted tomography
DBD	DNA-binding domain
DDG	German Dermatological Society
DKG	German Cancer Society
DKH	German Cancer Aid
DRG (G-DRG)	Diagnosis-Related Groups (German Diagnosis-Related Groups)
EASR	European age-standardised rate
EC	Expert consensus
EDC	Early detection of cancer

Abbreviation	Explanation
EIS	Electrical impedance spectroscopy
ENT	Ear, nose and throat
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Federal Joint Committee
GEKID	Society of Epidemiological Cancer Registries in Germany
GGPO	German Guideline Program in Oncology
GL	Guideline
HA	Health Assistant
HCA	Human capital approach
HPV	Human papillomavirus
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IG	Intervention group
IQWiG	Institute for Quality and Efficiency in Health Care
IW	Incapacity for work
KBV	National Association of Statutory Health Insurance Physicians
KDIGO	Kidney Disease: Improving Global Outcomes
LDH	Lactate dehydrogenase
LMM	Lentigo malignant melanoma
LOH	Loss of heterozygosity
MFS	Medical fee schedule (fee schedule outside the German statutory health insurance)
MM	Malignant melanoma
MPT	Multiphoton laser tomography
NBCC	Naevoid basal-cell carcinoma syndrome
NCCP	National Cancer Control Plan
NCN	Naevus cell naevus
NER	Nucleotide excision repair
NiSG	Act on Protection against Non-Ionising Radiation
NM	Nodular melanoma

Abbreviation	Explanation
NMSC	Non-melanocytic skin cancer
NNE	Number needed to excise
OCT	Optical coherence tomography
OR	Odds ratio
OStrV	Ordinance on the Protection of Employees against Hazards caused by Artificial Optical Radiation
PPV	Positive predictive value
QI	Quality indicators
QLQ	Quality of Life Questionnaire
QOL	Quality of life
RCT	Randomised controlled trial
ROS	Reactive oxygen species
RR	Relative risk
SAB	Scientific Advisory Board
SCC	Squamous cell carcinoma
SCREEN	Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany
SCS	Skin cancer screening
SHH-Gen	Sonic hedgehog
SHI	Statutory health insurance
SIGN	Scottish Intercollegiate Guidelines Network
SMO	Smoothened protein
SPF	Sun protection factor
SSE	Skin self-examination
SSK	Radiation Protection Commission
SSM	Superficial spreading melanoma
TNM classification	Staging of malignant tumours (tumour, lymph nodes (nodes), metastases)
UICC	International Union Against Cancer
UNEP	United Nations Environment Programme
UPF	Ultraviolet protection factor
URS	Uniform rating standard (fee schedule in the German statutory health

Abbreviation	Explanation
	insurance regarding outpatient care)
UV radiation	Ultraviolet radiation
UVI	UV index
UVSV	Ordinance on the Protection from Adverse Effects of Artificial Ultraviolet Radiation
WHO	World Health Organization
ZI	Central Institute for Outpatient Care Provision in Germany

3. Status quo of skin cancer

3.1. The aetiology of skin cancer

3.1.1. The causes of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM)

3.1.	Consensus-based statement
EC	On the basis of current knowledge, ultraviolet (UV) radiation is considered to be the most significant risk factor in the aetiology of skin cancer, even if not all details of the induction, promotion and progression of skin cancer in humans have been elucidated.
	Consensus strength: 96.2%

R. Greinert, B. Volkmer

In 2009, the International Agency for Research on Cancer (IARC) classified solar and artificial ultraviolet radiation (UV radiation) used in solariums as a class I carcinogen (“carcinogenic to humans”) [4]. This categorisation was made without any restriction as to specific wavelength ranges (UVA, UVB) because of the proven epidemiological and basic scientific evidence.

Principles of the biological effect of UV radiation

UV radiation encompasses the region of the electromagnetic spectrum that covers the wavelength range from 100 to 400 nm. Historically, this wavelength range is subdivided into UVC (100-200 nm), UVB (200-315 nm) and UVA radiation (315–400 nm) [5]. Solar UV radiation exerts a biological effect only through the UVB and UVA part, as UVC is absorbed by molecular oxygen in the earth’s stratosphere [5].

UV radiation can interact with a variety of cellular components (including membrane lipids, proteins and intracellular photosensitive molecules such as flavins or porphyrins) [6], but particularly through the absorption of UV photons by nucleic acids [7].

UVB radiation can be absorbed directly by the DNA molecule. Photochemical processes then result in dimerisation reactions of neighbouring pyrimidines on a DNA strand (cis-syn cyclobutane pyrimidine dimers (CPD), or (6-4)-pyrimidone photoproducts ((6-4)-PP)) [8].

Moreover, UVB and UVA radiation can contribute to the formation of reactive oxygen species (ROS) via indirect pathways in which the radiation energy is first absorbed by photosensitive molecules in the cell. ROS can then cause oxidative base damage, such as 8-oxo-7,8-dihydro-2’-deoxyguanosine (8-oxo-dG) in the DNA [8, 9]. More recent findings, however, show that UVA radiation is also capable of generating CPDs in the DNA [10-13].

DNA lesions such as CPDs and 8-oxo-dG can be eliminated by efficient repair systems (nucleotide excision repair (NER) or base excision repair (BER)). If these repair pathways are defective or deficient (e.g. NER in xeroderma pigmentosum patients, who are at greatly increased risk of skin cancer), mutations can occur in the genome. CPDs result predominantly in C→T or CC→TT mutations, known as UV signature mutations, while UVA-induced oxidative base damage can result in less significant GG-T fingerprint mutations. In general, two models are proposed for UV-induced mutagenesis in order to explain the predominance of C-T mutations in UV-irradiated cells. One pathway involves defects in DNA lesion bypass with the participation of translesion polymerases (pol ζ , pol κ) [14, 15]. In the other pathway, initial deamination of (methylated) CPDs is then followed by an error-free lesion bypass by pol η [15-18].

The study of mutation profiles in skin tumours, particularly those that occur in xeroderma pigmentosum (XP) patients confirmed the importance of UV-induced bipyrimidine photoproducts and oxidative DNA damage in the development of skin cancer. In addition, it has been possible to identify genes whose UV-dependent mutations exert an effect on elemental cellular pathways associated with the development and progression of basal cell carcinomas (BCC), squamous cell carcinomas (SCC) and malignant melanomas (MM).

The correlation UV radiation and the development of different types of skin cancer has been demonstrated in many epidemiological studies, in animal experiments and in a number of basic experimental studies [7]. Recent studies dealing with the sequencing of human tumour genomes additionally confirm the relationship between UV-induced DNA damage and MM at the molecular genetic level. For example, Pleasance et al. (2010) showed that the mutations found in the sequencing of a melanoma genome predominantly belonged to the UV signatures [19].

Basal cell carcinoma (BCC)

Basal cell carcinoma (BCC) is the most common skin cancer worldwide. It develops on sun-exposed areas such as the nose and forehead, amongst others. For this reason, its occurrence was initially assumed to be dependent on the cumulative UV dose. However, a proportion of BCCs, which is not negligible, also occur on “sun-protected” parts of the body, such as the torso. It has been recently assumed that, as is the case with MM, intermittent UV exposure such as sunburn in childhood and adolescence is (jointly) responsible for BCC as well [20-27].

In the meantime, intensive worldwide research results indicate a significant genetic determination in the development of BCC. For example, it has been shown that patients with naevoid basal cell carcinoma syndrome (NBCC) who often develop multiple BCC at an early age [28, 29] frequently exhibit a loss of chromosome 9q. These findings led to the identification of the localisation of a possible tumour suppressor gene in the 9q22-q32 region, the PTCH gene [30-32]. They also resulted in further characterisation of the important sonic hedgehog-patched-smoothened signalling pathway, which is reported to be impaired in up to 100% of all sporadically occurring BCCs [33].

In the skin, a sonic hedgehog (SHH) gene-dependent signalling chain is involved in hair follicle growth and morphogenesis. The protein product encoded by the PTCH gene, PATCHED1, acts as a cell surface receptor for the secreted signalling molecule SHH. In the absence of SHH, Patched1 inhibits the smoothened protein (SMO), a G protein-

coupled receptor. Following binding of SHH to PATCHED1, SMO is released and initiates a signal transduction chain that causes activation of the transcription factor Gli. Defective regulation of the hedgehog-patched-smoothened signalling pathway can occur as a result of loss of function of PTCH or increased expression of SMO. This results in an increased concentration of the transcription factor Gli and consequently in the induction of hair follicle-associated BCC [34-37] by inhibition of cell cycle arrest and differentiation [38]. It has been demonstrated in the mouse model that disorders of the SHH-PTCH-SMO signalling pathway in hair follicle stem cells are responsible for the development of BCC [39, 40]. Mutations in PTCH or SMO were found in the majority of all sporadic BCC [41-44].

UV-specific signature mutations (C→T transition mutations) were found in the p53, PTCH and smoothened genes [34, 44-52]. This finding must be interpreted as a further important indicator of the significance of UV exposure for the development of BCC. UV-induced p53 mutations in skin cells accumulate in hotspots, which differ from those in internal tumours. There is evidence that UV-specific mutations of the p53 gene might be specific to BCC [53].

A number of articles recently pointed to the fact that stem cells in the bulge region of the hair follicle or interfollicular epidermal stem cells are of major importance for the development of types of non-melanocytic skin cancer (NMSC, i.e. BCC, SCC). As stem cells and their differentiation or neoplastic transformation depend essentially on regulation by their microenvironment, intercellular communication and its signal-mediating pathways assume considerable significance. In this respect, the WNT, SHH, NOTCH and EGFR signal transmission pathways in animal models and in-vitro studies (including human skin cells) associated with BCC and SCC merit particular mention (see review [54]).

In addition to the previously described changes in the hedgehog-patched-smoothened signalling pathway, it is striking that in the genetics of BCC, only a few numerical chromosomal aberrations can be demonstrated in tumour cells [55]. However, BCC are characterised by a marked intratumour heterogeneity. In a cytogenetic analysis of 44 BCC, genetically unrelated subclones were found in 21 tumours and genetically related subclones in only 10 [56]. The authors conclude from this that a large number of BCC are of multiclonal origin. They were also able to show that a large proportion of BCC are characterised by the gain of chromosomes 18, X, 7 and 9 and that chromosomal losses frequently affected the distal regions of chromosomes 6q, 13q, 4q, 1q, 8q and 9p [56].

Squamous cell carcinoma (SCC)

Squamous cell carcinoma (SCC) is the only skin cancer to have a known precursor stage: actinic keratosis (AK, also known as solar keratosis). AK is a small, intraepidermal lesion that occurs on chronically sun-(UV-) exposed areas such as the face, scalp, lips, lower arms and hands in middle-aged and elderly light-skinned people. Cumulative UV exposure to the sun is regarded as the main reason for the occurrence of AK [57, 58]. The incidence of AK therefore increases with age.

AK constitutes a precursor stage of SCC [59]. In the literature there are conversion probabilities, i.e. of transition from AKs to invasive SCC, ranging from <1% up to 16% [60-63]. There have even been reports of up to 70% occurrence in individual cases [64]. In a more recent prospective study by Criscione et al. (2009) that included more than

6,000 people with actinic keratosis, the probability of transition from AK to SCC is given as only 0.06%. However, six years after the first diagnosis of actinic keratosis, all the SCC that occurred arose in AK [65]. The presence of multiple actinic keratoses over a 10-year period is given with a lifetime risk for the development of SCC in the range of 6-10% [60]. As a hallmark of increased UV exposure, AK represents an important risk factor for the development of SCC.

The risk of developing an NMSC or an MM for patients with AK is six times greater than for those without this lesion [66]. However, the underlying mechanisms of this increased risk of skin cancer are only incompletely understood.

For AK, the likelihood of transition from AK to a SCC or other skin cancer entities has not been sufficiently elucidated (see above) [67, 68], nor are there at present robust molecular biological or molecular genetic findings to demonstrate which genetic alterations might prompt the transition from AK to SCC [69, 70]. However, some dermatologists and dermatohistopathologists interpret indications that seem to confirm malignant progression from AK to SCC [71-73] in such a way as to classify AK per se as a SCC that is confined to epidermal dissemination (carcinoma in situ) [72, 74-77]. However, after viewing the literature data, Feldmann and Fleischer (2001) come to the conclusion in a more recent study that "Presently there is insufficient evidence to support the concept that AK is frank SCC" [68].

Because of the uncertainty over this categorisation, there is currently no reason to include AK in the group of skin cancer entities to be screened in a skin cancer screening programme.

There is a relatively well-described model for the aetiology of SCC, in which early-onset UV-specific mutations in the p53 gene in the tumour initiation phase promote the development of a precursor of SCC, AK. It is assumed that in AK only one allele of the p53 gene is mutated initially. As a result, the p53-dependent apoptosis of UV-damaged cells ("sunburn cells") is prevented in some of the cells. As "neighbouring" cells at the same time exhibit normal apoptosis, p53-mutated cells have a "selection advantage" and can expand clonally to AK. If the second p53 allele in these cells mutates in the tumour promotion phase, the p53-dependent cell cycle checkpoint function is switched off. Uncontrolled cell growth occurs and invasive SCC form as a result of the induction of further (possibly UV-induced) mutations in other genes (e.g. ras) in the tumour progression phase [78-80].

75-80% of p53 mutations in the white population occur in patients with AK (30-40% in Japanese and Koreans) [81] and these mutations occur in more than 90% of patients with in-situ SCC (i.e. still non-invasive SCCs) [82]. In the latter case, and also in the case of p53 mutations in AK, these have been shown to be caused predominantly by UV-induced dimerisation of neighbouring DNA pyrimidines and to result in C-T and CC-TT base substitutions (tandem mutations) [82] that are accepted as a UV signature mutation [83]. These mutations develop as a result of the defective repair/ replication of UVB- and UVA-induced DNA damage, such as the cyclobutane pyrimidine dimer and the pyrimidine(6-4)pyrimidone dimer [83-87]. This points unequivocally to the involvement of UV radiation in the aetiology of SCC. In the p53 gene, these mutations occur in certain mutation hotspots in the gene located in regions in which enzymatic repair of the DNA damage by nucleotide excision repair (NER) is impaired or prevented (repair coldspots) [88, 89].

A pioneering p53-dependent model for the development of SCC has been established by studies in the hairless mouse and its variants, in which the p53-DNA binding domain (DBD) has been replaced by the homologous human segment (Hupki mouse) [90, 91]. UV-induced p53 mutations can be demonstrated in this model by the immunofluorescent detection of clonal “cell patches” (up to several thousand cells) in the epidermis. The origin of this clonal expansion of p53-mutated cells might be seen in the induction of individual, severely UV-damaged, non-apoptotic, persistent CPD-retaining basal cells (CRBC), which have been detected both in the mouse model and also in human epidermis [92, 93]. CRBCs are probably interfollicular epidermal stem cells whose UV-induced damage is held responsible for the development of SCC [54, 82, 94]. Interfollicular epidermal stem cells, whose characterisation and possible isolation at the moment is best described for murine epidermis, are distinguished by the fact that they only rarely proliferate and therefore accumulate UV-induced DNA damage (label-retaining cells, such as CRBCs) [54, 95, 96]. Epidermal stem cells therefore represent the “suitable” target for the carcinogenic action of UV radiation, as they can also accumulate mutations because of their long persistence in the otherwise constantly self-renewing epidermis. This is consistent with early [97] and, in relation to skin cancer, recent models of cancer development [54, 98, 99].

In line with the dependence of SCC on the cumulative UV dose and the multistage nature of the development of SCC (see above), SCC exhibits a very much greater karyotype complexity and cytogenetically confirmed heterogeneity than BCC, for example. Nevertheless, some chromosomal aberrations can be detected in SCC that are probably specific to this entity. For example, it has been shown that the loss of heterozygosity (LOH) of a “9q marker” occurs frequently in SCC [100, 101]. In addition, LOHs in 3p, 13p, 17p and 17q appear to be specific for SCC and its precursor, AK [102]. Using multiplex fluorescence-in-situ hybridisation (m-FISH), it has also been shown that complex chromosome translocations occurred to an increased extent in cell lines obtained from SCCs [103], which points to the particular significance of genetic instability in the development of SCC. In this context, it is important to point out that UVA radiation is capable of inducing DNA double-strand breaks via the induction of ROS, which are known to be necessary precursor lesions for the development of chromosomal aberrations [104, 105].

Malignant melanoma (MM)

There is a considerable amount of unambiguous evidence that malignant melanoma (MM) occurs as a result of intermittent UV exposure and severe episodes of sunburn in childhood and adolescence [20, 106]. MMs occur very frequently in light-skinned individuals with red or blond hair (skin type I), who tend to develop freckles, do not tan and sunburn very easily (cf. also risk factors 3.4). There is a relationship between the risk of developing MM and specific mutations in the melanocortin-1 receptor [107, 108]. This receptor is responsible for the type of melanin that is formed in melanocytes after UV exposure. It is postulated that individuals with these receptor mutations are unable to form the photoprotective eumelanin and instead produce the photosensitising, and hence potentially mutagenic, pheomelanin [109].

There is strong evidence that MM is inherited via an autosomal dominant trait, since 5-12% of sufferers have one or more first-degree relatives who also develop MM. Cancer occurs at an early stage in these individuals with familial melanoma. It is frequently accompanied by multiple other (skin) tumours [110-114]. Genetic analysis of families with a high melanoma incidence resulted in the identification of susceptibility

genes such as the cycline-dependent kinase inhibitor CDKN2A (p16INK4A) and genes for the cycline-dependent kinases CDK4 and CDK6. It has been shown that p16INK4A, which is genetically encoded on the chromosome 9p21 section, is mutated in 25-40% of familial melanomas. It is now considered proven that this gene constitutes a predisposition gene for MM [115-117]. p16INK4A inhibits the progression of cells through the G1 phase of the cell cycle by suppressing the binding of cycline D1 to CDK4/6. This is necessary for phosphorylation of the retinoblastoma protein that governs the controlled transition of cells from the G1 phase to replication (S phase). Mutations in the INK4A gene, which codes for the inhibitor CDKN2A (p16), suppress this regulation and result in uncontrolled cell division. In addition, germ cell mutations and sporadic mutations have been demonstrated in the CDK4 gene of the tumours, which prevent the binding of p16INK4A to CDK4 and thus abolish the inhibitory function of p16INK4A [118].

The INK4A locus also codes for a structurally and functionally different protein, p14ARF, that acts as a further tumour suppressor [119]. p14ARF activates the p53 pathway as a result of oncogene-mediated signals (such as by c-Myc or ras oncogene) by binding to the p53 negative regulator Mdm2. This prevents the breakdown of p53 and allows the induction of cell cycle arrest or apoptosis. As p14ARF has been shown to be mutated in cells from MM [120, 121] and isolated germ cell mutations have been found in patients with MM [122, 123], p14ARF also represents a candidate for a predisposition gene of MM. More recent studies show that mutations in the BRAF gene may be highly significant for the development of MM [124-129].

In melanoma progression models, benign naevi (moles) are assumed to be a possible precursor stage of MM [130-132]. It is suspected that p16INK4A controls the growth of naevi and that these have arisen by clonal proliferation from melanocytes, which stop proliferating probably due to cell ageing [133-135]. This growth inhibition can be abolished e.g. by ras mutations that have been demonstrated in some forms of naevi [136-139]. Mutations in the BRAF gene may also contribute to this, as recent studies show [140-144]. This can result in the formation of dysplastic naevi and subsequently in the radial growth phase of MM [145], for which deficiencies in p16INK4A and in the retinoblastoma gene (RB) in these cells are regarded as necessary. In a subsequent stage, nodular melanomas develop in a vertical growth phase, penetrate deep into the dermis and are already capable of metastasising [146].

The number of acquired, UV-induced benign naevi in early childhood (0-6 years) is a significant (if not the main) risk factor for the formation of MM [106]. MMs not only develop from naevi, but many develop de novo, i.e. naevus-independently [147], so that the risk marker "number of benign naevi" should initially be regarded merely as an important indicator of pigmentation disorders, which then, in an as yet unexplained way, are associated with an increased risk of development of MM. This suggests that various pathways may be responsible for the formation of MM, even if UV radiation plays a causal role in its initiation. Thus, Maldonado et al. (2003) [148] in an analysis of 115 patients with invasive MM were able to show that BRAF mutations occur far more frequently in melanomas that develop on intermittently sun-exposed parts of the skin. They occurred only very rarely in MM on chronically exposed skin areas. This is indicative of the fact that various genetic changes may be held responsible for the formation of MM.

It is now accepted, however, that 50-60% of all MM exhibit BRAF mutations, 90% of which result in valine-glutamate mutations in codon 600 (BRAFF600). These BRAF

mutations result in kinase activation in the constitutive MAPK pathway [149]. At the same time, phosphorylation of the tumour suppressor LKB1 (of a serine/threonine protein kinase) results in its negative regulation, thereby contributing to the proliferation of melanoma cells and the attenuation of the apoptotic response to metabolic stress [150-152].

In contrast to squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), UV-induced mutations in the p53 gene appear to be of secondary importance. Only about 20% of MMs exhibit p53 mutations [153]. There is evidence that the involvement of p53 in the aetiology of MM is complex [154] and requires more precise elucidation. Other mechanisms, such as the induction of genetic instability, possibly play a more important role.

The aetiology of MM is characterised by a high degree of UV-induced genomic instability, which increases in the course of development of MM until metastasis. Genomic instability is expressed in the gain or loss of chromosomes (or chromosomal sections) and in the occurrence of chromosomal aberrations and loss of heterozygosity (LOH). Two genetically different subtypes can be distinguished according to the site: eye or skin. Losses of chromosome 3 and 1p and gain of 8q are often observed in melanomas of the eye, whereas the gain of 6p and the loss of 6q are apparently specific for melanomas of the skin [155]. Studies using spectral karyotyping (SKY) on cell lines from melanoma metastases show that genomic instability at the chromosomal level in the late stage of metastatisation of the melanoma can be so severe that almost every chromosome is involved in numerical or partially complex structural aberrations [156].

The gain of 7q which is associated with overexpression of c-MET (localised on 7q33-qter) appears to be a late event in melanoma progression. The tyrosine kinase receptor c-MET for the hepatocyte growth factor (HGF) is found in both keratinocytes and melanocytes. Stimulation of the HGF-MET cascade not only supports cell proliferation and mobility, but in particular destroys the important adhesion between keratinocytes and melanocytes by downregulating E-cadherin and desmoglein [157], thus encouraging melanoma progression.

LOH were found in MM for a number of chromosome loci: 1p, 3p, 3q, 6q, 9p, 9q, 11q, 17p, 17q and 22q [158]. The sites of tumour suppressor genes that play a particular role in the aetiology of MM (e.g. 9p21 as the site of CDKN2A) are often mapped to these loci. In addition, LOH in chromosome 10q23 are found in 30% of metastatic melanomas [159] and in melanoma cell lines [160]. This LOH relates to the PTEN phosphatase gene, another tumour suppressor gene, which acts as a negative regulator of the phosphatidylinositol-3-kinase pathway, supporting proliferation and cell survival [161].

A relationship between UV exposure and induction of skin MM is repeatedly doubted, because MMs also occur at sites of the body that are not usually UV-exposed. However, on closer examination of the literature on the subject, it can be found that only about 6% of all diagnosed melanomas in men and women occur in regions of the body that are purportedly less UV-exposed (lower abdomen, buttocks, genitoanal, mucous membrane, occult). The overwhelming majority of MMs (94%), however, are localised on body regions that may be frequently or intermittently exposed to UV radiation, such as the face, rest of the head, neck, chest, back, upper arm, lower arm, hand, thigh, calf and foot [162].

The relationship between UV exposure and MM development, however, is consistently confirmed by recent studies. In 2010, Pleasance and coworkers for the first time catalogued the entire spectrum of somatic mutations in the total genome of a melanoma metastasis [19]. This revealed that the majority (approximately 70%) of single base substitutions detected were of the C-T type and approximately 70% of the dinucleotide substitutions were of the CC-TT type. As these are known to be signature mutations for the effect of UV radiation, this finding clearly demonstrates the relationship between the development of MM and UV exposure.

3.1.2. **Clinical course of BCC, SCC and MM in relation to histopathological classification and TNM classification (WHO Classification of tumours)**

E.W. Breitbart

3.1.2.1. **Basal cell carcinoma (BCC)**

BCC arises from clinically unremarkable skin without a precursor stage. It is a slow-growing tumour with such slight growth initially that it is barely noticed. In this stage, it presents as a greyish-white induration of a few millimetres in size with a few telangiectases. In most cases, it is skin-coloured and grows slowly and only locally. The greatest risk from this tumour lies specifically in this constant slow growth, which can encompass and destroy all local tissue structures. Metastases are described in very rare cases [163].

BCC can occur anywhere on the integument, but in terms of the frequency of occurrence it has a predilection for areas exposed to UV radiation such as the head, throat, neck, lower arms and backs of the hands. BCC can also be found to a lesser extent on the upper body, arms and legs.

As it continues to grow, BCC develops a broad spectrum of clinical variations.

Various types of presentation are therefore distinguished according to their growth and pigmentation pattern:

1. Nodular BCC

Nodular BCC is the most common presentation. It usually develops on UV-exposed areas of the head, throat and neck region and presents first as a small, sharply delineated, broad-based, dome-shaped, firm consistency on the skin with a pearly border permeated with telangiectases. Following a prolonged period of growth, a central indentation develops that tends intermittently to bleeding, crust formation and weeping and ultimately is transformed into a permanent, slowly growing ulceration.

If treatment is not administered and tumour growth continues, deeply infiltrating tumours, known historically as *ulcus rodens*/*ulcus terebrans*, arise from it and destroy all tissue structures.

2. Pigmented BCC

Pigmented BCC is regarded as a variant of nodular BCC. The increased deposition of melanin can mean that the conventional criteria of BCC, such as a glassy surface with telangiectases and the pearly border, can no longer be identified. This can cause problems in the differential diagnosis between malignant melanoma and other pigmented changes, such as naevi, seborrhoeic warts, etc.

3. Superficial BCC

Superficial BCC is also known as BCC of skin of trunk because of its preferential localisation on the trunk. Since clinically it elicits the impression of a multiple occurrence at one site, it is also frequently referred to as multicentric BCC.

Superficial BCCs differ from the other subtypes in both their clinical and their biological behaviour, as a result of which they are frequently misdiagnosed and confused with inflammatory dermatoses.

Clinically, they are sharply but irregularly delineated, reddish to reddish-brown, very flat changes that may resemble eczema on the skin. Generally, they can cause fine scaling and even pruritus, but they also exhibit crust formation and the typical pearly nodules in the marginal regions. They can become very large, but even very large tumours do not ulcerate.

4. Sclerodermiform BCC

Sclerodermiform BCC is often overlooked because of the minor clinical findings. This tumour is frequently only detectable as a scar-like change that is readily permeated by telangiectases and feels hard to palpation. Following further growth, it occasionally resembles a slightly raised scar. The particular problem of sclerodermiform BCC lies in the fact that the often very delicate but extremely richly branched associations of tumour cells extend far beyond the border of the clinically detectable, often somewhat raised, yellowish, scar-like central plaques. This growth pattern is of particular significance, particularly in later treatment, as sclerodermiform BCC tend to infiltrate even deep anatomical structures very rapidly.

Histopathological classification of BCCs

(in accordance with WHO 2006 Histological classification of keratinocytic skin tumours [164])

- Superficial basal cell carcinoma,
- Nodular basal cell carcinoma (solid, adenoid and cystic),
- Micronodular basal cell carcinoma,
- Infiltrating basal cell carcinoma (non-sclerosing, sclerosing),
- Fibroepithelial basal cell carcinoma,
- Basal cell carcinoma with adnexal differentiation (follicular, apocrine, eccrine),
- Basosquamous carcinoma,
- Keratotic basal cell carcinoma.

Mixed forms of these types are frequently found [165]. Collision tumours with squamous cell carcinoma are also possible.

3.1.2.2. **Squamous cell carcinoma (SCC)**

SCC develops in more than 90% of cases on chronically UV-exposed skin such as the face, ears, lower lip and back of the hand. It has a precursor stage, actinic keratosis (AK) (see section 3.1.1). AK presents in most cases as a sharply delineated, faint

redness with very fine, firmly adherent scales (sandpaper phenomenon). In the subsequent disease course, brownish-yellow horns develop that are easy to remove by scratching. This hyperkeratosis continues to form until it is firmly attached, causes a fine, bright pain when any attempt is made to remove it by scratching and then transforms into a clinically clearly visible, firmly adherent, brownish-yellow horn, the cutaneous horn. At the base of this horn, the SCC develops in the form of a nodule that subsequently increases rapidly in size, can break up centrally and can then developing weeping tumours of varying size.

After a prolonged presence, this invasive growth results in metastases, initially to regional lymph nodes but later also organs.

SCCs develop primarily on chronically UV-damaged skin, but can also occur on X-ray damaged skin. The chemical carcinogens arsenic and tar, as well as the human papillomaviruses HPV 16 and 18, also result in SCC.

Histopathological classification of SCCs

(in accordance with WHO 2006 Histological classification of keratinocytic skin tumours [164])

- Acantholytic squamous cell carcinoma,
- Spindle-cell squamous cell carcinoma,
- Verrucous squamous cell carcinoma,
- Pseudovascular squamous cell carcinoma,
- Adenosquamous squamous cell carcinoma,
- Bowen disease.

TNM classification of SCC and BCC after AJCC (2006) (excluding eyelids, penis, vulva) [166]

Table 5: T category of skin cancer

T category of skin cancer	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour \leq 2 cm in greatest dimension
T2	Tumour $>$ 2 cm, but \leq 5 cm, in greatest dimension
T3	Tumour $>$ 5 cm in greatest dimension
T4	Invasion of deep structures, i.e. cartilage, skeletal muscle or bone

In the case of multiple simultaneous carcinomas, the tumour with the highest tumour category is classified and the number of separate tumours is indicated in parentheses, e.g. T2 (5).

Table 6: N category of skin cancer

N category of skin carcinomas	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Table 7: M category of skin cancer

M category of distant metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis present
M1	Distant metastasis present

Table 8: Clinical stages of skin cancer

Clinical stages	T category	N category	M category
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

3.1.2.3. Malignant melanoma (MM)

MMs frequently present as brownish to reddish-blue, blackish or greyish-white, frequently asymmetrical skin changes. However, they can be completely pigment-free. MM occurs in a wide variety of different clinical manifestations and can be found on all areas of the human skin, hairy scalp, mucous membranes of the eye, mouth and genitals, as well as under the toenails and fingernails. They can also occur in all organs of ectodermal origin, such as the meninges, gallbladder, etc.

The different forms, the frequent asymmetry, which is not necessarily present, the different types of discolouration and secondary changes such as weeping and crust formation underline the extraordinary variety of this tumour in terms of its clinical presentation. Malignant melanoma has no defined precursor stage. The clinical diagnosis therefore also requires many years of experience, as there is an extraordinarily large number of possible differential diagnoses.

Depending on their growth pattern, four skin types are distinguished clinically.

- Lentigo malignant melanoma (LMM), the prerequisite for which is chronically UV-damaged skin and for this reason it also occurs in UV-damaged areas,
- superficial spreading melanoma (SSM),
- nodular melanoma (NM) and
- acral-lentiginous melanoma (ALM).

Because of its vertical tumour growth, MM very rapidly metastasises and is responsible for the highest mortality rate among skin cancers.

Histopathological classification of MM

(in accordance with WHO 2006 Histological classification of melanocytic tumours [164])

- Superficial spreading melanoma,
- Nodular melanoma,
- Lentigo malignant melanoma,
- Acral-lentiginous melanoma,
- Desmoplastic melanoma,
- Malignant blue naevus,
- Melanoma on large congenital naevus,
- Naevoid melanoma,
- Spitzoid melanoma,
- Persistent melanoma.

A “final” TNM classification and staging of malignant melanoma was proposed by the AJCC in 2009 (see Table 5 to Table 8) and now forms the basis for the classification of malignant melanoma [167].

Table 9: T category of primary tumour in MM

T category	Tumour thickness	Other prognostic parameters
Tis	Melanoma in situ, no tumour invasion	Tis
Tx	No data	Stage not assessable *
T1	< = 1.0 mm	a: without ulceration, mitotic rate < 1/mm ² # b: with ulceration or mitotic rate ≥ 1/mm ²
T2	1.01-2.0 mm	a: without ulceration b: with ulceration
T3	2.01-4.0 mm	a: without ulceration b: with ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration

* Tumour thickness and/or ulceration not determined or unknown primary tumour

The mitotic rate is determined in the HE section. Source: WHO Classifications of Tumours, Pathology & Genetics, Skin Tumours

Table 10: N category of regional lymph nodes in MM

N category	Number of metastatic lymph nodes (LN)	Extent of lymph node metastases
N1	1 LN	a: micrometastasis/es only (clinically occult) + b: macrometastasis/es only (clinically detectable)
N2	2-3 LN	a: nodal micrometastasis/es only + b: nodal macrometastasis/es only c: Satellite(s) or in-transit metastasis/es without metastatic regional lymph nodes
N3	> 4 LN, or matted lymph nodes or satellites or in-transit metastases with metastatic regional lymph nodes	

+ in the new AJCC classification, the detection of micrometastases is now also the discovery of an individual cell with a positive immunohistochemical response. These cases should be characterised additionally. Source: WHO Classifications of Tumours, Pathology & Genetics, Skin Tumours

Table 11: M category of distant metastases in MM

M category	Type of distant metastasis	LDH
M1a	Metastases to skin, subcutis or lymph nodes beyond the regional lymph nodes	Normal
M1b	Pulmonary metastasis/es	Normal
M1c	Distant metastasis/es at other site or Distant metastasis/es at any site with elevated serum lactate dehydrogenase (LDH) levels	Normal Elevated

The M1a category also includes the iliac lymph nodes. Source: WHO Classifications of Tumours, Pathology & Genetics, Skin Tumours

Table 12: Staging of MM

Stage	Primary tumour (pT)	Regional lymph node metastases (N)	Distant metastases (M)
0	In-situ tumours	None	None
IA	< 1.0 mm, no ulceration	None	None
IB	< 1.0 mm with ulceration or mitotic rate/mm ² ≥ 1	None	None
	1.01–2.0 mm, no ulceration	None	None
IIA	1.01–2.0 mm with ulceration	None	None
	2.01–4.0 mm, no ulceration	None	None
IIB	2.01–4.0 mm with ulceration	None	None
	> 4.0 mm, no ulceration	None	None
IIC	> 4.0 mm with ulceration	None	None
IIIA	Any tumour thickness, no ulceration	Micrometastases (clinically occult) in up to 3 lymph nodes	None
IIIB	Any tumour thickness with ulceration	Micrometastases (clinically occult) in up to 3 lymph nodes Up to three nodal macrometastases	None
	Any tumour thickness, no ulceration	None, but satellite and/ or in-transit metastases	None
	Any tumour thickness, no ulceration		None
IIIC	Any tumour thickness with ulceration	Up to three nodal macrometastases or satellite(s) or in-transit metastasis/es without metastatic regional lymph nodes	None
	Any tumour thickness ± ulceration	Four or more nodal macrometastases or matted lymph nodes or satellites and/or in-transit metastases with metastatic regional lymph nodes	None
IV			Distant metastases

Source: WHO Classifications of Tumours, Pathology & Genetics, Skin Tumours

3.2. Incidence and prevalence of skin cancer

A. Waldmann

In principle, it is possible to make population-based statements about disease incidence and disease burden on the basis of data from the epidemiological cancer registries. Only recently all new cancer cases in Germany have been extensively recorded, with some federal states having a long tradition of registration (like Hamburg, Saarland and the federal states of Eastern Germany) and others having only operated cancer registries for a few years (Baden-Württemberg, Hessen). International experience shows that it takes several years for cancer registration to become established and for complete data to be expected. Consequently, there are regional differences in the predictive value of cancer registry data. This applies both to nationally and internationally available data. These differences are due, among other reasons, to different regulations governing reporting (obligation of reporting, right of reporting, extensive coverage, recording of model regions, recording of primary tumours with/without recording of metastases and relapses), the differing degrees of completeness of the reports and, not least, the quality of the reports (e.g. proportion of missing data on tumour size).

As far as the epidemiological cancer registries in Germany are concerned – and also most international cancer registries –, it may be remarked that the recording of malignant melanoma (MM) can currently be regarded as good (systematic, high degree of completeness), whereas non-melanocytic skin tumours (basal cell carcinomas (BCC), squamous cell carcinomas (SCC)) are not systematically recorded in all federal states. As the epidemiological cancer registries are incidence registries, only new cases are recorded. If the disease burden is to be estimated from cancer registries, the problem arises in the case of non-melanocytic skin cancer (NMSC) types that multiple metachromatic tumours with the same histology or recurrences occur frequently (multiple BCCs occur in about 15% of patients, multiple SCCs in about 10%; [168]), but are not registered. However, these constitute a major burden for the patients and the health system.

3.2.1. Malignant melanoma (MM)

In Germany, population-based cancer registration is undertaken at the federal state level. On the basis of these data, estimates of the incidence in Germany are published by the Society for Epidemiological Cancer Registries and the Centre for Cancer Registry Data at the Robert Koch Institute. Currently, approx. 18,000 people in Germany develop an invasive MM, 51.5% of whom are male (Table 13) [169]. In men, MM is the eighth most common new cancer and in women the fourth most common [170]. The disease incidence increases with age. Young women develop MM more often than young men. This ratio and the very high incidence at a young age compared with other tumours are unusual. From the age of 60 years, the ratio is inverted and the incidence in men increases to twice that in women [169]. An almost continuous increase in incidence has occurred over the course of the last 30 years, with a tripling of the incidence from about 5 to around 15 cases per 100,000 inhabitants [169]. With the introduction of skin cancer screening in 2008, the incidence has increased further and more markedly than before [169].

Survival after MM has improved markedly in the last 20 years and is high compared to other forms of cancer [171]. The relative 5-year survival of all melanoma patients is

currently estimated to be 80% (Table 13). In contrast to the increasing incidence, the age-standardised mortality has remained at a consistently low level over the past 30 years. Currently, about 2,700 people in Germany die each year from melanoma, 57.8% of whom are men (Table 13) [172]. One of the main reasons for the consistently low mortality despite the increasing incidence is probably the improved early detection of melanomas with good prognosis. In Schleswig-Holstein, a decline in melanoma mortality was observed following the pilot study (SCREEN) for skin cancer screening [173]. Future monitoring of the national data for Germany will provide an indication as to whether this effect will also occur following the introduction of national skin cancer screening.

It is assumed that in 2004 there were about 58,500 people living in Germany who had developed MM in the past five years. As a result of the increasing incidence with a comparatively unchanged mortality, it may be assumed that the 5-year prevalence will rise in the future. For 2010, it has already been estimated to reach 65,500 people (Table 13) [174].

Compared internationally, Germany, together with other European countries, the USA and Australia, is among those countries with the highest melanoma incidence [175]. Within Europe, Germany is in the upper third of countries in terms of the incidence and prevalence of melanoma (see Figure 4) [175, 176]. However, mortality in Germany is lower than in most other European countries (see Figure 5) and lower than in the USA and Australia/New Zealand [175].

Table 13: Current key indicators for MM in Germany

Key indicators	Men	Women
Incidence 2009*		
New cases of disease	9,250	8,725
Age-standardised rate (European standard) per 100,000	17.4	16.0
Mortality 2010**		
Deaths	1,568	1,143
Age-standardised rate (European standard) per 100,000	2.8	1.6
Relative 5-year survival***		
Total	83.1%	91.7%
pT1	99.7	100.0
pT2	83.7	97.7
pT3	67.8	86.1
pT4	47.8	67.7
Prevalence****		
Absolute frequency 2004	24,300	34,200
Absolute frequency 2010 (predicted)	27,600	37,900
Data sources: * [169] ** [172] *** [171] **** [174]		

Whereas an increased incidence has been observed in Germany in the past 30 years, various studies have been published in the last 10 years that describe either a slight regression or stabilisation of incidence. In a worldwide analysis of the incidence of melanoma, Erdmann et al. (2012) showed that the incidence is continuing to rise in most European countries, whereas a stabilisation of the incidence is apparent in Australia, New Zealand, the USA and Canada, as well as in Israel and Norway. This can be explained primarily by declining or stabilised incidences in the 25- to 44-year-old age group [177].

The sex-specific differences and the time-related incidence and mortality trends in Germany for the most part reflect the differences and trends found in other industrialised countries. One feature stands out for Australia and New Zealand, however: here, MM is the third most common new cancer [178] and the eighth most common cancer-related cause of death [175]. The incidence has increased in the last few years (men: twofold increase from 27 cases (1982) to 57 cases per 100,000 inhabitants (2004; age-standardised to the Australian population); women: 1.5-fold

increase from 26 to 38 cases per 100,000) [178] – with a plateauing of the increase in the last ten years [177]. For melanoma mortality, a comparatively weak increasing trend has been seen in the last 26 years [178]. Differentiated by age, a slight regression in mortality was observed for persons < 55 years, stable rates for subjects aged 55-79 years and an increase in melanoma mortality for subjects over 80 years of age up to the year 2002 [179].

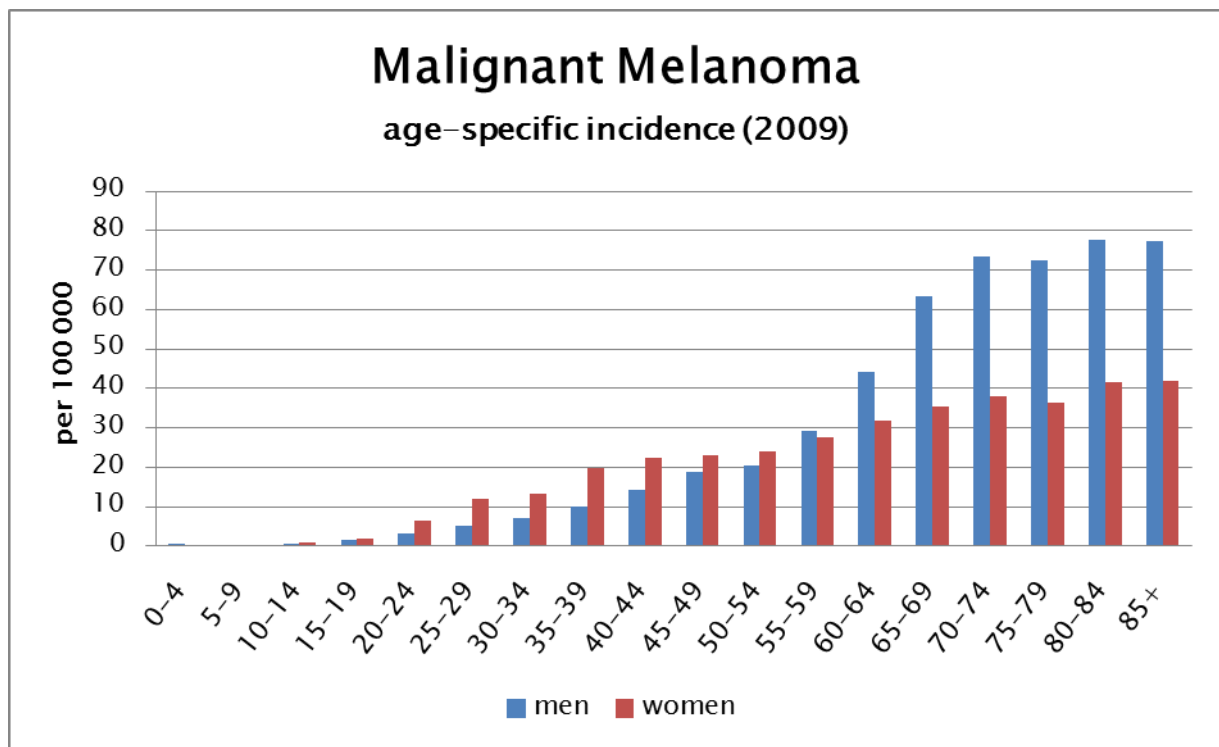


Figure 2: Age-specific melanoma incidence rates in 2009 differentiated by sex

Source: German Society of Epidemiological Cancer Registries

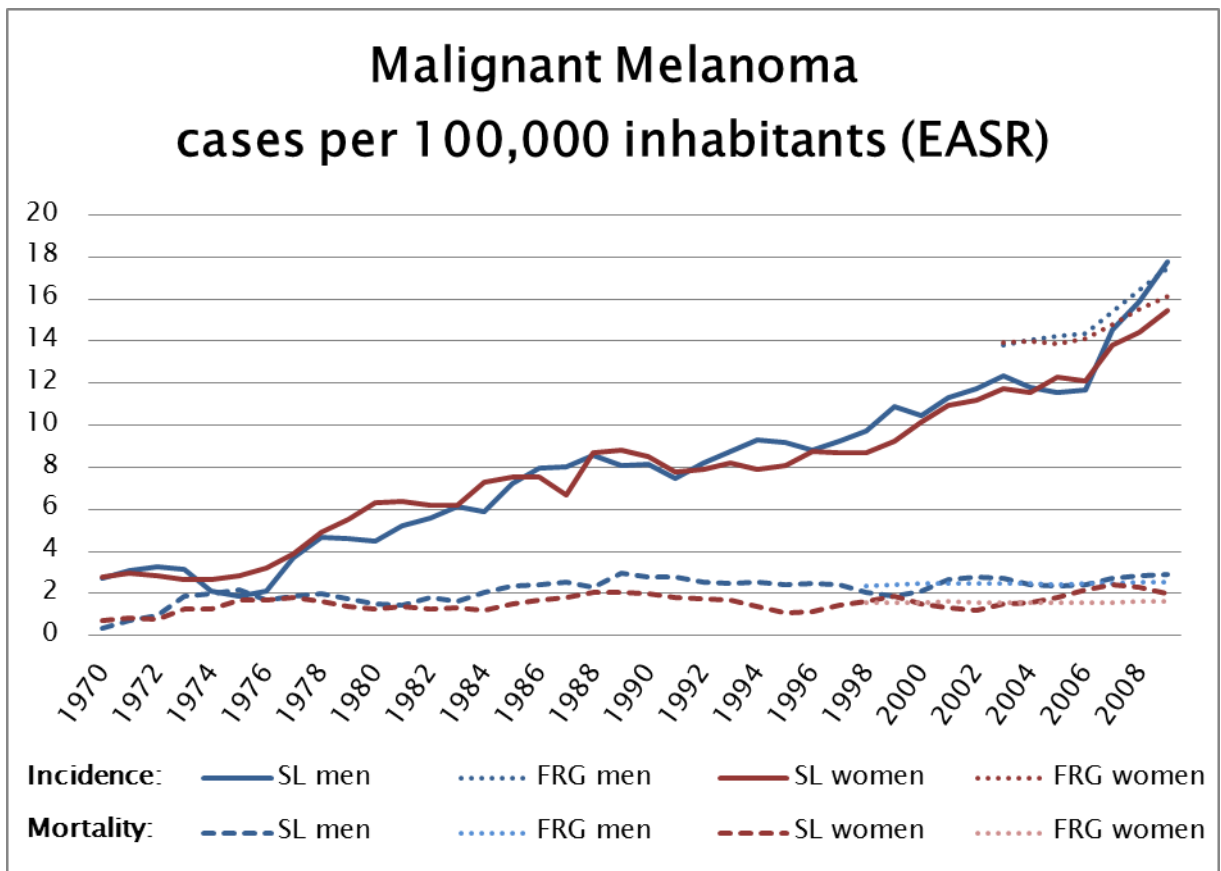


Figure 3: Time course of incidence rates in Saarland and Germany)

(smoothed; 3-year floating means; European standard; SL=Saarland, FRG =Germany)

Source: [169, 180]

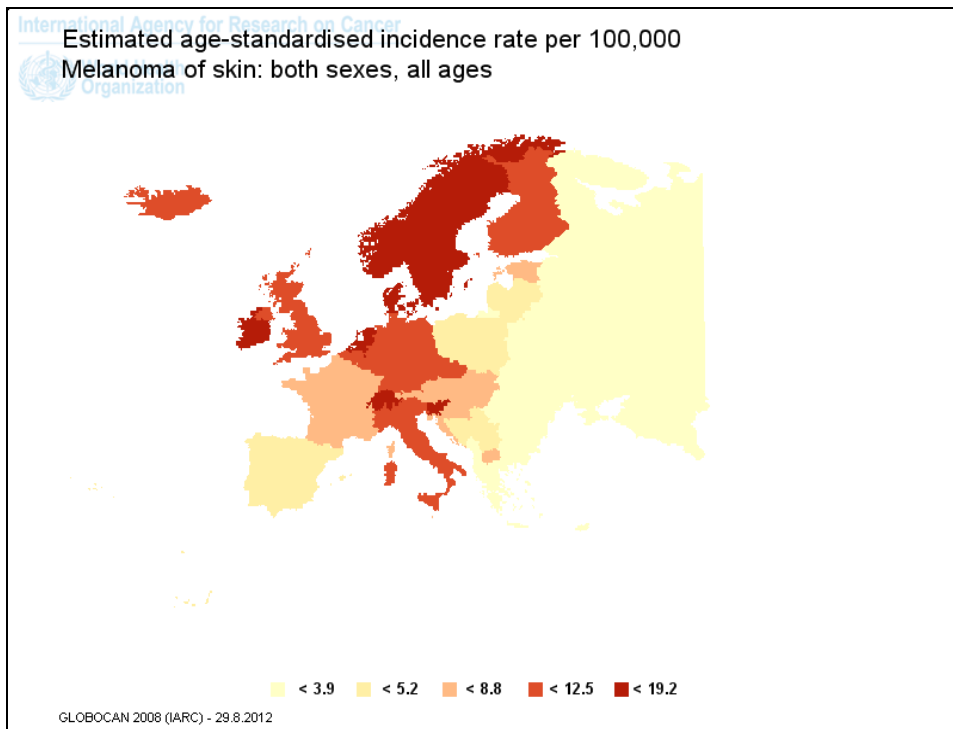


Figure 4: Age-standardised melanoma incidence in Europe in 2008 (world standard)

Source: [181]

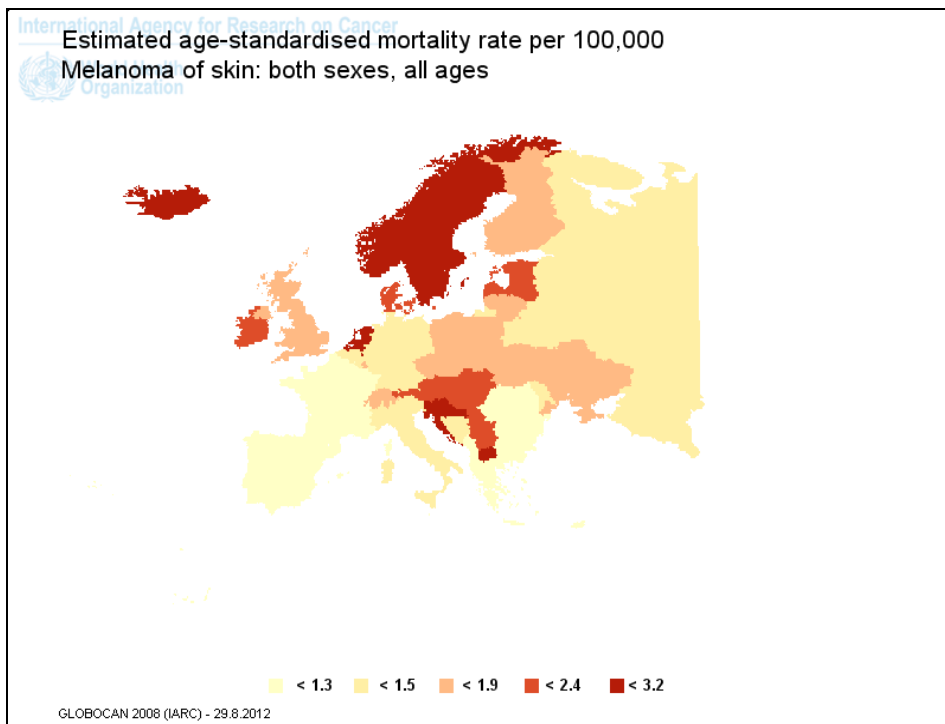


Figure 5: Age-standardised melanoma mortality in Europe in 2008 (world standard)

Source: [182]

Need for further research

Monitoring of stage-specific incidences in Germany (and worldwide) could provide conclusions as to whether the procedure of early detection/screening of skin cancer by whole body examination results in an increase in the early stages and a decrease in the late stages of melanoma. This requires reducing the currently high proportion of missing tumour stages in cancer registry reports and, where possible, recording information on tumour stage for all melanomas. Five to ten years after the introduction of skin cancer screening in Germany, the monitoring of melanoma mortality could provide an answer as to whether early detection leads to a reduction in mortality.

3.2.2. Non-melanocytic skin cancer (NMSC)

With nearly 119,000 new cases registered annually, NMSC occurs 6.5 times more frequently in Germany than MM [169]. The actual number, however, is probably higher because of under-registration [183]. Approximately 53.3% of all patients are men (Table 14). Among men, the estimated number of new cases is roughly the same as the incidence of prostate carcinoma (107.8/100,000 EASR; 2009), which is the most common cancer in men. The estimated incidence of NMSCs in women is between the incidence of the most common tumour (breast cancer; 123.8/100,000; EASR, 2009) and that of the tumour generally mentioned as the second most common (bowel cancer; 38.0/100,000; EASR; 2009). The disease incidence increases with age. In men aged 60 and over, the incidence increases more markedly than in women. In the group aged 85 years and over, the incidence in men is twice as high as in women (Figure 6) [169]. Over the course of the last 30 years, a fourfold (men) to fivefold (women) increase in incidence has been seen (Figure 6) [170, 180]. Mortality, however, has remained at a constant very low level over the last 30 years (Figure 7). At present, fewer than 650 people die from an NMSC in Germany annually; of these, 55.7% are men (Table 14) [172].

Table 14: Current key indicators for non-melanocytic skin tumours in Germany

Key indicators	Men	Women
Incidence 2009*		
New cases	63,543	55,655
Age-standardised rate (European standard) per 100,000	108.2	77.8
Mortality 2010**		
Deaths	346	275
Age-standardised rate (European standard) per 100,000	0.6	0.3

Data sources:

* [169]

** [172]

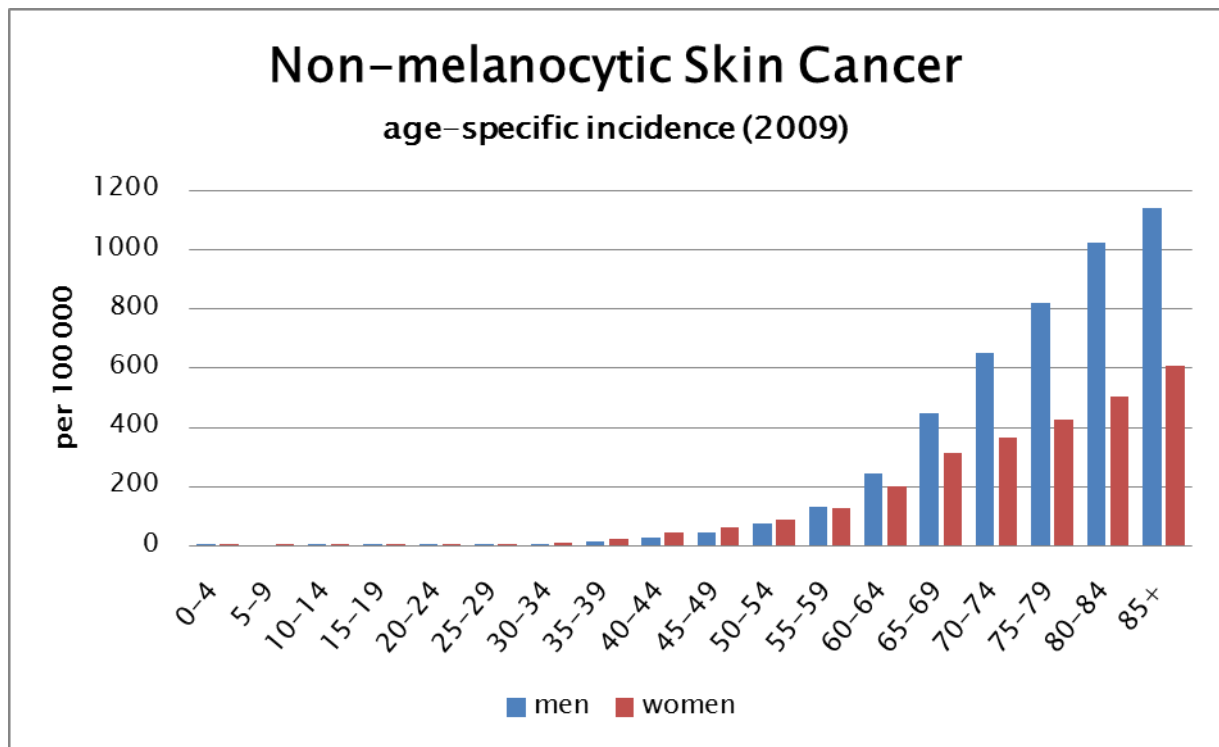


Figure 6: Age-specific incidence rates of NMSC in 2009 differentiated by sex

Source: Society of Epidemiological Cancer Registries

Unlike MM, there is a lack of data for types of NMSC. Comparative international data on incidence and mortality are frequently obtained from studies or model regions and only rarely from epidemiological cancer registries. For New Hampshire, USA, an increase in the incidence of BCCs in men of 235% and in women of 350% was observed from 1979/1980 to 1993/1994, as well as an increase of 82% in the incidence of SCCs [168]. For younger Americans (i.e. < 40 years) also, a twofold increase in the incidence of non-melanocytic skin tumours was found for the period 1976-2003 [184]. Canadian cancer registry data [185] and comparative data from Scotland [186] and Great Britain [187] also confirm the sex-specific differences and time-related incidence trends reported for Germany.

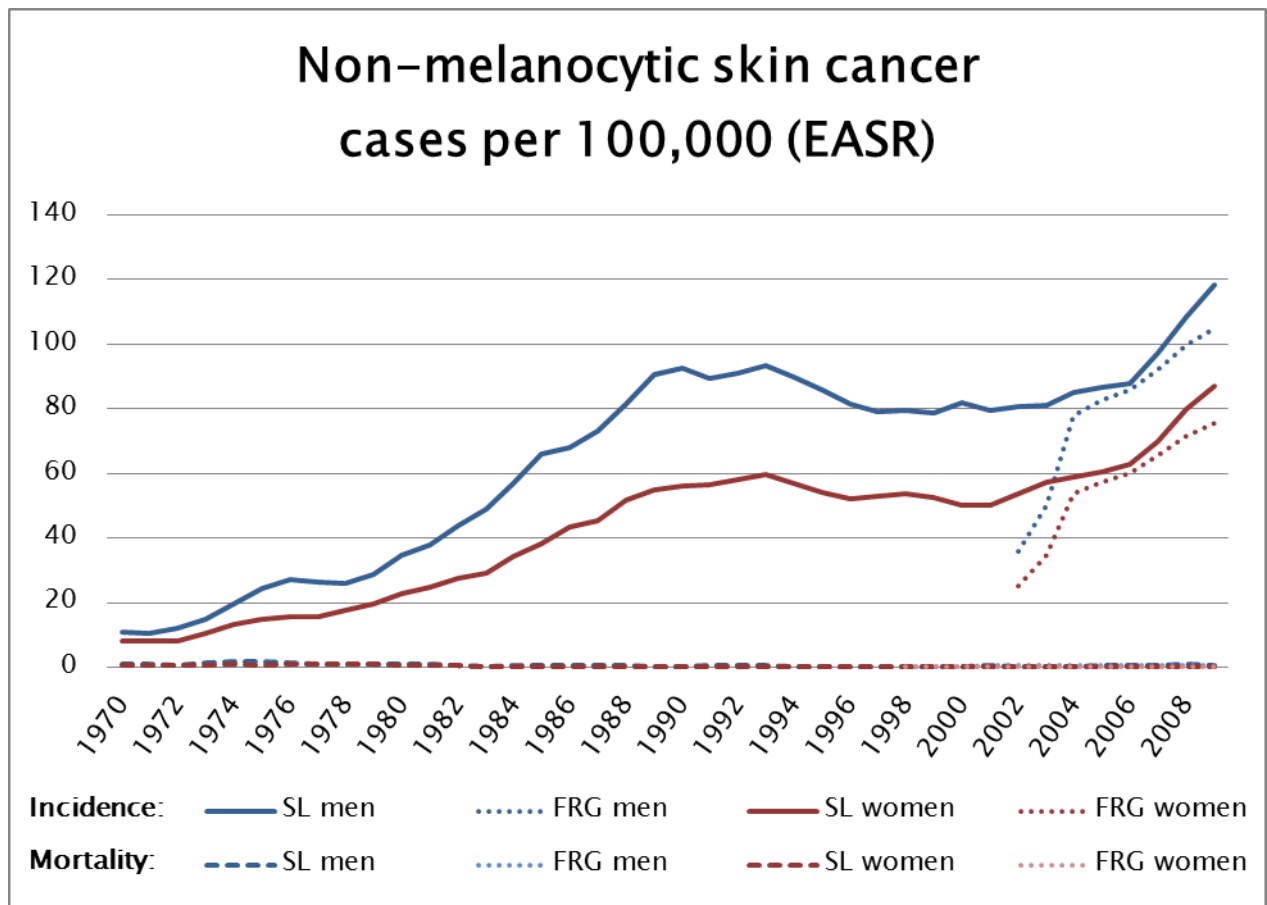


Figure 7: Time course of incidence rates in Saarland and Germany

(smoothed; 3-year floating means; European standard; SL=Saarland, FRG =Germany)

Source: [169, 180]

Need for further research

Compared with data for melanoma, the database for types of NMSC may be described as defective. In order to be able to describe definite epidemiological trends in future, stricter reporting of all incident types of NMSC to epidemiological cancer registries will be required.

3.2.3. Effects of skin cancer screening on incidence

On the basis of data from the epidemiological cancer registries, chronological trends for new cancers can be described at the population level. A precondition for a valid description of the cancer process is a high degree of completeness of reporting to the registry, i.e. (where possible) all newly occurring cancers are reported to the register, as well as (where possible) complete data for a description of the tumour, such as histology, morphology and tumour spread. In national health reporting, for the most part only invasive new diseases are described, whereas the epidemiological cancer registries in some cases also contain data on in-situ tumours. Some cancer registries are therefore able to describe the incidence of in-situ as well as of invasive tumours.

During the period 7/2003 to 6/2004, the SCREEN project was carried out in Schleswig-Holstein [2]. This was a pilot study for the skin cancer screening introduced throughout Germany in 2008. The effects of skin cancer screening on the population-based incidence were investigated on the basis of data from the cancer registries of Schleswig-Holstein and Saarland (comparator region). Saarland served as a comparator region, since no population-based skin cancer screening was being undertaken during the SCREEN period.

It can be seen from Table 15 that in Schleswig-Holstein both incidence of in-situ melanomas and invasive melanomas was substantially higher during the SCREEN period than in the period before the pilot study (1998-2000), whereas incidence in Saarland increased only slightly over the course of time. Following the end of the pilot study (2005-2007), a slight regression was seen in the incidence of in-situ melanomas and a marked regression in the incidence of invasive melanomas in Schleswig-Holstein, compared with only slight changes in Saarland over the same period [188].

Table 15: Age-standardised incidence rates of MM

	Schleswig-Holstein (SH)		Saarland (SL)		p value (comparison of SH and SL)	
	women	men	women	men	women	men
	Incidence rate, age-standardised (European standard)					
Before SCREEN project (01/1998-12/2000)						
MM (in situ) (ICD-10 D03)	5.7 (5.0; 6.4)	3.7 (3.2; 4.3)	2.4 (1.8; 3.2)	1.0 (0.6; 1.6)	<0.001	<0.001
MM (invasive) (ICD-10 C43)	16.8 (15.7; 18.0)	15.2 (14.1; 16.4)	9.2 (7.8; 10.6)	10.7 (9.3; 12.4)	<0.001	<0.001
SCREEN project (07/2003-06/2004)						
MM (in situ) (ICD-10 D03)	13.3 (11.5; 15.2)	7.7 (6.4; 9.2)	3.5 (2.1; 5.3)	3.1 (1.8; 4.8)	<0.001	<0.001
MM (invasive) (ICD-10 C43)	25.7 (23.2; 28.3)	19.2 (17.2; 21.5)	10.9 (8.4; 13.8)	11.8 (9.2; 14.9)	<0.001	0.003
After SCREEN project before NSCS² (01/2005-12/2007)						
MM (in situ) (ICD-10 D03)	10.4 (9.5; 11.4)	6.6 (5.9; 7.3)	4.0 (3.1; 5.0)	3.6 (2.8; 4.6)	<0.001	<0.001
MM (invasive) (ICD-10 C43)	15.1 (14.0; 16.2)	15.1 (14.1; 16.3)	12.2 (10.6; 13.9)	11.5 (10.0; 13.1)	0.044	0.002
	Absolute differences in incidence rates, age-standardised (European standard) [observed incidence - previous incidence as described above]					
SCREEN project						
MM (in situ) (ICD-10 D03)	7.6 (5.6; 9.6)	4.0 (2.5; 5.5)	1.1 (-0.5; 2.7)	2.1 (0.6; 3.6)	<0.001	0.164
MM (invasive) (ICD-10 C43)	8.9 (6.1; 11.7)	4.0 (1.6; 6.4)	1.7 (-1.3; 4.7)	1.1 (-2.0; 4.2)	0.005	0.373
After SCREEN / before NSCS						
MM (in situ) (ICD-10 D03)	-2.9 (-5.0; -0.8)	-1.1 (-2.7; 0.5)	0.5 (-1.2; 2.2)	0.5 (-1.2; 2.2)	0.019	0.264
MM (invasive) (ICD-10 C43)	-10.6 (-13.3; -7.9)	-4.1 (-6.5; -1.7)	1.3 (-1.8; 4.4)	-0.3 (-3.4; 2.8)	<0.001	0.252

¹ Poisson-based 95% confidence interval (CI).² National Skin Cancer Screening

The data from Schleswig-Holstein are compared with the estimates for Germany in Figure 8 and Figure 9.

In Schleswig-Holstein, the incidence of both invasive malignant melanoma (Figure 8) and invasive NMSC (Figure 9) increased from the start of SCREEN, whereas in Germany as a whole no peak incidence can be seen for the years 2003 and 2004. The increase is less pronounced among men than women, who showed a greater willingness to participate than women [188]. Following the end of the pilot study, the incidence in Schleswig-Holstein fell back as anticipated.

With the start of national skin cancer screening in 2008, the incidence of both tumour groups increased in both men and women in Germany (Figure 8 and Figure 9). These increases were most pronounced among men.

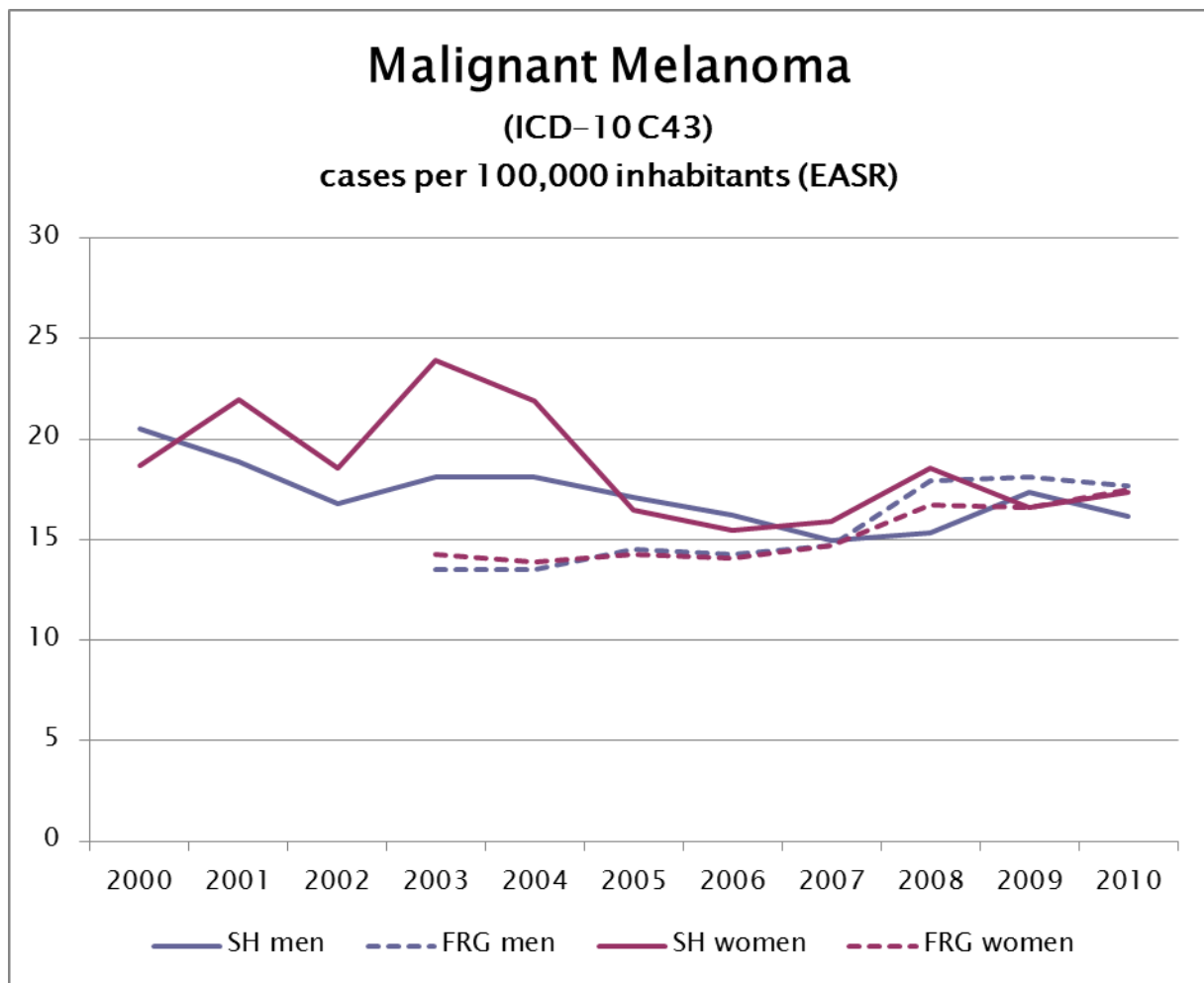


Figure 8: Time course of the incidence (EASR; European age-standardised rate) of MM in Schleswig-Holstein (unbroken line) and Germany (dotted line) [169]

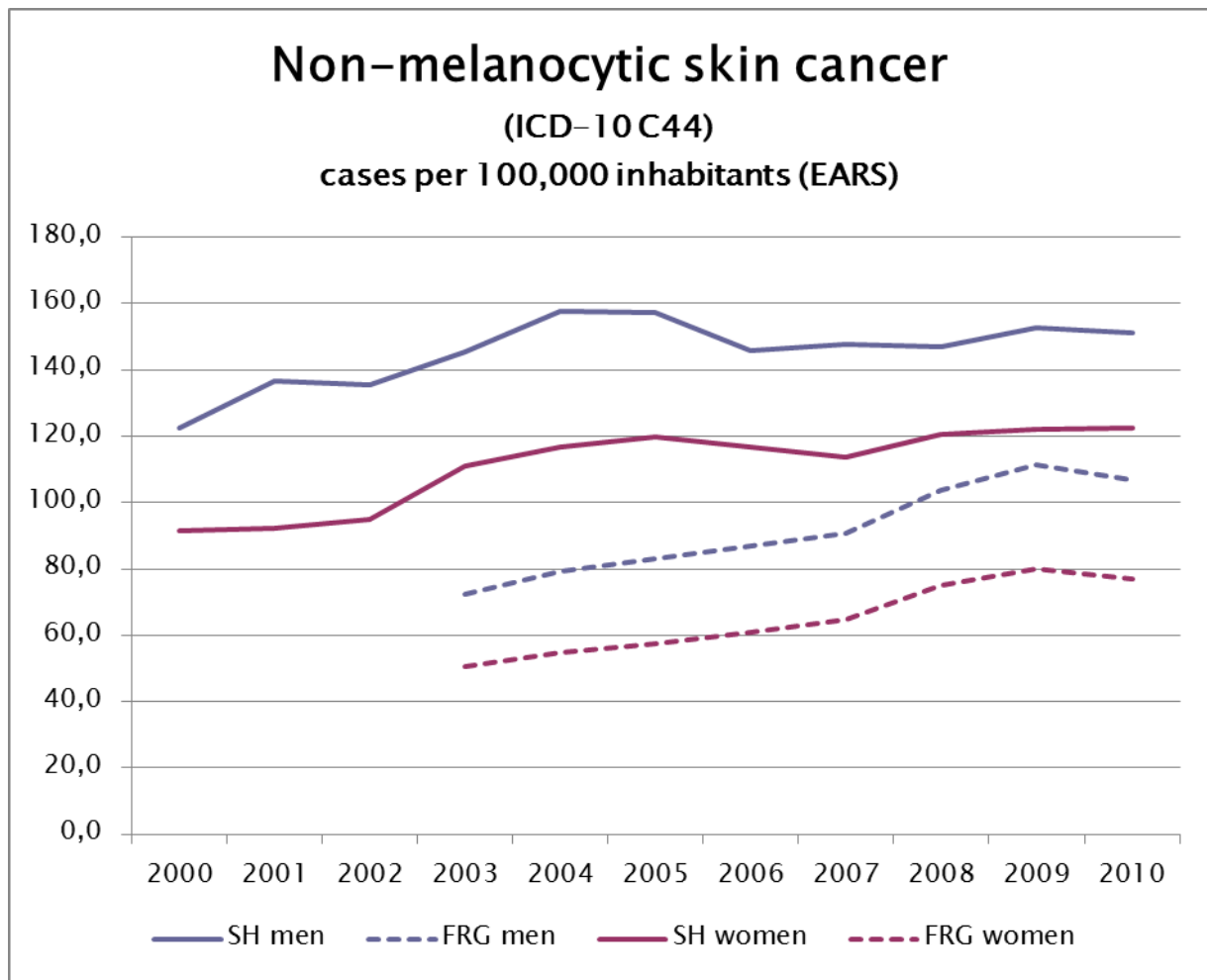


Figure 9: Time course of the incidence (EARS; European age-standardised rate) of NMSC in Schleswig-Holstein (unbroken line) and Germany (dotted line) [169]

Need for action: if skin cancer screening is to be studied for its effects on population-based incidence, then data from the epidemiological cancer registries are available for use. By analysing tumour stage-specific incidences, it can be determined whether skin cancer screening results in a reduction in incidence with a reduction in late tumour stages over the course of time, following the initially expected increase in incidence. This is regarded as a precondition for a subsequent reduction in mortality. Regular reporting of in-situ tumours would also be desirable in order to be able to estimate the existence and the extent of overdiagnoses on the basis of cancer registry data.

To generate valid estimates and hence to be able to draw reliable conclusions, cancer registries are dependent on prompt, complete and full reporting of tumour data, such as histology, morphology and tumour stages, by the diagnosing and treating physicians and pathologists.

3.3. The individual, social and economic burden of skin cancer

K. Beifus, J. Köberlein-Neu

3.3.1. Introduction

The limited financial resources of the healthcare system require an efficient distribution of the available means. Opportunities for rationalisation must be utilised to resolve problems of efficiency and to distribute medical services fairly on the basis of criteria of optimum quality. Resource allocation decisions of this nature should be taken on the basis of health economics. This is described as a science halfway between economics and medicine that uses various methods and analytical models so as to be able to offer a cost- and, above all, a benefit-oriented decision-making tool.

In the context of this guideline, the disease burden of skin cancer should be assessed from a health economic perspective. This requires a description of firstly, where the disease burden arises and secondly, whom it affects. The variety of players in the healthcare system involved in the treatment of a case shows how many perspectives can be included in health economic considerations. Each of the perspectives describes its own disease burden or its benefit. In order to define standard designations that can be applied to each player in a differentiated fashion, health economics divides costs into different types. A distinction is drawn between direct costs, indirect costs and intangible costs (effects).

Direct costs cover the utilisation of resources incurred for medical interventions in a treatment case and directly related to the disease itself. Indirect costs describe expenditure that occurs as a result of a disease. These involve costs due to productivity losses as a result of temporary or permanent incapacity for work, employment losses and mortality. As well as cost factors, intangible effects are included that are difficult to quantify in monetary terms. Effects describe the repercussions of the disease on the patients' quality of life. They can also be defined in a very large variety of different ways.

Health economics seeks ways on the one hand of reducing financial expenses and on the other of developing benefit factors, such as quality of life. Prevention represents a step in this direction. Preventive measures serve to prevent diseases (primary prevention) or can reduce the effects of existing diseases (secondary prevention). The intention is to influence morbidity and mortality in individuals and also in the population as a whole [189].

Within the context of the evidence-based guideline "Prevention of skin cancer", this section will examine the health economic potential of measures in the area of primary and secondary skin cancer prevention on the basis of the three main skin cancer entities, MM, BCC and SCC. In order to be able to assess the disease burden of skin cancer and its tumour stages from a health economic perspective, it is first necessary to describe out of what the disease burden arises and whom it affects. Subsequently, in order to elicit the health economic potential of skin cancer prevention measures, the potential costs savings are estimated in relation to cases of disease avoided and deteriorations prevented; savings that may be expected primarily from a stage shift

towards non-invasive or less invasive tumours due to early detection of skin cancer. The subsequent section of this guideline will examine the amount of costs that can be avoided if preventive measures are implemented or successfully carried out.

3.3.2. Malignant melanoma (MM)

3.3.2.1. Direct costs

In connection with the further development of the German Early Detection of Cancer Programme, the Association of Dermatological Prevention (ADP) undertook a pilot study (SCREEN) in the northernmost federal state of Germany, Schleswig-Holstein, in 2003/4 [2]. This involved a partial disease cost analysis of the direct costs for MM, BCC and SCC (www.g-ba.de/downloads/40-268-580/2008-03-31-Abschluss-Hautkrebscreening.pdf). On the basis of data from the corresponding cancer registry from 2002, extrapolations were applied to the whole of the national territory to estimate the incidence of these three skin cancer entities in Germany. Outpatient and inpatient measures were also included in the assessment. With the aid of the accounting data from the Schleswig-Holstein Association of Statutory Health Insurance Physicians (2nd quarter, 2003), the figures were extrapolated to the whole of the national territory in order to calculate care provision in the outpatient panel doctor sector. Costs of other medical care structures were also determined. The bottom-up assessment undertaken in the disease cost analysis comprises the following data material [190]:

- Treatment pathways consistent with clinical practice and guidelines,
- Incidence data from extrapolations from the corresponding cancer registry,
- The distribution of BCC between outpatient and inpatient management was taken from clinical practice or from the literature,
- Outpatient costs were calculated on the basis of the Uniform Rating Standard (URS) of the National Association of Statutory Health Insurance Physicians (individual services were multiplied by a point value of 0.046 cents),
- Drug costs were taken from the Rote Liste (schedule of all medications) 2004,
- Inpatient costs correspond to reimbursement in accordance with the German diagnosis-related groups (G-DRG) system 2004; costs of the individual case examples were determined by means of Webgrouper and the basic case value was €2,900. Multiple morbidity was not included in the considerations,
- Transport costs for histology and laboratory tests, as well as doctor's letters, reports to the cancer registry or travel costs for surgery, etc., were not quantified,
- The timeframe for observation was one year; it was assessed using an incidence-based approach.

The procedure described was applied for MM, BCC and SCC. To calculate the disease costs caused by MM, the incidences of each stage obtained from extrapolations from the Schleswig-Holstein Cancer Registry were used (see number of cases in Table 16).

As previously described, the treatment options were quantified in cost terms on the basis of the URS, accounting data from the National Association of Statutory Health Insurance Physicians and price information from the Rote Liste.

Table 16: Costs of treatment options for MM

	Minimum costs	Sensitivity	Maximum costs	Average costs
	€	%	€ (rounded)	
Detection and 1st treatment:				
Consultation	15.00	100%	30.00	25.00
Intensive medical counselling	13.80	100%	27.60	21.00
Local anaesthesia	6.90			10.00
Excision biopsy	7.36	338%	32.21	20.00
Histopathological diagnosis	92.23			95.00
Lump-sum payment	7.71	63%	12.19	10.00
Outpatient treatment:				
Local anaesthesia	6.90			10.00
Re-excision with safety margin	32.21			32.00
Histopathological diagnosis	92.23			95.00
Supplement outpatient surgery	18.40	100%	36.80	28.00
Follow-up treatment	1.97	16%	2.30	2.00
Outpatient staging:				
Lymph node ultrasound	9.20			10.00
Upper abdominal ultrasound	13.80			14.00
Chest X-ray in 2 planes	20.70			20.00
CT chest	134.00			135.00
CT abdomen	151.00			150.00
Bone scan	92.00	100%	184.00	138.00
Magnetic resonance imaging	256.00			256.00
Inpatient treatment:				
Re-excision with safety margin	2,485.30			2,490.00
Two-stage (with transplant)	4,970.60			5,000.00
One-stage with SLN biopsy	3,572.80			3,600.00
Two-stage	6,058.10			6,100.00
One-stage and lymphadenectomy	6,174.10			6,200.00
Two-stage	8,659.40			8,700.00
Outpatient follow-up treatment:				
Immunotherapy low-dose	1,4349.06	14%	16,357.93	15,400.00
Immunotherapy high-dose	34,065.95	14%	38,835.18	36,400.00

Infusion cytostatics at least 10 min.	5.14	16%	5.98	6.00
Infusion cytostatics > 90 min.	17.40	16%	20.24	19.00
Oncology	25.56	100%	51.13	38.00
Oncology continuing care	41.41			42.00
Visit	18.40	100%	27.60	23.00
Radiotherapy				
Consultations	1.97	16%	2.30	2.00
<i>Hyperthermia:</i>				
Doctor-patient contact and planning	427.80			430.00
Heat and irradiation	959.10	32%	681.00	810.00
Lymph drainage	6.90			7.00
Drugs:				
Analgesics	1.80		21.00	11.50
Psychotropics (N3 pack size)	13.60		55.21	35.00
Sedatives (N2 pack size)	12.42		13.44	13.00
Drugs for cognitive disorders	197.19			200.00
Outpatient chemotherapy:				
Monotherapy	1,207.98	10%	1,220.05	1,215.00
Polychemotherapy	4,222.35	10%	4,264.57	4,250.00
Follow-up:				
<i>Physical examination:</i>				
Lump-sum payment	7.71	63%	12.19	10.00
Counselling	13.80	100%	27.60	21.00
Laboratory tests order	0.23			0.25
Protein S 100 (laboratory)	29.10			29.00
Lymph node ultrasound	9.20			10.00
Upper abdominal ultrasound	13.80			15.00
Chest X-ray in 2 planes	20.70			20.00
Bone scan	92.00	100%	184.00	138.00
Magnetic resonance imaging	256.00			260.00

Source: [190]

The determining factor for the treatment options is the staging after excision of the first tumour.

The annual direct costs of all new cases of MM were about €132 million per year. The costs per case amounted to an average €720 for stage 0, €1,760 for stage I,

€14,420 for stage II, €43,450 for stage III and €38,910 for stage IV. The highest costs here were caused by palliative treatment approaches and treatments with interferon and surgical measures. For the annual follow-up costs, an average of €5,280 was calculated, excluding stage IV patients. The follow-up costs of the first year were quantified as €130 per case.

Table 17: Direct costs of MM

Stage	Number of cases	Costs per case (€)	Cost per year(€)
Melanoma in situ	6,595	720	4,757,300
Stage I	10,987	1,760	19,321,600
Stage II	2,816	14,420	40,609,200
Stage III	1,231	43,450	53,486,300
Stage IV	354	38,910	13,774,500
Total incidence and costs	21,983		131,948,900
Costs 1st year after tumour excision	2,816		14,872,700
5% discount	2,816		14,129,065
3% discount	2,816		14,426,519
Follow-up costs	21,983		2,881,800
5% discount	21,983		2,737,700
3% discount	21,983		2,795,300
Source: [190]			

The inpatient costs of MM were described in the study by Stang et al. (2008) [191]. Inpatient stays including all treatment procedures were evaluated using three assessment methods. In the first method, the G-DRG calculation for 2003 of 148 voluntarily participating hospitals was analysed. This yielded a proportional cost of €2,624.91 for melanoma in situ (D03) and €2,885.05 for malignant melanoma (C43) as a weighted mean per hospitalisation during the year. In the second procedure, the mean hospital day rate for skin tumours of €363 (according to the German Federal Statistical Office) was adopted. With the third method, costs per hospitalisation were determined on the basis of health insurance data from the Company Health Insurance Funds of €1,889 (men) and €2,394 (women) for MM in situ and €2,376 (men) and

€2,474 (women) for MM. From these data, the authors calculated annual hospital costs of €50-60 million for MM.

A total of 153,001 days of hospitalisation for MM were counted in 2003.

Table 18: Costs of hospitalisation with MM

Diagnosis/Method	Malignant melanoma (C43)	Melanoma in situ (D03)
G-DRG calculation (per case)	€2,885.05	€2,624.91
Costs per hospital day	€363.00	€363.00
Data of the company health insurance funds (per case)		
Men	€2,376.00	€1,889.00
Women	€2,474.00	€2,394.00
Source: own presentation, modified after [191]		

3.3.2.2. Indirect costs

While diagnoses of other cancers and also those of other malignant skin tumours are frequently observed in elderly patients over 60 years of age, MM affects younger people to a greater extent. 49% of men and 52% of women with MM are under 60 years of age, according to estimates by the Robert-Koch Institute [192]. The cancer registry in Schleswig-Holstein reports a particularly high incidence in women aged between 30 and 50 years.

The indirect costs, as described in section 3.3.1, are defined by the productivity loss that arises and the early retirements that are brought about. Insufficient data in terms of indirect costs in the case of MM entail the need to make certain assumptions in order to be able to estimate the mean productivity loss resulting from this tumour entity. The figures on economically active people in Germany are taken from the analyses of the German Federal Statistical Office.

According to the Federal Statistical Office, employee wages and salaries in 2011 were €1,326.30 billion [193]. The number of occupationally active people in 12/2011 amounted to 41,495 million [194]. From these data, a figure of €87.57 can be calculated per working day lost (the calculation formula is explained in the guideline report).

The data on incapacity for work were taken from the calculations of the OVIS study (Oncological Care of Tumour Patients in Schleswig-Holstein) conducted by the cancer registry of Schleswig-Holstein [195]. This yields an average of 20.8 days' incapacity for work for male patients of all stages. For female patients, a figure of 35.6 days was calculated. On the assumption of this loss of productivity calculation, this gives rise to incapacity costs in men of €16,848,468 for an incidence rate of 9,250 cases in 2009. For female melanoma patients, productivity losses of €27,200,118 are incurred with an incidence of 8,725 cases [196].

Table 19: Days of incapacity for work due to MM

Sex	Stage	Mean	Standard deviation
Male	T1	25.9	38.6
	T2	15.4	14.6
	T3	25.6	16.9
	T4	26.3	29.5
	Tx	11.7	10.6
	Total	20.8	25.5
Female	T1	11.5	16.1
	T2	15.5	14.4
	T3	76.2	114.7
	T4	59.8	61.5
	Tx	40.3	89.5
	Total	35.6	74.0
Source:[195]			

Data on early retirement due to MM are available from the Federal Statistical Office for 2002. According to these data, 318 men and 268 women with a mean age of 50.8 and 48.0 years, respectively, took early retirement. In 2002, therefore, 9,060 occupationally active years were lost due to MM [197].

The mortality rate of MM in 2010 was 2,711 deaths annually [198]. It is assumed here that men on average lose five years of their further life expectancy and women three years [197].

3.3.2.3. Intangible effects/quality of life (QOL)

In the case of MM, 288 titles with abstracts were identified in the literature search using the keywords “malignant melanoma” and “quality of life”.

Full texts of a total of 14 articles from this search were read. Four articles did not meet the inclusion criteria or had to be excluded on the grounds of the previously defined criteria. Of the ten selected full texts, three articles involved systematic reviews of the QOL and psychological aspects in melanoma patients. Five articles described studies

determining the quality of life of patients by means of questionnaires. Two of the articles assessed the reliability and validity of a questionnaire within a study.

Beutel et al. (2009) [199] in their German-language publication undertook a purely systematic review of the literature on “psycho-oncological aspects, determination of the factors influencing the QOL and determination of the need for further psycho-oncological research” in the period 1990-2008. Most studies in this review emanate from the English-speaking world. Only a few studies from Germany were available. The methodological quality and comparability of the studies found was poor. From the point of view of content, it was possible to conclude that psychosocial features (disease management, social support) have a substantial effect on patients’ QOL, independently of tumour stage. Corroborating results were obtained with applied psychotherapy for MM patients.

A systematic review by Cornish et al. (2009) [200] on the health-related QOL showed that patients’ psychological characteristics (e.g. coping strength, positive attitude to life) affect the perceived QOL. In a third of patients with melanoma, a major disease burden in terms of emotional distress at the time of diagnosis and the impending treatment was found in the studies that were included.

Cashin et al. (2008) [201] in their systematic literature review discussed studies on both economic aspects and QOL in MM. Thirteen QOL studies were included in the review, which defined the QOL on the basis of various questionnaires or scales. The result showed that patients who faced up to their illness with less anger, resentment and suffering rated their QOL better than others and exhibited a greater probability of survival.

The study by Sigurdardottir et al. (1993) [202] describes the QOL of MM patients using various questionnaires to determine various dimensions of their personal mind-set. Using the QLQ-C36 (Quality of Life Questionnaire), it was possible to ask about and document symptoms such as dyspnoea, sleep disturbances, loss of appetite, constipation, diarrhoea, fever, hot flushes, etc. A further questionnaire in this study, known as the *Hospital Anxiety and Depression Scale*, documented anxiety states and depression in the MM patients questioned. Correlations were also demonstrated between symptoms.

Burdon-Jones et al. (2010) [203] undertook a survey in patients with MM and NMSC. The questionnaire used was the Skin Cancer Quality of Life questionnaire. In answering their questionnaires, MM patients described the gratitude and relief they felt, as well as a more positive attitude to life after treatment. Compared with NMSC patients, they also reported experiencing a stronger feeling of anxiety, depression, guilt and stress towards themselves and their relatives or friends. Patients with NMSC, however, complained of the public lack of understanding and the lack of recognition of skin tumours. These patients also reported their worry about cosmetic defects, scarring or other people’s responses. Both patient groups also reported an awareness of their own mortality.

In a further study, Burdon-Jones and Gibbons [204] evaluated and validated the Skin Cancer Quality of Life Impact Tool (SCQOLIT) questionnaire. The 10-item questionnaire was designed for patients with non-metastatic MM and non-melanocytic skin tumour and validated in a group of 120 patients. In the study, patients with MM reported greater impairment of their QOL than the cohort with a non-melanocytic skin tumour.

Schlesinger-Raab et al. (2010) [205] recorded in their study the QOL of patients from the Munich Cancer Registry. During the study period, 1,085 patients answered the QLQ-C30 questionnaire of the EORTC (European Organisation for Research and Treatment of Cancer) and sections from the QLQ-BR-23 questionnaire, Mental Adjustment to Cancer Scale and the Functional Assessment of Cancer Therapy Scale. The main focus of the study was directed at the physical, cognitive, emotional and social aspects. The survey also related to aspects of the medical treatment, the healing process and the prognosis and effects of the disease over the course of time. The outcome showed that patients with MM do not necessarily suffer from a reduced QOL per se. In essence, the results matched the findings in the rest of the population. 50% complained of a lack of communication with the treating physician. QOL was also found to correlate with age. The younger the patients were the better quality of life values were measured. This was attributed to better physical functioning.

A further study from Germany by Waldmann et al. (2011) [206] using the QLQ-C30 questionnaire recorded health-related QOL in 450 melanoma patients. The patients completed the questionnaire for the first time 15 months after diagnosis. A follow-up survey was held after two years. The hypothesis established prior to the study, postulating that the QOL of melanoma patients is worse than that of the rest of the population and is also affected by tumour size and site, could not be confirmed. In addition, deterioration in patients' QOL was observed during the course of the disease.

Vurnek et al. (2007) evaluated QOL in two studies in Croatian melanoma patients. In the first study [207], the authors assessed various coping skills and the QOL of melanoma patients. These were investigated using the *Beck Depression Inventory* and the *COPE Inventory* questionnaire. It was found that patients perceived only a minor effect from the disease on their QOL, which they generally found to be good. Depressive symptoms were rarely described. The most common methods of coping were acceptance, active management and a positive approach to the situation. Generally, it was found that coping strategies resulted in a subjectively better QOL. The second study [208] describes disease perception in melanoma patients as well as their psychological state. Cognitive and emotional aspects of the approach to the disease were investigated using a self-assessment instrument, the Brief Illness Perception Questionnaire (Brief IPQ). A *Visual Analogue Scale (VAS)* was used to examine subjective QOL. Depressive symptoms were evaluated using the *Beck Depression Inventory*. Women displayed greater knowledge about the disease than men, described a stronger effect of the disease on their QOL and exhibited pronounced depressive symptoms. Mild symptoms of depression were observed in 78% of patients overall, 14% exhibited moderate symptoms and 8% severe depression.

In summary, it may be noted that, in terms of the measurement of QOL with MM regardless of tumour stage, this is adversely affected by accompanying reactions such as anxiety, depression, anger, resentment and associated psychological symptoms. Management strategies, however, can help to achieve improvements in subjective perception of quality of life. In addition, experienced support from the patient's immediate circle exerts a positive effect on QOL.

As well as revealing disease-related cost factors in the case of individual patients, the data found in cancer registries also offer the possibility of a robust analysis of the QOL of MM patients. This requires the acquisition of further data, e.g. directly from the patient or by linking these data directly with other sources of data.

Table 20: Included references on the QOL in MM

Author	Title	Journal	Study design	Country	Questionnaire
Beutel M.E., et al.	Psychoonkologische Aspekte des malignen Melanoms	Der Hautarzt 2009, 60:727-734.	Systematic review	Germany	
Burdon-Jones D., et al.	Quality of life issues in nonmetastatic skin cancer	Br J Dermatology 2010, 162: 147-151.	Cohort analysis (patients with MM and non-melanoma skin tumour)	UK	Skin Cancer Quality of Life Question Sheet
Burdon-Jones D., et al.	The skin cancer Quality of Life Impact Tool (SCQOLIT): a validated health-related quality of life questionnaire for non-metastatic skin cancer	JEADV 2012. [Epub ahead of print]	Cohort analysis (patients with MM and non-melanoma skin tumour)	Australia	SCQOLIT
Cashin RP., et al.	Advanced Cutaneous Malignant Melanoma: A Systematic Review of Economic and Quality-of-Life Studies	Value in health 2008, Vol.11, Nr. 2: 259-271.	Systematic review	Canada	
Cornish D., et al.	A systematic review in health-related quality of life in cutaneous melanoma	Annals of Oncology 2009, 20 (Suppl 6):vi51-vi58.	Systematic review	Netherlands	
Schlesinger-Raab A., et al.	Quality of life in localised malignant melanoma	Annals of Oncology 2010, Vol 21(12): 2428-2435	Cross-sectional study of patients from the Munich Cancer Registry	Germany	QLQ-C30, QLQ-BR23 (both EORTC tools)
Sigurdardottir V. et al.	The impact of generalized malignant melanoma on quality of life evaluated by the EORCT questionnaire technique	Quality of life Research 1993, Vol 2:193-203	Cohort analysis	Sweden	EORTCs QLQ-C36 (preliminary version of this questionnaire), a study-specific module on MM, HAD Scale (Hospital Anxiety and

Author	Title	Journal	Study design	Country	Questionnaire Depression)
Vurnek M., et al.	Psychological Status and Coping with Illness in Patients with Malignant Melanoma	Coll. Antropol. 31 (2007) Suppl. 1: 53-56	Cohort study	Croatia	General Quest. (sociodemogr.), visual analogue scale (QoL), BDI (Beck Depression Inventory), COPE inventory
Vurnek-Zivkovic M., et al.	Psychological Status and Illness Perceptions in Patients with Melanoma	Coll. Antropol. 32 (2008) Suppl. 2: 75-78	Cohort study (patients following tumour excision)	Croatia	General Quest. (sociodemo.), VAS (subjective QoL and effect of disease on QoL), BDI, Brief IPQ (Brief Illness Perception Quest.)
Waldmann A., et.al.	Different Aspects of Self-Reported Quality of Life in 450 German Melanoma Survivors	Cancers 2011, 3, 2316-2332	Cohort study (patients after MM Questionnaire 1 (Q1) 15 months after diagnosis, questionnaire 2 (Q2) 2 years after Q1)	Germany	QLQ-C30

Source: own presentation

3.3.3. Basal cell carcinoma (BCC)

BCC is one of the types of NMSC. All NMSC are combined under the ICD 10 code C44. If, therefore, ICD codes are used for further analyses, then a precise differentiation between the entities BCC and SCC is not possible in these analyses. Kraywinkel et al. (2012) [209] in their epidemiological observations confirmed a distribution between the two tumour types, BCC and SCC, of 80% to 20%. Accordingly, 80% of diagnoses under the ICD 10 code C44 can be ascribed to BCC.

3.3.3.1. Direct costs

The direct costs of BCC, like those of MM, have also been taken from the analyses of the skin cancer screening pilot study (SCREEN) by the ADP [190]. The methodological procedure for the calculations has already been described in section 3.3.2 in the analyses on MM.

The mortality rate for BCC may be described as low. However, BCC exhibits constant and destructive growth and is localised in particular in the head and neck region. Extensive treatment measures are undertaken in the case of BCC for the purpose of functional and cosmetic preservation of the affected areas of skin. Treatment options are dependent on site and tumour size. In this case, the assessment has also been made on the basis of the current treatment pathways.

The costs of the various treatment options have been determined on the basis of the URS, the Rote Liste and accounting data from the National Association of Statutory Health Insurance Physicians and are listed in Table 21.

Table 21: Costs of treatment options for BCC

	Minimum costs	Sensitivity	Maximum costs	Average costs
	€	%	€ (rounded)	
Detection and 1st treatment:				
Consultation	15.00	100%	30.00	25.00
Intensive medical counselling	13.80	100%	27.60	21.00
Local anaesthesia	6.90			10.00
Excision biopsy/sample biopsy	7.36	338%	32.21	20.00
Histopathological diagnosis	70.00			70.00
Small excision (shave)	7.36		32.21	20.00
Histopathological diagnosis	92.23			95.00
Cryosurgery	41.40			42.00
Immunotherapy ointment	249.42			250.00
Lump-sum payment	7.71	63%	12.19	10.00
Outpatient treatment:				
Local anaesthesia	6.90			10.00
Re-excision with safety margin	32.21			32.00

	Minimum costs	Sensitivity	Maximum costs	Average costs
Histopathological diagnosis	70.00		92.23	81.15
Supplement outpatient surgery	18.40	100%	36.80	28.00
Follow-up treatment	1.97	16%	2.30	2.00
Radiation:				
Discussion, explanation doctor-patient contact	36.80			37.00
Radiation planning	25.30			26.00
Radiation with accelerator, per fraction	48.30			49.00
Inpatient treatment:				
Re-excision with safety margin	2,485.30			2,490.00
Two-stage (with transplant)	4,970.60			5,000.00
Excision with conventional histology	1,874.00			1,900.00
Two-stage	3,748.00			3,750.00
Re-excision with safety margin 2 > 2 tumours	3,059.00			3,060.00
Two-stage				6,100.00
Prosthetic face care	11,449			12,000.00
Outpatient follow-up treatment:				
Oncology	25.56	100%	51.13	38.00
Oncology continuing care	41.41			42.00
Consultation	1.97	16%	2.30	2.00
Visit	18.40	100%	27.60	23.00
Drugs:				
Analgesics	1.80		21.00	11.50
Psychotropics (N3 pack size)	13.60		55.21	35.00
Sedatives (N2 pack size)	12.42		13.44	13.00
Outpatient chemotherapy:				
Systemic chemotherapy	24,204.00			24,200.00
Follow-up:				
<i>Physical examination:</i>				
Lump-sum payment	7.71	63%	12.19	10.00
Counselling	13.80	100%	27.60	21.00

Source: [190]

On the basis of these cost data and the available incidences, BCC engenders direct total annual costs of €145,555,600 as the total amount for all subtypes. Given the current number of cases, this equates to mean costs of €1,741.50 per case.

Table 22: Direct costs of BCC

BCC type	Number of cases	Costs per year (€)
superficial	29,420	47,791,100
invasive	49,564	87,476,600
sclerodermiform	4,513	8,170,300
metastasis	84	2,117,600
Total costs	83,581	145,555,600
Follow-up	83,498	5,704,000
5% discount		5,418,800
3% discount		5,532,900

Source: modified after [190]

The study by Stang et al. (2008) [191], already referred to in section 3.3.2, also describes hospital day costs for the ICD 10 diagnosis C44 (all non-melanocytic skin tumours). For the ICD 10 diagnosis C44, a weighted mean of €3,150.33 per case was reported for hospitalisation based on G-DRG data from 2003. Data from the company health insurance funds revealed costs of €2,442 for male patients and €2,494 for female patients per case for a hospital stay. The observation period was one year. The total costs for NMSCs were quantified as €105-€130 million annually.

324,085 hospital days for patients with the diagnosis C44 were counted in 2003.

Table 23: Hospitalisation costs for non-melanocytic skin tumours

	Non-melanocytic skin tumours (C44)
G-DRG calculation (per case)	€3,150.33
Costs per hospital day	€363.00
Data of the company health insurance funds (per case)	
Men	€2,442.00
Women	€2,494.00
Source: own presentation, modified after [191]	

3.3.3.2. Indirect costs

In the case of BCCs, the only data that can be used to determine incapacity for work are those from the German Federal Statistical Office. The indication code for BCC is summarised for all non-melanocytic skin tumours as per ICD 10 code C44: "Other malignant neoplasm of skin". According to the Federal Statistical Office, there were 12 days' incapacity for work per case for this diagnosis group in 2009. As the diagnosis and therapy of these cancer entities exhibit strong parallels, 12 days' incapacity for work is assumed for both BCC and SCC. In conjunction with the incidence rate of 133,000 cases per year in 2009 [209], this yields a mean annual loss of productivity of €139,761,720.

The data on BCC are lacking in many details. For this reason, early retirement figures from 2002 were used. Accordingly, in 2002, 62 men and 32 women with a mean age of 51.3 and 50.3, respectively, were obliged to retire due to a non-melanocytic skin tumour [197].

The figures for mortality are also simply presented globally in the data for NMSCs, i.e. including SCC. In 2010 the diagnosis C44 resulted in death in 621 cases [198].

3.3.3.3. Intangible effects/quality of life (QOL)

The keywords "basal cell carcinoma" and "quality of life" used in the systematic literature search yielded 104 hits. From these, 6 full texts were selected and examined. Of these full texts, three articles were included as meeting the inclusion and exclusion criteria (Table 24).

Blackford et. al. [210] conducted a survey using two questionnaires, the *UK Sickness Impact Profile* and the *Dermatology Life Quality Index*, in patients diagnosed with BCC. The QOL was recorded via the dermatologist during the initial visit, one week after treatment and 3 months after treatment. The results confirm that there was no connection between lesion size after excision treatment and QOL. Overall, BCC caused few handicaps, which might offer a possible explanation for the late consultation with a doctor generally observed in the presence of this disease.

In the QOL study by Rhee et. al. [211], changes were recorded in the QOL after surgery for non-melanocytic skin tumours. The results show only slight handicaps due to NMSC at the time of diagnosis. Only two questions showed a statistically significant improvement in QOL as a result of surgery, with the subsequent occurrence of a reduction in pain and pruritus.

Shah et al. (2011) [212] in their analysis showed the effect of demographic, medical and social effects on the QOL. Using the Center for Epidemiological Studies Scale (CES-D) questionnaire, a particularly high prevalence of depressive symptoms was uncovered. This was correlated with the number of relatives involved. The better cared for the patients felt themselves to be, the lower appeared to be the CES-D score. The site and number of tumours had no effect on the QOL.

Two studies by Burdon-Jones et al. (2010/2012) [203, 204] were described in section 3.3.2 which assessed patients with BCC as well as those with MM. The patients reported psychological distress in particular, such as worry about cosmetic defects, scarring or other people's responses. Essentially, BCCs in these studies caused only minor distress and appear not to prompt patients to consult a doctor until an advanced stage. This reveals a particular need for information about positive health-related behaviour.

The limited data for BCCs points to a need for further research in respect of factors that exert a positive effect on the health-related behaviour of the population. Both, screening methods and training in health-awareness behaviour by the patient himself, but also a sensitive approach on the part of the treating physician offer some potential in this respect.

Table 24: Included references on QOL with BCC

Author	Title	Journal	Study design	Country	Questionnaire
Blackford S. et al.	Basal cell carcinomas cause little handicap	Quality of life Research 1996, Vol. 5: 191-194	Cohort analysis (interview at initial treatment, 1 week later and 3 months later)	UK	DLQI (Dermatology Life Quality Index); UKSIP (UK Sickness Impact Profile)
Rhee J.S., et al.	Skin Cancer and Quality of Life: Assessment With the Dermatology Life Quality Index	Dermatol Surg 2004, 30:525-529.	Prospective cohort analysis	USA	DLQI
Shah M., et al.	Quality of life and depression assessment in nevoid basal cell carcinoma syndrome	Int J Dermatol 2011, 50: 268-276	Cohort analysis	USA	Skindex-29

Source: own presentation

3.3.4. Squamous cell carcinoma (SCC)

SCC, like BCC, is listed under ICD 10 code C44. It is assumed that 20% of cases of disease in the diagnosis C44 are due to SCC [209].

3.3.4.1. Direct costs

The direct costs of SCC are also cited from the calculations of the skin cancer screening pilot study [190]. The methodological procedure for the cost calculation for MM in section 3.3.2 also applies in this case.

90% of SCC are localised in the head and neck region and on the hands. At least one second tumour occurs in 70% of new cases. The determining factor in the choice of treatment of SCC is the staging following removal of the first tumour. The costs for SCC are described on the basis of cost units according to the URS, price information from the Rote Liste and G-DRG reimbursement.

Table 25: Costs of treatment options for SCC

	Minimum costs	Sensitivity	Maximum costs	Av. costs
	€	%	€ (rounded)	
Detection and 1st treatment:				
Consultation	15.00	100%	30.00	25.00
Intensive medical counselling	13.80	100%	27.60	21.00
Local anaesthesia	6.90			10.00
Excision biopsy	7.36	338%	32.21	20.00
Histopathological diagnosis	92.23			95.00
Lump-sum payment	7.71	63%	12.19	10.00
Outpatient treatment:				
Local anaesthesia	6.90			10.00
Re-excision with safety margin	32.21			32.00
Histopathological diagnosis	92.23			95.00
Supplement outpatient surgery	18.40	100%	36.80	28.00
Follow-up treatment	1.97	16%	2.30	2.00
Outpatient staging:				
Lymph node ultrasound	9.20			10.00
Upper abdominal ultrasound	13.80			14.00
Chest X-ray in 2 planes	20.70			20.00
CT chest	134.00			135.00
CT abdomen	151.00			150.00
Inpatient treatment:				
Re-excision with safety margin	2,485.30			2,490.00
Two-stage	4,970.60			5,000.00
One-stage and lymphadenectomy	6,174.10			6,200.00
Two-stage	8,659.40			8,700.00
Outpatient follow-up treatment:				
Infusion cytostatics at least 10 min.	5.14	16%	5.98	6.00
Infusion cytostatics > 90 min.	17.40	16%	20.24	19.00
Oncology	25.56	100%	51.13	38.00
Oncology continuing care	41.41			42.00
Visit	18.40	100%	27.60	23.00
Consultations	1.97	16%	2.30	2.00

	Minimum costs	Sensitivity	Maximum costs	Av. costs
Lymph drainage	6.90			7.00
Drugs:				
Analgesics	1.80		21.00	11.50
Psychotropics (N3 pack size)	13.60		55.21	35.00
Sedatives (N2 pack size)	12.42		13.44	13.00
Multimodal chemotherapy				
Excision/radiation/cytostatics	4,222.35	10%	4,264.57	4,250.00
Follow-up				
<i>Physical examination:</i>				
Lump-sum payment	7.71	63%	12.19	10.00
Counselling	13.80	100%	27.60	21.00
Laboratory tests order	0.23			0.25
Lymph node ultrasound	9.20			10.00
Upper abdominal ultrasound	13.80			15.00
Chest X-ray in 2 planes	20.70			20.00

Source: [190]

New cases of SCC engender total annual costs of €50,501,100. Additional risk factors such as immunosuppression and radiation exposure require closer follow-up and thus entail greater costs.

Table 26: Direct costs of SCC

SCC stage	Number of cases	Costs per year(€)
Stage 0	9,605	16,163,000
Stage I	15,481	26,048,600
Stage II	2,451	4,195,600
Stage III	234	586,400
Stage IV	305	3,507,500
Total costs		50,501,100
Follow-up costs (total)		1,822,587
5% discount		1,731,500
3% discount		1,767,900

Source: modified after [190]

There are no studies identifying the inpatient costs for SCC. Only the study by Stang et al. (2008) [191], which was first described in section 3.3.2, records data for hospital stays with the ICD 10 code C44. Inpatient costs engendered by the individual diagnoses, however, are not identified separately by tumour entity (see also Table 23). According to Stang et al. (2008), expenditure for hospital stays with the diagnosis C44 amount to €105-130 million annually for 324,085 hospital days [191]. According to Kraywinkel et al. (2012), 20% of cases in the diagnosis group C44 have SCC [209].

This also assumes that a proportion of 20% of the reported costs are due to SCC.

3.3.4.2. Indirect costs

The calculation of the indirect costs of SCC is based on data from the Federal Statistical Office. In this case, 12 days' incapacity for work were assumed for the ICD 10 code C44 in 2009. On the basis of the incidence figures for SCCs from the Schleswig-Holstein cancer registry, the mean productivity loss was €36,569,232 for 34,800 incidence cases [196].

Again, the mortality and early retirement figures are not available individually for SCC but only for all NMSC as a whole. They have already been reported in section 3.3.3 on BCC.

3.3.4.3. Intangible effects/quality of life (QOL)

The systematic literature search for SCC in the previously mentioned meta-databases yielded a total of 1,906 potentially relevant articles. As with the previously described diagnoses, the titles and abstracts were reviewed. None of the available studies could be included on the basis of the inclusion and exclusion criteria.

Only two studies by the authors Burdon-Jones et al. (2010/2012) [203, 204] (see also section 3.3.2) considered the effects of non-melanocytic skin tumours on QOL. Patients with NMSC here complained predominantly about worry over cosmetic defects, scar formation or other people's responses. The second article underlined the validity of the SCQGGPOIT questionnaire used in the case of NMSC patients.

3.3.5. Summary and prospects

The disease burden of skin tumours can be defined on the basis of a very large variety of factors.

From a social perspective, cost components representing an extreme economic burden were demonstrated. On the one hand, the sometimes very demanding medical treatment procedures account for a large proportion of the costs. For all the tumour entities mentioned, hospitalisation, surgical treatment procedures and an intensive follow-up period incur high direct costs. At the same time, the disease and treatment engender productivity losses that cause economic damage.

The proportion of direct costs for MM is quantified as €131,948,900 per year. The follow-up of patients in the first year engenders costs amounting to €14,872,700. The hospitalisation costs per case and per year were quantified in one study as €2,376 (men) and €2,474 (women), and in the case of melanoma in situ as €1,889 (men) and €2,394 (women).

Indirect costs resulting from productivity losses were estimated as €44,048,586 per year. The German Federal Statistical Office here calculated 9,060 lost years of productivity due to early retirement and recorded 2,711 deaths in 2010.

A reduction in the QOL as a result of the diagnosis of MM was occasioned by mental factors such as anxiety, depression, anger, resentment, etc.

BCC was associated with a proportion of direct costs of €145,555,600 per year. Furthermore, follow-up costs of €5,704,000 are incurred.

The total direct costs for SCC according to the calculations presented here amount to €50,501,100. Follow-up entails annual costs amounting to €1,822,587.

Loss of productivity as a result of SCC engenders annual costs of €36,569,232.

Because of the ICD 10 coding, hospitalisation costs can only be recorded for all non-melanocytic skin tumours combined. In one study, annual costs per case were calculated as €2,442 for men and €2,494 for women with the ICD 10 code C44 (non-melanocytic skin tumours). Incapacity for work as a result of the diagnosis C44 engendered annual costs amounting to €139,761,720. In 2010, 621 deaths due to non-melanocytic skin tumours were recorded.

Intangible effects were also measured for the diagnosis of a non-melanocytic skin tumour. It can be observed for both tumour entities, BCC and SCC, that slight distress is caused by these skin tumours themselves. Only after-effects of treatment such as scarring, cosmetic defects or other people's reactions cause worries and psychological distress.

Although the disease rates for basal cell and squamous cell carcinomas exceed those for MM, the latter is associated with significantly more days of incapacity for work and cases of early retirement. One possible reason for this trend is that with basal cell and squamous cell carcinomas the age in the event of disease is higher. These therefore make only a small contribution to productivity losses. In general, when interpreting the direct and indirect costs presented here, it should be borne in mind that the calculations were based on the common ICD 10 coding of BCC and SCC. It is therefore not possible to compare the costs of these two tumour entities.

In terms of patient-relevant factors, no specific conclusion could be drawn regarding direct and indirect costs in this analysis. This would require the collection of data quantifying, for example, out-of-pocket expenses, sick leave or even loss of employment. However, the documentation held by the cancer registries provides a good basis for collecting such data.

In the analysis of patients' QOL, only very limited conclusions could be drawn for the different tumour entities. In this case it was necessary to resort to international studies to a large extent, since hardly any data are available from Germany. As QOL relates to subjective feelings, the complete transposability of the results to the national context remains a matter of discussion.

In summary, however, it may be observed that psychological factors such as anxiety, depression, resentment or anger are associated with the diagnosis of cancer and the treatment modalities and negatively impact on the QOL. Physical symptoms such as pain also significantly affect the perceived QOL. In the case of BCC, it was also established on the basis of studies that the limited impact on the QOL experienced at the beginning of the disease are probably the reason for the late diagnosis. In this

condition, a physician is usually not consulted until a very advanced stage of the tumour. This points to the urgent need to implement preventive measures. In view of the high and constantly growing incidence figures, the concept of prevention must not only be promoted among physicians, but also more firmly anchored in the general population.

Cases of melanoma in situ are included in cancer registration in only a few federal states of Germany. As the precursor of an invasive melanoma, however, this non-invasive type of melanoma assumes a particular medical and hence economic significance.

Simply due to the less extensive range of treatments, fewer costs are incurred here. More successful treatment may probably be assumed, as a result of which it may also be assumed that there is a greater potential gain in terms of the avoidance of productivity losses, early retirement and years of life lost. In addition, the persons concerned are spared a reduction in their QOL.

Bringing forward the time of diagnosis is a primary goal of the screening measures for the early detection of skin tumours.

Taking into account the stage shift of the current prevalences of all tumour entities (e.g. melanoma in situ 6,595 cases, stage I 10,987 cases), then the number of cases in which an already large proportion of tumours in a non-invasive stage could be detected and treated becomes clear. Consequently, the proportion of invasive MM and later stages of BCC and SCC could be reduced.

For each tumour entity, the cost differential between the individual stages relative to the next highest tumour stage suggests the potential for savings from early detection.

Need for further research

There is a need for further research in respect of the cost calculation for screening measures for all the tumour entities considered here. Extensive national data are lacking, both for the cost factors of the diseases and also for statements on the individual disease burden and hence the QOL. A thorough disease cost analysis designed from a multiple perspective as well as QOL studies could provide a consistent statement on the current situation relating to costs and disease burden. An analysis of the costs of preventive measures in relation to the prevention of cases of disease and the associated cost savings is also a necessary step before and after the implementation of preventive measures. It can thus be shown how essential disease prevention measures are in the population.

3.4. Risk factors of skin cancer

R. Greinert, B. Volkmer

3.4.1. Constitutional risk factors (phenotypical or genotypical) of skin cancer

Among the risk factors for non-melanocytic skin cancer (NMSC) and malignant melanoma (MM), a distinction must be drawn between constitutional, acquired and exposure-related risk factors. Purely constitutional risk factors in non-melanocytic skin cancers (BCC, SCC) include skin type. In the case of MM, these factors are skin type and congenital naevi.

3.2.	Consensus-based statement
EC	<p><u>Constitutional risk factors:</u> Non-melanocytic skin cancer (NMSC) An important constitutional risk factor for NMSC (basal cell carcinoma and squamous cell carcinoma) is</p> <ul style="list-style-type: none"> • skin type. <p>All other risk factors can be acquired during the course of life.</p>
	Consensus strength: 100%

3.3.	Consensus-based statement
EC	<p><u>Constitutional risk factors:</u> Malignant melanoma (MM) The class of constitutional risk factors for MM includes</p> <ol style="list-style-type: none"> a) skin type and b) (large) congenital naevus. <p>All other risk factors can be acquired during the course of life.</p>
	Consensus strength: 100%

Non-melanocytic skin cancer (NMSC)

On the basis of a variety of epidemiological, medical and experimental studies, skin type has been identified as the most important constitutional risk factor for NMSCs. The risk of developing an NMSC is higher for light skin types (I, II) than for skin types III and IV (for skin types see Table 27). Gallagher and co-workers in two large-scale studies [21, 213] comparing skin type I and II with skin type IV, give crude odds ratios (OR) of 5.1 (95% confidence interval (CI): 1.4-11.3) and 5.3 (95% CI: 1.7-10.6) for the occurrence of a BCC and OR of 1.4 (95% CI: 0.5-3.0) and 2.2 (95% CI: 0.7-3.8) for the occurrence of an SCC.

Malignant melanoma (MM)

a.) Skin type

Skin type represents an important constitutional risk factor for MM. It has been shown that people with skin type I, II or III are at significantly higher risk of MM than those who never suffer sunburn and always tan (skin type IV). Relative risks (RR) for skin type I, II and III (vs. skin type IV) were determined in a meta-analysis with an RR of 2.09 (95% CI: 1.67-2.58), 1.87 (95% CI: 1.43-2.36) and 1.77 (95% CI: 1.23-2.56) [214].

b.) Congenital naevi

Congenital (i.e. present at birth) melanocytic naevi indisputably present a risk of malignant degeneration, which is particularly significant in the case of very large congenital naevi. "Giant naevi" (> 40 cm in diameter) in particular are at increased risk of developing into MM [215-217]. However, such naevi are extremely rare [218].

According to the current international classification based on good clinical practice [219], congenital melanocytic naevi (CMN) with a diameter of more than 20 cm to 40 cm are defined as "large congenital naevi" and naevi over 40 cm as "giant naevi". This classification is based on the expected maximum diameter of the naevus in adulthood.

The risk of degeneration of congenital naevi is correlated with size. The development of melanomas on CMN of up to 20 cm in diameter has been described [220], but epidemiologically the risk of degeneration is not demonstrably increased in comparison with "acquired", non-congenital naevi. In particular, up until puberty the development of a melanoma on these CMN appears to occur only very rarely. "Small" (up to 1.5 cm diameter) and "intermediate" CMN (1.5 to 20 cm) should therefore be examined (like all naevi) in the skin cancer screening programme and any changes recorded.

By contrast, "giant CMN", which frequently exhibit a number of what are known as satellite naevi as well as central nervous system pigment cell proliferation in some cases, are a pathogenetically distinct entity due to NRAS mutations of the embryonal neural crest [221]. These CMN are associated with a markedly higher risk for the development of a cutaneous or even central nervous system melanoma from early childhood onwards [215]. Cutaneous melanomas that arise from these naevi are typically deep, dermal or subcutaneous nodules that can be detected by palpation. On a molecular pathological level, these melanomas must be differentiated from what are known as benign proliferative nodules [222].

Table 27: Skin types (Act on Protection against Non-Ionising Radiation (NiSG)) [223]

Skin type	I	II	III	IV	V	VI
<i>Description</i>						
Natural skin colour:	very light	light	light to light brown	light brown, olive	dark brown	dark brown to black
Freckles/ sunburn spots:	very common	common	rare	none	none	none
Natural hair colour:	reddish to reddish-blond	blond to brown	dark blond to brown	dark brown	dark brown to black	black
Eye colour:	blue, grey	blue, green, grey, brown	grey, brown	brown to dark brown	dark brown	dark brown
<i>Reaction to the sun</i>						
Sunburn:	always and painful	almost always, painful	rare to moderate	rare	very rare	extremely rare
Tanning:	none	slight to moderate	progressive	fast and deep	none	none
Erythema-effective threshold radiation dose:	200 Jm ⁻²	250 Jm ⁻²	350 Jm ⁻²	450 Jm ⁻²	800 Jm ⁻²	> 1,000 Jm ⁻²

3.4.2. Acquired risk factors of skin cancer

3.4.	Consensus-based statement
EC	<p><u>Acquired risk factors:</u> Non-melanocytic skin cancer (NMSC) The main acquired risk factors for NMSC (basal cell carcinoma and squamous cell carcinoma) are:</p> <ol style="list-style-type: none"> actinic keratosis, previous history of NMSC, immunosuppression, chronic radiation keratoses.
	Consensus strength: 100%

3.5.	Consensus-based statement
EC	<p><u>Acquired risk factors:</u> Malignant melanoma (MM) The main acquired risk factors for MM are:</p> <ol style="list-style-type: none"> a) previous history of melanoma, b) family history of melanoma, c) number of acquired naevi, d) clinically atypical moles.
	Consensus strength: 93%

3.6.	Consensus-based statement
EC	<p>The probability of developing a squamous cell carcinoma is correlated with the UV dose to which a person is exposed during their life (cumulative dose).</p> <p>For basal cell carcinoma, the cumulative UV exposure appears to be of secondary importance. Intermittent UV exposure and sunburn are important in the case of BCC.</p> <p>For malignant melanoma, intermittent UV exposure and sunburn (at any age) are of major importance.</p>
	Consensus strength: 100%

Non-melanocytic skin cancer (NMSC)

In the case of BCC and SCC, the risk factors that can be acquired by UV exposure or other external influences in the course of life include:

- a.) actinic keratosis (AK),
- b.) personal history of NMSC,
- c.) immunosuppression,
- d.) chronic radiation keratoses.

a.) Actinic keratosis (AK)

AK represents a precursor of SCC [59]. In the literature, there are conversion probabilities from AK to invasive SCC ranging from < 1% up to 16% [60-62]. There have even been reports of up to 70% in individual cases [64]. The presence of multiple AK over a 10-year period is reported as being associated with a lifetime risk for the development of SCC in the range of 6-10% [50]. AK thus represents an important risk factor for NMSC, particularly SCC.

b.) Personal history of NMSC

Epidemiological studies show that individuals with a previous personal history of BCC or SCC are at considerably higher risk of developing another NMSC in their subsequent

life [224]. The risk of developing a second SCC within 5 years of treatment of the first SCC is 30% [225]. The corresponding 3-year risk is about 18%, which equates to a 10-fold increase in probability compared with the occurrence of a primary SCC in the population. The 3-year risk for a second BCC if the primary tumour was also a BCC is 44% even, which also equates to a 10-fold increase in probability compared with the occurrence of a primary BCC in the population [224]. The risk of a BCC developing in patients with a previous SCC is approximately the same as that in people with a previous BCC (about 40%). The risk of developing an SCC as a second tumour [226] when the first tumour was a BCC is comparatively small (6%) [224]. Against this background, follow-up strategies (e.g. continuous screening of risk groups) are required for patients with SCC and BCC, as the existence of a previous history of non-melanocytic tumours constitutes a significant risk factor for the development of other non-melanocytic tumours.

c.) Immunosuppression

Organ transplant patients are at significantly increased risk for the occurrence of NMSC types due to the administration of immunosuppressant drugs [227-232]. SCC develop up to 65 times more frequently in transplant patients than in controls [233]. Patients who have undergone a heart transplant are apparently at greatest risk of developing an SCC, followed by kidney and liver transplant recipients [230, 234-238]. The ratio of SCC to BCC following heart transplant in an Australian study is about 3:1 to 4:1 and thus represents an inverse relationship to the occurrence of SCC and BCC in the general population [239].

Individuals with non-drug-induced immunosuppression can also exhibit a greater risk for non-melanocytic skin tumours. Generally, HIV-infected subjects have a slightly increased incidence of SCC at a younger age than non-immunosuppressed individuals [240]. HIV-infected patients with a light skin type and high leisure time UV exposure or who exercise an outdoor occupation exhibit an increased risk for SCC and BCC [241-243]. Furthermore, HIV patients appear to develop aggressive, fast-growing SCC associated with a high risk of local recurrence and metastases [240].

d.) Chronic radiation keratoses

Patients required to undergo radiotherapy with ionising radiation (e.g. X-ray radiation) are at risk of developing chronic radiation keratosis at a later stage. These are keratotic skin lesions that have been found in radiotherapy patients or in clinical staff exposed to ionising radiation over a number of years or working with radioactive material [244]. Chronic radiation keratoses are significant because there is a greater probability of BCC or SCC developing from them. More recent findings, however, show that exposure to therapeutic (ionising) radiation tends to contribute more to the formation of BCC and probably not to that of SCC [245]. The risk for an SCC arising from a chronic radiation keratosis increases with the UV exposure of individuals who sunburn readily (skin type I, II) [246].

Malignant melanoma (MM)

Many of the risk factors for MM mentioned in this chapter were investigated in studies that were used for three systematic reviews including meta-analyses [214, 247, 248]. These included studies published between 1966 and 2002 on risk factors for MM. Following an analysis of approximately 600 original articles using various inclusion criteria (only case-control, cohort or cross-sectional studies were included; ecological studies, case studies, reviews and editorials were excluded), it was possible to

calculate pooled RRs for the number of acquired and atypical naevi, family history, skin type, freckles, skin colour, eye colour and hair colour (Table 28).

The risk factors that can be acquired by UV exposure or other external influences during the course of life for MM include:

- a) previous history of MM,
- b) family history of MM,
- c) number of acquired naevi,
- d) clinically atypical moles.

a) Previous history of MM

The RR for a second melanoma with a previous personal history of MM is high and reported as 8.5 [249]. It is therefore approximately 4 times higher than the RR of developing an MM if an MM is present in a first-degree relative (RR = 2.2) [250, 251]. Further studies confirm that approximately 3% of patients with MM are at high risk of developing another MM as a second primary tumour [252, 253]. Standardised incidence ratios (compared with people without a primary tumour) of 2-10 are reported [254, 255].

b) Family history of MM

There is strong evidence that MM is inheritable as an autosomal dominant trait, as 5-12% of patients with the disease have one or more first-degree relatives who have also developed MM. Cancer occurs at an early stage in these individuals with a familial disposition. It is frequently accompanied by multiple other (skin) tumours [110, 111, 113, 256]. These people have a particularly high risk of developing a melanoma. The RR of developing melanoma can be increased up to 500-fold if two first-degree relatives suffer from MM and also have dysplastic naevus syndrome. The lifetime risk of developing a melanoma is then greater than 50% [162, 256, 257]. Studies on the aetiology of melanoma also offer strong evidence for the importance of familial melanomas in the development of melanomas in members of the subsequent generation (see above).

c) Number of acquired naevi

Numerous studies confirm that the number of benign acquired naevi (naevus cell nevi, NCN) may be regarded as the most significant risk factor quantitatively for the development of melanoma [258-268].

Risk estimates reported in these studies are in the range of 1.3-30. Twin studies show that the number of naevi is genetically controlled [269, 270] and that they are dependent on constitutional factors such as skin type, hair colour and a tendency to freckling [271, 272]. A clear relationship has been demonstrated between severe sunburn (intermittent UV exposure) in childhood and the number of acquired benign naevi [106, 263, 264, 273-276]. New studies show that the tendency to UV-related formation of melanocytic naevi in early childhood (0-6 years) is important [106] and in the case of a certain genetic predisposition can be activated by suberythral UV exposure [277].

The articles listed confirm the close relationship between UV exposure and the development of melanocytic naevi, regarded as a determining risk factor for the development of the MM.

d) Clinically atypical moles (naevi)

Clinically atypical (dysplastic) moles (naevus cell naevi) can occur over the whole body. They are defined by their vague and irregular outline and the often variable colour components. The presence of atypical naevi as a risk marker for the formation of MM is well documented.

In the German-speaking regions, atypical melanocytic naevi, together with the number of common melanocytic naevi, were described as the second most important risk indicator for the development of melanoma in a multicentre study in 1994. According to this study, the presence of a few (1-4) atypical naevi is associated with a 1.6-fold increase in risk (compared with subjects without atypical naevi). If 5 or more atypical melanocytic naevi are observed, there is a marked, 6-fold increase in the risk of developing melanoma. This finding was interpreted to mean that at least 5 of these moles must be present to identify persons at risk [263, 264]. Grob et al. (1990) [278], however, found that the mere presence of an atypical mole increases the RR of melanoma development 3-fold. A relative risk of 3.8 has been calculated for 1-5 atypical naevi and a value of 6.3 in the presence of 6 or more atypical naevi [279].

About 40% of patients with sporadic MM (especially of the superficial spreading type) exhibit atypical naevi, in contrast to a 10-15% prevalence in the rest of the population [280].

Table 28: Relative risks for MM

Risk factor	Reference	Relative risk (95% CI)
Number of acquired naevi	101-120 vs. < 15	6.89 (4.63-10.25)
Number of atypical naevi	5 vs. 0	6.36 (3.80-10.33)
Family history of melanoma	yes vs. no	1.74 (1.41-2.14)
Skin type I	I vs. IV	2.09 (1.67-2.58)
Numerous freckles	high density vs. low density	2.10 (1.80-2.45)
Skin colour	light vs. dark	2.06 (1.68-2.52)
Eye colour	blue vs. dark	1.47 (2.80-2.55)
Hair colour	red vs. dark	2.02 (1.24-3.29)
Precursor stage and skin cancer lesions*		4.28 (2.8-6.55)
Actinic damage**		2.02 (1.24-3.29)

* actinic keratosis, SCC, BCC

** solar lentigines, elastosis

Source: [214, 247, 248]

3.4.3. Risk factors for UV exposure

There are no data on the incidence of skin cancer according to geographical latitude in Germany. However, it will be difficult to demonstrate a clear causal relationship should any sort of correlation emerge between latitude-dependent UV exposure and the occurrence of skin cancer, since the induction of cellular UV damage that can lead to skin cancer can occur regardless of geographical location (e.g. on holiday, behaviour).

Furthermore, the form taken by the dose-response relationship has not been sufficiently elucidated for UV-induced skin cancer diseases. Whether there is a threshold value for the emergence of certain skin diseases or a linear dose-response relationship without a threshold value can only be established by future research. This applies also to the possibility of quantifying the increased risk per dose (risk coefficients).

Types of NMSC

With NMSC, UV exposure from natural or artificial radiation is the most important factor in the development of the disease [20, 79, 281]. The fact that SCC and BCC predominantly develop on chronically UV-damaged skin or on parts of the body constantly exposed to light elucidates this relationship. While the probability of developing an SCC is correlated with the increasing, lifelong acquired UV dose (cumulative dose) and occupational exposure, the UV dose-response relationship for BCC has not yet been fully elucidated. In the case of BCC, cumulative UV exposure appears to be of only secondary importance. The converse relationship is found for occupational exposure (Table 29). It is clearly apparent in this table that intermittent UV exposure and sunburn can be held responsible for MM [20]. This applies to a lesser extent also to BCC.

Table 29: Relative risks of occurrence of BCC, SCC and MM with different types of sun exposure

Type of exposure	BCC	SCC	MM
Total (cumulative)	0.98 (0.68–1.41)	1.53 (1.02–2.27)	1.20 (1.00–1.44)
Occupational	1.19 (1.07–1.32)	1.64 (1.26–2.13)	0.86 (0.77–0.96)
Non-occupational or intermittent	1.38 (1.24–1.54)	0.91 (0.68–1.22)	1.71 (1.54–1.90)
Sunburn at any age	1.40 (1.29–1.51)	1.23 (0.90–1.69)	1.91 (1.69–2.17)

Relative risk in comparison with control groups with the lowest possible exposure (95% CI)

Source: [20]

Malignant melanoma (MM)

Although the form of the dose-response relationship is largely unknown, as long ago as 1991 the “Consensus Development Conference on Sunlight, Ultraviolet Radiation, and the Skin” determined that the only established reason for the occurrence of melanomas – in the white population – is to be found in UV exposure from the sun [282]. Since 1992 (and again in 2012), the International Agency for Research on Cancer (IARC) has also regarded exposure to sunlight as the main reason for the development of MM in humans [7].

However, since then further questions were raised that primarily concern the role of UV exposure pattern in the development of MM. In the literature, a distinction is drawn between intermittent, chronic and total UV solar exposure and sunburn. However, it is often difficult, particularly retrospectively, to distinguish between these exposure patterns when reconstructing the “UV history” of individual persons. Thus, it is difficult to separate interactions between sunburn, general exposure behaviour in the sun, individual tanning capacity and other phenotype factors (eye colour, hair colour, skin type, etc.). UV radiation can act as an initiator, e.g. through sunburn or intermittent exposure, but also as a promoter through subsequent chronic exposure [7, 260, 283, 284]. Recent meta-analyses have shown that the number of acquired, UV-induced naevi is closely related to the melanoma risk and that their number is increased in individuals with high UV exposure [106, 247]. Acquired UV-induced naevi thus assume a central role in the causal chain between UV exposure and development of MM.

Gandini et al. (2005) [248] in a meta-analysis report (pooled) RRs for different UV exposure patterns and their association with MM (Table 30).

Table 30: Effect of UV exposure pattern on the relative risk of developing melanoma

UV exposure pattern	RR for association with MM (95% CI)
Total (intermittent + chronic + sunburn)	1.34 (1.02-1.77)
Intermittent	1.61 (1.31-1.99)
Chronic	0.95 (0.87-1.04)
Sunburn	2.03 (1.73-2.37)

Source: [248]

As the control groups differed in the individual studies, in each case the control group with the lowest possible exposure was used to calculate the pooled RR in the meta-analysis.

In this analysis, the differences between the studies analysed in the determination of risk estimates (e.g. odds ratio, rate ratio, risk ratio) were ignored and each risk estimate of an association was converted to logRR and its associated variance in accordance with a procedure by Greenland [285]. Four hundred and thirty-eight studies (up to 2002) were found in the literature search, 87 of which appeared potentially suitable for a meta-analysis and 57 ultimately met the authors' inclusion criteria [248]. The meta-analysis encompasses 38,671 cases, distributed between 32 studies in Europe, 19 in North America, two in Australia and one each in New Zealand, Argentina, Brazil and Israel. Fifty case-control studies, five cohort studies and two nested case-control studies were included.

Despite the lack of well-designed cohort studies and systematically recorded UV exposures in case-control studies and against the background of difficulties in retrospective surveys of UV exposure (recall bias) and in the recruitment of representative control groups, Gandini et al. (2005) [248] in their meta-analysis come to the conclusion that the overwhelming majority of data document the importance of intermittent sun (UV) exposure in the development of melanoma. In particular,

irregular and intensive exposure (as for example with sunburn) significantly increases the risk of melanoma (Table 30).

Table 30, however, shows that fairly regular (chronic) exposure is possibly even inversely associated with the occurrence of melanomas [248]. This is demonstrated in particular in studies by Elwood and Jopson (1997) and Nelemans et al. (1995) [286, 287]. When considering the topographical distribution of cutaneous melanomas, the highest incidence rates for MM in studies in Lithuania, Finland and Germany [288, 289] are found on the trunk in men, whereas in women the incidence of MM is greatest on the legs. This distribution characteristic is also used as an argument that MM arise as a result more of intermittent than of chronic UV exposure. However, the topographical comparison of incidence ignores the fact that the areas of the body to be compared differ very considerably in body surface area and/or melanocyte count. The estimated body surface area of the trunk, for example, accounts for 32% of the total body surface area, whereas the proportion of the face including lips and eyelids constitutes only about 2.7%. If the topography-specific incidence rates are adjusted to the body surface area concerned (body surface adjusted rates, RSA), a different possibility of interpretation emerges in respect of the predisposition of skin areas to MM. The highest RSA in women and men is then found on the face, which is classed more as chronically UV exposed.

Further studies are needed to explain whether chronic UV exposure, possibly in connection with intermittent periods, is important for certain types of melanoma.

Sun studios, solariums

In the past decades, as well as UV exposure patterns that result from solar radiation in the open air and that are associated with a risk of melanoma (Table 30), consideration has also had to be given to the importance of exposure to artificial UV radiation, particularly in solariums. A meta-analysis by the IARC showed that such exposures can no longer be ignored in terms of the development of MM. It has been shown that the risk of developing an MM later in life is increased by 75% if people have started using solariums regularly before the age of 35 (regularly = once a month) [290]. In 2009, these findings and a variety of publications in the field of epidemiology and basic research prompted the IARC to classify UV radiation used in solariums also as a group 1 carcinogen (“carcinogenic in humans”), just like solar UV radiation [4]. UV radiation is thus categorised in the group of substances and radiation qualities that have the highest proven carcinogenic potential in humans.

3.4.4. Other risk factors for skin cancer

3.7.	Consensus-based statement
EC	Other risk factors that are described for non-melanocytic skin cancer are exposure to arsenic or tar, particularly in the work environment. HPV infections are discussed both as a risk factor for skin cancer in their own right and as a cofactor in combination with ultraviolet (UV) radiation.
	Consensus strength: 100%

Arsenic

Arsenic (in the drinking water) is seen as a risk factor for skin cancer (particularly SCC and BCC). According to the IARC classification, arsenic belongs to class I of carcinogens (“carcinogenic in humans”). It has been reported that, among other effects, arsenic can contribute to numerical chromosomal aberrations and to changes in the epigenetic regulation of tumour suppressor organs.

Limit values for arsenic in drinking water are set at $\leq 10 \mu\text{g/L}$. However, these values are exceeded for almost 100 million people, particularly in Bangladesh, Taiwan, Mongolia, India, China, Argentina, Mexico, Canada and the USA.

Nevertheless, there are no robust epidemiological studies on the contribution of arsenic-induced types of skin cancer to the total incidence of skin cancer.

Tar

Chronic exposure to tar and tar derivatives, particularly in the work environment, is a risk factor for NMSC [291, 292]. An increased risk from the therapeutic use of tar has not been demonstrated to date [293].

HPV infection

HPV infections are discussed both as a risk factor for skin cancer (squamous cell carcinoma) in their own right and as a cofactor in combination with UV radiation. Extensive UV exposure at the site of skin biopsies is described as a strong risk factor for the occurrence of HPV infections, with local immunosuppression possibly playing an exacerbating role [294, 295].

However, since both the degree of UV exposure and the severity of the HPV infection are difficult to quantify, large epidemiological studies are required first of all to document possible causal relationships between UV exposure and HPV infection and to quantify the number of HPV-associated SCCs in the total number of all SCCs that occur [294].

3.4.5. Absolute and relative risks

In the following statements on the absolute and relative risks, the figures from the previous sections on constitutional risk factors, the risk from different UV exposure patterns and the risk from using solariums are summarised by way of conclusion and examples listed.

3.8.	Consensus-based statement										
EC	<p>Values for relative risks (RR) or lifetime risks are given in the literature in various studies for the constitutional risk factors described. Examples of such values are listed below for non-melanocytic skin cancer:</p> <table border="1" data-bbox="432 759 1348 1025"> <thead> <tr> <th>Risk factor</th> <th>RR (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Skin type I vs. IV (BCC)</td> <td>5.1 (1.4-11.3)</td> </tr> <tr> <td>Skin type II vs. IV (BCC)</td> <td>5.3 (1.7-10.6)</td> </tr> <tr> <td>Skin type I vs. IV (SCC)</td> <td>1.4 (0.5-3.0)</td> </tr> <tr> <td>Skin type II vs. IV (SCC)</td> <td>2.2 (0.7-3.8)</td> </tr> </tbody> </table> <p>Sources: [21, 213]</p> <p>The presence of multiple actinic keratoses over a 10-year period is reported as being associated with a lifetime risk for the development of a squamous cell carcinoma (SCC) in the region of 6-10%.</p> <p>With a personal history of SCC, the risk of developing another SCC within 5 years is 30% and of developing a basal cell carcinoma (BCC) about 40%.</p> <p>With a personal history of BCC, the risk of developing another BCC within 3 years is 44% and of developing an SCC about 6%.</p> <p>SCC occurs up to 65 times more frequently in immunosuppressed transplant patients than in controls. Immunosuppressed transplant patients develop more SCC than BCC (4:1).</p>	Risk factor	RR (95% CI)	Skin type I vs. IV (BCC)	5.1 (1.4-11.3)	Skin type II vs. IV (BCC)	5.3 (1.7-10.6)	Skin type I vs. IV (SCC)	1.4 (0.5-3.0)	Skin type II vs. IV (SCC)	2.2 (0.7-3.8)
Risk factor	RR (95% CI)										
Skin type I vs. IV (BCC)	5.1 (1.4-11.3)										
Skin type II vs. IV (BCC)	5.3 (1.7-10.6)										
Skin type I vs. IV (SCC)	1.4 (0.5-3.0)										
Skin type II vs. IV (SCC)	2.2 (0.7-3.8)										
	Consensus strength: 86%										

3.9.	Consensus-based statement												
EC	<p>Values for relative risks (RR) or lifetime risks are given in the literature in various studies for the constitutional risk factors described. Examples of such values are listed below for malignant melanoma:</p> <table border="1" data-bbox="432 546 1436 860"> <thead> <tr> <th data-bbox="438 555 1054 589">Risk factor</th> <th data-bbox="1059 555 1430 589">RR (95% CI)</th> </tr> </thead> <tbody> <tr> <td data-bbox="438 595 1054 629">Number of acquired naevi (100-120 vs. < 15)</td> <td data-bbox="1059 595 1430 629">6.89 (4.63-10.25)</td> </tr> <tr> <td data-bbox="438 636 1054 669">Skin type (I vs. IV)</td> <td data-bbox="1059 636 1430 669">2.09 (1.67-2.85)</td> </tr> <tr> <td data-bbox="438 676 1054 710">Family history of melanoma (yes vs. no)</td> <td data-bbox="1059 676 1430 710">1.74 (1.41-2.14)</td> </tr> <tr> <td data-bbox="438 716 1054 750">Number of atypical naevi (5 vs. 0)</td> <td data-bbox="1059 716 1430 750">6.36 (3.80-10.33)</td> </tr> <tr> <td data-bbox="438 757 1054 790">Personal history of melanoma (yes vs. no)</td> <td data-bbox="1059 757 1430 790">8.5 (5.8-12.2)</td> </tr> </tbody> </table> <p data-bbox="432 866 1436 900">Sources: [214, 247, 249]</p> <p data-bbox="432 938 1436 1032">Congenital naevi with a diameter of > 10 to 20 cm are known as “large congenital naevi”. They are associated with a risk of approximately 2-10% of developing a melanoma during the course of life.</p>	Risk factor	RR (95% CI)	Number of acquired naevi (100-120 vs. < 15)	6.89 (4.63-10.25)	Skin type (I vs. IV)	2.09 (1.67-2.85)	Family history of melanoma (yes vs. no)	1.74 (1.41-2.14)	Number of atypical naevi (5 vs. 0)	6.36 (3.80-10.33)	Personal history of melanoma (yes vs. no)	8.5 (5.8-12.2)
Risk factor	RR (95% CI)												
Number of acquired naevi (100-120 vs. < 15)	6.89 (4.63-10.25)												
Skin type (I vs. IV)	2.09 (1.67-2.85)												
Family history of melanoma (yes vs. no)	1.74 (1.41-2.14)												
Number of atypical naevi (5 vs. 0)	6.36 (3.80-10.33)												
Personal history of melanoma (yes vs. no)	8.5 (5.8-12.2)												
	Consensus strength: 96%												

3.10.	Consensus-based statement
EC	<p>The relative risks (RR) for the development of different skin cancer entities (basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM)) depend on the UV exposure pattern. BCC does not depend on the cumulative UV dose (RR = 0.98, 95% CI 0.68-1.41), whereas SCC is more strongly dependent on the cumulative dose (RR = 1.53, 95% CI 1.02-2.23). MM is intermediate between the two in relation to the cumulative dose (RR = 1.2, 95% CI 1.00-1.44). For MM, however, there is an increased risk from intermittent UV exposure (RR = 1.71, 95% CI 1.54-1.90) or from sunburn at any age (RR = 1.91, 95% CI 1.69-2.17) [20].</p>
	Consensus strength: 96%

3.11.	Consensus-based statement
EC	The relative life risk (RR) for a malignant melanoma is $RR = 1.75$ (95% CI: 1.35-2.26) if solariums are used regularly (at least once a month) before the age of 35 [290].
	Consensus strength: 96%

4. Primary prevention

4.1. Individual behaviours

H. Siekmann, M. Diensberg, H. Grundhewer

The effect of UV radiation on the skin is the main cause of skin cancer. The aim of primary prevention is therefore to prevent excessive UV exposure of the skin. This applies first and foremost to UV exposure from the while being outdoors. Various measures are suitable, but the individual sensitivity of the skin to UV radiation needs to be borne in mind.

4.1.1. Risk-minimising behaviours

4.1.	Consensus-based recommendation
EC	Protective measures against solar ultraviolet radiation must be applied in the following order: <ul style="list-style-type: none"> • avoidance of exposure to strong solar radiation, • wearing suitable clothing, • using sunscreens.
	Consensus strength: 100%

4.1.1.1. Avoidance of exposure to strong solar radiation

4.2.	Consensus-based recommendation
EC	The following measures must be taken to avoid exposure to strong solar radiation in the relevant weather conditions: <ul style="list-style-type: none"> • remain outside as little as possible, • avoid staying outside in the middle of the day, • the length of time in the sun should not exceed the individual intrinsic protection time of the skin, • seek shade, • undertake outdoor activities in the morning and evening hours, • accustom the skin slowly to the sun (e.g. in spring / on holiday), • avoid sunburn at all events.
	Consensus strength: 100%

The avoidance of exposure to strong sunlight is the most important sun protection measure and has the highest priority.

The level of possible exposure to UV rays depends on:

time of year, time of day, weather conditions (cloud thickness and degree of cloud cover), altitude (sea level, mountains), reflection from the ground (earth, sand, snow, water), shade.

The strength of solar radiation is generally easy to estimate by looking at the sky. However, if the sky is cloudy, UV exposure can be underestimated since even with a thin, closed cloud cover UV radiation can penetrate the clouds and is dispersed on the clouds. In this case, what is known as the UV index helps assess the possible exposure to UV rays. It is determined by measurements and calculations and is published by the weather service and other institutions in the media (internet, newspaper, television). Various sun protection measures are recommended by the WHO according to the level of the UV index.

If the UV index is not known, the “shadow rule” can be used to establish whether dangerous exposure to the sun is to be expected. The sun stands more than 45° above the horizon when the shadow is shorter than the object casting the shadow. In this case, strong UV radiation may be expected. However, solar radiation can contain high proportions of UV radiation even when the sun is lower in the sky (approx. 35° - 40°).

The strongest solar radiation occurs at the sun’s highest point in the middle of the day and when there is little cloud. About 50% of the total UV dose for one day occurs in the timeframe of 2 hours before and after the sun’s highest point, hence the recommendation, where possible, to avoid going outside altogether in very strong sunlight between the hours of 11 a.m. and 4 p.m.. Strong UV exposure can also occur before and after these times if there is a clear sky, so that appropriate sun protection measures are also to be recommended then. Sporting and recreational activities should where possible be switched to the morning and evening hours if weather conditions dictate.

It should be noted that the highest point of the sun within a time zone depends on geographical longitude. In the east of Germany the sun is highest in summer at 1 p.m. (Central European Summer Time), but not until 1.40 p.m. in the west of Germany. Over the whole Central European Summer Time zone, for example, there is a time window for the highest point of the sun of between 12.30 p.m. (Poland) and 2.30 p.m. (Spain). Therefore, the recommendation to avoid the midday sun (+/- 2 hours either side of the sun’s highest point) should be adapted to local circumstances, particularly when travelling abroad.

The intrinsic protection time of the skin depends on skin type. To avoid sunburn, the length of time spent in the sun should not exceed this intrinsic protection time.

If it is not possible to avoid being outside in the sun in strong sunlight, the length of time spent out in the sun should be kept as short as possible to minimise the UV radiation dose. If it is not possible to limit the length of time in the sun, shade should be sought or created as a further measure. At the same time, it should be noted that not all types of shade are sufficient. UV radiation not only emanates directly from the direction of the sun, but also from the blue background of the sky through the dispersion of solar UV radiation by air molecules. For this reason, shading from direct solar radiation (e.g. with a sunshade) is not sufficient on its own. Even if the sun is blocked out, up to 50% of the total UV radiation load is still received if there is insufficient shade. In this case, additional sun protection measures are needed. If the blue background of the sky as well as direct solar radiation is largely blocked out (e.g. in deep alleyways between houses or in a dense wood), the proportion of dispersed solar UV radiation is less and the shade is sufficient.

Avoidance of sunburn

In the Nambour Skin Cancer Study, a strong association was found between basal cell carcinomas (SCC) on the upper body and the number of reported episodes of sunburn. Study participants who had suffered sunburn more than 10 times had almost twice the risk of basal cell carcinoma (BCC) on the upper body as people without sunburn (Odds Ratio (OR) OR 2.49, 95% Confidence Interval (CI) 1.04-5.99). The incidence of BCC on the head increased with the number of sunburns (OR 1.79, 95% CI 0.93-3.45 for > 10 sunburns) [296].

Slow habituation to the sun

In principle, the skin should always be accustomed gradually to the sun. This applies in particular with increasing solar radiation in the spring or with increased UV exposure on holiday. Habituation can be done by repeated brief outings in the sun that are short enough to ensure that the skin does not turn red.

4.1.1.2. Wearing suitable clothing

4.3.	Consensus-based recommendation
EC	When staying outside in the sun, suitable clothing, headwear and sunglasses should be worn for protection.
	Consensus strength: 100%

If it is not possible to avoid being outside in strong sunlight and insufficient shade is available, then the UV exposure of the skin should be reduced as far as possible by individual protection against solar radiation. This can be done for example with suitable clothing that covers as much of the skin as possible.

Suitable clothing should be preferred to the use of sunscreens for individual sun protection. Clothing absorbs UV radiation. The unit of measurement of absorption is the UV protection factor (UPF), which is comparable to the sun protection factor (SPF) of sunscreens. Simple T-shirts have a UPF of 20 and over, which is usually sufficient for individual sun protection. More robust clothing and special UV protective clothing can exhibit a UPF of 50, 80 or more even. In contrast to the SPF of sunscreens (see below), the UPF is immediately present and effective as long as the article of clothing is worn. With very thin materials (e.g. shirts, blouses, night shirts, some swimwear) the UPF is less than 20 and may not suffice, in which case a second layer of clothing can provide a remedy. As the UPF is inversely proportional to the degree of penetration of UV radiation through the clothing, the UV protective factors of two articles of clothing are multiplied when they are worn on top of one another. If, for example, a T-shirt and a shirt each with a UPF of 20 are worn over one another, then this combination provides effective protection with a UPF of 40.

4.1.1.3. Protection of the eyes against UV radiation

4.4.	Consensus-based recommendation
EC	Suitable sunglasses must be worn in strong sunlight. Never look directly at the sun in the sky. This applies even when wearing sunglasses.
	Consensus strength: 96%

As well as skin protection, protection of the eyes against solar radiation is very important, particularly as basal cell and squamous cell carcinomas can also occur in the eye. It has therefore also been included in the recommendations for the primary prevention of skin cancer. Suitable sunglasses serve to protect the eyes from strong sunlight [297]. Sunglasses are considered to be suitable if they comply with European standard EN 1836 for sunglasses. This standard defines five different shade categories (degree of darkening). For everyday use, sunglasses of shade category 2 or 3 are sufficient. Sunglasses of shade category 4 are used for extreme conditions, e.g. on glaciers, but are not suitable for driving in traffic.

Looking directly at the sun when it is high in the sky can cause irreversible damage in a minimal amount of time, to the extent even of causing blindness. This also applies when wearing sunglasses. Sunglasses are not suitable for observing the sun. Solar eclipses of the sun, for example, can only be safely observed with special sun protection filters with very high radiation absorption. Only at sunrise and sunset is the use of eye protection filters not necessary.

4.1.1.4. Use of sunscreens

4.5.	Evidence-based recommendation
Degree of recommendation A	Where possible, physical measures (avoidance of exposure, textiles) must be used in the first place for protection from sunlight. Sunscreens must be used for areas of the skin that cannot otherwise be protected. The use of sunscreens must not result in staying out longer in the sun.
Level of evidence 1+	Primary studies: [298-303]
	Consensus strength: 96%

4.6.	Consensus-based recommendation
EC	<p>Sunscreens should be applied carefully to free areas of skin that are not covered by clothing (head, face, hands, arms, legs) and the following should be observed:</p> <ul style="list-style-type: none"> • use an appropriate sun protection factor, • apply as thick a layer as possible (2 mg/cm²), • apply evenly to all uncovered areas of skin, • apply before exposure to the sun, • repeat the application after 2 hours and after bathing (the protective time is not prolonged as a result).
	Consensus strength: 96%

4.7.	Evidence-based statement
Level of evidence 1 ++	There are contradictory data as to whether the risk of melanoma is reduced by using sunscreen.
	Primary studies: [301-305]
	Consensus strength: 96%

The correct use of sunscreens is important. Used wrongly, their effect can be severely reduced.

Sunscreens should be applied in as thick a layer as possible. An application layer of 2 mg/cm² is taken as a basis when determining the sun protection factors of sunscreens (see e.g.

http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/sunscreen_mandate_en.pdf).

In order to achieve the stated SPF for a sunscreen product, an adult (approx. 1.5 - 2 m² skin) must use about 30 to 40 ml for the whole body. This equates to about 1/5 of a commercially available bottle. Sunscreen must be applied evenly and to all uncovered areas of skin. It is estimated that in practice only about 1/3 to 1/5 of the stated SPF is actually achieved, resulting in an overestimation of the protective effect. The sunscreen should be applied before the start of exposure to the sun and not just once the subject is outside in the sun. Sweating and bathing dissolve the sunscreen from the skin after a time. For this reason, water-resistant sunscreen should be preferred and the application repeated no later than every 2 hours. The sunscreen must be reapplied after bathing. The lips also should be protected with a suitable product.

As the predictive value of the sun protection factor is limited for practical use, the efficacy of sunscreens are now no longer described by numerical values, but verbally in four categories for different levels of protection (low, medium, high, very high) in accordance with Commission Recommendation 2006/647/EC.

Sunscreens were originally developed to protect the skin from sunburn. They absorb UV radiation to a large extent, but not completely. They allow part of the UV radiation to pass through to the skin, so that the UV dose can accumulate there and contribute to long-term effects such as the emergence of skin cancer.

Systematic reviews and meta-analyses of observational studies showed that the incidence of malignant melanomas (MM) in sunscreen users is not increased, but is also not reduced [305, 306]. Other studies find evidence that the use of sunscreen may even be associated with an increased risk of melanoma [300]. It is suspected that this is due to a false sense of security engendered by the use of sunscreen and the resultant longer periods of time spent in the sun [298]. People who used screens with a higher SPF sunbathed for longer [299]. The use of what are known as “self-tanning sunscreens” containing psoralens (bergamot oil) appears to be associated with an even higher risk of developing melanoma [300].

Different skin types (see Table 27) respond differently to UV radiation and the associated risk of skin cancer.

Gorham et al. (2007) describe how the use of sunscreen in light-skinned people possibly increases the risk for melanoma development. Overall, the authors find no significant increase in the risk of melanoma associated with sunscreens in their systematic review. However, if studies conducted in the northern hemisphere above a latitude of 40° are pooled, the odds ratio is 1.6 (95% CI 1.3-1.9). The authors conclude that the use of sunscreen with UVB filters only could at least contribute to the risk of melanoma in populations residing above latitude 40° [301].

Lin et al. (2011) reported in a systematic review that the regular use of sunscreen reduces the risk of SCC, but not the risk of developing BCC [303]. After a 10-year follow-up, a reduced risk of melanoma was found in the intervention group [302]. In subtropical areas, the development of solar keratoses can be reduced by using sunscreens [304].

4.1.1.5. UV exposure from artificial sources

4.8.	Consensus-based recommendation
EC	In accordance with international and national recommendations (WHO, ICNIRP, EUROSkin, SSK, DKH and ADP), the use of sun studios must be avoided to reduce the risk of development of skin cancer.
	Consensus strength: 96%

R. Greinert

UV exposure from artificial UV sources can also result in skin and eye damage. In the private life, particular mention may be made here of visits to solaria. The artificial UV exposure that exists in solaria is just as dangerous as natural sunlight in terms of the development of skin cancer (section 3.1, Aetiology).

A meta-analysis by the IARC (section 3.1) shows that this type of exposure cannot be neglected in respect of the development of MM [290]. The IARC shows that the risk of developing MM later in life is increased by 75% if people have started using solarium regularly before the age of 35 years (regularly = once a month; section 3.1). An update of the data from 2012 confirms that the risk is almost doubled [7]. This finding and a variety of publications from the field of epidemiology and basic research prompted the IARC additionally in 2009 to classify the UV radiation used in solariums as a group 1 carcinogen (“carcinogenic in humans”) and thus, the same as solar UV radiation [4]. UV radiation is therefore classed in the group of substances and radiation qualities that possesses the highest proven carcinogenic potential for humans.

In Germany, there has been a Law on the Protection of Humans from Non-Ionising Radiation (NiSG) and an associated UV Protection Ordinance, <http://www.gesetze-im-internet.de/uvsv/index.html>) governing the operation and use of solarium since July 2009. In particular, it was laid down that adolescents under 18 years of age may not use solarium (section 4, NiSG). The ordinance also stipulates that people with skin type I and II should not use solarium and that specialist staff must be on hand to comply with the duties of information under the UVSV. Since January 2012, the maximum erythema-effective UV radiation strength in solariums is defined as $\leq 0.3 \text{ W/m}^2$.

Generally, the use of solariums is not recommended by WHO, ICNIRP, EUROSkin, SSK, DKH and ADP.

UV exposure can occur in the occupational sphere, e.g. during welding or from the use of UV radiation sources. The use of suitable protective measures against damage from UV radiation is required by the relevant health and safety regulations. The necessary measures must be implemented in a consistent way in the daily work environment.

4.1.1.6. Food supplements

4.9.	Evidence-based recommendation
Degree of recommendation A	Food supplementation with selenium, vitamin A and beta-carotene must not be recommended as a measure for skin cancer prevention.
Level of evidence 1++	Primary studies: [304, 307, 308]
	Consensus strength: 100%

A meta-analysis of randomised clinical trials showed that the incidence of BCC and SCC of the skin was not reduced by taking antioxidative supplements (selenium, beta-carotene, vitamin A) [308]. Likewise, the development of actinic keratosis (AK) was not reduced by taking beta-carotene [304].

There are no confirmed results from cohort or intervention studies that suggest a particular form of diet as a prevention strategy.

The consumption of antioxidative substances such as selenium, beta-carotene and vitamin A is strongly advocated in the lay press as an additional means of UV protection. Beta-carotenes have no sun-protective effect [307]. A meta-analysis also

showed no clinical evidence of the preventive effect of antioxidative supplements on skin cancer [308].

4.1.2. Behaviours for certain groups

H. Grundhewer, M. Diensberg, H. Siekmann

Although many studies are concerned with sun protection behaviour, particularly of children and adolescents, and focus on the sustained nature of any changes (e.g. [309-312]), there are only very few articles that recommend scientifically justifiable differences in sun protection measures for certain groups (see also section 4.2.2).

All the articles universally emphasise the health damage that can occur in all the observed groups from increased or intensive solar radiation.

4.10.	Consensus-based recommendation
EC	Intensive solar / ultraviolet (UV) radiation represents a risk for skin cancer to all certain groups and must be avoided.
	Consensus strength: 100%

In assessing the need for and the nature of sun protection measures, the individual sensitivity of the skin to solar radiation is an essential factor. The extent and nature of the required sun protection depends on the skin type. People with skin types I and II are particularly sensitive, as well as people with a genetically or pathologically increased sensitivity to UV radiation.

4.1.2.1. Children

4.11.	Consensus-based recommendation
EC	Children must not be allowed to develop sunburn.
	Consensus strength: 96%

4.12.	Consensus-based recommendation
EC	Babies must not be exposed to direct sunlight.
	Consensus strength: 100%

4.13.	Consensus-based recommendation
EC	Children must be required to wear skin-covering clothing in strong sunlight.
	Consensus strength: 100%

4.14.	Evidence-based recommendation
Degree of recommendation A	Children with a light skin colour in particular must use sunscreens as well as avoid strong ultraviolet (UV) radiation exposure and additionally wear sun-protective textiles.
Level of evidence 1++	Primary studies: [313]
	Consensus strength: 96%

4.15.	Consensus-based recommendation
EC	Children's eyes must be protected by suitable children's sunglasses that meet the previously mentioned requirements (see Recommendation 4.4.).
	Consensus strength: 92%

H. Grundhewer, M. Diensberg

Children's skin is very susceptible to the effect of solar radiation. This applies in particular to those with a light skin colour and freckles. Sunburn in children increases the risk of developing skin cancer later on. Children therefore require very careful sun protection. As in adults, this includes first of all the avoidance of strong UV exposure, then wearing suitable clothing that covers as much of the body as possible, including suitable headwear, and lastly, as a supplementary measure, the use of sunscreens on unprotected areas of skin.

In a randomised controlled trial, Gallagher et al. (2000) show, that the number of naevi in children with light skin can be reduced (statistically significantly in children with freckles) by the extensive use of sunscreen [313].

4.1.2.2. Immunosuppressed / transplant patients

4.16.	Evidence-based recommendation
Degree of recommendation A	Immunosuppressed transplant recipients must use sunscreens to protect themselves from skin cancer as part of a consistent, comprehensive ultraviolet (UV) radiation protection strategy.
Level of evidence 2+	Primary studies: [314]
	Consensus strength: 96%

4.17.	Consensus-based recommendation
EC	Immunosuppressed people must ensure they have a consistent, comprehensive ultraviolet (UV) radiation protection strategy.
	Consensus strength: 100%

Ulrich et al. (2009) conducted a two-year prospective study with 120 organ transplant patients. In addition to information about sun protection, the study group also received sunscreen; the control group received information material only. It was shown that in immunosuppressed organ transplant recipients the regular use of sunscreen – as part of a consistent strategy of protection against UV radiation – protects against the development of further actinic keratoses, invasive SCCs and also, to a lesser extent, against BCC [314].

These recommendations chime with the international Kidney Disease Improving Global Outcomes Guidelines on the care of renal transplant recipients, which advocate consistent, intensive UV protection, regular self-examinations and annual whole-body examinations by a dermatologist for all transplant recipients [315].

For the risk of low vitamin D levels as a result of consistent UV protection in immunosuppressed patients, see the following section 4.1.3.

4.1.3. Potential side effects

R.Greinert, B. Volkmer, H. Siekmann

UV radiation has been shown to trigger skin cancer. The risk of developing MM as well as SCC and BCC is increased by UV exposure. As this is a well-known relationship, the most important primary preventive measure is the avoidance of increased UV exposure. This can be achieved by various individual behaviours and measures (e.g. sun-protective textiles, sunscreen, and avoidance of the midday sun).

UV radiation is necessary for vitamin D synthesis in the skin; one potential adverse effect of sun protection measures may be an associated reduction in vitamin D levels.

Additionally, the avoidance of increased outdoor UV exposure could bring with it the adverse effect of a lack of movement. The issue of adverse effects has been investigated in some studies.

4.1.3.1. Role of vitamin D

4.18.	Consensus-based recommendation
EC	In people at high risk for skin cancer (e.g.: transplant recipients, immunosuppressed patients) who practice consistent, extensive sun protection, vitamin D levels should be checked and vitamin D supplements given where necessary.
	Consensus strength: 100%

Vitamin D plays an important role in the calcium balance and in bone metabolism.

Sun protection measures reduced cutaneous vitamin D synthesis. Consistent sun protection in certain groups of people can promote vitamin D deficiency [316].

Srikanth et al. (2007) found an inverse association between skin cancer and fractures: elderly people with a fracture presented more rarely with NMSC, which was interpreted as a lower cumulative lifetime exposure to the sun [317]. The avoidance of exposure to the sun can have long-term detrimental consequences for future bone health. A review reports contradictory studies on the reduction of fractures by administration of calcium and vitamin D [316]. However, the analysis revealed a reduction in falls in elderly people as a result of administration of vitamin D.

Ulrich et al. (2009) observed no differences in vitamin D levels after 24 months in organ-transplant recipients who practised maximum sun protection compared with the control group. However, particularly in risk groups (immunosuppressed patients, transplant recipients, etc.) who practise intensive sun protection, they recommend that vitamin D levels must be checked and, where necessary, vitamin D supplements given [314].

4.1.3.2. Effect of vitamin D on the development of various types of cancer

4.19.	Evidence-based statement
Level of evidence 2+	Moderate exposure to ultraviolet (UV) radiation and high vitamin D levels possibly have a protective effect against the occurrence and development of various types of cancer, including malignant melanoma. However, the existing evidence for a relationship between the risk of cancer and vitamin D intake is insufficient.
	Primary studies: [316, 318-320]
	Consensus strength: 100%

4.20.	Consensus-based statement
EC	The Guideline Group is currently unable to answer the question as to the optimal (reasonable) ultraviolet (UV) radiation exposure to ensure sufficient endogenous vitamin D production without incurring an increased risk of skin cancer.
	Consensus strength: 100%

A review examined the question of whether exposure to the sun has a protective effect on the development of other types of cancer. There were possibly protective effects of sunlight against the development of breast and prostate cancer. The situation revealed by the studies, however, was equivocal; no relationship could be established in the other types of cancer [320].

Tuohimaa et al. (2007), in a historical cohort study, showed that people with skin cancer (all types) were at increased risk for further primary cancer. People living in sunnier latitudes had a somewhat lower risk for a second tumour, which was attributed to a possibly protective effect of vitamin D [319].

A review by Krause (2006) collated studies that pointed to a protective effect of sunlight on colon and breast cancer [318].

Schwalfenberg (2007) in a review presented studies that point to a protective effect of vitamin D on heart diseases and certain types of cancer. However, the review was not methodologically unimpeachable [316].

4.21.	Dissenting opinion of DEGAM on section 4.1.
	The German Society of General Practice and Family Medicine (DEGAM) generally does not pass on recommendations with the strength of recommendation “must” to the general population. On the one hand, the data relating to a possible vitamin D deficiency and the need to spend time outdoors does not suffice to issue a general recommendation to avoid sunlight. Secondly, it is not DEGAM’s policy to give well-intentioned-generalised recommendations for behaviour in terms of cancer prevention to the population, which fail to take into account the particular aspects and preferences of the individual subjects.

4.2. Primary prevention measures for the population

4.2.1. Behavioural preventive measures

M. Asmuß

Knowledge about the effects of UV radiation and about appropriate UV protection behaviour forms the basis for risk awareness and for a positive attitude towards UV protection recommendations. These in turn are essential prerequisites for appropriate sun protection behaviour. The successful communication of knowledge is therefore an underlying and necessary part of primary prevention.

In terms of the communication of knowledge about the effects of UV radiation and UV protection measures, there is evidence that a significant improvement in the state of knowledge can be successfully achieved with different methods and in various target groups. At least some studies also document a certain persistence of this improved state of knowledge.

4.22.	Evidence-based recommendation
Degree of recommendation A	Knowledge about the effects of ultraviolet (UV) radiation and sun protection measures must be passed on constantly.
Level of evidence 1+	Primary studies: [310, 321-325]
	Consensus strength: 100%

Bränström et al. (2003), in a randomised controlled trial in randomly recruited adult participants from the Swedish population register, showed that a significant increase in knowledge and a decrease in the positive attitude towards sunbathing and tanning could be achieved, particularly in younger women [321]. A follow-up of the persistence of the effect of the intervention was not performed.

Results from a randomised controlled trial by Buller et al. (2008) in schoolchildren aged 5 to 13 years show a significant increase in knowledge from computer-based education about sun protection, which was enhanced further through the combination with a one-hour presentation by teachers [322]. Effects on sun protection behaviour, however, were dubious and only significant in younger children, and then only in the combination group (computer-based education with an additional presentation by teachers).

Gritz et al. (2007) in a randomised controlled trial in association with the “Sun Protection is Fun!” campaign established that the state of knowledge about sun protection in preschool staff was still significantly improved 2 years after the end of an intervention involving the use of training units, a video, a newsletter and a curriculum [323]. This improvement in the state of knowledge was associated with an improvement in sun protection behaviour (use of sunscreen, sun-protective textiles, seeking shade).

Loescher et al. (1995) in a randomised controlled trial show that knowledge and understanding of sun protection can be improved in preschool children as young as 4-5 years old with the aid of a curriculum adapted to their age group, compared with a control group. However, the study shows that children in this age group are not able to put this theoretical knowledge to practical use on their own and without the help of adults [310].

A similarly school-based campaign, in which adolescents were used as information mediators for younger fellow pupils and gave lectures on the subject of UV protection, still showed a significant increase in knowledge 6 months after the end of the intervention (controlled pre-post study, endpoint studied: communication of knowledge) [324].

Bastuji-Garin et al. (1999) in an interventional study show a significant improvement in knowledge in 9-year old children 3 months after a 4-week school-based campaign using teaching materials produced with the aid of dermatologists and health experts [325]. This improvement in knowledge was associated with improved sun protection behaviour (use of sun-protective textiles and sunscreen as well as avoiding going out during the most sun-intensive time of day) after the intervention compared with behaviour before the intervention.

4.2.1.1. Behaviour-changing interventions

Information about the risks of UV radiation and knowledge about how to protect oneself are a necessary prerequisite for appropriate sun protection behaviour, but are not sufficient for consistent conversion into practice [310, 326, 327].

For this reason, particular attention must be paid to strategies that produce as permanent a change in behaviour as possible. A successful intervention strategy cannot be deduced from the available studies. The approaches and methods are too disparate for that. The effects of individual components in the overall outcome of multicomponent campaigns cannot be determined. Additionally, there is often a lack of evidence about the sustainability of the observed effects and the transposability to the situation in Germany. Nevertheless, some basic recommendations can be established.

4.23.	Evidence-based recommendation
Degree of recommendation B	To improve sun protection behaviour, interventions about ultraviolet (UV) radiation protection should be conducted in schools and playschools or day care centres, with particular regard to the target group of younger children.
Level of evidence 1+	Primary studies: [323, 328-330]
	Consensus strength: 100%

Most existing interventions are addressed either directly or indirectly via parents, teaching staff, kindergarten teachers or other carers to the target group of children. This is logical for several reasons. Firstly, childhood and adolescence are an essential phase in life for the later risk of skin cancer; and secondly, several studies document the potential for at least a short- and medium-term positive effect on sun protection behaviour in 9-year-old primary school children [325], 5- to 6-year-old primary school children ("Kidskin", [328, 329]) and preschool children [323]. In intervention groups, use of sun-protective textiles [323, 325, 328, 329], use of sunscreen [323], avoidance of staying outdoors during the most sun-intensive time of the day [325] or finding shade [323, 328, 329] increased in comparison with control groups. In addition, the behaviour of the supervising adults could also be influenced through child-targeted interventions [323].

Even in children as young as 4 to 5 years, knowledge about sun protection could be improved with the aid of an age-adapted intervention using e.g. games, songs and picture books compared to a control group. The effect was also still significant in the intervention groups of a randomised controlled trial (sample of 12 classes of preschool children aged 4-5 years) 7 weeks after the end of the intervention. However, help from

adults is required to put this knowledge into practical effect. The authors therefore highlight the need to include parents in the intervention [310].

Only a few studies examine the effects on endpoints such as skin tanning or number of naevi. The fact that suitable school-based campaigns have the potential to influence these endpoints to at least a moderate extent is demonstrated by the “Kidskin” intervention study undertaken over 5 years in 5- to 6-year-old primary school children. After 2 years, reduced exposure to the sun and less tanning were described in the intervention groups compared with the control group. After 5 years, a slightly (albeit statistically non-significantly) smaller number of naevi was observed in the intervention groups compared with the control group [329, 330].

By contrast, the SoleSi SoleNo-GISED intervention programme conducted in Italian primary schools [331] showed no effect on the endpoint “number of sunburns” or number of naevi one year after the intervention. Possible explanations for the negative result discussed by the authors include the high level of sun protection already present in the study population before the intervention, the more generally available information material and the overly short follow-up of only one year in respect of the number of naevi.

There is no evidence from the available studies of detrimental effects of interventions in schools to improve appropriate sun protection behaviour. In particular, no difference was found between children from sun protection intervention groups and control groups in terms of body-mass index or self-reported outdoor activity [303].

4.24.	Evidence-based recommendation
Degree of recommendation B	Interventions that target a sustained effect on behaviour should involve several components and should be implemented intensively and repeatedly.
Level of evidence 2+	Primary studies: [323, 326, 332-335]
	Consensus strength: 100%

Buller and Borland (1999) studied 24 sun protection programmes for children aged under 14 years. Short-term interventions such as individual lessons or information day visits (“sun safety health fair”) were suitable for improving knowledge about sun protection, but had little effect on attitude and behaviour. More intensive, several-day-long to several-week-long interventions combining series of lectures, information materials, workbooks, etc., had a greater effect [326].

Dietrich et al. (2000) report on a two-year multicomponent programme “SunSafe”, in which schools, kindergartens, medical practices and recreational facilities in several communities took part. The sun protection behaviour of children was successfully promoted. This effect was enhanced by a second, less intensive follow-up campaign [332].

Comparatively successful long-term programmes such as “Kidskin” [335] or “SunSafe” [332], as well as the 2-year intervention “Sun Protection Is Fun” directed at preschool

staff [323], have been developed with a view to influencing behaviour. They combine different components, e.g. age-specific teaching plans, training units for teachers and lifeguards on the beach, information and training material, posters, computer-based teaching modules, etc., and include parents and others with a supervisory role [333].

Weinstock et al. (2002) confirm moderate but sustained positive effects from a two-year multicomponent intervention with information material, sunscreen, a personal test of sensitivity to the sun, and written and verbal feedback among beachgoers. Reported sun protection behaviour improved in the intervention group compared with a control group, with the effect being most pronounced in the 16- to 24-year-old age group (Weinstock et al. 2002).

The one-off provision of information material to parents of young children is obviously not sufficient to exert a significant effect on sun protection behaviour, even when accompanied by the free supply of sunscreen [336]. An intervention confined to swimming lessons for primary school children – consisting of 3- to 5-minute lectures before the swimming lesson in combination with information material for use at home – was also unsuitable for exerting an effect on sun protection behaviour and tanning [337].

4.25.	Evidence-based recommendation
Degree of recommendation B	Doctor-patient communication (e.g. in connection also with skin cancer screening) should be used for primary preventive measures. (see also section 5.4 Doctor-patient communication)
Level of evidence 1+	Primary studies: [312, 338-340]
	Consensus strength: 100%

The importance of a personal approach, e.g. as part of a doctor-patient discussion, in effectively influencing behaviour is particularly apparent in adolescents and adults. There is evidence from several studies that individualised interventions (individual risk assessment, personal doctor-patient discussion) increase the chances of influencing behaviour. Medical counselling with individually tailored feedback reports showed significant differences in terms of sun protection behaviour between intervention group and control group in 11- to 15-year olds even 24 months after the intervention [312]. Falk and Magnusson (2011) show that personal counselling about sun protection behaviour during a medical consultation, combined with an examination of existing naevi, resulted in improved sun protection behaviour in adults three years even after the intervention – although it was significantly improved only in terms of the use of sunscreen. Written information in the form of a letter on its own had no effect. An intervention tailored to the target group of solarium users and focussing on appearance showed effects on attitude and behaviour (number of visits to solariums) in young female solarium users [338, 339].

4.26.	Consensus-based recommendation																																						
EC	<p>The following recommendations must be given in the doctor-patient discussion on cancer prevention:</p> <table border="1" data-bbox="432 477 1410 1379"> <thead> <tr> <th data-bbox="432 477 1267 521">Content</th> <th data-bbox="1267 477 1410 521">Done?</th> </tr> </thead> <tbody> <tr> <td data-bbox="432 521 1267 566">• Information about the risks of ultraviolet (UV) radiation</td> <td data-bbox="1267 521 1410 566"></td> </tr> <tr> <td data-bbox="432 566 1267 611">• Motivation to change behaviour</td> <td data-bbox="1267 566 1410 611"></td> </tr> <tr> <td data-bbox="432 611 1267 656">• Avoid exposure to strong solar radiation</td> <td data-bbox="1267 611 1410 656"></td> </tr> <tr> <td data-bbox="432 656 1267 701"> ○ Avoid the midday sun</td> <td data-bbox="1267 656 1410 701"></td> </tr> <tr> <td data-bbox="432 701 1267 745"> ○ Stay out in the sun for as little as possible</td> <td data-bbox="1267 701 1410 745"></td> </tr> <tr> <td data-bbox="432 745 1267 790"> ○ Seek shade</td> <td data-bbox="1267 745 1410 790"></td> </tr> <tr> <td data-bbox="432 790 1267 835"> ○ Avoid sunburn</td> <td data-bbox="1267 790 1410 835"></td> </tr> <tr> <td data-bbox="432 835 1267 880"> ○ Be aware of the ultraviolet (UV) radiation index</td> <td data-bbox="1267 835 1410 880"></td> </tr> <tr> <td data-bbox="432 880 1267 925">• Accustom the skin slowly to the sun</td> <td data-bbox="1267 880 1410 925"></td> </tr> <tr> <td data-bbox="432 925 1267 969">• Wear protective clothing</td> <td data-bbox="1267 925 1410 969"></td> </tr> <tr> <td data-bbox="432 969 1267 1014">• Use sunscreens without prolonging exposure time</td> <td data-bbox="1267 969 1410 1014"></td> </tr> <tr> <td data-bbox="432 1014 1267 1059"> ○ Be aware of individual skin sensitivity</td> <td data-bbox="1267 1014 1410 1059"></td> </tr> <tr> <td data-bbox="432 1059 1267 1104"> ○ Give information about the different skin types</td> <td data-bbox="1267 1059 1410 1104"></td> </tr> <tr> <td data-bbox="432 1104 1267 1193">• Advice on individual protective measures according to the patient's skin type</td> <td data-bbox="1267 1104 1410 1193"></td> </tr> <tr> <td data-bbox="432 1193 1267 1238">• Pay attention to possible side effects of medicines in the sun</td> <td data-bbox="1267 1193 1410 1238"></td> </tr> <tr> <td data-bbox="432 1238 1267 1283">• Protect children in particular</td> <td data-bbox="1267 1238 1410 1283"></td> </tr> <tr> <td data-bbox="432 1283 1267 1328">• Avoid sun studios (refer to NiSG)</td> <td data-bbox="1267 1283 1410 1328"></td> </tr> <tr> <td data-bbox="432 1328 1267 1373">• Wear sunglasses</td> <td data-bbox="1267 1328 1410 1373"></td> </tr> </tbody> </table>	Content	Done?	• Information about the risks of ultraviolet (UV) radiation		• Motivation to change behaviour		• Avoid exposure to strong solar radiation		○ Avoid the midday sun		○ Stay out in the sun for as little as possible		○ Seek shade		○ Avoid sunburn		○ Be aware of the ultraviolet (UV) radiation index		• Accustom the skin slowly to the sun		• Wear protective clothing		• Use sunscreens without prolonging exposure time		○ Be aware of individual skin sensitivity		○ Give information about the different skin types		• Advice on individual protective measures according to the patient's skin type		• Pay attention to possible side effects of medicines in the sun		• Protect children in particular		• Avoid sun studios (refer to NiSG)		• Wear sunglasses	
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	Consensus strength: 100%																																						

4.2.1.2. Ultraviolet (UV) radiation index

4.27.	Consensus-based recommendation
EC	<p>The ultraviolet (UV) radiation index should be more intensively publicised, firmly anchored in the media and used as an aid in UV protection campaigns. At the same time, the limits of its value should be observed.</p>
	Consensus strength: 96%

The UV index (UVI) was developed by the WHO in association with the ICNIRP (International Commission on Non-Ionizing Radiation Protection), the World Meteorological Organisation, the UNEP (United Nations Environment Programme) and other co-operation partners as an internationally standardised measure of the erythema-effective (= sunburn-effective) radiation strength and as an indicator of the skin-damaging potential of the solar UV radiation reaching the earth's surface. The

higher the UVI, the more rapidly sunburn will occur on unprotected skin. Protective measures are recommended from a UVI of 3 (seek shade in the midday period, sun-protective textiles, use of sunscreens).

The UVI should serve as a means of promoting risk awareness and drawing attention to the need for suitable UV protection [341]. It can be published as part of the weather forecast, particularly on the internet. Further explanations of the UV index and international protection recommendations for the different UVI values can be found e.g. on the website of the German Federal Office for Radiation Protection, http://www.bfs.de/de/uv/uv2/uv_messnetz/uvi.

The UVI can be used to assess the level of erythema-effective UV radiation strength from the sun, for example as part of information campaigns and interventions on sun protection or in information materials. It can also help to assess the necessary sun protection measures and provide guidance. As an instrument of behavioural prevention, the UVI currently plays no appreciable role [321, 342, 343]. A need is therefore seen to give the UVI a firmer place among sun protection recommendations, at the same time as using the opportunities offered by the new media (internet, mobile communication devices). However, the limits of the UVI must also be clearly communicated. The UVI is defined for a horizontal surface. Oblique radiation from the sun to inclined areas of skin such as the nose, forehead or shoulders can be higher than to the horizontal surface of the earth. The UVI can – for example in environments with strong UV reflection such as snow or water – underestimate the actual erythema-effective radiation strength and cannot take into account a person's individual sensitivities.

Effect of UV photographs and self-examination on behaviour

Hollands et al. (2010) find only limited evidence that the use of images visualising individual "UV damage" or signs of skin ageing contribute to behaviour change [344]. Other studies indicate that, for example, UV photograph-based evidence of the negative consequences of excessive UV radiation on appearance may have a positive influence on sun protection behaviour, at least in some target groups [338, 339, 345, 346]. The, for the most part, inadequate explanation of the health relevance of visualising pigmentations for the purpose of influencing behaviour is usually regarded as a matter for criticism. No recommendation is therefore given in this guideline.

There are no systematic studies on the question of whether and to what extent risk assessment or sun protection behaviour can be affected by skin self-examinations. A gap is seen here. Robinson et al. (2007) point out that, in the randomised controlled trial they undertook in a high-risk group, concern about UV-induced skin damage *decreased* in one intervention group. In this intervention group, self-examination was performed jointly with a partner (definition of high-risk group: melanoma patients, persons with family members with melanoma or persons with > 50 naevi or > 2 atypical naevi). By way of explanation, the authors suggest that the trust in their own abilities to examine the skin was possibly increased [347]. Whether and how subjects' sun protection behaviour was actually affected by the intervention was not investigated.

Need for further research

In evaluating screenings and/or studies of skin self-examination (SSE), the effects on risk awareness and sun protection behaviour should be recorded at the same time.

4.2.1.3. Interventions in children and adolescents

4.28.	Evidence-based recommendation
Degree of recommendation A	Parents of babies and young children must be informed about appropriate sun protection for their children. (see also Recommendation 4.7.)
Level of evidence 1++	Primary studies: [348]
	Consensus strength: 100%

S. Singer

Crane et al. (2006) regularly and extensively informed parents of babies and young children about age-appropriate sun protection at medical check-ups in the first three years of life. Over the course of the three years, knowledge in the intervention group increased markedly and sun protection behaviour also improved [348].

4.29.	Evidence-based recommendation
Degree of recommendation A	Schoolchildren and adolescents must be intensively informed about skin cancer risks, instructed in the practical use of protective measures and receive appropriate support from teachers.
Level of evidence 1++	Primary studies: [332]
	Consensus strength: 100%

As a result of a two-year multicomponent campaign involving schools, kindergartens, medical practices and recreational facilities, the proportion of children practising sun protection in the intervention towns was increased from 58% to 73%. This increase was due to the use of sunscreen [332].

4.30.	Evidence-based recommendation
Degree of recommendation A	The tendency to acquire risk factors for skin cancer (e.g. naevi) must be reduced by interventions at school age with a long-term and repetitive approach.
Level of evidence 2+	Primary studies: [328, 330, 335, 349, 350]
	Consensus strength: 92%

Milne et al. (2008) reported in their study that there was slight evidence after a six-year follow-up that the intervention resulted in a smaller increase in the number of new naevi on boys' upper body. No difference was found for girls [350].

4.2.2. Structural preventive measures

S. Singer, M. Asmuß

4.2.2.1. Introduction

There are no studies investigating the systematic effects of structural preventive measures. Where structural preventive components are part of the interventions, such as the installation of shade sails in schools in Dobbinson's case (2009) or sun protection measures at the swimming pool as part of the "Pool-Cool" programme (Escoffery, 2009), it is not possible to define what role they play in the effect of the intervention as a whole [351, 352]. The need for structural preventive measures, however, is postulated in many studies, particularly as the efficacy of interventions targeted solely to changing behaviour frequently proved unsatisfactory (e.g. [337, 353]). It is known from the area of smoking prevention that structural preventive measures are markedly more efficient – i.e. cheaper and more effective – than behavioural preventive measures [354].

In Germany, the *Act on Protection against Non-Ionising Radiation (NiSG)*, which has been in force since July 2009, and the *Ordinance on the Protection from Adverse Effects of Artificial Ultraviolet Radiation (UVSV)*, which has been effective since January 2012, are important measures for protection against artificial UV radiation and hence for primary prevention.

In accordance with [section 4 NiSG \(only available in German\)](#), the use of solarium is prohibited to minors. Infringements are a regulatory offence. The intention of this ban is to influence by law the behaviour of minors in respect of the use of artificial UV radiation for cosmetic purposes. However, there are no studies of whether and how far the attitude or behaviour of the general population in relation to UV protection is altered by this structural preventive measure.

The UVSV governs, among other things, the operation of UV radiation devices. Since 1 August 2012, in Germany, all devices must comply with maximum sunburn-effective radiation strength of 0.3 Watts per square metre of skin for UVA and UVB radiation. Since 1 November 2012, qualified specialists must be on hand in order to comply with

the duties of information under the UVSV – including that relating to the effects of UV radiation and the risks associated with the use of solaria. There are no studies on whether and how far risk assessment and behaviour in the population are affected by these structural preventive measures.

4.2.2.2. Environmental prevention for children and adolescents

4.31.	Evidence-based recommendation
Degree of recommendation A	Sufficient shaded areas must be established in day-care centres, kindergartens and schools.
Level of evidence 1++	Primary studies: [351]
	Consensus strength: 100%

Several studies discuss the need to establish shaded areas in day care centres, kindergartens, schools or above sports grounds [323, 333, 355, 356]. Evidence for the basic acceptance of the shaded areas provided among the target group of adolescents, that is otherwise difficult to reach, is supplied by the randomised and controlled study of Dobbinson et al. (2009), conducted in 51 Australian secondary schools [351]. Although it is unclear how far the outcomes are transposable to other countries, the results of this study indicate that providing shaded areas has the potential to reduce UV exposure of pupils during school time. The provision of shaded areas is regarded as a basic building block of environmental prevention. The recommendation issued by the WHO and other national and international organisations to seek shade during the midday hours when the UV index reaches 3 or higher (e.g. [357]) is meaningless if no shaded areas are available. This applies in particular to institutions such as day-care centres, kindergartens and schools, under whose responsibility children and adolescents usually spend the hours of the day that are associated with the strongest UV intensity.

4.32.	Evidence-based recommendation
Degree of recommendation B	Technical and organisational measures to minimise ultraviolet (UV) radiation exposure, particularly during the midday hours (e.g. provision of shaded areas, structuring of the timetable, consideration of UV radiation protection in the timetabling of sports events), should be an essential part of primary prevention.
Level of evidence 2+	Primary studies: [323, 333, 355, 356]
	Consensus strength: 100%

Quéreux et al. (2009) showed that instruction of 8- to 11-year-old schoolchildren could increase their knowledge about the effects of the sun and sun protection, but that this

did not result in any change in sun protection behaviour. They therefore recommend that sun protection education should be associated with appropriate environmental preventive measures (provision of shade particularly in the lunch breaks, avoidance of outdoor activities between 11 a.m. and 3 p.m.) [356]. Similarly, Hart and Demarco (2008), Buller et al. (1997) and Gritz et al. (2007) also recommend structuring timetables in such a way that outdoor activities are avoided in the midday period [323, 333, 355]. Buller et al. (1997) and Gritz et al. (2007) also supplement behavioural preventive interventions with structural and organisational measures such as the provision of shaded areas [323, 355].

4.2.2.3. UV protection in the working environment

4.33.	Consensus-based recommendation
EC	For outdoor workers, suitable technical and organisational ultraviolet (UV) radiation protection measures (shaded areas, work organisation, rules governing breaks) should be promoted and take precedence over personal protective measures.
	Consensus strength: 100%

M. Asmuß, H. Siekmann

Technical and organisational UV protection measures are highly important for employees predominantly or partly engaged in outdoor work. In Germany, under section 4 of the *Law on the Implementation of Protective Measures to Improve the Safety and Health of Employees at Work (ArbSchG)*, the employer is obliged to organise work in such a way as to avoid any risk to life and health as far as possible and to minimise any remaining risks. For personal protective measures (body-covering clothing, headwear, appropriate sunglasses, correctly used sunscreens), the same recommendations apply in principle as for the general public. However, the measures must be practicable and compatible with work procedures. They may not in any way increase the risk of accidents at work. In addition, they must be accepted by employees. Studies for example by the Austrian General Accident Insurance Institute (AUVA) on the UV load when working out of doors (Report No 49) and on the solar UV radiation load of highway workers (Report No 34) show that the latter requirement is often not the case [358, 359]. For example, UV protective textiles are found to be too hot and thus not worn. Sunscreens must also be easy to apply with dirty hands, should not be greasy and should be water- and sweat-resistant.

Technical and organisational work measures to reduce UV exposure can generally only rarely be influenced or even instigated by individual workers. Glanz et al. (2007) in their review of studies on the UV protection and efficiency of skin cancer protection at outdoor workplaces see the conflict with defined work procedures as a reason why strategies to reduce UV exposure such as seeking shade or minimising working time in the sun are implemented only reluctantly, if at all, among the workers questioned (construction and transportation workers, mail carriers). They highlight the importance of structural and organisational protective measures by the employer [360]. German professional associations such as the Professional Horticultural Association or the Professional Association of the Energy Textile Electrical and Media Products Sector (BG ETEM) support these views. The Professional Horticultural Association in their Information Sheet 24.1. "Sun protection in horticulture" give precedence to technical and organisational measures (e.g. shelters, use of sunshades or shade sails, switching work where possible to shaded areas, adapting work and break times if possible or bringing forward the start of work) over personal protective measures [361]. Similarly,

the BG ETEM gives precedence to technical protective measures (UV absorbing shelters, sunshades and shade sails) as well the “judicious organisation of work” over personal protective measures. There are no systematic studies on the question of how far these recommendations can be implemented in practice and how far they affect the behaviour of employees or the general public.

4.34.	Evidence-based recommendation
Degree of recommendation A	Outdoor workers must be informed of the ultraviolet (UV) radiation risks and UV radiation protection measures by means of training measures.
Level of evidence 1+	Primary studies: [309, 346, 362-364]
	Consensus strength: 100%

Outdoor workers in some cases have a comparatively high UV exposure. Various studies showed that training measures are effective in these groups of people and can lead to improved sun protection behaviour. Azizi et al. (2000) in a prospective cohort study in Israeli maintenance workers show that an integrated intervention (involving skin and eye examination at the workplace, health information with personal feedback and information on protective measures) resulted in a significant improvement in sun protection behaviour [364]. A randomised controlled trial in American employees in ski resorts (“Go Sun Smart” programme) shows an improvement in sun protection behaviour and a decrease in self-reported sunburns in the intervention group compared with the control group [309]. Glanz et al. (2001) in a randomised controlled trial as part of the SunSmart programme show that an intervention geared primarily to the target group of children also improved the state of knowledge and sun protection behaviour in recreational staff (moderators, lifeguards, etc.) [362]. As part of the “Sunwise” project, Mayer et al. (2007) in a randomised controlled clinical trial in American mail carriers document the positive effect of a two-year intervention directed primarily to promoting individual sun protection measures. In particular, the wearing of hats and the use of sunscreen was encouraged [363].

A randomised controlled trial in American highway workers comes to the conclusion that an intervention based on UV photographs and videos on the subject of skin cancer can promote risk awareness and sun protection behaviour even in the longer term (follow-up 2 months and 1 year post-intervention) [346].

4.35.	Consensus-based recommendation
EC	Outdoor workers must be protected by detailed legal regulations as they are at particular risk from intensive ultraviolet (UV) radiation.
	Consensus strength: 96%

In Germany, the primary prevention of skin cancer due to occupational UV exposure under the [Arbeitsschutzgesetz](#) (Law on the Implementation of Protective Measures to Improve the Safety and Health of Employees at Work (ArbSchuG)) is the responsibility of the employer, who must ensure this with the assistance of the occupational physician and health and safety experts on the basis of risk assessments. Where there is exposure to artificial UV radiation at the workplace, appropriate preventive measures must be implemented under the Ordinance on the Protection of Employees against Hazards caused by Artificial Optical Radiation ([OStrV](#)) based on [EU Directive 2006/25/EC](#). Unfortunately, neither the Directive of the European Union nor the German [OStrV](#) contain concrete measures for health and safety protection against exposure to solar UV radiation. Thus, while the employer is now obliged to establish and assess risks from solar radiation, how he must do that and what protective measures are to be used, if any, is not discussed further. There is therefore a lack of detailed provisions and recommendations for action that would allow a risk assessment, for example, on the basis of the UV index.

Need for further research:

- The level of awareness of legal requirements for the use of sunbeds among the lay public and medical personnel should be increased.
- Occupational, school and community-related behaviour prevention measures should be studied for feasibility and efficacy.

4.2.3. Side effects of primary prevention measures

The available literature for this guideline is not able to answer the question as to the side effects of extensive population-based UV prevention measures (behavioural prevention). Reference is made to the remarks in section 4.1.3 regarding potential side effects of sun protection recommendations.

5. Secondary prevention

5.1. Early detection of skin cancer

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5.1.1. Introduction

Where reference is made in this chapter to “skin cancer screening”, the term “skin cancer” is intended here, as in the whole of the guideline, to mean the three most common malignant skin cancer entities: malignant melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

5.1.1.1. Definition of secondary prevention, early detection and screening

Distinguishing between secondary prevention, early detection and screening constitutes a challenge. The definitions are similar, but the terms cannot be used synonymously.

Secondary prevention is generally targeted at healthy persons or populations. Its aim is to reduce or avoid mortality, morbidity and the resultant impairment of quality of life by detecting diseases in an early stage. To be suitable for secondary prevention, diseases must therefore have a long asymptomatic phase and be detectable already in the precursor or early stages of the disease.

Screening is a key component of secondary prevention. Skin cancer screening includes the recruitment of apparently healthy participants, history-taking and the whole-body visual examination (screening test) for the early detection of malignant skin tumours. In this context, advice can also generally be given about risk factors and prevention of skin cancer.

According to Morrison (1992) [365], screening divides participants into “persons with a low probability of having a disease” and “persons with a high probability of having a disease”, with the second group requiring follow-up diagnostic tests (presumptive and/or confirmatory diagnostic procedures, see sections 5.2.4 and 5.3) to confirm the diagnosis. Consequently, screening relates neither to the diagnostic procedure nor to treatment. If the examination is extended to the whole body for the diagnosis of a self-discovered skin lesion, this also can be referred to as “screening”.

Overall, secondary prevention or early detection can be defined as follows: screening plus measures to confirm the presumptive diagnosis in order to state a definite diagnosis.

5.1.1.2. Underlying principles of screening measures

The primary aim of screening and early detection is to reduce mortality. Secondary aims are to reduce morbidity, reduce the costs of expensive treatments of advanced diseases and improve the quality of life (QOL).

The core concept of screening is the assumption that, by diagnosing a disease (e.g. cancer) at an early stage, treatment is more likely to be successful and the mortality risk is reduced. This assumes that in the case of an untreated disease the prognosis will worsen as the disease progresses. In the case of MM and SCC, a thinner tumour (i.e. a skin lesion in a less advanced stage) is the most important prognostic factor for improved survival.

For a cancer entity to be eligible for screening, a (long) “preclinical phase” in which early detection is possible is an essential precondition [366]. The disease starts at a specific point in time, but at that stage is not yet detectable. It is not until a later stage that the disease can be diagnosed, e.g. when a solid tumour has reached a minimum size. The phase before a disease can be diagnosed without screening is known as the preclinical phase or sojourn time [367]. Consequently, it is only during this preclinical phase that screening can provide an earlier diagnosis. The length of time by which the diagnosis can be brought forward is known as the lead time. Neither lead time nor preclinical phase can be determined in individuals. The distribution of these two time spans, however, can be estimated for a population that has been screened. At the same time, it is expected that the mean age in a screened group at the time of diagnosis will be lower (by the value of the lead time concerned) than in a control group without screening [367].

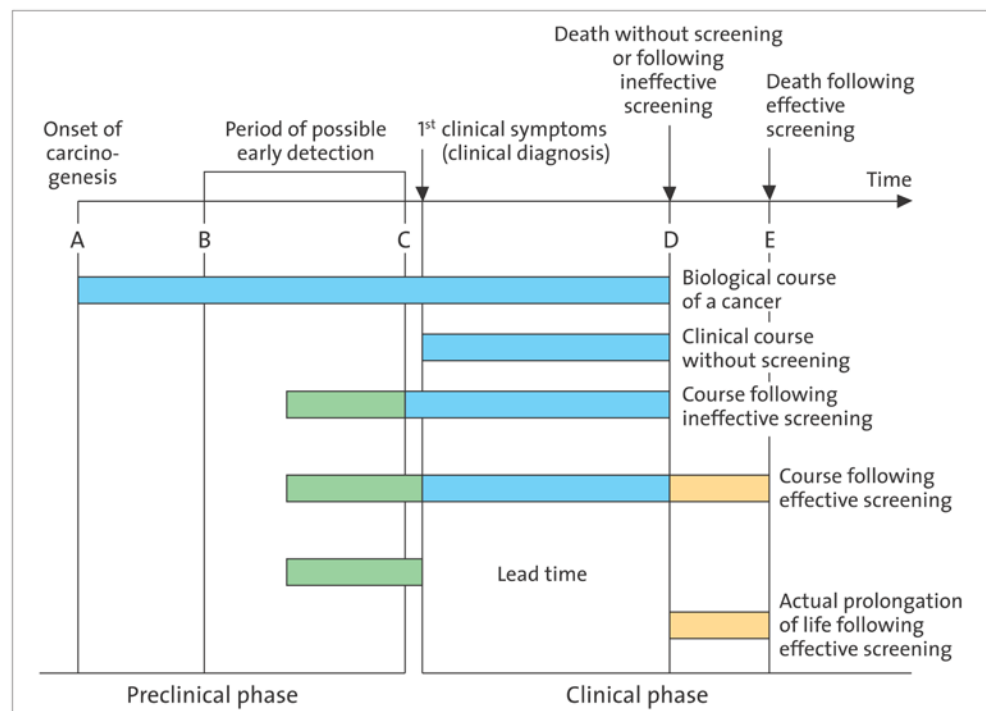


Figure 10: Time course of cancer following effective screening [368]

Other important screening parameters are the sensitivity and specificity of the screening test. A screening test should correctly assign diagnosable preclinical cases (sensitivity) and at the same time correctly identify negative cases (specificity). Cancer is a progressive disease and generally, the aim of screening is to discover a cancer at an earlier time than usual in the normal care system – in particular, before the tumour has reached an invasive stage.

A screening test is rarely 100% sensitive (i.e. all individuals who have the disease are detected as “true-positive”), precisely because it is not a diagnostic test. Normally there is no “gold standard” for comparing the disease status. Most participants in skin cancer screenings are “true-negatives” (negative test result and free from disease) or “false-positives”, i.e. a positive test result even though the disease is not present. Only a fraction of people screened are “true-positives”, i.e. they have a positive test and suffer from the disease.

The positive predictive value (PPV) indicates the probability that a person with a positive test result is actually ill. The PPV is affected by the prevalence of the disease in the population. The higher the prevalence, the higher also is the PPV [369].

5.1.1.3. **Possible harm and risks of early cancer detection examinations**

Although screening measures have the potential to reduce mortality from a disease and save lives, death as an “outcome” cannot always be avoided. Some people will die from cancer despite their participation in screening because the diagnosed tumour does not respond to the treatment or because it is already in an advanced stage at the time of diagnosis.

In patients with a false-negative test result (they have a negative test result despite having the disease) the deceptive certainty can lead to a delay in the diagnosis. In this case, the tumour remains undiscovered until it produces symptoms or is detected at the next screening examination.

In patients with a false-positive test result (they have a positive test result although no disease is present), there may be a number of unnecessary excisions; in addition, the time until the negative histopathological report is received is perceived by many patients as a major psychological burden.

Interval carcinomas, in other words tumours that are discovered between two screening examinations [369], can also occur despite an effective screening programme. These are not false-negative results. Interval carcinomas occur either because the screening interval is too long or because the patient suffers from a particularly fast-growing tumour.

Lastly, screening can also reveal very slow-growing tumours that are unlikely ever to have harmed the patient or to have become life-threatening for the patient at any stage (overdiagnosis). In these cases, further diagnostic procedures or treatment are more likely to do harm to individuals than prove beneficial to them.

5.1.1.4. **Screening programme**

In a screening programme, screening is normally performed by specially trained physicians. Screening can be performed firstly in a whole population (population-based or mass screening) without division into subgroups. Another option is risk-group screening in certain population groups only, for example in people with a higher probability of disease, e.g. skin cancer [366]. Because the PPV is dependent on the prevalence of a disease in a specific population and because by definition the prevalence in risk groups is higher, a screening programme will normally exhibit the greatest productivity and efficacy when it is directed at high-risk persons (better PPV in risk groups than in non-risk groups).

A screening programme can be performed systematically, by which is meant a highly organised programme with a standardised and quality-assured screening examination.

By contrast, decentralised unsystematic screening is also referred to as “opportunistic” screening [366]. Because of the lack of a standardised screening procedure, evaluations of opportunistic screenings are only possible with difficulty.

A screening programme – in this case, skin cancer screening – should contain the following components [367, 370]:

- A target population. In the case of skin cancer screening in Germany, these are individuals with statutory health insurance aged 35 years and above (mass screening).
- A recruitment strategy. Strategies often include campaigns in the mass media with information tailored to the target group, as well as invitation or reminder letters addressed personally to those eligible for participation (as in the German breast cancer screening programme). In Germany, skin cancer screening can be combined with the routine health check, an early detection examination for cardiovascular diseases in particular, for people aged 35 years and above. For this reason, participants in skin cancer screening are often recruited during consultations with doctors.
- A screening test. The screening test for skin cancer is the visual standardized examination of the whole body. This is a simple, safe, non-invasive and inexpensive method which is acceptable to the population to be screened.
- A standardised training programme for the physicians performing the screening. In Germany, physicians are only qualified to carry out skin cancer screening if they have taken part in an eight-hour advanced education course. This ensures the quality of the screening programme.
- A screening interval. In Germany, participation in statutory skin cancer screening is possible every two years.
- Follow-up of patients. This topic is discussed further below.
- Evaluation. In order to generate evidence on the effectiveness of each screening programme, it is essential to develop a comprehensive evaluation strategy. This includes both an evaluation of the results in terms of mortality, incidence of stages (stage shift to earlier, less aggressive stages of the tumours discovered), morbidity and quality of life, and also process evaluation, evaluation of the training and evaluation of the campaigns and general recruitment strategy.

5.1.1.5. **Impact and evaluation of population-based screening programmes**

As mentioned earlier, the principle aim of a screening programme is to reduce mortality by preventing disease progression. An actual reduction in mortality will only be seen several years after the introduction of a population-based screening programme. In order to predict the effects of mass screening on mortality, other interim parameters can be analysed. The concept described below was developed and recommended by Hense et al. (2011) to evaluate the German breast cancer screening programme [371]:

With the start of a population-based screening intervention, the total incidence of the target disease – in our case the incidence of MM, BCC and SCC – should initially increase, since existing but previously undiagnosed skin tumours are discovered (prevalence round of screening). The increased incidence consequently indicates that the screening test is appropriate for detecting the disease.

The principle of screening is the identification of precursors of cancers or early tumour stages. Subsequently, an effective screening programme should result in an increase in

the proportion of early tumour stages. A temporary increase in the proportion of late tumour stages should also be observed due to the presence of existing but previously undiagnosed tumours in the prevalence round.

Some years after the introduction of a screening programme, the development of later tumour stages should be prevented by improved detection and immediate treatment of early tumour stages. A decrease in the incidence of late tumour stages should therefore be apparent.

In the final outcome, the above-mentioned effects should result in a substantial reduction in mortality.

Some time after the beginning of a screening programme, the initial increase in incidence should also decrease. If that does not happen, and at the same time mortality remains stable (tumours regress or are not aggressive), this suggests that the screening intervention has resulted in overdiagnosis [371].

In summary, an effective population-based screening programme is characterised by an initial increase in total incidence, a stage shift towards early tumour stages and a subsequent reduction in mortality.

5.1.2. Measures for the early detection of skin cancer

5.1.	Evidence-based statement
Level of evidence 2++	Population-based screening with the target diseases of malignant melanoma, basal cell carcinoma and squamous cell carcinoma, in which a standardised examination of the skin over the whole body is performed by trained physicians, has been shown to result in an increase in the detection rate of tumours at an early stage.
	Primary studies: [2, 188]
	Consensus strength: 100%

5.2.	Evidence-based statement
Level of evidence 2++	Skin cancer screening of the general adult population results in an initial increase in the incidence of skin cancer (prevalence phase of screening) and an increase in the detection rate of skin cancer at an early stage. This result could impact on the morbidity of malignant melanoma, basal cell carcinoma and squamous cell carcinoma.
	Primary studies: [2, 188]
	Consensus strength: 96%

5.3.	Evidence-based statement
Level of evidence 2+	A single study indicates that population-based skin cancer screening could reduce mortality from melanoma.
	Primary studies: [2]
	Consensus strength: 96%

Population-based skin cancer screening

Whereas non-melanocytic skin cancers (NMSC), e.g. BCC and SCC, are the most widespread types of malignant skin cancer tumours and contribute to the increasing morbidity, MM causes most deaths from skin cancer as it metastasises earlier than NMSC. Survival with MM depends in the first place on the tumour thickness at the time of diagnosis. Consequently, the early detection of melanomas theoretically has the potential to save lives as a result of the identification of thinner lesions. Population-based as well as individual measures are described in the literature for the early detection of MM. The evidence regarding the efficacy of these measures, i.e. a shift from late tumour stages to early tumour stages and a reduction in mortality, is weak. The existing evidence is based almost exclusively on epidemiological rather than randomised controlled trials (RCT), which would have allowed the generation of higher levels of evidence in relation to the efficacy of population-based screening measures. The current lack of evidence of efficacy from RCTs is the main reason why organisations worldwide [372, 373] do not recommend such interventions for the early detection of malignant skin tumours [374, 375].

Despite the lack of RCTs and of evidence on the efficacy of population-based screening measures, a national skin cancer screening programme was introduced in Germany in 2008. The decision to implement this programme was based on the results of the SCREEN (Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) project, conducted between 2003 and 2004 [2, 188].

This population-based skin cancer screening project was conducted in Schleswig-Holstein, the northernmost state of Germany. In SCREEN, a two-stage skin cancer screening procedure was tested, in which the standardised whole-body examination was carried out by trained physicians (dermatologists, but also family physicians and other specialists). With 360,288 participants and a participation rate of 19% within 12 months, this is the largest study to date on the early detection of MM, BCC and SCC. An analysis of epidemiological endpoints of this study, such as incidence, stage shift and mortality, points to the very probable efficacy of this screening measure. Apart from the initial increase in the incidence of skin cancer (an indicator of effective screening), an increase in the proportion of thin tumours (less than 1 mm in depth) from 52% to 64% was also observed during the study. Furthermore, 90% of the invasive melanomas detected had a tumour depth of less than 1 mm. Five years after the end of SCREEN, a reduction of approximately 50% in the mortality rate was registered, whereas no regression was found in other regions of Germany without a screening programme [2, 188].

As only 19% of the population were screened and mortality in Schleswig-Holstein had declined before the start of the SCREEN project, other factors may possibly have contributed to the rapid fall in mortality. One plausible explanation is provided by the media campaigns that had begun before SCREEN and the fact that a higher proportion of risk persons participated. In addition, the persons in the control groups were possibly not similar enough to the persons in the intervention region and also data from other cancer registries (in this case Saarland, [188]) may generally be liable to bias because of the time variation in the incidence. Nevertheless, the SCREEN project offers the best available evidence to date that large-scale skin cancer screening is feasible and effective.

A number of studies show modest evidence of efficacy of population-based interventions for the early detection of skin cancer. In a systematic review, the effectiveness of interventions in increasing cancer awareness and promoting the early diagnostic investigation of possible symptoms (referred to as early presentation in the original article) was studied at community level. The scientists found evidence of the efficacy of information measures (brochures, posters and media campaigns), i.e. a reduction in the mean tumour depth of MM and a reduction in the time between the discovery of symptoms and presentation for investigations [376].

In a population-based case-control study conducted in Australia, there was an association between clinical whole-body examinations and a decline in the incidence of thick MM [377].

By contrast, a community intervention in Great Britain to promote early detection of MM in the adult general population showed no effect on mortality rates. An implemented health information programme consisted in distributing brochures on the signs or distinguishing features of MM and encouraging early presentation. Skin self-examination was not part of the information. Despite an increase in the incidence of thin melanomas, nine years after the conclusion of the programme the researchers found no significant reduction in cumulative mortality in the intervention regions compared with other regions of Great Britain [378].

Furthermore, a systematic review of routine skin cancer screening by primary care providers concluded that there was insufficient evidence of the efficacy of such a programme [379].

Individual measures for early detection of skin cancer

In terms of individual measures, routine skin self-examination (SSE) could be a promising method for early detection of malignant skin tumours as it is free of charge and free from inconvenience. The evidence relating to SSE, however, is limited in terms of quality and quantity and it remains unclear as to whether SSE results in an improved outcome in respect of morbidity and mortality [380]. The reliability of using mole mapping diagrams was tested in an RCT and was more successful in the intervention group than in the control group. The authors describe how the increased accuracy of the identification of new skin lesions with the use of mole mapping diagrams has the potential to reduce mortality from melanomas and how it is a simple and cheap measure [381]. Mortality and tumour thickness, however, were not investigated in this study.

Further studies indicate that photographic documentation combined with SSE can increase the diagnostic quality of SSE, resulting in a reduced excision rate [382, 383].

Muhn et al. (2000), however, concluded from their study that SSE is only a moderately effective method for determining changes in the size of existing skin lesions. They studied the capacity of high-risk persons to recognise changes in the size of moles on their back. These high-risk patients were trained in SSE at the beginning of the study. The authors report that a large proportion of study participants (25%) discovered no changes or incorrectly discovered changes when none were present (38%) [384].

Overall, there are only a limited number of studies that provide substantial evidence of the efficacy of population-based and individual measures for the early detection of skin cancer. Many do not relate to screening or do not refer adequately to the increase in the proportion of early disease stages or a reduction in mortality.

Need for further research

There is a need for research to evaluate the efficacy of population-based and individual screening measures for skin cancer. The most pressing need is to provide evidence that screening results in a decrease in mortality.

The highest possible evidence is generated with an RCT. However, RCTs are difficult to conduct as they require a long follow-up time and a large sample size (compared with other cancer entities, MM occur rarely), engender high costs and in most cases there is no adequate control group/control region without screening activities.

The SCREEN project conducted in Schleswig-Holstein is the best available evidence to date and shows that population-based skin cancer screening is feasible and effective. This was shown by the results for the incidence of early skin cancer stages and mortality [2, 188]. Evaluation of the nationwide skin cancer screening will provide more high-grade evidence with regards to the effects of a population-based screening programme. A comparison between mortality in Germany after the introduction of skin cancer screening and neighbouring countries without such a programme is of particular importance. A multiple time series study of this nature will provide strong evidence to answer the question as to the effectiveness of skin cancer screening. A study of this kind could be combined, for example, with a case-control study to establish whether screening participants have lower mortality than unscreened persons. This will provide further substantial evidence as to whether a reduction in mortality is attributable to routine skin cancer screening.

In the German setting, a RCT is no longer possible because of the non-availability of a control region (a region without routine skin cancer screening). Possible types of study for assessing effectiveness include:

- Cohort studies comparing the outcomes of participants and non-participants in the screening programme,
- Case-control studies comparing the previous screening history of cases (e.g. people with advanced melanomas or people who died from melanoma) and controls (e.g. people who do not have melanoma),
- Ecological studies comparing endpoints such as incidence, stage-specific incidence and mortality between Germany and countries without routine skin cancer screening,
- Studies on the potential harm of routine skin cancer screening, such as unnecessary biopsies, negative psychological effects and overdiagnosis,
- Cost-effectiveness analyses of routine skin cancer screening (direct and indirect costs),

- Studies comparing the outcomes of risk-group screening with screening of the general population,
- Studies on the performance of SSE in risk groups and also in the general population in connection with the corresponding patient outcomes,
- Communication strategies and health information programmes for recruiting and motivating the population to participate in screening measures.

5.1.3. Performance of skin cancer screening

5.4.	Evidence-based recommendation
Degree of recommendation B	Skin cancer screening should be offered as part of the prevention of skin cancer.
Level of evidence 2+	Primary studies: [2]
	Consensus strength: 82%

5.5.	Dissenting opinion of DEGAM
	The German Society of General Practice and Family Medicine (DEGAM) regards the evidence for the benefit of a general skin cancer screening programme as insufficient. In individual cases, early detection of skin cancer can be performed following balanced information about the pros and cons.

5.6.	Evidence-based recommendation
Degree of recommendation A	The standardised whole-body skin examination to screen for malignant skin tumours must be performed by physicians. The precondition for this is participation in special advanced education courses on the early detection of skin cancer.
Level of evidence 2++	Primary studies: [2, 188]
	Consensus strength: 93%

5.7.	Consensus-based recommendation
EC	On the basis of the current evidence, it is not possible to make any statement about examination intervals for people not at increased risk.
	Consensus strength: 100%

5.8.	Consensus-based recommendation
EC	In the context of skin cancer screening, the time to presentation for further confirmation of the findings following the suspicion of a malignant melanoma, basal cell carcinoma or squamous cell carcinoma should not exceed ten working days.
	Consensus strength: 89%

5.9. Dessenting opinion of DEGAM

In the context of skin cancer screening, people with a suspected malignant melanoma must be given the opportunity to attend for further, where necessary surgical, investigations within ten working days.

According to the screening criteria of Wilson and Jungner (1968), cancer screening should cover the following points [366]:

1. The condition sought should be an important health problem,
2. The natural course of the disease should be adequately understood,
3. There should be a detectable early stage,
4. Treatment should be more effective in the early stage than the later stage,
5. There should be an effective test for detecting early stages,
6. The test should be acceptable,
7. The examination intervals should be known/defined,
8. Appropriate health system facilities to cover the added demand resulting from the screening,
9. Both physical and psychological risks should be less than the benefit,
10. The costs should be in a balanced ratio to the benefit.

Skin cancer fulfils most, if not all, of these criteria and consequently is suitable for screening. However, more evidence is required to assess all 10 of these criteria, e.g. the harm from skin cancer screening, cost-effectiveness and the question as to the appropriate examination interval. In German skin cancer screening programme, a screening interval of two years is recommended, although there is no high-level of evidence to show that this is an appropriate interval. This applies in particular to people at high risk for skin cancer.

5.1.3.1. The standardised whole-body examination

The only option for detecting skin cancer in an individual is to perform a standardised whole-body examination. This type of skin examination can be carried out by dermatologists or other physicians qualified in the early detection of skin cancer.

However, the decision to carry out a whole-body examination must remain with the patient. After comprehensive explanation of the screening test, including the potential

benefits and harms, it must be the individual's decision whether or not to undergo a whole-body skin examination (see also section 6.1.2 "Informed decision").

In an Australian case-control study, it was shown that use of the whole-body examination resulted in a reduction in the incidence of thick melanomas [377].

A large-scale project on skin cancer screening, the SCREEN project in Schleswig-Holstein, showed the feasibility of population-based screening using the standardised whole-body examination. In this project, an appropriate training programme in the early detection of MM, BCC and SCC for dermatologists, physicians engaged in family practice and other specialists (gynaecologists, urologists and surgeons) was implemented. The advanced education sessions included targeted history-taking from the patient, the performance of the whole-body examination and advice on risk factors and prevention. The whole-body examination was carried out in a brightly lit room (or with a bright lamp), an examination couch and a mat on which the patient could stand. After the patient had undressed and removed glasses, if any, the following parts of the body were examined: the scalp through the parted hair, ears, eyelids, oral mucosa, lips, gums, neck, upper body, axillae, arms, hands and interdigital areas, submammary region in women, perianal region, legs, external genitalia and feet, including the soles and the interdigital spaces (for a detailed description of the screening procedure, see section 5.5 "Implementation and quality assurance of skin cancer screening").

5.1.3.2. Skin cancer screening procedure

In the SCREEN project, the population-based screening was performed as a two-stage procedure (Figure 11). When an appropriately trained physician, including a gynaecologist or urologist, made a presumptive clinical diagnosis or identified the patient as an at-risk person, the patient was referred to the dermatologist for a second examination. If the dermatologist also diagnosed a suspicious skin lesion, a skin biopsy was taken. The histopathological examination of the biopsy was performed by a pathologist. Alternatively, patients could also be screened directly by the dermatologist. Apart from the dermatologists, the trained physicians therefore served as gatekeepers and could only refer patients with suspicious lesions and/or risk factors to a dermatologist. In addition, only the dermatologist was allowed to take biopsies [2, 188].

Delays in the referral of patients with a suspected skin cancer to a specialist could have an impact on patients' probability of survival. The results of a British study showed a smaller tumour thickness and improved survival in patients with suspicious lesions who were referred to a plastic surgeon for consultation and immediate treatment within two weeks. These results support the "two-week rule" for referral for several types of cancer introduced in Great Britain in 2000 [385].

Apart from the skin cancer screening procedure described above, alternative population-based screening approaches are mentioned in the literature. In a RCT of community-based screening, family doctors were trained in the early diagnosis and treatment of skin cancer. The screening was conducted as a whole-body skin examination and the local physicians were supported by special "skin screening clinics". The number of whole-body examinations increased in the intervention regions in comparison with the control regions in which no "skin clinics" were established. The authors concluded that the provision of additional "screening clinics" could improve screening participation rates [386, 387]. Because of a lack of funding, this RCT was never completed and to date there are no comparative data on tumour thickness and/or mortality between the intervention and control regions.

Janda et al. (2006) report a significant increase in screening examinations in centrally organised “skin screening clinics” compared with screenings in everyday primary care [388]. In addition, “pre-screening”, i.e. the identification of skin lesions requiring further investigations by a specialist, undertaken in hospitals by minimally trained nursing staff has the potential for a cost-effective and reliable screening intervention [389].

In summary, there is a lack of evidence regarding the efficacy of the above-mentioned screening approaches in reducing mortality. In terms of feasibility, however, such mass screening programmes would not be possible without a “gatekeeper” approach of this kind.

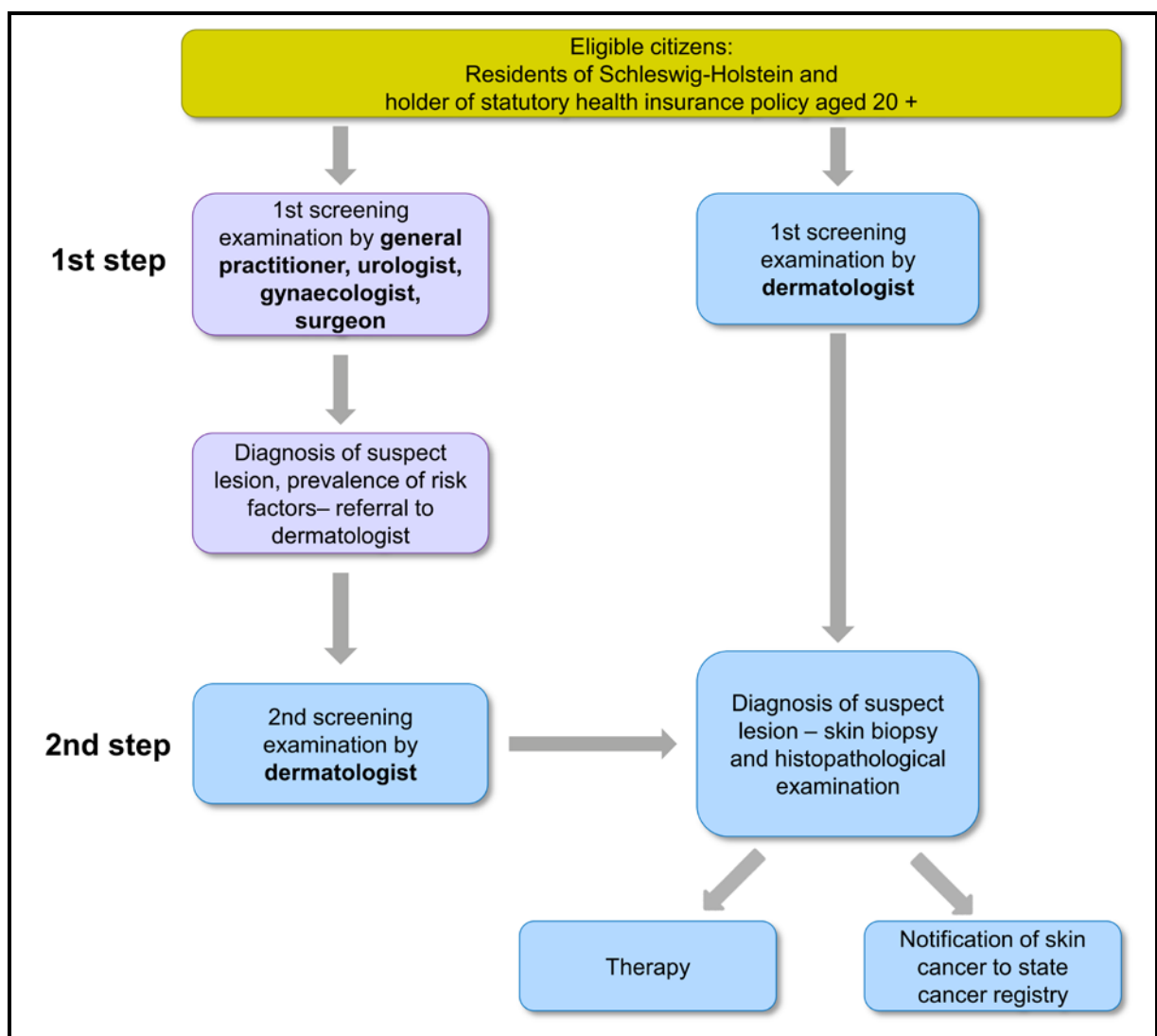


Figure 11: Schematic representation of a multidisciplinary two-stage approach to population-based early detection of skin cancer

Need for further research

The evidence regarding the diagnostic accuracy of dermatologists and other specialised physicians is sparse. Additional studies are needed to support either the gatekeeper approach or direct access to dermatologists [390]. Future studies comparing the results of dermatologists with those of other specialised physicians should link diagnostic accuracy to outcome data for patients and also include the cost-effectiveness of the two approaches (gatekeeper vs. direct access to dermatologists). In addition, any shortcomings in the training and teaching of physicians in early detection and treatment of skin cancer will be exposed. Future studies on training and teaching of physicians will help to improve the appropriate curriculum [391]. They should focus on the following three questions:

- How extensive should training in the early detection of skin cancer be and at what intervals should dermatologists and other physicians be offered refresher courses?
- Which professional group(s) should be considered to conduct the screening test (just dermatologists or family physicians and other specialists as well)?
- What should be the content matter of the teaching programme?

5.1.4. Screening of at-risk persons

5.10.	Consensus-based recommendation
EC	At-risk persons (see section 3.4) must be taught to carry out skin self-examination so as to be able to identify abnormal skin lesions. At-risk persons must be informed about their individual risk and be regularly examined (at intervals to be defined individually) by a trained physician by means of a whole-body skin examination.
	Consensus strength: 96%

There are two target groups for skin cancer screening: at-risk persons and persons without risk factors. This gives rise to the possibility of mass screening, as has now been introduced in Germany, or targeted screening of persons at highest risk (see section 5.1.1.4).

As described in section 3.4, the individual risk of developing skin cancer varies considerably. It depends on environmental, genetic and acquired risk factors (e.g. immunosuppression). A standardised population-based screening programme is feasible both for people at high risk and for those without particular risk factors [2].

Engelberg et al. (1999) recommended that particular focus should be placed on elderly people because in this population group, and especially in men aged 59 years and older, MM continues to be associated with a high mortality rate [392]. At the same time, it is important that at-risk persons understand what factors contribute to their high risk. Therefore, comprehensive counselling is necessary in particular for those people who are at increased risk for developing skin cancer.

There are differing results regarding the benefit of skin self-examination (SSE). Because the efficacy of SSE has already been discussed in sufficient detail in section 5.1.2, it is outlined here only briefly in connection with the recommendation of SSE for people at increased risk for skin cancer.

Oliveria et al. (2004) showed that regular SSEs are of benefit in detecting thin lesions. The identification of factors associated with the performance of SSE (sex, age, education, marital status, skin awareness, previous benign biopsy, presence of atypical moles) will enable healthcare providers to concentrate on those people who do not carry out SSE despite an increased risk of melanoma. They emphasise the importance of identifying factors that increase the probability of a person examining their skin themselves, since early detection and excision of lesions has the potential to reduce morbidity and mortality from MM [393].

A guideline from Australia and New Zealand (Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand) states that regular surveillance reduces the mean thickness of MM. For high-risk persons, this guideline recommends a combination of SSE and screening and advises a screening interval of six months. However, there are no studies that systematically compare alternative methods; these recommendations are based on expert opinion only. The individual frequency of skin examinations in at-risk persons should be made dependent on the individual risk factors, i.e. the frequency should be defined in such a way as to achieve a reduction in mortality and morbidity as well as a stage shift.

Guther et al. (2012) studied a model for identifying people at increased risk for skin cancer who would benefit from regular skin cancer screening. They used an open prospective point-prevalence study of consecutive patients presenting to dermatologists for complete examination of the skin. Demographic characteristics and risk factors for skin cancer were documented, together with the histology of the skin lesions. The results were subjected to univariate and multivariate analysis and a risk group model was developed to identify patients most likely to develop MM or NMSC [394].

Need for further research

Studies should be conducted to compare the effectiveness of mass screening with risk-group screening for people at increased risk for skin cancer and to assess this in relation to mortality, morbidity and stage shift. In this context, economic aspects should also be taken into consideration.

5.1.5. Examination intervals

5.11.	Consensus-based recommendation
EC	For people at increased risk for skin cancer, the physician, together with the person to be screened, should define an appropriate interval, based on an assessment of the individual risk profile.
	Consensus strength: 100%

The time interval between screening examinations for skin cancer should be chosen so as to meet the criteria for screening: identification of early stages, stage shift and reduction in mortality as well as morbidity.

Taking into account the age-specific incidence of MM, BCC and SCC and their respective (and different) clinical courses, the examination interval in the German skin cancer screening programme for people without risk factors is set at two years. Apart

from this practice in Germany, there is insufficient evidence of optimum screening intervals either for people at increased risk for skin cancer or for people without special risk factors (see 3.4).

According to Spix and Blettner (2012), both the examination frequency (the screening interval) and the screening test and target group in the population must be defined (see also the introduction to this chapter [367]). The literature, however, provides no evidence of confirmed assertions of how to achieve the greatest effectiveness with a screening programme. The main reason for this is the lack of evidence on skin cancer screening of high-risk persons and persons without risk factors. The available guidelines [372-375] offer no information in this respect.

Need for further research

An evaluation of skin cancer screening in Germany, taking into account the long-term clinical course, should be undertaken in relation to the screening interval for people at increased risk for skin cancer and people without risk factors in order to determine optimum screening intervals. This must include a study of interval carcinomas. This study should preferably be in the form of an RCT in order to define the possible screening intervals (e.g. one year for people at increased risk for skin cancer in one region compared with a different interval, e.g. three or four years, in another region).

5.1.6. What negative consequences can be associated with which screening?

5.12.	Evidence-based statement
Level of evidence 2+	Negative consequences of skin cancer screening involve excisions with a benign histology (false-positive tests). The number-needed-to-excite described in studies ranges from 3.25 to 179, i.e. between 3.25 and 179 excisions are needed to confirm one malignant skin tumour histologically.
	Primary studies: [2, 392, 394, 395]
	Consensus strength: 100%

5.13.	Consensus-based recommendation
EC	With the exception of false-positive tests, there is little evidence to date about potential risks and negative consequences of skin cancer screening. Possible negative consequences are overdiagnosis, overtreatment, negative psychological consequences and possible delays in diagnosis as a result of false-negative tests. These potential risks and negative consequences of skin cancer screening should be reduced as far as possible by appropriate physician training and teaching measures. Physicians should discuss potential risks and negative consequences with their patients before the screening.
	Consensus strength: 100%

Numerous studies have looked at the potential benefit of skin cancer screening for individuals as well as for the general public (e.g. reduction in mortality and morbidity and increase in the quality of life). However, because screening is geared to examinations and tests in *healthy* humans, the possible harm and risks associated with these procedures must be studied even more carefully.

Despite the worldwide increase in incidence rates of MM, BCC and SCC, Germany is the only country in the world with a nationwide population-based skin cancer screening programme. Many countries with a higher skin cancer burden still hesitate to introduce such a programme. For a screening programme to be introduced, the possible benefit must outweigh the possible risks and harms. Only then can the examination of apparently health populations be justified. Because of a lack of studies investigating the burden on individuals and the health system represented by a screening programme and because the effectiveness has yet to be conclusively demonstrated, many organisations, including the United States Prevention Services Task Force [372, 373] and the Australian Cancer Council with the New Zealand Guidelines Group [374] do not undertake routine skin cancer screening.

Screening tests can occasion considerable stress because these tests can also produce “false-positive” (positive test result, but healthy) and “false-negative” (i.e. the disease is present, but the test result indicates that there is no disease) results.

The following potential risks and harm are associated with **false-positive** test results:

- Many studies showed that suspicious skin lesions turn out to be benign lesions. The proportion of histopathologically confirmed benign lesions ranges from 70% to almost 90% [2, 392, 394, 395]. Only a small proportion of patients receive a “true-positive” screening result. If physicians were to convey this knowledge to their patients, this could reduce the pressure and anxiety for patients with possibly “false-positive” test results.
- Superfluous further tests and/or examinations can lead to complications and cause harm to the patient. In the case of skin cancer screening, unnecessary biopsies can cause complications and can also lead to numerous, unsightly scars. If these scars occur on visible parts of the body, such as the face, this can cause the patient psychological stress. Differing statements are made about the number needed to excise (NNE) in order to find one malignant skin tumour. For example, one study on skin cancer screening showed an excision rate per newly diagnosed MM of 179:1, which points to poor diagnostic specificity [395]. By contrast, in the German SCREEN project, only 27 excisions needed to be performed in order to discover one MM, while the NNE for BCC was 8:1 and for SCC 41:1 [2]. In the SCREEN project, the dermatologists and other qualified physicians received additional training in early detection [2], which was not the case in the study by Schmitt et al. (2011) [395]. This may have resulted in the lower NNE and underlines the importance of special teaching measures and advanced education courses for physicians taking part in skin cancer screening.
- Costly superfluous excisions, as well as overdiagnoses and unnecessary treatments, can be a burden on the health system, given that some age-related NMSC discovered during skin cancer screening would never have caused a clinical problem.
- The quality of life can be affected by worry and stress in the waiting period for the definitive (negative) examination result. These negative psychological

effects depend predominantly on the amount of information available to the screening participant and also on the communication skill of the physician.

- Legal proceedings may be brought by people who suffer complications during the subsequent procedures. This can reduce public trust in screening.

The following potential risks and harms are associated with **false-negative** test results:

- False-negative results can provide a deceptive sense of security; for example, the patient may cancel doctors' appointments because the previous screening has suggested that everything is fine. In this case, the tumour remains undiscovered until it makes itself apparent or is discovered in the next screening round. It is then possibly too late for treatment or the tumour is in a more advanced stage than might have been the case with a correct diagnosis in the first place. This can result in increased morbidity, expensive treatments and reduced quality of life because of the delay in diagnosis. In the extreme case of MM, which is associated with a potentially high probability of metastases, a false-negative test result may result in death. Osborne et al. (2003) report on the accuracy of the diagnosis of "false-negatives" in different clinics. They discovered that the number of "false-negatives" was lowest in specialised skin clinics (pigmented lesion clinics). They concluded from this that the experience of dermatologists working in such specialist clinics may be responsible for the improved diagnostic accuracy [396].
- Legal proceedings may be brought by people who suffer from late stages of skin cancer despite participating in skin cancer screening. That also can reduce public trust in screening measures.

Most participants in skin cancer screening have a "true-negative" test result and as such benefit from skin cancer screening because the medical confirmation that they are healthy is viewed as positive. Patients with "true-positive" results can be placed under pressure by the diagnosis because their disease phase is prolonged by the earlier diagnosis as a result of the screening and they must wait and see whether they benefit from the immediate treatment [367, 392]. In addition, delays in the referral of suspicious lesions (due to a consultation with the dermatologist or further procedures) can increase the potential harms, e.g. through an increase in the tumour thickness of MM and a decline in the survival rate from MM [385].

The whole-body examination is performed without technical aids. This is a safe, cheap and non-invasive screening test. It is also not painful for patients or excessively time-consuming for physicians. There are to date no known disadvantages that arise directly from a whole-body examination, apart from the fact that it can be uncomfortable for participants to have to undress completely for a screening.

A skin tumour that has not been discovered during a screening can reach a symptomatic stage before the next screening examination is due. These tumours are known as "interval carcinomas". Consequently, "false-negative" test results can be used to define the appropriate screening interval for skin cancer screening. This will reduce the potential negative consequences of "false-negative" results. A screening interval that is too short, e.g. every three months for high-risk persons, could cause long-term psychological stress and adversely affect a person's quality of life.

Need for further research

Most studies of negative consequences of skin cancer screening focus on unnecessary biopsies and the NNE. Further research is needed into *other factors* that exert an effect on potential harms.

The following aspects should be considered:

- Study of risk factors for “false-positive” and “false-negative” results, both in risk groups and in people without risk factors,
- Overdiagnoses in skin cancer screening must be studied,
- Studies of interval carcinomas to define the optimum screening interval and reduce “false-negative” results,
- The NNE of trained vs. untrained physicians and the resultant consequences for patients,
- The communication skills of physicians and auxiliary medical staff in explaining the potential benefits and risks of skin cancer screening to participants,
- The negative psychological effects associated with the uncertainty of possible “false-negative” and “false-positive” results of skin cancer screening,
- Negative effects of screenings for physicians (time demands, etc.).

5.2. Screening test / presumptive diagnostic procedures

5.2.1. Introduction

The subject of the secondary prevention of skin cancer is the performance of a screening test and the investigation of a clinical suspicion of malignancy as part of the presumptive diagnostic procedure.

The screening test is the beginning of the early detection chain and involves the use of a simple, valid test in healthy individuals.

Morrison (1992) defines screening as an examination of asymptomatic people with the aim of dividing the examinees into two groups in terms of disease: those with a high probability of disease and those with a low probability. The screening test here constitutes a filter method that makes it possible to identify people with a high probability of disease in a population. They can then be investigated further in a procedure subsequent from the screening and where necessary be treated [365].

For the skin cancer screening test, only measures that can also be performed in larger population groups and as such are time- and cost-effective are suitable. Whole-body examination of a completely undressed person with the naked eye is the appropriate measure for use as a screening test method (see also section 5.1).

As soon as a clinical suspicion of malignancy is established by the examiner during the screening, the screening test is ended and the presumptive diagnostic procedures begin.

Various methods and techniques for presumptive diagnostic testing have been studied and published as aids to investigating a clinical suspicion of malignancy and these are detailed below. These measures include:

- Dermatoscopy,
- Use of algorithms,
- Photography,
- Teledermatology,
- Spectrophotometry,
- Near-infrared spectroscopy,

- Confocal laser scanning microscopy,
- Multiphoton laser tomography,
- Optical coherence tomography,
- Electrical impedance spectroscopy,
- High frequency ultrasound.

If there is a continued suspicion of malignancy of a skin change, confirmatory diagnostic tests should then be performed (see section 5.3).

5.2.2. Screening test

5.14.	Evidence-based recommendation
Degree of recommendation A	A whole-body examination must be performed for skin cancer screening.
Level of evidence 2++	Primary studies: [2, 389, 397, 398]
	Consensus strength: 100%

5.15.	Consensus-based recommendation
EC	For a whole-body examination, the examination room must be well-lit and the examiner must approach the person to be screened close enough to be able to detect skin changes with the naked eye.
	Consensus strength: 100%

5.16.	Evidence-based statement
Level of evidence 1 -	The diagnosis of non-melanocytic skin cancer by whole-body examination has a sensitivity of 56-90% and a specificity of 75-90%.
	Primary studies: [397]
	Consensus strength: 100%

5.17.	Evidence-based statement
Level of evidence 2+	In a cross-sectional study with Australian family physicians, sensitivity in the diagnosis of skin cancer types by whole-body examination was 100% for melanomas (n=1), 89% for basal cell carcinomas (n=62), 80% for dysplastic naevi (n=30), 58% for benign naevi (n=69), 42% for squamous cell carcinomas (n=18) and 10% for actinic keratoses (n=31), while specificity for these entities was 76-99%.
	Primary studies: [398]
	Consensus strength: 100%

5.18.	Evidence-based statement
Level of evidence 2-	In the diagnosis of melanoma by clinical examination, the sensitivity of non-dermatologically trained practitioners was 86-95% and the specificity 49-77%. Training in the diagnosis of melanoma did not produce any substantial increase in sensitivity and specificity in general practitioners.
	Primary studies: [399, 400]
	Consensus strength: 100%

C. Berking

The whole-body examination of the undressed person without any other aid is a simple and cheap examination method that has been used for decades for detecting skin cancer during screening. There are a number of variable factors that affect the achievement of the optimum results with this method, but their significance and weighting has yet to be tested in studies. This includes the illumination of the examination room. Experience shows that daylight and bright white or yellow artificial light are beneficial. The illumination strength of the ambient light of normal examination rooms in accordance with DIN 12464-1 is between 300 and 500 Lux. For whole-body examinations, therefore, illumination strength of the ambient light of at least 500 Lux appears appropriate, whereas for detailed skin examinations about 1,000 Lux is required. A further factor is the distance of the examiner from the examinee. A close visual distance is recommended to be able to detect and assess small skin changes with the naked eye. However, there is a lack of studies on the minimum distance required for different degrees of visual acuity.

The examiner's experience is absolutely fundamental to the whole-body examination. Measurement parameters in this respect are the sensitivity and specificity in the detection of skin cancer and different studies have measured the detection of melanomas, the detection of NMSC or the distinction between benign and malignant lesions.

The data relating to the sensitivity and specificity of the diagnosis of melanocytic and NMSC and its precursor stages by whole-body examination are very limited.

In a systematic review, Mogensen and Jemec evaluated all studies between 1990 and 2006 that examined the diagnostic accuracy of NMSC using various diagnostic test procedures and technologies. A total of 48 studies were included. In terms of the purely clinical examination, according to various studies the sensitivity for diagnosis of NMSC was between 56-90% and the specificity between 75-90%, with the best values being found for BCCs (sensitivity 66-89%) [397].

In an Australian single-centre study with 199 consecutive patients with 287 histologically examined lesions, the sensitivity (and specificity) of the referring family physicians for the diagnosis of BCC was 89% (76%), dysplastic naevus 80% (93%), SCC 42% (93%), actinic keratosis 10% (98%) and benign naevus 58% (99%) [398].

In a comparison of 31 general practitioners who had undergone a training course and 32 general practitioners without previous teaching who carried out melanoma screening on 109 people, there was no significant difference in sensitivity with 98% versus 95% and specificity with 52% versus 49% [399]. The applicability of these results, however, is limited, as the selection of general practitioners was not representative and they had been informed beforehand that some study participants had suspicious skin lesions. Among surgical oncologists with several years' experience in melanoma diagnosis, sensitivity was 86% and specificity 77% for a purely clinical examination of suspicious pigmented skin lesions [400].

In a one-arm, prospective cohort study, 256 patients at increased risk for skin cancer underwent an examination by specially trained nurses who had to assess whether suspicious skin cancer lesions were present or not [389]. The results were compared with a subsequent assessment by plastic surgeons. The nurses correctly recognised 95% of the suspicious lesions, while 16% were diagnosed as false positives. Because of limitations in the design of this study, only a limited interpretation of the results is possible.

5.19.	Evidence-based statement
Level of evidence 2++	<p>According to a systematic review, the available study data are insufficient to draw conclusions about statistically significant differences between dermatologists and primary care physicians in terms of accuracy in classifying suspected melanoma lesions.</p> <p>In terms of diagnostic accuracy, the sensitivity of dermatologists was 0.81-1.0 and of primary care physicians 0.42-1.00. In terms of biopsy or referral accuracy, the sensitivity was 0.82-1.0 (dermatologists) and 0.70-0.88 (primary care physicians).</p>
	Primary studies: [390]
	Consensus strength: 92%

All studies from the period 1966 to 1999 investigating sensitivity and specificity in the diagnosis of melanomas by dermatologists compared with primary care physicians were analysed in a systematic review. The studies measured the correct detection of melanomas versus non-melanomas (diagnostic accuracy) or/and the correct determination of whether a lesion might be malignant and hence will be biopsied or result in referral to a melanoma expert (biopsy or referral accuracy). A total of 32 studies were included in the final analysis. In terms of diagnostic accuracy, the

sensitivity for dermatologists in all prospective studies was between 81% and 100% and for primary care physicians between 42% and 100%. Specificity was calculated in none of the studies for dermatologists and in only one study for primary care physicians (98%). In terms of biopsy and referral accuracy, the sensitivity for dermatologists was between 82% and 100% and for primary care physicians between 70% and 91%. Specificity was between 70% and 89% for dermatologists and 51% to 87% for family doctors. The authors came to the conclusion that the data were unsuitable for the purpose of distinguishing between dermatologists and primary care physicians in respect of diagnostic accuracy and biopsy or referral accuracy [390].

5.2.3. Previous history and self-examination

5.20.	Consensus-based recommendation
EC	The person to be screened must be asked about skin changes at the beginning of the screening / presumptive diagnostic procedures.
	Consensus strength: 100%

5.21.	Evidence-based recommendation
Degree of recommendation B	The results of the self-examination of the person to be screened should be included at the beginning of the screening / presumptive diagnostic procedures to identify and differentiate between malignant and benign skin changes.
Level of evidence 2-	Primary studies: [383]
	Consensus strength: 100%

In patients with dysplastic naevi who examined their skin in the trunk area themselves, the sensitivity for changed or new moles was 60.2% and the specificity 96.2% [383]. When digital photographic images of the first examination were included, the sensitivity increased to 72.4% and the specificity to 98.4%.

As far as the previous history is concerned, study data only exist to indicate that it is highly reproducible: in a repeated interview of 236 people, 116 of whom were patients with a previous history of BCC or SCC, good reproducibility of the responses was found after a period of 18-26 months in terms of pigmentation properties, sun exposure and sunburn episodes in childhood, while the number of sunburn episodes showed the lowest concordance [401]. In a comparison of the diagnosis of difficult-to-classify pigmented lesions by six dermatologists who were only shown photos of clinical and dermatoscopic findings, low values were found for the correct diagnosis of melanomas without (38.3%) and with dermatoscopy (40.8%) and only 70% of melanomas and BCC were referred for surgical therapy [402]. The authors speculated that the absence of direct examination of the patient could have had a negative impact on the results.

Studies comparing the accuracy of the examiner's diagnosis in skin cancer screening with and without the aid of the patients' previous history and self-examination are lacking in the review.

5.2.4. Presumptive diagnostic procedures

5.2.4.1. Dermatoscopy

5.22.	Evidence-based recommendation
Degree of recommendation B	Dermatoscopy should be performed in the presumptive diagnostic procedure. It should be used to improve the clinical diagnosis of melanocytic lesions.
Level of evidence 2++	Primary studies: [403, 404]
	Consensus strength: 82%

5.23.	Evidence-based recommendation
Degree of recommendation A	Dermatoscopy must be performed only after appropriate practical training.
Level of evidence 2++	Primary studies: [404]
	Consensus strength: 100%

5.24.	Evidence-based recommendation
Degree of recommendation 0	Dermatoscopy can be performed in people at increased risk undergoing an individualised check-up.
Level of evidence 2++	Primary studies: [405]
	Consensus strength: 100%

T. Eigentler

Dermatoscopy (also known as reflective light microscopy, epiluminescence microscopy or dermoscopy) is a non-invasive diagnostic procedure for evaluating skin lesions. The principle is based on a magnified image of the skin structures, which are usually illuminated with a light source. The dermatoscope is then placed directly on the skin

lesion to be examined. To prevent reflection of the light, either a contact medium (immersion oil, disinfectant spray, ultrasound gel) or a light source with polarising light must be used. In this way, structures as far down as the upper dermis can be evaluated by dermatoscopy. Diagnostic properties of skin lesions that are not detectable to the naked eye can be visualised by dermatoscopy.

Dermatoscopic devices work either with an analogue optical unit or with photosensors. In principle, there is the possibility with both procedures of documenting findings, depending on the device used.

Dermatoscopy of melanocytic lesions

Dermatoscopy is suitable for examining melanocytic lesions and in particular for diagnosing melanomas [403, 404]. Kittler et al. (2002) submitted 27 articles on diagnostic accuracy with and without dermatoscopy to a meta-analysis. This showed the accuracy of a diagnosis of melanoma to be significantly higher with the aid of dermatoscopy (log odds ratio 4.0 [95% confidential interval 3.0-5.1] vs. 2.7 [1.9-3.4]; 49% improvement, $p=0.001$). The diagnostic accuracy, however, was dependent on the physician's level of practical training. Dermatoscopy was only superior to the conventional, purely visual diagnosis with an increasing level of training and experience [404]. This systematic review also showed no significant advantage from the use of an algorithm for the assessment (sample analysis vs. ABCD rule of dermatoscopy vs. point systems (3- and 7-point list)).

There are individual studies on the diagnostic validity of dermatoscopy in general medical practice. These show improved sensitivity for the diagnosis "melanoma" or at least the identification of suspicious lesions requiring a biopsy as a result of the use of dermatoscopy [406, 407]. However, it should be noted that these studies were all conducted with clinicians with training in dermatoscopy (although in some cases only through seminars or literature).

Some publications also indicate a reduced excision rate of benign lesions as a result of the use of dermatoscopy (reduced ratio of excised benign to excised malignant lesions; reduction in the number of patients referred for biopsy) [408, 409].

Only patients with an appropriate risk profile (multiple atypical naevi, several cases of melanoma in the family) seem to benefit from regular follow-up by dermatoscopy. The melanomas diagnosed during follow-up using dermatoscopy were significantly thinner than those not diagnosed dermatoscopically [405].

For people with an increased risk for skin cancer, the physician, together with person to be screened, should define an appropriate time interval based on an assessment of the individual risk (see also 5.1.5).

Dermatoscopy of non-melanocytic lesions

In contrast to melanocytic lesions, there are markedly fewer studies on dermatoscopy of non-melanocytic lesions. In some studies of pigmented lesions [397, 410, 411], non-melanocytic lesions are listed in the margin. In the article by Lorentzen et al. (2008), the diagnostic specificity of dermatoscopy for basal cell carcinomas is reported as 99%.

In principle, dermatoscopy is suitable for non-melanocytic lesions. As well as the typical features of individual lesions, attention should be focussed here primarily on vascular structures [412].

5.25.	Consensus-based recommendation
EC	For all lesions of the skin and the adjacent mucosae in the facial, genital or anal region that would be insufficiently investigated by diagnostic procedures involving the use of dermatoscopy, the patient must have a consultation with further specialist diagnostic procedures.
	Consensus strength: 97%

G. Mehlhorn

For melanocytic and non-melanocytic skin lesions, such as precursor stages of SCC or carcinomas in the genital or anal region that cannot be sufficiently investigated by diagnostic procedures involving the use of dermatoscopy, a consultation about the further gynaecological or/and surgical diagnostic tests is necessary. These diagnostic tests should primarily be clinical, involving a close inspection, supplemented by the use of differentiated vulvoscopy, vaginoscopy or anoscopy. A tissue sample should be taken in the event of abnormal findings.

In the event of suspected melanocytic or non-melanocytic (squamous epithelial) precursor lesions or tumours of the oral mucosa, a further oral and maxillofacial consultation and diagnostic tests are required. Here again a tissue sample must be taken in the event of suspicious findings. The same applies to lesions in the facial region that cannot be sufficiently investigated by diagnostic procedures involving the use of dermatoscopy.

In this respect, reference is made to the currently existing interdisciplinary guideline for the diagnosis and therapy of vulvar carcinoma and its precursor stages of 2009 (AWMF registration number: 015/059) and the guideline for the diagnosis and management of precursor lesions of oral squamous cell carcinomas in oral medicine and dentistry of 2010 (AWMF registration number: 007/092).

5.2.4.2. Algorithms

5.26.	Evidence-based recommendation
Degree of recommendation B	Algorithms for describing pigmented lesions and instant cameras for observing the disease course with the aim of reducing the proportion of excised benign lesions relative to melanomas should not be used.
Level of evidence 1++	Primary studies: [413, 414].
	Consensus strength: 100%

5.27.	Evidence-based statement
Level of evidence 2-	The value of whole-body photography in melanoma risk patients remains unproven.
	Primary studies: [415, 416]
	Consensus strength: 96%

C. Berking

One problem with presumptive diagnostic procedures is the relatively low specificity in the clinical diagnosis of melanomas, in other words against the background of a relatively low incidence of melanomas, a relatively large number of benign lesions are excised unnecessarily. For example, in general practices in Australia, this ratio is 10-35 naevus cell naevi and seborrhoeic keratoses to one melanoma [413]. In a randomised controlled trial with 468 participating family physicians in Australia, the provision of an algorithm (description of morphological changes and clinical symptoms) and an instant camera (for follow-up over 4-8 weeks) to support the detection of melanomas as distinct from other pigmented lesions (naevus cell naevi, seborrhoeic keratoses) produced no reduction in the ratio of benign lesions to melanomas excised [413]. In an older, very similar study with about 100 Australian primary care providers, these aids resulted in a 4.8% lower proportion of excised benign lesions, although this study exhibited methodological deficiencies [414].

Serial, automated, digital whole-body photography with 48 images per patient was presented in a historical cohort study as a new method for the regular examination of melanoma risk patients and allowed the earlier detection of melanomas, as measured by the thinner mean Breslow depth, than for other patient cohorts [415]. The combined use of digital whole-body photography and digital dermatoscopy at mean intervals of 5 months in patients with atypical naevus cell naevus syndrome resulted in a higher diagnostic accuracy with the discovery of early and small melanomas and savings in terms of biopsies [416]. However, these conclusions by the authors are based on inaccurate data in their study results with only a small number of histopathological reports relative to the total cohort in the way of confirmatory diagnostic procedures and the absence of a control group.

5.28.	Evidence-based statement
Level of evidence 2-	Special image processing programmes for the detection of melanomas have been developed, but their value remains unproven.
	Primary studies: [417]
	Consensus strength: 100%

A programme for processing digital images to distinguish between melanomas and melanocytic naevi on the basis of 3 variables relating to geometry, colour and colour texture was presented with a sensitivity of 60.9% and a specificity of 95.4% for

predicting the diagnosis of melanoma and an overall accuracy of 89.4% [417]. Because of a lack of data on study details, only a limited assessment of the results and their applicability is possible.

5.2.4.3. Tele dermatology

5.29.	Evidence-based recommendation
Degree of recommendation 0	Tele dermatology can be used to assess benign and malignant skin tumours.
Level of evidence 2++	Primary studies: [418-420]
	Consensus strength: 100%

Tele dermatology makes use of digital photographs of suspicious skin findings sent over the internet to medical colleagues to be assessed by them. The intention is to improve the diagnostic quality (second opinion), reduce the number of personal medical consultations and reduce the time to diagnosis or treatment. The latter was demonstrated by Ferrandiz et al. (2007) in a trial with 134 preoperative patients with a clinical suspicion of NMSC or a rapidly growing vascular tumour and 784 teleconsultations. They observed a significant reduction in dermatological consultations and waiting time to surgery compared with the conventional referral system [418]. The concordance rate between diagnosis by teleconsultation and that by histopathology was 0.86, while 12 of 20 non-concordant diagnoses related to lesions that were not originally included in the study.

In another study of 2,009 patients with benign or malignant skin tumours presenting to primary care centres, two digital photos (panoramic image and close-up) of their skin tumours were sent over the internet to dermatologists at a skin cancer centre for evaluation [419]. The teleconsultation filtered out 51.2% of patients, while 48.8% of the patients attended the skin cancer centre in person. The referral times were markedly shorter than with conventional procedures. The concordance of the diagnoses via teleconsultation was 0.95 for the same dermatologist and 0.85 between two dermatologists. Concordance between the general practitioner and the teleconsultation dermatologist was 0.46. The sensitivity of the teleconsultation-based diagnosis was 99% and the specificity 62%.

In a prospective controlled trial, a dermatologist was presented with a digital plain film, a close-up and a dermatoscopic image of the dubious lesions of 451 patients and on the basis of his assessment determined the urgency of the patient's personal attendance at the clinic [421]. As a result, waiting times for patients with urgent tumours, i.e. melanomas or SCCs, to be seen at the clinic was reduced by an average of 10 days compared with the conventional referral procedure.

In a British study, the diagnostic accuracy was tested of a dermatologist who initially established the diagnosis on the basis of a conventional clinical examination of patients referred with pigmented lesions and then months later on the basis of anonymised, stored video images of the same lesions [420]. No differences were found

in diagnostic accuracy, which argued in favour of the possibility of using teleconsultations. However, the authors expressed the reservation that this method only examines a snapshot and not the whole patient, no palpation of the lesion is possible and the results depend on the quality of the images. They also require a cost-benefit analysis before the methodology can be recommended for implementation.

Teledermatology was negatively assessed in the study by Warshaw et al. (2009) of 519 patients with pigmented lesions, in which diagnostic accuracy was markedly poorer than in the clinical examination of patients (sensitivity 64% vs. 80.3%) and was also not improved by the additional assessment of dermatoscopic images [422]. However, the study population was confined to men with a mean age of 66 years.

A comparison between the evaluation of conventional photographic slides and compressed digital photographic images showed no differences in sensitivity and specificity in the diagnostic accuracy of pigmented skin lesions [423].

5.2.4.4. Spectrophotometry

5.30.	Evidence-based statement
Level of evidence 2-	Spectrophotometric analysis of pigmented lesions has shown no improvement in sensitivity and specificity in the diagnosis of melanoma.
	Primary studies: [400, 424, 425]
	Consensus strength: 100%

With telespectrophotometry, the reflection of a lesion is measured at wavelengths between 420 and 1,040 nm with a CCD camera with 17 interference filters. The 17 spectral images are stored on computer and processed further. In a study of this method, four descriptors were defined, corresponding to the clinical properties of the lesions in accordance with the ABCD rule: roundness (asymmetry), evenness (border), mean reflection (colour) and size (dimension) [424]. One hundred and eighty-six patients with 195 pigmented lesions were evaluated. All variables differed significantly between melanomas and non-melanomas, with colour representing the most important parameter. Because of deficiencies in the study design and an uncertain bias potential, the predictive nature of the results is vague. The same working group examined 313 suspicious skin lesions in 298 patients by clinical examination, dermatoscopy and telespectrophotometry [400]. In terms of the correct diagnosis of the 66 histologically confirmed melanomas, sensitivity was 86%, 91% and 80% and specificity 77%, 74% and 49%, respectively. Telespectrophotometry therefore offered no advantage

In another more recent study, a spectrophotometric analysis of 881 skin lesions in 860 patients was performed by a dermatologist [425]. Compared with his assessment based on clinical examination and dermatoscopy, no improvement in sensitivity (94% vs. 91%) and specificity (87% and 91%) was found in relation to the diagnosis of melanoma.

5.2.4.5. Near-infrared spectroscopy

5.31.	Evidence-based statement
Level of evidence 3	The value of near-infrared spectroscopy in distinguishing melanocytic and non-melanocytic skin changes from one another and from normal skin remains unproven.
	Primary studies: [426]
	Consensus strength: 100%

With near-infrared spectroscopy at wavelengths of between 700 and 2,500 nm, absorption by haemoglobins, cytochromes, water (O-H groups), lipids (C-H groups) and proteins (N-H groups) in tissue is measured for each wavelength, which can provide conclusions about tissue composition and oxygen supply [426]. In a study, in-vivo images were taken of a total of 195 benign and malignant skin tumours in the visible and near-infrared range (400-2,500 nm), of which 130 were evaluable [426]. Significant group differences were seen, as for example between dysplastic naevi and other skin lesions (e.g. actinic keratoses, BCCs, lentiginos) and between BCCs and common naevi as well as seborrhoeic keratoses. MMs were not investigated in this study.

5.2.4.6. Confocal laser scanning microscopy (CLSM)

5.32.	Evidence-based statement
Level of evidence 1 -	Confocal laser scanning microscopy (CLSM) has a high resolution in assessing pigmented and non-pigmented skin lesions. Following suitable training, CLSM can improve the diagnostic accuracy of individual lesions.
	Primary studies: [397, 427, 428]
	Consensus strength: 89%

C. Berking, P. Mohr

Confocal laser scanning microscopy is a modern technical procedure that can produce cross-sectional images of the epidermis and papillary dermis at almost histological resolution by means of focussed laser light and its reflection from the various structures of the skin. The various media act almost as endogenous chromophores through different refractive indices (examples of refractive indices: water 1.33, keratin 1.5, melanin 1.7). The standard wavelength of the laser is 830 nm, while wavelengths of 400-1,064 nm are available with what are known as multiwave devices. The lateral resolution is 0.1-1 µm, the axial resolution 3-5 µm and the maximum penetration depth ranges up to about 250-300 µm depending on the wavelength, and even up to 450 µm in the nail organ. In-vivo examination of the patient is performed in real time by placing the device on the lesion to be examined with the use of a coupling medium such as gel and oil – similarly to dermatoscopy.

There are now more than 300 publications on the method in the area of dermatological diagnosis, but to date there is no meta-analysis of the value of confocal laser scanning

microscopy in the diagnosis of pigmented and non-pigmented skin changes [397, 427, 428].

5.2.4.7. Multiphoton laser tomography (MPT)

5.33.	Consensus-based statement
EC	The value of multiphoton laser tomography in the diagnosis of melanoma remains unproven.
	Consensus strength: 100%

P. Mohr

Multiphoton laser tomography (MPT) is a non-invasive examination technique that can be used to assess both cellular and extracellular structures at subcellular resolution. MPT is based on stimulation of biogenic fluorophores by two or more long-wavelength, low-energy photons and induction of second harmonic generation. A resolution of less than a micrometre can be achieved. Studies are investigating the extent to which the technique is helpful in the diagnosis of melanoma.

5.2.4.8. Optical coherence tomography (OCT)

5.34.	Consensus-based statement
EC	The value of optical coherence tomography (OCT) in distinguishing melanocytic and non-melanocytic skin changes from one another and from normal skin remains unproven.
	Consensus strength: 100%

C. Berking, P. Mohr

Optical coherence tomography (OCT) is a modern optical procedure that allows non-invasive, real-time images of the epidermis and upper dermis. The basis of OCT is white light interferometry. The travel time of a signal within the tissue sample is compared with a reference signal of known optical path length. OCT is similar to B-mode in the ultrasound pulse-echo procedure, although the optical and not the acoustic reflection is measured. The examination procedure allows a penetration depth of up to a millimetre and a resolution of 3-15 μm . The image is depicted vertically as with histological sections, but more recent apparatuses also allow a horizontal presentation. Both melanocytic and non-melanocytic skin tumours have already been depicted with the method and the results published, although the most convincing results are available for BCC. However, there is a lack of larger-scale controlled studies, so that the value of the diagnosis cannot be definitively assessed [397].

5.2.4.9. Electrical impedance spectroscopy (EIS)

5.35.	Consensus-based statement
EC	The value of multifrequency electrical impedance spectroscopy (EIS) in distinguishing melanocytic and non-melanocytic skin changes from one another and from normal skin remains unproven.
	Consensus strength: 100%

P. Mohr, C. Berking

Multifrequency electrical impedance spectroscopy (EIS) is a procedure that sends an electrical current with different frequencies from various electrodes into the superficial skin by means of a small probe and measures and analyses changes in the current, frequency and electrical field. The electrical properties of biological material reflect cellular properties of the tissue such as cell density, architecture, cell shape and intracellular and extracellular water content. In pilot studies, significant differences were found between BCCs and normal skin, as well as the differentiation of BCCs from benign naevi, with a sensitivity of 96% and a specificity of 86% [397].

5.2.4.10. High-frequency ultrasound

5.36.	Consensus-based statement
EC	The value of high-resolution ultrasonography in distinguishing melanocytic and non-melanocytic skin changes from one another and from normal skin remains unproven.
	Consensus strength: 100%

P. Mohr

High-resolution ultrasonography of the skin (also known as ultrasound) is a non-invasive diagnostic procedure for evaluating skin lesions. The principle is based on the representation of skin structures using high-frequency sound waves. The sound waves are reflected off skin structures, captured by the transducer and then converted back into electrical impulses by means of the piezoelectric effect. Images are generated from the electrical impulses. Water or ultrasound gel serve as contact medium.

According to Lassau et al. (1997), high-frequency ultrasound is a simple, reliable, non-invasive method for the accurate preoperative assessment of skin tumour dimensions. There was a very strong correlation between ultrasound and histological measurement of tumour thickness (Breslow index) of 13 melanomas ($R^2 = 0.9959$); however, there were no differences in the ultrasound characteristics of melanomas and naevi. Thirty-one of the 32 BCCs were detected with high-frequency ultrasound. One lesion was not a BCC, but actinic keratosis. Resection was complete in 24 cases and incomplete in 7 cases [429].

Krahn et al. (1998) demonstrated sensitivity in the determination of tumour thickness of melanomas (± 0.2 mm): < 0.76 mm: 79.3%, 0.76-1.5 mm: 42.9%, > 1.5 mm: 100%. The technique allows surgical planning and avoids re-excisions. However, its use is confined to differential diagnoses of malignant and benign skin lesions [430].

Wortsman and Wortsman (2010) studied the value of ultrasound for differential diagnosis. The proportion of correct clinical diagnoses on referral was 73%, while the proportion of correct diagnoses following diagnosis by ultrasound was 97%. The diagnostic accuracy for ultrasound [95% confidential interval] is reported with a sensitivity of 99% [98.9-99.5] and a specificity of 100% [96.4-99.9]. The inclusion criteria, however, are not described and not all patients underwent a biopsy with histopathological confirmation. Equally, the investigators were aware of the previous clinical diagnosis (lack of blinding). Because of the study design and the lack of description of the patient population, the results provide only a very limited basis for recommendations for action [431].

5.3. Confirmatory diagnostic procedures

5.3.1. Confirmatory diagnostic methods

5.37.	Consensus-based recommendation
EC	The histopathological examination of a suitable tissue sample is the standard confirmatory diagnostic method. The histopathological diagnosis must be used to confirm a suspicious lesion.
	Consensus strength: 96%

5.38.	Consensus-based recommendation
EC	At the time of tissue sampling, consideration must be given to the relevant specific functional features in each case (e.g. in the facial and genital region) to prevent a functional disorder (e.g. ectropion, facial nerve paralysis) simply as a result of the tissue sampling.
	Consensus strength: 100%

C. Rose, A. Gerstner

The histopathological examination of the tissue sample is performed by a trained pathologist (specialist grade) or dermatohistologist (subspecialty). In the quality assurance agreement for skin cancer screening [432], the reporter must also have performed a minimum number of personal histopathological reports of skin samples and must be able to demonstrate this (see also section 5.3.4).

As a rule, the skin tissue is processed after formalin fixation. In rare cases, the histological examination is performed using the frozen section technique. This requires appropriate experience in the technical performance and assessment of these preparations [433].

The presence of a suitable tissue sample is the precondition for a histopathological examination. The process of tissue sampling is dependent on the clinical findings and the presumptive clinical diagnosis (see also section 3.2.3 in the evidence-based guideline on diagnosis, therapy and follow-up of melanoma [1]).

At the time of tissue sampling, due account must be taken of specific anatomical features in relation to function and aesthetics by calling upon the expertise of the relevant specialties (e.g. ENT, oral and maxillofacial surgery, ophthalmology, gynaecology) in order to prevent the development of e.g. nerve damage (in the face, for example, the facial nerve) or stenoses and distortions due to scarring (lacrima glands, eyelids, genitalia).

5.3.2. Conduct of confirmatory diagnostic procedures

5.3.2.1. Confirmatory diagnostic procedures for MM

5.39.	Consensus-based recommendation
EC	On clinical suspicion of a malignant melanoma, this lesion must first of all be completely excised with a small safety margin.
	Guideline adaptation: [1], [374]
	Consensus strength: 100%

5.40.	Evidence-based statement
Level of evidence 2+	The optimal tissue sample for histopathological assessment of a skin lesion suspected of being malignant melanoma is the complete excision (excision biopsy) with a safety margin of 2 mm, including the removal of fatty tissue.
	Guideline adaptation: [375]
	Consensus strength: 100%

C. Rose

On the basis of the SIGN guideline No 72 “Cutaneous Melanoma” (2003) and the “Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand” (2008), an MM should be completely excised with a small safety margin of 2 mm [374, 375]. A larger excision margin, on the other hand, destroys lymph drainage ducts and possibly interferes with the detection of sentinel lymph nodes [1, 434].

5.41.	Consensus-based recommendation
EC	In the case of large, extensive tumours on the face or acral skin that are suspicious for melanoma and for which a primary diagnostic excision is difficult, a sample biopsy or partial excision can be performed.
	Consensus strength: 100%

In specific situations, particularly in the case of large, extensive tumours on the face or acral skin that are suspicious for melanoma and for which a primary diagnostic

excision is difficult, a sample biopsy or partial excision can be performed [374]. Studies have shown that this process does not adversely affect patients' prognosis [435].

For tissue sampling, a distinction is usually made between incisional and excisional biopsies. Incisional biopsies include punch biopsies and shave biopsies; for excisional biopsies, the elliptical excision is available [436]. A superficial shave biopsy of suspicious lesions is not indicated [375]. The various biopsy techniques each have their pros and cons. A correctly performed shave biopsy covers a wider area than a punch biopsy. It extends as far as the middle dermis and allows a better assessment of the architecture. A punch biopsy generally reveals deeper sections of the dermis [1, 434].

5.3.2.2. Confirmatory diagnostic procedures for BCC and SCC

5.42.	Evidence-based recommendation
Degree of recommendation 0	On clinical suspicion of a basal cell carcinoma or a squamous cell carcinoma, the tumour can undergo complete primary excision with a small safety margin or a sample biopsy can be taken beforehand.
Level of evidence 3	Primary studies: [437]
	Consensus strength: 100%

Communication between clinicians and histopathologists is of particular importance in a sample biopsy. To prevent misdiagnoses and a delayed diagnosis, the histopathologist must be informed that a sample biopsy from a relatively large tumour is present. This involves specifying exactly the excision site from the lesion (e.g. marginal zone, nodular areas, regression zone). Forwarding a clinical image at the same time can be helpful.

A BCC or SCC can usually be diagnosed by punch biopsy [437].

5.3.3. The histopathological diagnostic procedure

5.43.	Consensus-based recommendation
EC	Each histopathological report (cf. quality assurance agreement) must contain a description of the microscopic findings and the formulation of a diagnosis. The type of tumour must be stated in accordance with the WHO classification and the histological staging in accordance with the currently valid TNM classification (UICC).
	Consensus strength: 100%

In Germany, the contents of the histopathological report of a malignant skin tumour are governed by the quality assurance agreement on histopathological examinations in

association with SCS (2008), which is legally binding for German pathologists and dermatohistologists [432].

In Appendix 1 to this quality assurance agreement, requirements are defined for the medical documentation of histological findings (see Figure 12). In the evidence-based guideline on diagnosis, therapy and follow-up of melanoma, parameters for the histological reporting of MM were established and consented in section 3.2.5 [1].

The most important part of each histological report is the correct diagnosis of a tumour, including the clinical-pathological correlation. For a malignant tumour, this involves describing the growth pattern, the degree of differentiation and the cytomorphological characteristics of a malignant neoplasm. The tumour must be typed in accordance with the WHO classification. The stage must be defined in accordance with the currently valid TNM classification, while at the same time a grading must be given for SCCs.

As defined in the quality assurance agreement, the size of the preparation to be examined and the nature of the sampling technique must be documented (Figure 12).

In the diagnosis of a malignant tumour, details must be given about the examination of the surgical margin. Where feasible, a micrometric measurement of the safety margin is performed laterally and in depth. In addition, the micrometric penetration depth must be measured and stated for all malignant tumours. The lateral and deep margins are assessed for the absence or presence of tumour cell clusters (residual tumour (R) classification).

<p>Patient data: Skin cancer screening: yes/no Sampling date: Clinical question: Localisation: Sample: excisional biopsy / sample biopsy Sampling technique: excision / punch biopsy / shave biopsy / curettage / electrocautery / other</p> <p>Date received: Date dispatched:</p> <p>Histology No:</p>
<p>1) Details of tissue processing Size of preparation Examination of surgical margin yes/no¹</p> <p>2) Microscopic findings¹: Growth pattern Degree of tumour differentiation Cytomorphological characteristics Micrometric measurement of penetration depth for all malignant tumours Micrometric measurement of safety margin laterally and in depth, where feasible Details on ulceration, also regression and, where applicable, mitotic rate for malignant melanoma Micrometastases</p> <p>3) Diagnosis: Diagnosis Indication of subtype/differentiation pattern² Invasiveness¹ Indication of ICD code¹ UICC classification, indicating pTNM and grading¹, also Clark level and Breslow index for malignant melanoma</p> <p>4) Case conference: no/yes, outcome¹:</p> <p>Comments: In the event of special features, additional recommendations for secondary excision, diagnostic tests, etc.</p> <p>Advice to forward a copy of the report to the referring physician, where applicable</p>
<p>¹ do not indicate for benign skin changes ² indicate for benign skin changes, where possible</p>

Figure 12: Content of the medical documentation of histopathological examinations

Source: Skin Cancer Screening Histopathology Quality Assurance Agreement, Appendix 1 [432]

The currently valid AJCC classification of MM of 2009 includes the determination of the maximum Breslow thickness (measured from the underside of the stratum corneum to the deepest tumour cell), ulceration of the primary tumour (epidermis interrupted by melanoma growth) and the mitotic rate for MM of less than 1 mm tumour thickness [167]. As distinct from the previous classification, the determination of the Clark level is no longer relevant for classification. A German-language working group has presented detailed recommendations in this respect for determining the mitotic rate [438]. The mitotic rate is determined on the basis of haematoxylin-eosin sections and the assessment of 1 mm² or, in the case of thin MM, a smaller tumour area is sufficient. Only mitoses localised unequivocally in the dermis are considered and given in whole numbers.

The histopathological reporting of a MM must include the following criteria:

- Indication of whether the excision margins are microscopically tumour-free,
- Determination of the maximum Breslow thickness (measured from the underside of the stratum corneum to the deepest tumour cell),
- Ulceration of the primary tumour (epidermis interrupted by melanoma growth),
- The mitotic rate for melanomas of less than 1 mm tumour thickness,
- Indication of special histopathological features such as vascular invasion and special morphological features (e.g. portions of a desmoplastic melanoma).

5.3.4. Quality assurance

5.44.	Consensus-based statement
EC	[In Germany,] the aspects of quality assurance are defined in accordance with the agreement on quality assurance measures laid down in section 135(2) SGB V ¹ on the histopathological examination in association with skin cancer screening [432] of 12 August 2009.
	Consensus strength: 100%

C. Sander

The Skin Cancer Screening Histopathology Quality Assurance Agreement is a binding operating procedure. This was required and defined on the basis of the directive of the Joint Federal Committee (G-BA), which is the highest decision-making body of the German statutory health insurance, on early cancer detection 2009 [370].

In addition to the technical qualification (specialty of dermatological and venereological diseases with subspecialty of dermatohistology, or specialty of pathology), this agreement defines the facilities as well as the possibilities for conducting immunohistological examinations, storing residual formalin-fixed tissue for at least six weeks, storing tissue blocks for at least two years and storing sections and written findings for at least ten years [432].

Dermatohistologists are required to show evidence of having reported personally on at least 6,000 dermatohistological preparations, at least 1,000 of these within 24 months before the application for authorisation, or evidence of discipline-specific

¹ German social act

dermatohistological advanced education in the period mentioned. This is documented by eight advanced education credit points or by KV- (Association of Panel Doctors -) certified advanced education of the appropriate scope [432].

Pathologists are required to show evidence of 15,000 histopathological preparations, at least 1,000 of these within 24 months before the application for authorisation, or qualification of professional dermatohistological advanced education [432].

Further aspects of this operating procedure include medical documentation, the conduct of case conferences and conditions for maintaining technical skills. For malignant tumours, the ICD code must be given [432].

5.4. Doctor-patient communication

5.4.1. Structure of the doctor-patient conversation prior to screening

5.45.	Consensus-based recommendation
EC	<p>Prior to the doctor-patient conversation, the patient should be issued with an information sheet on the early detection of skin cancer (skin cancer screening) that provides information about the pros and cons of early detection in simple language without engendering any anxiety. The subject matter should be kept to the checklist agreed in connection with the German National Cancer Control Plan <i>Recommended content of information about early detection measures</i> [439]. In addition, reference should be made to the possibility that outstanding queries can be clarified in the subsequent doctor-patient conversation.</p> <p>During the doctor-patient conversation, which should take place in a quiet and undisturbed atmosphere, the checklist should also serve as a guide. Emphasis should be placed on the following aspects:</p> <ul style="list-style-type: none"> • Procedure of the skin cancer screening, • Pros and cons of skin cancer screening, • Primary prevention information, • Personal risk profile and resultant consequences (risk communication). <p>A period of time commensurate with the patient's personal preferences should be allowed to elapse between the provision of information and the decision. Associated professional groups and, where applicable, relatives should be included in the communication process.</p>
	Consensus strength: 92%

M Anders

The doctor-patient² conversation is important for communicating information to the potential participant about primary and secondary skin cancer prevention measures. This can reduce gaps in knowledge and uncertainties on the part of the potential participant regarding modes of behaviour and measures (for example whole-body examination). In addition, the potential participant should be given the opportunity to weigh up the pros and cons in relation to his own preferences, attitudes and capacities and to make an “informed decision” for or against a measure/behaviour [439]. The information content required in this respect has been elaborated by the members of the Objectives Paper 1 within the framework of the German National Cancer Control Plan. This is summarised in a checklist (see section 6.1.2). This serves as a basis for the information of potential participants in early detection examinations. It is planned to supplement this checklist with a criteria list in a subsequent step. This criteria list will serve to check and assess information concepts (e.g. brochures, folders, verbal communication processes) [439].

In the doctor-patient interview, consideration must be given to the preferences, attitudes, capacities and prior knowledge of the potential participant. In addition, the potential participant should be made aware that he can ask questions at any time.

Within the doctor-patient conversation, successful risk communication is also important, showing the potential participant his individual risk and where applicable his risk behaviour and enabling him to assess this. The individual risk factors can be determined from personal and family history and his clinical presentation. In this context, it should be noted that a “positive” family history is sometimes inadequately communicated, if at all, within the subject’s own family and to health professionals. This may be due to the fact that health professionals on their part do not communicate the importance of this risk factor clearly and comprehensibly. These results are illustrated by a qualitative study using the example of MM, in which 22 people from seven families were questioned. In each family, people had developed MM (n=11). They were interviewed about (risk) communication within the family and from health professionals [440, 441].

Only one study looked at the capacity of recipients to remember possible risks following an information discussion, using the example of a dermatological surgical method (Mohs micrographic surgery). The study shows that the general recollection of risks 20 minutes and one week after the information does not differ significantly (arithmetic mean of remembered risks: 2.65 (20 minutes) vs. 2.44 (one week – difference: 0.21). In conclusion, it can be assumed that over a period of a week the knowledge base relevant to a decision remains relatively stable [442]. However, these results can be applied to early detection only to a limited extent, since the study participants are already patients, i.e. a disease is already present. That heightens the need for decision-making and prioritises the importance of information in a different way than from healthy persons.

² *Patient* in this context means a “*visitor*” to a medical institution or a (potential) participant in skin cancer screening. Since the term doctor–patient interview is widely used, however, this has been retained.

Finally, it should be pointed out that basic communication knowledge and techniques for medical discussions, as described for example by Schweickhardt and Fritzsche, are helpful for creating successful communication in the context of the doctor-patient conversation [443].

Need for further research

- Explanation of the significance of the time factor in the information and decision-making process in relation to the weighing up of the available factors and memory capacity.
 - Studies that repeatedly record knowledge and other decision-making factors over a prolonged period following the communication of information.
- Identification and description of predictors, moderators and mediators that act on the “informed decision”. In this context, particular attention must be paid to the areas of information, context and medium. This also involves clarifying the question about the skills and subject matter need to put health professionals in a position to enable potential participants to make an “informed decision” and how the subject matter concerned is to be communicated:
 - Intervention studies that investigate the different effects that an information intervention developed in accordance with the criteria of an “informed decision” has on different target groups.
 - Intervention studies that investigate the effects that different information channels and mediators have in transmitting an information intervention developed in accordance with the criteria of an “informed decision”.
 - Instrument development study recording possible dimensions of an “informed decision” and describing their validity in this respect in order to check or develop existing or new instruments for quantifying an “informed decision”.
 - Intervention studies that investigate the advanced education courses for health professionals intended to communicate the criteria of an “informed decision” in relation to the information of potential participants under controlled conditions.
- (Empirical) verification of the checklist e.g. by the development of criteria lists within validation studies.
- Risk communication within (skin cancer) early detection measures.
 - Intervention studies in which various types of risk communication and their effects on the decision-making process or on informed decision-making are studied under controlled conditions.

5.4.2. Structure of the doctor-patient conversation after screening

5.4.2.1. Structure of the discussion if there is no suspicion of skin cancer

5.46.	Consensus-based recommendation
EC	<p>A negative examination result must be communicated to the patient personally by the doctor carrying out the early detection in a counselling immediately after the examination.</p> <p>It must be pointed out that the result of the examination reflects the current status.</p> <p>In addition, the patient's individual risk factors must be explained to him and he must be motivated to practise primary preventive behaviour and skin self-examination. The patient must also be informed that he can visit the doctor again at any time in the event of any uncertainties about self-recorded skin findings.</p>
	Consensus strength: 100%

A. Rogge

Although the results of the study by Karri et al. (2009) do not confirm any difference in preference between a written report of the findings and face-to-face information, the communication of a negative report in a personal interview is recommended. In this way, the patient can be informed at the same time about risk factors and risk behaviour and the practitioner can respond in greater detail to the patient's questions [444].

5.4.2.2. Structure of the discussion if there is a suspicion of skin cancer

5.47.	Consensus-based recommendation
EC	<p>The suspicion of skin cancer must be communicated to the patient personally by the doctor carrying out the early detection in a counselling immediately after the examination.</p> <p><u>Family physicians (specialists in general medicine working in family practice, internal specialists, medical practitioners and non-specialist practitioners):</u> following the communication of a suspicion, the subsequent procedure must be explained, including a referral to the dermatologist for further investigations.</p> <p><u>Dermatologist:</u> the subsequent diagnostic investigations of the clinical suspicion must be communicated and explained.</p> <p>The patient must be informed that the findings will be communicated in a personal conversation and that he has the possibility of including a person of trust in this conversation. The patient must be asked about resources for psychological support during the waiting period and encouraged to practise self-care.</p> <p>The detailed interview must take place following receipt of the histological report.</p> <p>Information about the exclusion or demonstration of skin cancer (following histological confirmation of the findings) must not be given over the telephone.</p>
	Consensus strength: 92%

Although many patients want a detailed discussion as soon as a suspicion of skin cancer is mentioned, there is usually not sufficient time and tranquillity for this in an everyday practice environment. For this reason, it is recommended that the conversation should be held following receipt of the histological report [445].

During the conversation, the patient's fears must be taken seriously, but at the same time he must also be prepared for the possibility of a positive diagnosis of cancer.

In addition, it is pointed out that the diagnosis is communicated in a face-to-face conversation and the patient has the option to bring a relative along to this conversation [445].

As most patients describe, the time until the diagnosis is felt as a very distressing one [446], thus, patients are also given suggestions for psychological stabilisation.

5.4.3. Structure of the doctor-patient conversation for reporting findings

5.48.	Consensus-based recommendation
EC	<p>The period between the measures to confirm the diagnosis and the communication of the diagnosis must be kept as short as possible.</p> <p><u>Exclusion of skin cancer:</u> the patient must be told of the histological exclusion of skin cancer. In addition, the patient must be given an explanation about his individual risk factors and he must be encouraged to practise primary preventive behaviour and skin self-examination. The patient must also be informed that he can visit the doctor again at any time in the event of any uncertainties about self-recorded skin findings.</p> <p><u>Confirmation of skin cancer:</u> the finding of skin cancer must be communicated to the patient in detail with the diagnosis and grading in a personal (face-to-face) conversation. The existing diagnostic and therapeutic steps consistent with the current state of scientific knowledge must be conveyed comprehensibly to the patient over several sessions.</p>
	Consensus strength: 100%

A. Rogge, C. Schwarz

The delivery of bad news, such as the diagnosis of skin cancer, causes anxiety for many patients. For this reason, the diagnosis must be communicated in a quiet environment, in a comprehensible language and in an appropriate timeframe. The interview should be tailored to the patient, his intellectual capacities and preferences. At the same time, allowance must be made for the finding that in most cases only a little information can be absorbed at any one time. As little information is given as is compatible with the patient's need for information. A sensitive approach is required to ensure that only as much information is conveyed as patients indicate they can absorb and process [445]. In addition, emotional support for the patient is helpful. The patient should be offered the opportunity beforehand of including a person of trust in the conversation; this is particularly the wish of married people. The presence of other members of healthcare professions is to a large extent regarded as uncomfortable [446].

To provide some perspective, it may be necessary to tackle topics such as remaining life expectancy, impact of the disease on daily life and/or treatment options directly, depending on the patient's preference. For the prognosis, a reliable source of information should be chosen. Patients also prefer a concise information sheet with the most important frequently asked questions, as well as advice on further sources of support.

The above-mentioned recommendations for the information discussion are based on the standard publication for delivering serious diagnoses [447].

General aims of the information discussion are to convey information comprehensibly to the patients, to provide patients with psychosocial support and to develop coping strategies jointly with the patient. The discussion can be divided into six steps in accordance with Baile et al. (2000):

At the outset, an appropriate atmosphere must be created and important persons should be involved (e.g. partners). Subsequently, the patient's attitude must be ascertained and their state of information about the diagnostic process to date elicited. After obtaining permission to report the findings, this is done in an appropriate language (no specialist terms) and by not conveying too much information all at once. The understanding of the findings and the information communicated is checked regularly during the interview. After the findings have been reported, it is helpful to investigate the patient's feelings, identify his reactions and confirm these by way of acknowledgement. At the end, the forward planning is discussed [447]. Patients are encouraged to ask further questions themselves [445]. In particular, at the end of the interview the patient is again asked whether any questions remain unanswered. The patient is also given the opportunity to take up psychosocial support from cancer counselling organisations or self-help groups [445].

Need for further research

There is a need for further research into the average length of time patients have to wait for the communication of a confirmed diagnosis. This can be obtained by the retrospective recording of data from patient records, compiled by personnel within the medical practice, to be able to ensure data protection. The quality of the patient conversation should also be recorded, although this might prove difficult because of the sensitive nature of the situation. Qualitative and quantitative interviews with affected patients can play a role here.

5.5. Implementation and quality assurance of skin cancer screening

5.5.1. Training, advanced education and continuing professional development

5.5.1.1. Introduction

Even if a direct need for further research cannot be derived from some of the German directive on early detection of cancer recommendations in this section, the implementation of skin cancer screening as a whole and its quality assurance should be scientifically based or further developed using scientific methods. Following the implementation of skin cancer screening, the achievement of its underlying aims (reduction in mortality or morbidity) should be reviewed, as well as just the process quality. This requires the development of suitable concepts for a concomitant evaluation. The data recorded in connection with quality assurance should be exploitable for scientific purposes in order to be able to tackle rapidly any emerging new need for further research in the area of skin cancer screening without the need to record new data. The quality indicators for structure and process quality used for quality assurance and their reference values should be studied and confirmed using evidence-based methods, and where necessary new quality indicators developed. Suitable adjustments allowing for the different risk constellations for skin cancer must be made in order to present the quality assurance results. In terms of the education or training of family physicians and dermatologists, many questions still remain unanswered (e.g. efficacy, persistence, frequency). Such points should be researched further in conjunction with the on-going screening.

5.5.1.2. Professional requirements

5.49.	Consensus-based recommendation
EC	Skin cancer screening must be conducted only by qualified physicians who have successfully completed a recognised advanced education course lasting several hours on the conduct of skin cancer screening.
	Consensus strength: 100%

B. Löpker, M. Anders

In Germany, there are about 3,400 dermatologists, who in their everyday professional practice are engaged in the investigation, treatment and care of patients with non-infectious and infectious skin diseases and with benign and malignant skin tumours. To ensure extensive, population-based skin cancer screening, the Joint Federal Committee (G-BA) regarded family physicians (specialists in general medicine working in family practice, internal specialists, medical practitioners, non-specialist physicians) and dermatologists for its implementation and defined a two-stage skin cancer screening.

Independently of these statutory requirements, both urologists and gynaecologists have advanced experience of early detection and screening measures. That offers the possibility to include skin cancer prevention in specialty-specific early cancer detection examinations. It is expected that women will find it easier to submit to a close examination of their entire skin, particularly of intimate areas, when visiting their gynaecologist. The same also applies to urologists. The German pilot skin cancer screening project (SCREEN), conducted from 2003 to 2004 in Schleswig-Holstein, also shows that the organisation of population-based skin cancer screening with gynaecological support is useful [2, 448].

SCREEN also shows that the extension of medical skills by systematically developed and quality-assured advanced education is helpful in meeting the requirements placed on doctors by skin cancer screening. These requirements include, for example, the interpretation and communication of sensitivity and specificity of the screening test, communication skills (e.g. shared decision-making) and the standardised performance of the screening examination [448].

Need for further research

There is a need for further research; while there are studies that evaluate advanced education and teaching courses for their effect (increase in knowledge, diagnostic accuracy, etc.), there is a lack of studies that analyse the professional prerequisites necessary for advising on and carrying out skin cancer screening. This would require conducting a study in which the different specialist qualification profiles were compared in terms of their effect on epidemiological key performance indicators (sensitivity, specificity, positive predictive value, negative predictive value, etc.) in relation to the screening test and in terms of communication skills. In this way, it will then be possible in a subsequent step to identify the professional requirements necessary for the quality-assured performance of skin cancer screening to a large extent and to define a skills profile.

5.50.	Consensus-based recommendation
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EC	<p>A counselling approach and/or further advice on skin cancer screening can be offered and carried out by health professionals who are not medical practitioners (health assistants, practice nurses, nursing professions, other specialist professions within the healthcare system).</p> <p>The precondition for this is:</p> <ul style="list-style-type: none"> • completion of appropriate professional training and • successful completion of a recognised advanced education course lasting several hours on counselling in connection with skin cancer screening.
	Consensus strength: 100%

Personal communication, in other words direct discussion between physician and citizen, plays an important role in healthcare issues. In the pilot German skin cancer screening project (SCREEN), the particular importance of health assistants was also clearly apparent in this respect. They approached potential participants about their willingness to be counselled on skin cancer screening almost twice as often as doctors. A direct approach and counselling is particularly crucial in encouraging decision-making for or against early cancer detection measures (see also section 6.1) [448]. In everyday practice, health assistants often have more direct access to potential participants; in this case, counselling is possible without a threshold of access. The role of health assistants and other health professionals in general and their potential for prevention must also be optimised by participation in advanced education that imparts skills associated with counselling on the early detection of skin cancer.

Need for further research

There is a need for further research about the formative evaluation (see section 6.1) of advanced education and advanced education programmes on skin cancer screening for health professionals who are not medical practitioners. The results from this can provide conclusions as to how educational measures for these professional groups must be designed, offered and summatively evaluated.

5.5.1.3. Creation of the professional requirements

5.51.	Consensus-based recommendation
EC	<p>Advanced education/advanced education programmes in skin cancer screening for physicians and other health professionals (health assistants, practice nurses, nursing professions, other specialist professions in the healthcare system) must be extensively offered and carried out by certified trainers.</p>
	Consensus strength: 89%

M. Anders, B. Löpker

An important prerequisite for the conduct of skin cancer screening in the practice is the quality-assured teaching of practitioners and other health professionals so that they can fulfil their particular role in the prevention of diseases.

With its skin cancer screening, Germany was the first country in the world to introduce a comprehensively organised, standardised examination for the early detection of skin

cancer. To participate in this skin cancer screening, physicians must demonstrate successful participation in one of the eight-hour advanced education programmes recognised by the National Association of Statutory Health Insurance Physicians (KBV). Under the guidance of the Central Institute for Outpatient Care Provision in Germany, a trainers' programme was implemented first of all: training was given to 132 dermatological and 151 family medicine trainers, who in turn have run or are running advanced education courses. According to data from the KBV, by the end of 2012 around 44,000 physicians (family physicians and dermatologists) had qualified to carry out skin cancer screenings and 597 pathologists or dermatohistopathologists meet the required quality demands.

The contents of the advanced training course include:

- Incidence of skin cancer,
- Aetiology of skin cancer, risk factors and groups,
- Clinical presentations,
- German statutory programme for the early detection of cancer, medical examination, early enhancement of patient awareness,
- Potential benefits and harms of early detection measures, criteria for assessing early detection measures,
- Measures for addressing members of medical insurance schemes,
- Targeted history-taking,
- visual standardised whole-body examination,
- Practical exercise of the visual standardised whole-body examination on the screenee and at the same time reporting of findings with relevant advice,
- Presentation and discussion of case studies,
- Documentation measures,
- Interdisciplinary co-operation.

The teaching concept for physicians and health assistants during the German pilot skin cancer screening project (SCREEN) in Schleswig-Holstein made a decisive contribution to the large number of examinations for skin cancer and the increase in the (informed) uptake of other early cancer detection examinations. The training was generally well received by physicians; a 98% participation rate was achieved among dermatologists and 64% participation among the other qualified disciplines [2, 448]. In addition, health assistants were offered advanced education appropriate to their professional qualifications and their area of work and here again active participation was seen. This teaching concept was proven to be practicable and to result in increased knowledge in health professionals [448].

Need for further research

There is a need for further research involving an analysis of the actual situation to ascertain whether there is comprehensive advanced education provision for the individual professions and whether this is known to the target group. In addition, a target analysis must be defined in order to determine which aims are to be achieved in this respect. Where applicable, a concept must be developed for eliminating any inconsistencies between the actual and the target situation. Lastly, the effects, effectiveness and efficiency of the existing advanced education provision must be evaluated.

5.5.1.4. Content matter of the curriculum

5.52.	Consensus-based recommendation
EC	<p>Advanced education provision in skin cancer screening for physicians or other health professionals (health assistants, practice nurses, nursing professions, other specialist professions in the healthcare system) must impart practical and theoretical knowledge and methods. To this end, the following content matter must be included in a curriculum:</p> <ul style="list-style-type: none"> • Epidemiology of skin cancer (MM, NMSC), • Aetiology, risk factors and groups, • Clinical pictures (MM, NMSC), • Definition of prevention (primary, secondary and tertiary prevention), • Early detection of cancer as a screening measure, • Legal framework conditions, • Benefit and harms of early detection measures/screening programmes, • Criteria for assessing early detection measures, • Key performance indicators of a screening test, • Skin cancer screening, • Measures for targeting potential participants, • Requirements for advice about an informed decision in the context of skin cancer screening, • Screening test: visual standardised whole-body examination, • Targeted case history-taking, • Reporting of findings and advice, • Quality assurance of pathology (histopathological differential diagnoses), • Quality requirement of histopathology, • Histopathological diagrams, • The histopathological report (completeness, significance of contents), • Referral, • Documentation, • Invoicing, • Notification to cancer registries, • Interdisciplinary co-operation, • Principles of communication, • Communication between family physician and dermatologist, dermatologist and pathologist, physician and patient, • Communication tools for conversation techniques.
	Consensus strength: 92%

Under the co-ordinating leadership of the Association for Dermatological Prevention (ADP), together with the German Skin Cancer Screening Commission, composed of the ADP, the DDG, the BvDD, the ADO, the DGDC and the ADH, and in association with the German Association of Family Physicians, the German Institute for CME and CPD in General Practice (IhF) and DEGAM, an advanced education programme for the introduction of skin cancer screening was developed and published through the Deutsche Ärzte-Verlag, the contents of which are presented here [449]. This programme is regarded by the National Association of Statutory Health Insurance Physicians as being consistent in terms of its content with the German directive on early detection of cancer [370]. Content from the advanced education programme

successfully undertaken within the German pilot skin cancer screening project (SCREEN) was included.

5.53.	Evidence-based recommendation
Degree of recommendation 0	<p>Curricula for the training, advanced education and continuing professional development of physicians or other health professionals (health assistants, practice nurses, nursing professions, other specialist professions in the healthcare system) in primary care provision can include the following subject areas in relation to the primary and secondary prevention of skin cancer:</p> <ul style="list-style-type: none"> • Epidemiology, • Diagnostic procedures including dermoscopy and clinical algorithms, aided by photographic images of skin lesions, • Advice (primary and secondary prevention), • Communication, • Treatment. <p>Curricula can be divided into one or more intervention units and incorporate the following educational means and conditions: course attendance, web-based, interactive, multimedia, role play, conveyed theoretically and/or practically.</p>
Level of evidence 1-	Primary studies: [391, 400, 450-460]
	Consensus strength: 100%

M. Anders

A systematic literature search yielded 20 publications about 13 different educational programmes for health professionals on the early detection of skin cancer. In addition to the information contained in the various publications, 12 of the original authors provided further details on the individual analyses. The pooled information provides details on aspects from the areas of curriculum (technical content), forms of training and measured outcomes (evaluation). Within the individual educational courses, curricula were developed or adapted, implemented and ultimately evaluated in the subject areas of diagnosis (in 92% of studies), epidemiology (97%), treatment (62%), algorithms (46%) and dermoscopy (15%). The content matter was conveyed in various forms and using various educational means: course attendance (in 69% of studies), interactively (46%), multimedially (23%) or web-based (15%); with one intervention unit (23%), with two (46%) or with more than two intervention units (30%). Eighteen of 20 studies show a significant improvement in the measured outcomes as a result of the intervention. Specifically, the endpoints of knowledge, skills and competences, confidence in diagnostic, treatment and counselling skills, and the proportion of correct diagnoses was increased or enhanced [456].

In a further study in which the results of 17 general practitioners were analysed and the intervention consisted of course attendance and a brochure with 40 diagnostic pictures, sensitivity and specificity were improved in relation to the detection of various skin lesions. Specifically, the sensitivity for malignant lesions increased significantly from 63% to 76% (for MM from 65% to 81%) and for borderline lesions from 55% to 62%. A group consisting of six dermatologists was also interviewed. In this respect, it may be observed that, even after the teaching given to general

practitioners, the proportion of correctly made diagnoses is frequently higher among dermatologists (for example seborrhoeic keratosis: dermatologists (100%), general practitioners (54%)) [450]. Twenty-seven medical students with (n=20) and without (n=7) previous dermatological knowledge who received the same teaching also showed a significant increase in correct diagnoses. In this evaluation, no significant difference was seen between the group with and the group without prior knowledge [452].

Following an hour's teaching in the clinical and dermatological assessment of skin lesions using 20 pairs of photographic images (one clinical, one dermatoscopic), the evaluation showed that confidence in the diagnosis that was made was significantly increased in the subjects (19 physicians undergoing specialist training to become dermatologists) by the dermatoscopic presentation of malignant and benign lesions compared with clinical examination. The exception was the group of dysplastic skin lesions, in which no significant change was observed. It can also be inferred from these results that, following the teaching, the assessment is significantly shifted towards the correct diagnosis (for malignant and benign skin lesions). Again, the result in the group of dysplastic skin lesions did not change significantly. With images that had previously been classified as unequivocal in terms of their clinical diagnosis, no significant improvement was shown as a result of the dermatoscopic images after the intervention [451]. It should be noted that the analysis provides no information on a possible control group.

The determination of the diagnosis and the development of a plan for further diagnostic tests or treatment on the basis of 36 images as part of a web-based tutorial significantly increased the proportion of correct diagnoses in the intervention group for some skin lesions following teaching. No significant changes can be seen in the control group (without teaching). Seventy-one physicians took part in the study (intervention group: n=39; control group: n=32), of whom only 46, however, (intervention group: n=27; control group: n=19) remained until the end of the study [454].

In a one-week intervention, 32 nurses received instruction in the subject areas of clinical decision-making, epidemiology, risk assessment, diagnosis, prevention, symptoms and treatment in connection with the early detection of skin cancer (24 hours of theory, 20 hours of practice). This included the use of case analyses and photographic images of skin lesions. In addition to the theory, practical training was undertaken in a clinical setting. Outcomes (general knowledge, prevention knowledge, skills relating to the early detection of skin cancer) were recorded before the teaching, after the teaching and three months after the beginning of the teaching. It was found that the knowledge and skills parameters increased significantly, in addition to which the self-confidence of the participants increased regarding performance and advice on early detection of skin cancer. Overall, the values remain stable over the subsequent course of time. Significant differences were also seen in all aspects in relation to the results of the control group, which consisted of 87 nurses [457]. It should be noted that the result cannot be fully transposed to other countries, as the professional image of nurses in the USA differs markedly from that of healthcare and nursing staff in other countries.

In a two-hour intervention, health professionals (physicians, nursing staff, medical assistants) received instructions in the subjects of epidemiology, symptoms, diagnosis, prevention and counselling concepts associated with early detection of skin cancer. This involved course attendance, role-playing and additional information material (diagnostic algorithms, general brochures, scientific articles). In the follow-up

questionnaire (a total of 23 participants in the evaluation) general agreement with the early detection of skin cancer increased significantly. The same applied to agreements with the statements: “early detection of skin cancer is effective”, “the patient should be given the opportunity to take part in the early detection of skin cancer” and “early detection of skin cancer reduces mortality and morbidity”. The general attitude towards the importance of skin cancer counselling also increased significantly. Likewise, a significant increase can be observed in terms of the self-reported performance of preventive and cancer early detection measures (performance of whole-body examination, questions about sun protection behaviour, advice on skin cancer risk, provision of information material). In addition, the performance of preventive and skin cancer early detection measures as well as the whole-body examination of at-risk patients is significantly extended to include all patients. Likewise, the length of discussion of this topic and also the use of sunscreens by health professionals themselves increased. It can also be reported that the proportion of correct diagnoses increased significantly from 46% to 64% and the detection of suspicious skin lesions from 61% to 71%. Further significant increases are also found in the appropriate handling of patients’ uncertainty (from 49% to 70%) and in knowledge about the early detection of skin cancer (from 68% to 74%). The ability to provide the patient with prevention measures also increased significantly. In addition to these surveys (before and one month after teaching), patients (n=285) were interviewed by telephone in the institutions in which the participating health professionals were employed. Overall, preventive activities increased between the two surveys. Significant increases that are relevant in this context are the question by physicians about skin self-examination, use of solaria, use of sunscreens, severe sunburn episodes and advice about sun protection, skin self-examination and personal risk. In addition, the patient’s questions about early detection of skin cancer were answered more frequently and information material was provided more frequently [458, 459].

Dolev et al. (2011), with the aid of 252 medical students randomised to two groups and interviewed at three timepoints, studied the impact of an intervention consisting of the combination of web-based teaching about the diagnosis of skin lesions and practical training in a dermatological clinical department. The web-based teaching programme consisted of 17 teaching units on the diagnosis and, where applicable, treatment of pigmented and non-pigmented skin lesions (MM, NMSC, moles and other benign skin lesions). The learning units contained 85 clinical cases with photographic images and learning texts, which discussed visual features for assessing skin lesions. The practical part included the following areas: general dermatology, paediatric dermatology, dermatological surgery plus face-to-face learning, case discussions and analysis of the relevant literature. Group I completed the web-based teaching first and then the practice; group II the practice first and then the teaching. Interviews were held in both groups at the beginning and end as well as between the respective interventions. The students’ state of knowledge was recorded in terms of both the diagnosis and the treatment of skin cancer. A significant improvement was seen in both groups over the course of time. Overall, higher values generally were achieved with the combination of theory and practice than with only one of the two interventions. In addition, it can be observed that sequence plays a role in terms of knowledge of diagnostic procedures, i.e. the sequence of practice followed by teaching yields significantly higher values than the sequence of teaching followed by practice [453].

A training programme with 65 family physicians, 41 of whom completed the evaluation fully, comprised three learning units: a general, three-hour information session (epidemiology, diagnosis, treatment), which included the discussion of various skin

lesions on the basis of slides, a practical unit in a Melanoma Unit in a clinic and a unit that focussed on practical skills (e.g. excision methods). Confidence in medical counselling is shown to be increased. Specifically, the parameters of advice on screening interval (39.7% increase) and recognition of the signs of skin cancer (54.8% increase) were studied. In addition, the physicians' confidence in their diagnosis of malignant lesions was increased by 43.1%. In the control group, no significant increase was detectable over the course of time. Similarly, an increase was found in the intervention group in terms of correct diagnosis and correct treatment (based on the assessment of photographic images). The proportion of physicians who independently established a possible diagnosis prior even to the histological report also increased. However, no significant improvement was obtained in the concordance between the initially established and the histologically confirmed diagnosis. The teaching also did not produce any increase in the appropriate performance of excisions from a histological perspective [455].

An intervention conducted with community-based general practitioners and dermatologists involved an individual, 20-minute-long, face-to-face feedback. This was followed by the participants assessing skin lesions on the basis of analogue and digital images and the direct examination of the patient. The intervention also consisted of a two-hour interactive seminar focussing on pigmented and non-pigmented skin lesions. The subject matter was supported by a slide presentation, videos and case examples. Another topic involved instruction about the process of the whole-body examination. In addition, other materials were issued for more in-depth information (colour diagram, brochure, "melanoma prevention kit", magnifying glass, skin colour guide, photographic images). The analysis showed that the intervention significantly increased correct diagnoses and the associated correct treatment option(s) in the intervention group (n=26) compared with the control group (n=26). The education, however, was not able to bring up the level of skills of community-based general practitioners to that of dermatologists (n=13) [460].

In a study by Gannes et al. (2004), general practitioners were provided with a twelve-minute online video containing information on skin cancer (including risk groups, advice) and photographic images of the various skin cancer entities. The results showed that only a slight increase in knowledge (skin cancer generally, prevention strategies, treatment, suspicious skin lesions) was demonstrated in the intervention group (n=10), which was not significant in comparison with the control group (n=17). At the same time, there was no significant increase in the frequency of excisions and correctly established diagnoses between the intervention group and the control group [391].

Bono et al. 2002 show that the combination of clinical (including the ABCD algorithm) and dermatoscopic diagnostic procedures for the detection of MMs by experienced dermatologists (more than five years' professional experience) exhibits the most beneficial balance in terms of sensitivity and specificity compared with telespectrophotometric diagnostic procedures. The combination of clinical (86%) and dermatoscopic (91%) sensitivity yielded an overall sensitivity of 97%. By comparison, the telespectrophotometric examination had a sensitivity of only 80%; in addition, the specificity was only 49%. Conversely, with clinical and dermatological diagnostic procedures, values of 77% and 74%, respectively, were obtained. Overall, 313 suspicious skin lesions were investigated in 298 people [400]. The study did not examine a direct intervention, but nevertheless provides an indication of possible difficulties in the diagnosis of MMs in relation to the early detection of skin cancer.

Need for further research

There is a need for further research since, although the studies to date do yield results for individual projects, this is on the basis of small case numbers. In addition, recommendations for a comprehensive and complete evaluation, which is needed in order to be able to attribute effects to specific intervention measures, are not implemented. Greater emphasis must therefore be placed on quality and completeness in the evaluation of existing and future programmes and measures so that programmes and measures are improved and new programmes can be designed on a robust basis.

5.54.	Evidence-based recommendation
Degree of recommendation 0	Pharmacy staff can be trained in primary skin cancer prevention.
Level of evidence 1-	Primary studies: [461]
	Consensus strength: 96%

Fifty-four pharmacies belonging to three pharmacy chains were randomly allocated to an intervention group (n=27) or a control group. Each pharmacy staff was taught about primary preventive aspects in the prevention of skin cancer by means of video and written information. This encouraged the pharmacy staff to approach their customers about primary skin cancer prevention behaviour, give them advice and offer them a brochure and sunscreen samples. The campaign was supported by coffee cups, badges and posters for staff that were intended to refer to the campaign. In addition to pre/post data collection, test subjects were sent to the pharmacies. In total, 91% of pharmacy staff from the intervention group saw the video, 97% read the written information, 76% wore the badge and 74% used the results-based feedback given after a week by the test subjects. Verbal advice was offered by 34% of pharmacy staff; a brochure was handed out in 9% of cases. 17% of the test customers received advice and a brochure, 4% a brochure and a sunscreen sample. 36% were offered all three measures. Consequently, 87% in total received advice. In the pre/post test completed by the staff themselves, it was found that there was an increase in terms of counselling activities, attitude to the issue (importance of sun protection), knowledge and self-rated expertise in the intervention group following the intervention. Similar results were not found in the control group [461].

Need for further research

There is a need for further research as to how useful it is to include other professional groups who are in less direct contact with possible recipients in primary and secondary preventive measures.

5.5.2. Data documentation and flow

A. Katalinic

5.5.2.1. Introduction

If European Union requirements are taken as a basis for the assessment of early cancer detection programmes, the German skin cancer screening (SCS) may be classed as a non-population-based (opportunistic) early detection programme. It is offered population-wide as an statutory health insurance service, but vital elements of a systematic, population-based early detection programme are missing (e.g. population-wide invitation to SCS, monitoring of the requisite examination intervals, quality assurance-related and programme-related evaluation, outcome evaluation). In Germany, at present only breast cancer screening fulfils the requirements of a population-based early detection programme. According to the European guidelines for breast cancer screening and diagnosis [462], all eligible women are systematically invited for screening at specified intervals. There is also, for example, an organisation responsible for issuing invitations, detailed documentation of the mammography and on-going quality assurance with clearly defined indicators for process and outcome quality.

There are also corresponding guidelines for the early detection of colon cancer and cervical cancer at the European level [463, 464], although these have not yet been implemented in the German health system, or only to a limited extent. Thus, both programmes can also be described as an opportunistic screening service. Under the current Federal government bill, “Bill on the further development of early cancer detection and on quality assurance by clinical cancer registries”, an attempt is being made to convert the early detection of colon cancer and cervical cancer into population-based programmes [465].

Although there is no comparable guideline for skin cancer screening at the European level, progression towards a population-based early detection programme should also be the aim for skin cancer screening in order to ensure a homogeneous provision of services and high quality of the overall programme. Based on the European early cancer detection guidelines, individual aspects such as the invitation system (e.g. through registration offices or health insurance companies), monitoring of examination intervals, documentation of early detection examinations, definition and assessment of quality indicators and regular feedback on the quality of the examination provision to those involved (benchmarking) should be implemented.

The German College of General Practitioners and Family Physicians (DEGAM) has issued a contrary opinion on the subject (see section 5.5.2.2).

5.5.2.2. Data recording

5.55.	Consensus-based recommendation
EC	<p>In skin cancer screening, participating physicians must collect the following data for each patient examined for skin cancer:</p> <p><u>Family physician (specialists in general medicine working in family practice, internal specialists, medical practitioners, non-specialist physicians):</u></p> <ul style="list-style-type: none"> • Clear personal identification of the examinee (screening ID or pseudonym in the cancer registry), • Identification of the physician, • Age and sex of examinee, • Date of examination, • Presumptive diagnosis, differentiated by type of skin cancer (malignant melanoma, squamous cell carcinoma, basal cell carcinoma). <p><u>Dermatologists (specialists in skin and venereological diseases) must record the following data in addition to those mentioned above:</u></p> <ul style="list-style-type: none"> • On referral: presumptive diagnosis of the referring physician and date of first examination, • Date of examination (dermatologist), • Presumptive diagnosis (dermatologist), differentiated by type of skin cancer (malignant melanoma, squamous cell carcinoma, basal cell carcinoma), • Following excision: excision date, histopathological findings and where applicable tumour stage (tumour thickness or spread, where applicable TNM stage, grading).
	Consensus strength: 100%
5.56.	Consensus-based recommendation
EC	<p>If an invitation system is introduced for skin cancer screening, the following data on the invitation of the general population must be recorded:</p> <p><u>Agency issuing the invitation (central agency or health insurance company):</u></p> <ul style="list-style-type: none"> • Clear personal identification of the invitee (screening ID or pseudonym in the cancer registry), • Date of invitation • Age and sex of invitee, • Rejection / exclusion (active rejection of skin cancer screening or skin cancer screening not applicable, e.g. with prevalent skin cancer).
	Consensus strength: 84%

5.57.	Dissenting opinion of DEGAM
	In view of the unconfirmed evidence for skin cancer screening and the in any case already high level of doctor-patient contacts in general practices compared to international standard, the German College of General Practitioners and Family Physicians (DEGAM) does not recommend an invitation system.

Predefined quality dimensions and indicators are essential for monitoring the quality of population-based early detection programmes. The assessment of the quality of the individual components of a screening programme is facilitated by using normatively defined or empirically determined reference values or ranges [462].

The data listed in this guideline recommendation represent a minimum data set for describing the skin cancer screening examination and any investigations undertaken of suspected cases, including the primarily outpatient excisions. The data set coincides to a large extent with the range of documentation required by the Joint Federal Committee (G-BA) [370]. Additionally, – but of vital importance – it is proposed here to include an unequivocal personal identification of screening participants. Without this unequivocal personal identification, neither the screening process (first examination, second examination where applicable, follow-up by cancer registry where applicable), nor the previous screening history for participants (determination of participation rate, referral from general practitioner to dermatologist, time interval between first and second examination), nor compliance with screening intervals can be described, in addition to which no link can be established with the cancer registry data, for example in order to determine participant-specific skin cancer mortality and to identify interval carcinomas.

The administrative availability of basic data for those eligible (age, sex, etc.) is crucial for running a population-based invitation system. Non-participants could be reminded of their examination again at set intervals and those who are not to be invited (skin cancer patients undergoing follow-up, abstainers) could be excluded from further invitations.

The data from the invitation system are also essential to be able to derive indicators of uptake.

With the documentation of the range of data recommended above, SCS would be equivalent in essential respects to the German breast cancer screening in terms of process and outcome evaluation.

5.5.2.3. Data transmission

5.58.	Consensus-based recommendation
EC	<p>Data recorded about skin cancer screening must be forwarded by family physicians and dermatologists to an evaluation centre where, together with the invitation data where applicable, they must be collated and evaluated for the quality management of skin cancer screening.</p> <p>In order to determine interval carcinomas and to evaluate mortality, a comparison must be undertaken with the cancer registry. The comparative data must be provided for the purposes of scientific evaluation.</p> <p>When a malignant finding is obtained, the responsible cancer registry must be notified by the examining physicians (including pathologists).</p>
	Consensus strength: 100%

In terms of its content, this recommendation is based on breast cancer screening. Data from the family physician, dermatologist and organisation issuing the invitation must be collated by an evaluation and quality assurance body in order to determine indicators. The collation of a person's data is urgently required to determine essential quality indicators.

In order to ascertain how many participants with a presumptive diagnosis made by the family physician are then examined by a dermatologist, the data for that person must be collated from both data sources. Further indicators (e.g. participation rate [number of participants/number of invited persons eligible for screening]) require links to be established with the invitation data.

The recorded data must be compared with and linked to the data from the relevant cancer registries in order to identify interval carcinomas and to evaluate the results of the skin cancer screening (SCS) scientifically. The procedures for this are already described for breast cancer screening.

In order to support associated healthcare research, interested institutions must be provided with defined anonymised data from the SCS on request.

A population-based assessment of SCS becomes possible if the cases of skin cancer discovered on screening are notified to the appropriate cancer registry.

5.5.2.4. Methods of data transmission

5.59.	Consensus-based recommendation
EC	<p>Skin cancer screening data must be recorded electronically by all those involved and transmitted electronically.</p>
	Consensus strength: 100%

The German directive on early detection of cancer requires that all data should be recorded and transmitted in an electronic form for skin cancer screening [370]. The requirements for the record formats and the channels of transmission are specified bindingly by the National Association of Statutory Health Insurance Physicians in special requirements for practice management systems [466]. Supplementation of the data set with these additionally required data fields or procedures for generating clear personal identifications (compatible with cancer registries [467]) should also be included in future in these electronic documentation requirements.

5.5.2.5. Data protection aspects

5.60.	Consensus-based recommendation
EC	Documentation of the examination results for participants in skin cancer screening must be done under pseudonymised conditions taking due accounts of suitable methods and data protection concepts. The additional collection of a declaration of consent must be omitted. For non-participants, time-limited pseudonymised data storage of the invitation data is recommended for the purpose of evaluating outcomes (particularly skin cancer-related mortality). All data recording, data storage and transmission processes must be closely agreed with the data protection authorities.
	Consensus strength: 100%

By analogy with the German breast cancer screening, quality assurance documentation must be kept for all participants in skin cancer screening (SCS). As in the German breast cancer screening, a declaration of consent should be omitted since otherwise there is a risk of gaps in the data (see also the rationale for the German directive on early detection of cancer [370]). A particular problem is presented by the fact that participants not agreeing to a declaration of consent could no longer be distinguished from the group of non-participants. Comparison of participants and non-participants would therefore be meaningless.

In evaluating mortality, skin cancer mortality must be compared between participants and non-participants. This is only possible if data from non-participants are used for comparison with the cancer registry.

To comply with the right to self-determination over personal data, the participant's personal data must be pseudonymised at the time of first recording. If cancer registry-compatible pseudonymisation and security procedures are used [467], the re-identification of people is virtually impossible. The feasibility of pseudonymised data storage and comparison of these data with other data sources has already been successfully demonstrated by the North Rhine-Westphalia cancer registry, even where large amounts of data are concerned [468].

5.5.3. Quality assurance of skin cancer screening

5.61.	Consensus-based recommendation
EC	Quality assurance measures for skin cancer screening must include structure, process and outcome quality. Because of the absence of scientifically-based quality assurance measures, quality indicators must be confirmed by evidence-based methods and where necessary new indicators developed.
	Consensus strength: 96%

M. Anders

The task of quality assurance must be to ensure the quality of the *skin cancer screening* healthcare provision. As well as the *targeted history-taking* and the *standardised visual whole-body examination*, this service also includes the *reporting of findings* and *related advice*, as well as appropriate *documentation* [370]. In addition, *preliminary advice*, advice on primary preventive behaviour (*UV advice*) and the *confirmatory diagnostic procedure (histopathology)* must also be regarded as part of quality assurance. Furthermore, quality assurance measures relating to *qualification* (in Germany: Skin Cancer Screening Advanced Education Programme) are necessary. As there are insufficient scientific studies on quality assurance in the areas mentioned and at present practically no standardised, comprehensive measures of static and dynamic quality assurance are being conducted, no evidence-based recommendations can be given here. It is therefore necessary to record and further develop any existing individual quality assurance measures, but new procedures should also be developed. These can then be tested, evaluated and, where applicable, implemented on a large scale. In principle, quality indicators established on the basis of this guideline should be used for guidance. Since, however, no quality indicators could be developed (see Chapter 7), reference is made here to the need of generating parameters that are relevant to quality assurance from the relevant recommendations. An overview or summary of the content matter of the recommendations can be found in the following list. This contains additions to the Skin Cancer Screening Advanced Education Programme and is harmonised with the German directive on early detection of cancer, the German Skin Cancer Screening Histopathology Quality Assurance Agreement and Objectives Paper 1 of the German National Cancer Control Plan.

Targeted history-taking

- Determination of eligibility
- Completion of standardised case history form by participant
- Family history-taking
- Personal history-taking (including the possibility of immunosuppression)
- Current history-taking

Examination

Facilities

- The examination area is shielded from view (privacy)
- Use of a mat on which the participant can stand

- Use or presence of good lighting
- Use or presence of an examination couch

Aids

- Presence of spatulas/ use of three spatulas per examination
- Presence of examination gloves / use of one pair of examination gloves per examination

Visual standardised whole-body examination

- Scalp: with two spatulas by parting the hair in strips
- Ears: looking behind the ears and in the external auditory canal
- Eyelids, have patient remove glasses where necessary
- Examine oral mucosa and lips with a new spatula, raising the tongue and inspecting the gums
- Neck
- Upper body
- Axillae
- Arms
- Hands - in particular the interdigital areas
- Women: submammary region
- Perineal region: bending over, pulling buttocks apart
- External female genitalia: lying or seated
- Male genitalia: can be inspected following the standing examination, with the examinee raising the testes and retracting the foreskin
- Legs and feet, including the soles of the feet and in particular the interdigital areas

Interdisciplinary co-operation

- Feedback from the dermatologist/venereologist to the referring physician (general practitioner, internal specialist, medical practitioner, non-specialist physician) about the findings and the subsequent procedure

Reporting findings/advice (see also section 5.4.2 and 5.4.3)*Reporting in the absence of a clinical suspicion:*

- Following the examination, personally by the examining physician
- UV counselling
- Where appropriate, encouragement and motivation for skin self-examination

Reporting in the presence of a clinical suspicion:

- Following the examination, personally by the examining physician
- Family physician (specialists in general medicine working in family practice, internal specialists, medical practitioners and non-specialist physicians): explanation of the subsequent procedure (referral to the dermatologist)
- Dermatologist: explanation of the further measures for diagnostic investigations, explanation of the procedures for reporting findings (including the possibility of involving a person of trust)

Reporting in the event of negative skin cancer findings:

- Following the histopathological examination, by the examining physician personally
- UV counselling
- Where appropriate, encouragement and motivation for skin self-examination

Reporting in the event of positive skin cancer findings:

- Following the histopathological examination, by the examining physician personally
- Explanation of the findings with diagnosis, grading and prognosis
- Explanation of the therapeutic options, where necessary at several sessions
- Explanation of the next steps

Documentation requirements

General practitioners, internal specialists, medical practitioners and non-specialist physicians must provide the following parameters for complete documentation:

- Physician registration number
- Clear personal identification of the examinee (screening ID or pseudonym in the cancer registry)
- Age and sex of participant

- Examination date
- Presumptive diagnosis, differentiated by type of skin cancer:
 - Malignant melanoma
 - Basal cell carcinoma
 - Squamous cell carcinoma
- Participation in association with a routine health check

Dermatologists/venerologists must provide the following for complete documentation of these parameters:

- Physician registration number
- Clear personal identification of the examinee (screening ID or pseudonym in cancer registry)
- Age and sex of participant
- Examination date
- Presumptive diagnosis, differentiated by type of skin cancer:
 - Malignant melanoma
 - Basal cell carcinoma
 - Squamous cell carcinoma
- In the event of a referral for investigation of an abnormal finding from the skin cancer screening, the date of the first examination and the indication of the presumptive diagnosis:
 - Malignant melanoma
 - Basal cell carcinoma
 - Squamous cell carcinoma
- In the event of excision: date, histopathological findings, where possible tumour thickness or spread, TNM stage, grading
- Notification to the cancer registry

Preliminary information/advice (see also section 5.4.1)

The template for the following list is the Objectives Paper 1 checklist (German National Cancer Control Plan). In the list presented here, the individual items have been pooled so as to provide the following selection of requirements for written and supplementary verbal advice:

- Description of the target disease
 - Clinical presentations
 - Incidence
- Eligibility for the early detection service (age, interval, qualified service provider)
- Examination procedure
- Reference to directives/guidelines
- Diagnostic accuracy
 - Sensitivity
 - Specificity
 - Positive predictive value
 - Negative predictive value
- Benefits
- Side effects of the examination
- Risks
 - Description

- Probability
- Effect
- Measures
- Procedure in the event of an abnormal finding
- Symptoms/precursor stages
- Causes and risk factors
- Instructions and motivation for skin self-/partner-examination
- Primary preventive modes of behaviour (UV counselling)

UV counselling (see Chapter 4)

The following aspects need to be considered in counselling on UV:

- Information about the risk from UV radiation
- Advice on exposure to natural UV radiation
 - Avoid exposure to strong sunlight
 - Avoid the midday sun
 - Stay out in the sun as little as possible
 - Seek shade
 - Avoid sunburn
 - Accustom the skin slowly to sunlight
 - Take note of the UV index
 - Sun protection
 - Textiles, head cover, sunglasses
 - Sunscreens
 - Use sunscreens without prolonging the exposure time
 - Be aware of individual skin sensitivity
 - Provide information about the different skin types
- Advice on individual protection measures according to patient's skin type or state of health (immunosuppression)
- Restrictions on exposure to sunlight (cosmetics, medicines)
- Protect children in particular
- Restrict annual exposure to sunlight
- Advice about the use of artificial UV radiation
 - Avoid the use of solariums, particularly people under 18 years of age and people with skin type I (recommendation of abstention: ICNIRP, WHO, EUROSkin and the German Act on Protection against Non-Ionising Radiation (NiSG))
 - Radiation Protection Council recommendation on the use of artificial UV radiation
 - Recommendation for behaviour if solariums or other sources of artificial UV radiation are used

Confirmatory diagnostic procedure (histopathology)

- Compliance with requirements for the methodology and conduct of the confirmatory diagnostic procedures (excision/biopsy) (see also section 5.3 and 5.3.2)
- Completeness of the medical documentation of histopathological examinations (see section 5.3.3 and 5.3.4, see Figure 12), in particular:
 - Indication of tumour type in accordance with the WHO classification

- Indication of histological stage in accordance with the TNM classification (UICC)

Content matter of the qualification (see also section 5.5.1)

- Potential benefit and harm of early detection measures, criteria for assessing early detection measures
- Programme for the cancer early detection examination, health check and early enhancement of patient awareness
- Targeting measures
- Counselling
- Aetiology of skin cancer, clinical presentations, incidence, risk factors or group, previous history, standardised whole-body visual examination, visual diagnosis
- Procedure of the examination for the early detection of skin cancer
- Presentation and discussion of case examples
- Documentation measures
- Interdisciplinary co-operation

In addition to quality assurance measures, other parameters that serve to evaluate skin cancer screening should be noted when recording the outcome quality of skin cancer screening:

- Participation rate (differentiated by physician groups, age and sex)
- Proportion of combined skin cancer screening and health checks to all skin cancer screenings performed
- Number of presumptive diagnoses differentiated by physician groups
- Number of confirmed diagnoses by dermatologists
- Number of false-positive findings
- Detection rate (participation rate/number of detected skin cancers and histopathological grade)
- Overdiagnoses and overtreatment

6. Informing the general population / public

6.1. Informing the general population / public

6.1.1. Preamble

A working group of the German National Cancer Control Plan (NCCP) was concerned with the topic 'uptake of early cancer detection measures' (Objective 1 from field of Action 1). In connection with this process, a paradigm shift was effected that entailed placing the informed individual decision for or against early cancer detection measures above the highest possible participation rate [439]. It was then necessary to elaborate the concept of "informed decision". In this context, and following Rimer et al. (2004) [469], the members of this working group agreed on the following definition [439]:

An "informed decision" is present when an individual:

- understands the disease concerned and grasps what the medical service involves, including the benefits, risks, limitations, alternatives and uncertainties;
- has considered his preferences and
- makes the decision in accordance with these points,
- is of the opinion that he has been involved in the decision to the desired extent and
- has reached the decision voluntarily and with the highest degree of personal autonomy.

6.1.2. The "informed decision" about participation in an early detection examination

6.1.	Consensus-based recommendation
EC	Information about the early detection of skin cancer must be guided by the recommendations of the [German] National Cancer Control Plan on an "informed decision" to enable the potential screenee deciding for or against participation in skin cancer screening examination.
	Consensus strength: 75%

M. Anders

In 2008, together with representatives of the German Cancer Society, German Cancer Aid and the Association of German Tumour Centres, the German government brought into existence the National Cancer Control Plan to harmonise the activities of all those involved in combatting cancer and to optimise the care situation for cancer patients in Germany. The aims of the NCCP are primarily to develop early cancer detection and care structures further, as well as to introduce more quality assurance in oncology, to ensure effective drugs for treatment and to give guidance to patients. This also involves improving the communication skills of physicians, as well as providing information, advice and assistance [439].

In this context, Objective 1 (Improvement of information and participation in the early detection of cancer) from field of action 1 (Further development of the early detection of cancer) concerns the development of criteria necessary for the formal and content-related structuring of information provision to allow citizens an “informed decision”. Since early cancer detection examinations are directed towards asymptomatic persons and can be associated with risks as well as benefits, an “informed decision” for or against participation is particularly important. Potential screenees must therefore have access to objective, comprehensible and comprehensive information about potential pros and cons. To meet this requirement, the following *Recommended content of information about early detection measures* checklist was compiled by the members of the appropriate working group. It constitutes a consensual basis for compiling health information, which remains to be tested in research projects [439].

Checklist: Recommended content of information about early detection measures (modified) [439]

- Introduction,
- Target groups,
- Aims of the information,
- Explanation of the disease for which the measure is used,
 - Description of the disease and its course (without an early detection measure),
 - Health significance/handicaps,
 - Epidemiology (disease incidence, mortality; it may be helpful to present these risks in comparison with other diseases; presentation of risks as natural numbers and also where possible graphically),
 - Treatment options,
 - Prevention,
- Description of the early detection measure,
 - Aim of the measure (incidence reduction /morbidity/mortality),
 - Explanation of the method/description of the examination procedure,
 - Description of further investigations following the finding,
 - Reliability of the method (frequency of false-positive and false-negative findings; positive predictive value of a finding),
 - Description of the benefit and quantification (comparatively with and without the early detection measure),
 - Level of evidence (or with what certainty the measure is scientifically proven actually to achieve its aims),
 - Description of risks and drawbacks,
 - Direct risks associated with the examination (e.g. radiation, complications),
 - Indirect risks that result from a finding,
 - ... from false-positive findings,
 - ... from false-negative findings,
 - ... from bringing forward the diagnosis,
 - ... from overdiagnosis/overtreatment,
- Access to early detection,
- Information on costs arising or payment of costs,
- Information on the quality of the early detection measure,
- Description of quality assurance measures (e.g. certification of the service provider, continuing education programme, dual approval) and verifiability (quality indicators which the participant can check, such as counselling about possible findings, need to undress for skin cancer screening),

- Further information,
 - Reference to additional information not given due to lack of space,
 - Reference to the fact that other people who knew this information have reached different decisions,
 - Reference to the fact that there is no pressure in terms of content or time,
 - Reference to patient guidelines or other specific information,
 - Decision aids (where validated aids are available for the individual decision),
 - Reference to data protection or data utilisation or declaration of consent to data transmission,
 - Self-examination,
 - Reference to absence of symptoms (i.e. symptoms must be investigated regardless of eligibility to an early detection examination),
 - Own responsibility (each person is himself responsible for looking after himself and taking decisions for or against preventive measures. Knowledge about one's own risk, about efficacy, benefits, risks and limits of methods and consequences – including in the event of non-uptake – is the basis for assuming self-responsibility),
 - Risk groups,
 - Legal statements/indication of sources/date of information,
 - Funding of information medium, of information source, etc.,
 - Statement of conflicts of interest,
 - Expiry date of information.

Need for further research

There is a need for further research regarding the identification and description of predictors, moderators and mediators that impact on the “informed decision”. In this respect, consideration needs to be given to the areas of information, context and medium. In addition, as described, the checklist must be tested (empirically) and developed further, for example by criteria lists or other measurement instruments.

6.1.3. Addressing target groups

6.2.	Consensus-based recommendation
EC	Strategies and measures whose aim is to reach the population with prevention messages and to allow an “informed decision” for or against participation in skin cancer screening must be tailored to the different target groups.
	Consensus strength: 96%

M. Anders, E. Baumann

The fact that a decision for or against participation in skin cancer screening is optional and not obligatory for the potential screenee means that first of all the target persons' attention must be drawn to prevention options and they must be offered information and information sources that are relevant to the decision. Accordingly, this entails communication strategy-related considerations about the accessibility of the different target groups; bearing in mind, the individual factors affecting access to the target group concerned. In this context, it should also be realised that often precisely those individuals who are characterised by a fairly high risk status because of a poor risk

awareness and a low perception of self-efficacy that need to be reached. Exactly these groups often have only a limited awareness of their need for information, communication and decision, have little interest in the subject and/or do not want to modify their health-related behaviour. On the other hand, there are also individuals who display a high degree of commitment and a marked interest in the subject and whose information and communication needs – coming from a different direction from that of the high risk groups – must also be taken into account. As a result, a differentiated, target group-oriented approach and information are of particular importance. The communication strategy must be adapted to the information and communication needs, to the routines and the health-related everyday setting of the target group concerned. This also includes the identification of relevant multipliers (e.g. parents, partners, doctors, pharmacists, teachers, employers, peers), who play an essential role in reaching the actual target group(s). The first step therefore involves the need (for example as part of the formative evaluation, see section 6.1.5) to identify the different target groups (segmentation) so as then to be able to describe them and subsequently, in a second step, to be able to select, develop and compile suitable strategies and measures (targeting). It is the function of segmentation to distinguish more homogeneous subgroups from the heterogeneous overall group in order to be able to address and serve them more effectively and in a more targeted fashion [470].

Simultaneously, it is beneficial if segmentation is based on health psychology and behavioural science constructs, such as lifestyle, health-relevant attitudes and motives, risk perception and behaviour, as well as self-efficacy perception. These factors are associated with information and communication needs, preferences and barriers, with the type and intensity of the search for health-related information and media use, and with the awareness and processing of the issues. In terms of health communication, this entails the need to develop information and communication aims, communication pathways and message strategies tailored to this basis [471]. It is also necessary to ascertain the health literacy and media literacy as well as real-life settings of the target groups in order to be able to localise and define the individual segments. Since such comprehensive information is often not available, segmentation is mostly performed on the basis of more easily available determinants of the features mentioned. Sociodemographic, socioeconomic, sociological and psychographic criteria in particular, as well as health status, health awareness and risk profile, play an important role here. The combination of several criteria (hybrid segmentation) is also frequently possible and necessary. In addition, segmentation should be process-oriented, i.e. since a decision is often a constituent part of a process of behavioural modification involving several stages (cf. transtheoretical model), target group differentiation should also take into account that the target persons can be situated at different stages in the behaviour change process and thus present different information needs. In addition, target group segmentation should also be constantly adapted to changes in the target group's characteristics (dynamic segmentation) [470].

Need for further research

There is a need for further research to examine how the efficacy of target group-segmented measures differs from measures that address the whole population. There is also a need to document empirically which criteria used within a segmentation strategy are more efficient and effective than others. Furthermore, strategies and measures for disseminating messages and information must be evaluated in terms of their strategy by comparing target groups. This requires (see section 6.1.5) comparing measures with one another and testing their suitability for specific target groups.

6.3.	Evidence-based statement
Level of evidence 1 ++	Informing the adult population in a social setting can help promote cancer awareness.
	Primary studies: [376]
	Consensus strength: 96%

The systematic review by Austoker et al. (2009) considers interventions to promote cancer awareness and early presentation when cancer is suspected. Five studies which investigate interventions directed at individuals and involving the distribution of (personalised) information by mail or via the web were included in the analysis. A further ten studies describing public information campaigns in some cases, but also setting-related interventions (i.e. related to the surroundings, e.g. the workplace) were also analysed. Most studies focussed on one specific type of cancer. A total of four studies consider malignant melanoma exclusively. The intervention resources ranged from information brochures and telephone information via computer-based learning programmes to mass media information campaigns, information seminars and presentations, and information stands. The outcome shows that cancer awareness, alertness to possible cancer symptoms, actively seeking assistance in the event of suspicious symptoms or knowledge about melanoma risk reduction were increased by the interventions concerned. It may be inferred from the study that interventions geared to the individual (tailoring) are the most effective. Incorporating or adapting an information measure in or to the social setting is an option for personalisation [376].

The review itself is rated as level of evidence “1++” (see section 2.4.1). The question in hand, however, is examined only indirectly, so that the level of evidence can be applied only to a limited extent to the recommendation statement. As a result, the wording “can” has been chosen in the statement.

Need for further research

As the study situation shows, there are to date hardly any studies that evaluate setting-related interventions (e.g. at the workplace or in the kindergarten) against interventions that work without reference to the setting. It would be important to provide evidence for the advantages of a setting-related intervention and to generate detailed research results so as to be able to adapt interventions to the relevant setting, since it is precisely through such interventions that difficult-to-access target groups can also be reached.

6.4.	Evidence-based recommendation
Degree of recommendation 0	Children, adolescents and young adults with computer or online skills can be informed via computer or online.
Level of evidence 1-	Primary studies: [472-474]
	Consensus strength: 96%

S. Singer, C. Schwarz, M. Anders

As far as the approach to children, adolescents and young adults is concerned, there is evidence in the literature regarding suitable media to reach out to this target group. Thus, Adams et al. (2009) discovered that children and adolescents aged 10 to 16 years who participated in computer-based training behave more risk-aversely in terms of sun exposure than people from the control group [472]. This effect is probably due to a change in the decisional balance (subtraction of the pros of sun exposure from those of sun protection) as a result of the intervention. However, a direct relationship between intervention and behaviour is not observed in the study.

Hornung et al. (2000) report on an intervention aimed at third- and fourth-year schoolchildren. The subject matter of the intervention was knowledge about the risks of UV radiation, attitude towards suntans and behavioural practices for protecting against UV radiation. Various channels of communication were used in the process. One group was given the information by CD-ROM (IG 1), others by teacher-led instruction (IG 2) and a third group received no intervention (NG). In both interventional groups, the teachers received general information and information about how to carry out each measure. The results show that knowledge was most increased, attitude was most improved and possible behaviour was exhibited more frequently in IG 1 than in IG 2 and NG. After seven months the effects were attenuated in IG 1 and were no longer statistically significantly different from IG 2, but there were significant differences between these two groups and NG in knowledge about the risks of UV radiation. In respect of attitude, only IG 1 and NG differed significantly from one another, while there were no longer any differences between the groups in terms of behaviour [473].

Idriss et al. (2009) provide evidence that for internet-savvy young adults (18 to 39 years old) web-based communication resources (online videos) are superior to purely text-based media (print media) in their effectiveness in mediating knowledge about malignant melanoma. It was also observed that more participants would consult a dermatologist in the event of suspicious skin lesions [474].

6.5.	Consensus-based recommendation
EC	Information can also be given via agents of socialisation, peers and other multipliers.
	Consensus strength: 83%

Peers

The inclusion of peer communication in information measures about primary and secondary skin cancer prevention is highly promising because studies show that peer communication has a moderating effect on the relationship between descriptive norms (what the majority do or would regard as appropriate) and behaviour. This can be explained using the example of alcohol consumption among students. Alcohol consumption is affected by more than just descriptive norms. Communication between peers also has a determining effect here [475]. For this reason, peer communication is suitable for supporting behaviour changes.

Agents of socialisation

As one of the most important processes of internalisation, socialisation also offers the possibility for informing. Within the socialisation process, for example parents, nursery school staff, teachers, etc., assume the role of agents of socialisation [476]. By training and informing agents of socialisation, they can act as well informed multipliers.

Other multipliers

Training partners can improve the self-confidence of melanoma patients in self-examination [477].

Family physicians and pharmacists can be offered teaching videos with information about risk groups or internet-based tutorials. However, there is insufficient evidence of the effect of such teaching videos on specific skin cancer risk groups or of internet-based tutorials on family physicians [391, 454] and pharmacists [478].

6.6.	Evidence-based recommendation
Degree of recommendation B	Adults should be informed repeatedly.
Level of evidence 1+	Primary studies: [479-481]
	Consensus strength: 88%

6.7.	Evidence-based recommendation
Degree of recommendation B	Adults should be informed by means of multimedia.
Level of evidence 1+	Primary studies: [474, 479-483]
	Consensus strength: 75%

S. Singer, C. Schwarz

There is evidence in the literature that a repeated and multimedia approach to adults leads to better effects. Thus, several studies have documented the fact that repeated communication is associated with increased sun protection knowledge, self-efficacy in the use of sun protection and avoidance of sun. In addition, knowledge about melanomas and about performing the skin self-examination can be increased. These effects were significantly different from the results in the corresponding control group [479-481]. Group-related interventions can lead to better risk awareness. In this context, Austoker et al. (2009) describe an increase from 16% to 67% in medical consultations within 3 months of the detection of melanoma symptoms [376]. In addition, multimedia communication (e.g. videos) appears to be superior to purely text-based communication in terms of effectiveness [474]. The installation of a multimedia information stand with a touchscreen at central contact points (town pharmacy, library, health centre), however, did not produce any improvements in knowledge, attitude and behaviour [483]. Nevertheless, there is no evidence for the general superiority of pictures over texts in communication [482]. Boer et al. (2006) showed that when information about skin cancer is provided through slogans and public service announcements, both the addition of textual arguments and the addition of pictures increased knowledge about sun protection measures. Lastly, irrespective of educational level, women and men appear to be equally amenable to persuasion to attend screening facilities [484]. This is attributed to well-structured promotional materials [485]. In general, it should be pointed out that in some studies the effects cannot be attributed unequivocally to their repetitive or multimedia nature as both attributes were used together and therefore it is not possible to consider them separately.

6.8.	Evidence-based recommendation
Degree of recommendation B	People at increased risk should be informed by means of tailored communication.
Level of evidence 1+	Primary studies: [477, 479]
	Consensus strength: 91%

Tailored communication achieves better effects in modifying risk behaviour (sun exposure) than simply handing out a standard brochure [479]. Tailored communication means that individuals document their sun protection behaviour over a prolonged period, after which they are given personalised feedback on how to assess their behaviour from the point of view of sun protection and how they can reduce their risk of skin cancer [479].

Training partners can improve the self-confidence of melanoma patients in self-examination [477].

6.9.	Evidence-based recommendation
Degree of recommendation B	Schoolchildren should be offered information via multiple media, along with information for their teachers.
Level of evidence 2-	Primary studies: [473, 486, 487]
	Consensus strength: 89%

The conduct and results of an intervention by Hornung et al. (2000), aimed at schoolchildren and teachers and involving various channels of communication, have been described previously under Recommendation 6.20. [473].

The effects of standard information from the Office of Health Protection compared with the SunSmart package³ (with additional, further information and materials, as well as the possibility of direct feedback to the organisers) were studied in an intervention in primary and secondary schools in Australia. However, in the evaluation no significant differences could be found in the relevant outcomes between the two groups [486]. Multimedia information (written, visual, electronic and interpersonal communication) of parents in a ski resort resulted in parents being able to remember the displayed posters but had no effect on the use of sunscreens and protective clothing in children [487].

In general, there are insufficient studies on the provision of information to schoolchildren and adults on topics relating to primary prevention of skin cancer. Since the provision of such information was discussed in the consensus building as an important aspect of primary prevention, a “should” recommendation (degree of recommendation B) has been issued despite the low evidence base.

³ The SunSmart package contains various (in some cases multimedia) materials for both schoolchildren and teachers to structure the teaching and for information.

6.1.4. Presentation of information

6.10.	Evidence-based recommendation
Degree of recommendation B	Educational and training programmes on primary and secondary prevention of skin cancer should be structured multimedially and interactively and incorporate several channels of communication.
Level of evidence 1-	Primary studies: [472-474, 479, 480, 483, 484, 487-489]
	Consensus strength: 93%

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Even for individual means of communication such as (promotional) public service announcements, positive interaction effects can be shown to be obtained in young adults with the combined use of pictures and textual arguments compared with similar announcements using only pictures *or* only textual elements in addition to a slogan and logo. This can increase knowledge about the consequences of excessive exposure to the sun and improve awareness of the advantages of sun protection behaviour. Further, announcements combining text and pictures are perceived as more attractive and encourage reflection about the announcement [484]. However, in assessing these findings, consideration should be given to the limited external validity of the experiment in view of the laboratory situation and the variety of announcements presented to the subjects for assessment as well as indications of a ceiling effect in the control group in view of the marked awareness of the benefits of protective behaviour.

In respect also of educational and training programmes, the studies considered here indicate that, compared with the presentation of information using only one sensory channel without the possibility of selection and feedback by the recipient, a communication approach using several sensory channels (text, graphics/photo, moving picture/animation) as well as human-computer interaction in the training situation increases the likelihood of a more in-depth consideration or a greater depth of information processing and hence effectiveness. In addition, media and interpersonal forms of approach should be combined, as this increases the effectiveness of the communication.

Repeated multimedia health training with animations, photos and brief information in clinical institutions results in better knowledge about melanomas, improved sun protection behaviour and increased mole checking in risk subjects [488]. It has been shown that for adolescents two sessions of interactive PC training in clinical institutions combined with four telephone interviews with health advisers over a period of 24 months has a positive effect on protection behaviour, with decisional balance acting as a mediator variable [472]. Multimedia interactive training or intervention programmes have also already been conducted in other health-related settings, such as a pharmacy, with moderate success [483].

Repeated communication achieves better effects in changing risk behaviour than simply handing out a standard brochure [479, 480].

Setting-related, multimedia, interactive training materials have also been used effectively in primary prevention in third- and fourth-year children. Hornung et al. (2000) were able to show that information communication via CD-ROM can exert a positive effect at the knowledge and attitude level compared with teacher-led educational interventions using brochures [473]. Evidence of the superiority of multimedia presentations (video) over conventional pathways using brochures is also found in Idriss et al. (2009) and Janda et al. (2010) [474, 489].

However, on the basis of existing studies, the positive effect of such prevention programmes can only be assumed for complex training programmes that incorporate various textual, visual and audiovisual elements. In many studies [472, 483, 487, 488], the programmes were not tested against the effect of other programme profiles (other channels of communication or other forms or combinations of presentation and preparation of information), so that on this basis – despite the high level of evidence of the studies in some cases – it is not possible to make any statements about precisely *which measures* or which *components* of a training programme exert an effect and which do not contribute to improving knowledge, attitude and behaviour parameters. In studies in which different forms and ways of presenting information are compared with one another, e.g. [473, 474, 483, 489], other biases may in turn have exerted an effect, which are also reflected in the lower level of evidence. In addition, these studies only provide evidence of the effect of a complex and multicomponent bundle of measures, so that it is not possible to comment on the potential preventive effect of individual components.

Against this background, evidence for the use of multimedia interactive training materials in the area of skin cancer prevention or optimisation of the cognitive preconditions necessary for an “informed decision” about participation in screening must be regarded as limited.

Need for further research

There is accordingly a need for further research in order to test comparatively the short-, medium- and long-term effectiveness of different training programmes. At the same time, conclusions about effectiveness of *individual* forms of presentation or programme profiles are only possible if the presentational and communicational parameters are varied systematically, other parameters (such as target group, subject matter) are kept constant and confounding variables are controlled or excluded. In particular, it must be ensured that the information content of the different communication pathways used is comparable. In addition, comparative studies should check the transposability of findings on the effect of different training programmes in countries and regions with an above-averagely high risk potential from solar radiation (e.g. Australia, cf. [387, 489]) and on specific target groups (e.g. elderly men, cf. [481, 489]).

Furthermore, in the context of the content and formal planning and implementation of prevention and intervention programmes, there is a need for further research in the formative⁴, process-related and summative evaluation (see also the following section 6.1.5). The strategic planning and design of campaigns requires in the first place a discussion of which risk groups can be reached via which channel of

⁴ By “formative evaluation” is meant the evaluation of a process. By “summative evaluation” is meant the evaluation of the result, i.e. a target/actual comparison, what is planned versus what is achieved.

communication and what media format this should take in order to gain attention in the target groups' natural settings. In combination with formal structural elements, various message strategies (message frames) should also be tested for their efficacy.

6.11.	Evidence-based recommendation
Degree of recommendation B	Educational and training programmes on primary and secondary prevention of skin cancer should use the simplest, most realistic and vivid forms of visualisation possible in structuring materials and take account of the limits to the acquisition of new skills by individual target groups beyond the transmission of knowledge.
Level of evidence 1-	Primary studies: [481, 482]
	Consensus strength: 93%

Girardi et al. (2006) showed that the learning effect among lay people of cognitive training in the detection of malignant melanomas using suitable photos only is clearly superior to an analytical information strategy using "ABCD criteria". Accordingly, the effect of using pictures to recognise melanomas is regarded by the authors as greater than that of textual explanations based on ABCD criteria. The latter did not even prove effective as a supplement to the photos. Photos are considered to be a more realistic everyday form of presentation for lay people that is easier to transpose to the life context or to the examination of the skin in reality, whereas the ABCD criteria are more suitable for training health experts [482].

However, the potential impact of such information material as a measure on its own should not be overestimated. Even if learning effects can be demonstrated at the knowledge level with suitably well-structured materials, this is transposable to only a limited extent to the ability to distinguish benign and malignant lesions in reality (cf. [481]). In this case, a media-based communication measure on its own – particularly in risk groups with below-average health literacy – appears not to exert a sufficient effect, so that combining such measures with interpersonal counselling and support provision is probably required.

Need for further research

Accordingly, there is a need for further research to discover what depth of information and what sort of information presentation is appropriate for which target group, i.e. can be easily understood and converted into practical knowledge, and how far in each case a combination of media and interpersonal training measures is suitable. In this context, the process of gaining attention and of learning in particular should be analysed in a differentiated manner, taking into account the target group- and risk group-specific resources and barriers of information processing.

6.12.	Evidence-based recommendation
Degree of recommendation B	Educational and training programmes on primary and secondary prevention of skin cancer should address the target persons individually (individual-level interventions) and at the same time include individualised information and feedback elements.
Level of evidence 1+	Primary studies: [327, 376, 472, 479, 488]
	Consensus strength: 96%

Health information tailored to personal characteristics, behaviour patterns, needs and convictions are more likely to be perceived as personally relevant and therefore have a stronger motivational character than those containing general information and advice. This tailoring should occur for example in the form of personalised feedback about risk status, appropriate behavioural recommendations and reminders.

For prevention and intervention programmes that address single individuals – either through personal contact with a health expert or in the form of direct media –, there is stronger evidence of their effect on the awareness of a cancer risk than is the case with interventions designed on a collective level, i.e. that do not address single individuals specifically [376]. The systematic review also provides evidence that an individualised approach or information adapted to the individual risk status (tailoring) is more effective than general information.

Evidence for the efficacy of tailoring is also provided by Glanz et al. (2010). The authors demonstrated a positive effect of personalised feedback for adults with a moderate to high risk of skin cancer in association with an information package mailed three times at two-week intervals in comparison with a non-personalised intervention in the form of general training material about skin cancer prevention and self-examination as well as a brochure on sun protection measures and tips about behaviour. The feedback was personalised through the individual risk status and personal risk factors as well as on the basis of the sun protection and self-examination behaviour practised, the willingness to change behaviour and the perceived barriers to behaviour change. The constructs “risk perception”, “cost-benefit considerations of behaviour change”, “action-relevant knowledge and skills” and “social norms” were included as mediating variables [479].

Adams et al. (2009) also demonstrated positive effects on sun protection behaviour for adolescents using an interactive PC training programme with personalised feedback and telephone interviews with health advisers. Following the interviews, personalised feedback with tips on different types of sun protection behaviour and a bottle of sunscreen were sent out by post [472].

In their interactive PC training for risk subjects, Glazebrook et al. (2006) also worked with individualised feedback on risk status that served as a warning in order to increase awareness of the threat and at the same time to provide information to reduce the barriers to, and enhance the perceived benefit of practising protective behaviour. It contributed to an increase in knowledge in particular in people with a higher risk

status [488]. Here too, however, the programme was not tested against non-personalised training, so that indications of the evidence of individualised information and feedback elements remain limited despite a high level of evidence of the studies in this respect.

Over and above the need for an individualised approach, the studies provide unequivocal evidence that a theoretical grounding to the programme design is important and meaningful. According to Garside et al. (2010), the elements of the Health Belief Model in particular provide a coherent theoretical framework for personalisation that underlies many interventions, from which can be derived the information to be communicated individually about risks and protective behaviour for preventing skin cancer and which provides initial explanations for target group-specific efficacy of programmes for the prevention of skin cancer as well as starting points for structuring messages and levels of individualised feedback and evaluation [327]. Glanz et al. (2010) also included the previously-mentioned constructs for measuring the efficacy of personalised feedback as mediating variables derived from the Health Belief Model and social cognitive theory [479].

Need for further research

There is accordingly a need for further research to underpin empirically the short-term, medium-term and long-term efficacy of individualised training programmes and feedback elements in intervention measures in comparison with programmes that include no tailoring and feedback option elements. The programmes should be based on established theoretical approaches to programme modelling and to the explanation of changes in health behaviour. Accordingly, such programmes should be designed on a theoretical basis and be tested systematically against measures that involve no tailoring.

6.1.5. Evaluation of the communication process and outcome

6.13.	Consensus-based recommendation
EC	Communication interventions in connection with primary and secondary skin cancer prevention should be evaluated formatively and summatively. The evaluation parameters used should be derived from a theoretically established model.
	Consensus strength: 85%

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In order to develop and plan targeted communication interventions in connection with primary and secondary skin cancer prevention, data collection is required even before the actual implementation of the intervention (formative evaluation). In this process, two aims are pursued: collection of information to conceptualise and implement the intervention (preproduction research) and to undertake preliminary testing of the ready-to-use intervention measure and its instruments and materials (product testing). Measurements and monitoring of the whole process are also beneficial in order to allow for external and internal confounding variables over the course of time (process evaluation). In addition to recording content-related aspects, the process evaluation also involves the inclusion of variables that describe the quality of the organisation of the intervention (controlling) (e.g. organisational procedures). The summative evaluation makes it possible to test the defined aims of a communication intervention

and to record the effects, effectiveness and efficiency of the measure. The period on the whole, during and after the intervention, must be considered. The summative evaluation provides information needed to identify and, where applicable, quantify possible changes engendered by the intervention. To this end, the relevant variables must be recorded both before (can be done already in the formative evaluation (preproduction research)) and after the intervention. Furthermore, it is important in the evaluation not just to study variables that are directly related to communication, but also to include the relevant health indicators and their change over the course of time [490-492].

The evaluation parameters used in an evaluation should be derived from a theoretically established model. According to the transtheoretical model, different stages of information processing will be passed through before an intervention is considered behaviourally relevant. Continuum models such as the Health Belief Model and the Theory of Planned Behaviour also model the process of change in health behaviour initiated by a prevention or intervention measure in a differentiated fashion. The stage of behaviour change in which the target person or subject finds himself or the constellations of individual predispositions present in the members of a target group also affect their receptiveness to the different information and communication offerings that are part of an intervention, as well as their assessment and the resultant potentials for communication. The outcomes to be measured and evaluated at the attitudinal and behavioural level should therefore be derived from the theoretical model on the basis of which the measure was designed [493-495].

Need for further research

There is a need for further research in testing evaluation strategies for their reliability and in developing a criteria list for the quality testing of evaluation measures. In addition, the explanatory power and prognostic value of different theoretical models for identifying different aims and measures and the model parameters for the prevention of skin cancer should be specified.

6.14.	Consensus-based recommendation
EC	Evaluations of interventions in connection with primary and secondary skin cancer prevention must work with empirically established measurement procedures geared specifically to the particular outcomes.
	Consensus strength: 100%

The evaluation should be performed at several measurement time points and measure short-term as well as long-term effects. Validated and standardised scales for measuring the different endpoints must be used. Where these are not available, evaluation findings should be verified empirically by comparison of the findings generated by different recording and analysis procedures.

Austoker et al. (2009) in their systematic review of prevention measures to increase cancer awareness, which also includes studies on skin cancer prevention, come to the conclusion that a higher methodological quality and comparability of study designs is required: "Future research evaluating individual-level interventions to promote cancer awareness should attempt to use study designs that generate high-quality evidence,

measure outcomes over a longer term (months/years) and attempt to measure behavioural and stage outcomes, as well as knowledge and attitudes. We also highlight the need for standardised and validated measures of cancer awareness [...]” (P.38 in [376]).

From this derive the consequences formulated in the recommendation regarding the parameters to be evaluated and the type of measurement. This applies also to the choice of recording instruments used to measure attitude- and behaviour-related outcome variables. Accordingly, the risk and protection behaviour associated with sun exposure should generally only be recorded by self-reported information from the target groups as part of written or verbal surveys. A survey, however, is a reactive method, i.e. the nature of the questioning about behaviour can exert an influence on the outcome variables. In addition, different survey methods are suitable for different attitude and behaviour measurements. While standardised surveys which frequently work with Likert scales are more suited to measuring habitual behaviour and general attitudes, exact behaviour data and situational states of mind are more accurately recorded by diary studies.

In this respect, Glanz et al. (2010) demonstrate that data collected by means of diaries are significantly better suited to predicting sun protection behaviour than data from a standardised survey. In order not to underestimate possible effects of an intervention by virtue of the fact that the selected evaluation method possibly does not record certain effects because of the nature of the data collection, different methods for measuring dependent variables should be used that are complementary to one another and that, when combined, allow a more comprehensive picture [479].

Need for further research

There is a need for further study in methodological research to optimise study designs relating to the evaluation of prevention or intervention measures and the measurement procedures used in the process. The aim is to compile a criteria list for evaluating prevention or intervention measures in order to generate empirically better validated and comparable evaluation findings, while simultaneously, for example, developing standardised and validated scales.

6.15.	Evidence-based recommendation
Degree of recommendation B	In evaluating the efficacy of interventions for the primary prevention of skin cancer, skin cancer prevention-specific attitude and behaviour parameters should be used, as well as indicators of contact frequency/intensity, to assess methods of communication and their quality and effectiveness.
Level of evidence 1+	Primary studies: [479, 484, 488, 495]
	Consensus strength: 84%

The precondition for a prevention or intervention measure to exert an attitude- and behaviour-relevant preventive effect is how often and intensively the individual communication offerings and messages are perceived, whether they generate attentiveness, how they are assessed on the content and formal level and whether they

are understood, retained and perceived subjectively as useful. To measure the immediate success of communication in advance of the longer-term effect at the attitudinal and behavioural level, there is also a need for evaluation parameters that directly address the perception of the campaign message or training measure and that measure the subjects' dispositions in a differentiated fashion at each behaviour change stage [495]. Accordingly, effective interventions would also have to exert a positive effect on the outcome variables preceding the behaviour change if it is possible to attribute the behaviour change to the intervention. Also, only feedback from the recipient about the actual information or training material provides concrete indications as to how various target groups receive the information and training provision as a whole or as individual elements, as well as the content and formal preparation of information in multimedia interventions, and to what potential for optimisation this gives rise.

Thus, Boer et al. (2006) in an experiment on the effect of public service announcements on preventive sun protection behaviour showed that a variation in the media presentation of information acts on the parameters that precede an attitude and behavioural intention. The use of pictures or textual elements and a combination of the two significantly increases the *attractiveness* of the announcements. The use of pictures alone without a textual explanation, however, can reduce the *comprehensibility* of the message. Higher *credibility* is achieved in particular with textual arguments, which is also not increased by being combined with pictures. However, the use of pictures in particular significantly increases reflection about the announcement [484].

Glanz et al. (2010a) also evaluated the *assessment* of personalised and non-personalised stimulus material by subjects, even if this was not included statistically as a mediator variable in the effect model. However, it is shown that all personalised information is assessed significantly better across all items than non-personalised information. In Glazebrook et al. (2006) also, the positive view of the way in which the information was produced and presented and the perceived user-friendliness of an interactive PC training used in the risk group contributed to the success of learning [488].

A relevant concept in this connection is the *decisional balance*, derived from the decision-making model of Janis and Mann, which expresses the weighing-up of the positive and negative consequences of an action or behaviour by the target person. It plays an essential role in connection with (health-related) behaviour changes according to the transtheoretical model. Empirical social research has developed two main options for recording the concept of decisional balance. One option lies in contrasting the pros and cons of an action or behaviour, i.e. subtracting the cons from the pros. Another option for operationalising the decisional balance lies in contrasting or subtracting the pros of a particular behaviour with or from the pros of the opposite behaviour or of not adopting the recommended behaviour [472, 496, 497].

Against this background, Adams et al. (2009) studied changes in sun protection behaviour among adolescents. This involved comparing the pros of sun protection behaviour against the pros of sun exposure [472]. In the analysis, the decisional balance was identified as a mediator between the intervention (computer-based interactive sun protection training) and sun protection behaviour. Individual components of the decisional balance (pros of sun protection and pros of sun exposure), however, are in themselves not mediators of sun-protection behaviour. This means that decisions about sun protection behaviour are taken on the basis of

expected consequences of competing behaviour patterns. In conclusion, the decisional balance measured on the basis of the relationship between the pros of competing behaviour patterns is also suitable as a surrogate parameter for measuring behaviour or behaviour changes [472].

Accordingly, when evaluating skin cancer prevention interventions, the decisional balance should be included as a mediator or surrogate parameter of sun protection behaviour.

Need for further research

There is a need for further research to systematically evaluate the importance of direct communication-related parameters (e.g. scope and capacity to attract attention of the communication media, comprehensibility and assessment of the information provision or measure) for the effect of the prevention or intervention measure at the attitudinal and behavioural level. There is also a need to model the different variants of the decisional balance empirically and to test them for their mediating effect on sun protection behaviour in order to draw conclusions about suitable forms of approach in prevention campaigns.

Studies in which media messages are used and associated with attitude- and behaviour-related outcomes would have to fulfil the necessary preconditions for a conclusion about the effect on the campaign and may then only be interpreted as evidence of changes at the attitudinal and behavioural level if it is empirically verified that this change results from the contact of the target groups with the campaign content (scope) and the processing of these messages. Studies to date do not provide sufficient evidence for this. For example, Del Mar et al. (1997) do not show sufficient evidence that the increased number of excisions by doctors during two TV campaigns can be causally attributed unequivocally to these campaigns, so that assumptions of the causal relationship remain somewhat speculative in nature despite a statistical relationship between the campaign period and the number of excisions [498]. For Oivanen et al. (2008) also, skin examination visits cannot be causally attributed to contact with campaign messages [499].

Therefore, in evaluating such measures, detailed information about the disseminated messages and promotional measures as well as a measurement of the probability of contact with the campaign and its scope, including its perception and assessment by the target population, must be gathered or ensured before evidence for the efficacy of a campaign can be assumed.

6.16.	Consensus-based recommendation
EC	<p>To evaluate the effectiveness of a communication-based intervention in terms of informed decision-making in connection with primary and secondary skin cancer prevention, at least the following parameters must be determined:</p> <ul style="list-style-type: none"> • relevant knowledge, • attitude towards the measure, action or behaviour, • participation or behaviour.
	Consensus strength: 81%

On the basis of the definition, three dimensions involved in an “informed decision” can be derived: understanding, preferences and decision. Mullen et al. (2006) also describe a fourth: participation. The individual dimensions can be operationalised in a wide variety of ways. Understanding, for example, can be portrayed by recording knowledge and risk awareness. Some preferences can be recorded by means of parameters such as perceived benefits or barriers, values and attitudes. Aspects of participation can be portrayed using concepts such as self-efficiency or shared decision-making. Lastly, the decision dimension is reflected in the intention to participate or in participation itself [500]. It is not always unequivocally, comprehensively and/or exclusively possible to assign individual parameters to a specific dimension, i.e. in some cases a parameter also incorporates aspects of several dimensions or just fragments of an individual dimension.

Marteau et al. (2001) developed a multidimensional model for measuring an “informed decision”, incorporating knowledge; attitude and behaviour (participation), i.e. aspects of the previously mentioned dimensions of understanding, preferences and decision are taken into account. All three parameter are considered dichotomously in the model: knowledge (high, low), attitude (positive, negative), behaviour (participation, non-participation). From the resultant combinations of the three variables, it is finally deduced whether the decision made is informed or uninformed. It is important for an “informed decision” that there is consistency between attitude and behaviour with, simultaneously, a high state of knowledge (Table 31).

Table 31: Algorithm for an “informed decision”

Knowledge	Attitude	Participation	Decision
high	positive	yes	informed
high	negative	no	informed
high	negative	yes	uninformed
high	positive	no	uninformed
low	positive	yes	uninformed
low	negative	no	uninformed
low	negative	yes	uninformed
low	positive	no	uninformed

Source: [501]

Conversely, inconsistencies between attitude and behaviour are a sign of an uninformed decision (Table 31). The model acquires its theoretical basis from the Theory of Planned Behaviour [493].

Need for further research

There is a need for further research in respect of the development of a recording tool that covers all four dimensions (understanding, preferences, participation, and decision) of the “informed decision” and therefore allows a more exact measurement. In addition, predictors, moderators and mediators that impact on the “informed

decision” parameter as a global concept must be identified and described. In this context, consideration needs to be given to the areas of information, context and medium. Similarly, not only decision-making processes in secondary prevention (of skin cancer), but also those in primary prevention need to be evaluated in relation to informed decision-making. There is also a need to test whether people who have taken an informed decision actually achieve other short-term and long-term outcomes in terms of primary and secondary prevention behaviours compared with uninformed decision-making.

7. Quality indicators

The derivation of quality indicators (QI) from the strong recommendations in the evidence-based guideline on the prevention of skin cancer was subject to the standardised process defined in the German Guideline Program in Oncology (see guideline report). This process has previously been used only in guidelines for diagnosis, therapy and follow-up of tumours. The present guideline is the first to deal exclusively with the subject of prevention. This fundamentally different situation was discussed extensively in the QI Working Group. Specific considerations and consequences for the derivation of QI are presented below.

A key problem is posed by the lack of transposability of the guideline recommendations into clearly and unequivocally defined QI, as well as the availability of appropriate data on possible indicators. In the area of primary prevention, behavioural indicators are the most important component of the evaluation, the aim being to detect changes in behaviour through appropriate interventions. However, in the specific case of primary prevention, these behavioural indicators would frequently have to be recorded in the form of retrospective self-reported information; as a result, the data are more strongly subject to subjective biases than measurements near to behaviour or routine medical data and should therefore be regarded as relatively limited in their objectivity and validity. This applies also to some secondary preventive measures in which epidemiological data and care research data play a role, as well as behavioural indicators. In addition, if individual recommendations relate for example to modes of behaviour of large subpopulations or the population in general, complete recording from routine data is almost impossible.

To overcome the difficulties described here, the guideline provides comprehensive recommendations on the formative and summative evaluation of information and training programmes in the area of primary and secondary skin cancer prevention. In the process, two areas can be distinguished in which the efficacy of an intervention should be extensively evaluated, both process- and result-dependently: behavioural prevention and structural prevention.

In the area of behavioural prevention, answers are required to questions such as: *What information has the citizen or specific target groups (e.g. parents) received and from where? How is this perceived and processed?* This involves asking about knowledge, but also about the depiction of risk awareness or attitudes, as well as the subjective degree of informedness. Therefore it is necessary to incorporate intermediate factors reflecting the process of information dissemination and processing as well as behaviour-relevant outcomes.

In structural prevention, the focus is on environmental factors and structures in the public, such as in schools, kindergartens and at the workplace, but also in the area of town planning and development. A formative role is played here by political or technical administrative framework conditions and processes, which should be included in the evaluation. The evaluation can be carried out both in conjunction with field experiments and also by means of process-related, non-experimental, evaluation studies. Possible questions here are: *(How) were the necessary legal, political and financial framework conditions for implementing the measure created? How are the relevant decision-makers included in the planning process and informed? Which measures have been implemented how in which areas? How do the measures go down*

with the experts and multipliers and what effects do they have in the target groups, e.g. schoolchildren, workers? Furthermore, individual guideline recommendations refer to the basic, further and advanced training of multipliers such as doctors, health assistants or other professional groups. Possible questions in the corresponding evaluation could be: *How well is the training content tailored to the particular circumstances of the professional practice and the everyday professional life of the professional group concerned? How is the content of the programmes structured and how are the training documents prepared? Are preconditions for participation in such training created by the professional groups concerned? How are the programmes received in the professional group concerned, how are the transmitted skills integrated into professional practice and what related effects can be seen, e.g. in patient counselling?* In addition, changes in or additions to continuing professional education requirements, qualification requirements and nursing training, but also in the training of nursery staff, child carers or teachers, play a role as well. The question also arises: *How far are framework conditions for implementing prevention measures catered for in administrative systems, e.g. the medical invoicing system, for example in the form of a “counselling sum”.*

In evaluating skin cancer screening (SCS), hurdles resulting from documentation requirements also need to be explained. Each SCS examination must be fully documented electronically for the purpose of invoicing (in accordance with §34 of the German directive on the early detection of cancer) by means of software certified by the National Association of Statutory Health Insurance Physicians. This electronic documentation is also used for the evaluation defined in §35 of the German directive on the early detection of cancer. The target parameters of the evaluation include participation rates, suspected diagnoses and false-positive findings. A comprehensive assessment of SCS, however, also involves epidemiological outcomes such as mortality and morbidity (stage shift to tumours detected earlier) and interval carcinomas. These outcomes are very important in assessing the efficacy of an early detection of cancer programme and are also required internationally. However, on the basis of current data collection, a robust evaluation of SCS is not possible as documentation is undertaken without the necessary personal identification. With personal referencing, it would be possible to make a comparison with the epidemiological cancer registries and the target tumours of SCS could be subdivided into “discovered in screening” and “not discovered in screening”. In this way, a study can be conducted of, for example, the possible reduction in mortality in participants and non-participants.

It is also possible that, as a result of the two-stage nature of skin cancer screening, diagnoses are documented twice and therefore biases are introduced into the comparison of suspected and confirmed diagnoses. Personal identification would also eliminate these biases. To allow a comprehensive and scientific demonstration of the effects of SCS, it is recommended that the current electronic documentation should be extended and adapted with the relevant stakeholders to include the items mentioned.

For the reasons described above, no quality indicators can be derived from this guideline.

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