Promotor	Prof. Dr. Lieve Brochez Department of Dermatology
Copromotor	Prof. Dr. Lieven Annemans Department of Public Health
Jury	Prof. Dr. Koen Van Herck Department of Public Health
	Prof. Dr. Lutgart Braeckman Department of Public Health
	Dr. Evelien Verhaeghe Department of Dermatology
	Prof. Dr. Veronique Cocquyt Department of Medical Oncology
	Prof. Dr. Pol Specenier Department of Medical Oncology, University of Antwerp
	Prof. Dr. Mathieu Boniol International Prevention Research Institute, Ecully, France

UNIVERSITEIT GENT

Faculty of Medicine and Health Sciences

Department of Dermatology

Isabelle Hoorens

Preventive landscape of skin cancer in Belgium

A clinical and health economical analysis

Thesis submitted as fulfilment of the requirements for the degree of

Doctor in Health Sciences

2016

Colophon ISBN 978-9-4619738-6-3

ABCD	Asymmetry, border, color and diameter
AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
BADO	Belgian Association of Dermato-Oncology
BCC	Basal cell carcinoma
BIA	Budget impact analyses
CI	Confidence interval
DALY	Disability adjusted life years
DLQI	Dermatology life quality index
DRU	Dermatology Research Unit
EGFR	Epidermal growth factor receptor
EQ-5D	EuroQOL 5 dimensions questionnaire
HR	Hazard ratio
HE	Health economic
HPV	Human papilloma virus
HRQOL	Health related quality of life
iBCC	Infiltrative basal cell carcinoma
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
KCE	Federaal Kenniscentrum voor de Gezondheidzorg
LDS	Lesion directed screening
LYG	Life-years gained
MeSH	Medical subject headings
MM	Malignant melanoma
MMS	Mohs micrographic surgery
MSC	Melanoma skin cancer
nBCC	Nodular basal cell carcinoma
NEE	Naked-eye examination
NMSC	Non-melanoma skin cancer
NNE	Number needed to excise
OR	Odds ratio
PDT	Photodynamic therapy
POMC	Pro-opiomelanocortin

PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
PTCH	Patched homolog 1
QALY	Quality adjusted life years
QOL	Quality of life
sBCC	Superficial basal cell carcinoma
SE	Standard excision
Sens	Sensitivity
Spec	Specificity
SPF	Sun protection factor
SCC	Squamous cell carcinoma
SCI	Skin cancer index
SMO	Smoothened
TBE	Total body examination
TNM	Tumor-node-metastasis
UK	United Kingdom
US	United States
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
UVC	Ultraviolet C
VAS	Visual analogue scale
WHO	World Health Organization

Chapter 1

Introduction

SKIN CANCER

Skin cancer comprises different entities and is generally divided in two groups: melanoma and non-melanoma skin cancer (NMSC). Malignant melanoma arises from melanocytes and is the most aggressive type. Basal- and squamous cell carcinomas are the majority of non-melanoma skin cancers and originate from keratinocytes. Other more rare NMSC are among others Merkel cell carcinoma, Kaposi sarcoma and cutaneous T- and B-cell lymphomas. When reference is made to skin cancer in this thesis, these three most common forms of skin cancer are referred to: malignant melanoma (MM), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC).

Epidemiology

Skin cancer epidemic

In 2013, melanoma represented 1.8% of all new cancer diagnoses and 0.7% of all cancer deaths worldwide.[1] Annually 272 000 new melanoma cases are diagnosed. The crude incidence rates of MM and NMSC however strongly depends on the latitude of the geographic location and ethnicity. In countries at low latitude where Caucasians historically migrated, the incidence rate of MM and NMSC is strikingly higher (BCC and melanoma incidence in Australia respectively >1 000 and 49 per 100 000 person-years versus Africa < 1 per 100 000 person-years).[2] Melanoma is the 5th most frequent cancer in Australia and New Zeeland after NMSC, prostate-, colon- and breast cancer, and the 9th most frequent in Belgium, France and the United Kingdom. The lowest incidence rates of melanoma are seen in Asia (Japan, Singapore and South Korea).[1]

It is well known that the incidence of melanoma and NMSC is rapidly increasing in white populations. Over the last 25 years the absolute number of confirmed BCC increased with 700% in the Netherlands, currently 1 in every 5 men and 6 women will develop a BCC for the age of 85 years.[3] Melanoma incidence rates have tripled in Europe during the last four decades, similar to increases in the United States.[4,5] The rising trend is argued to be a result of increased exposure to ultraviolet (UV); due to increased travel and outdoor activities, changes in clothing style and use of sunbeds; aging of the population, ozone depletion and host factors. In addition, increased surgical treatment for NMSC and thus histological confirmation, as well as increased registration and awareness contributes to the rising incidence. Lastly, perhaps also overdiagnosis contributes, as supported by the observed increased proportion of early melanomas. Though this last point is the subject of major debates in the research field today.[6–8]

Skin cancer risk increases with advanced age, on the other hand melanoma affects young and middle-aged adults more frequent. In the age group of 20-30 years melanoma represents up to 10% of all new

cancer diagnoses worldwide, resulting in important premature mortality and morbidity.[1,9] Few cancer registries comprehensively record data on NMSC, nonetheless a recent study in the Netherlands showed that in 2009 more people were diagnosed with BCC than any other type of cancer.[10] Compared to other age groups, women younger than 40 years showed the most pronounced increase in BCC incidence.[10–12]

Belgian situation

The cumulative incidence of developing melanoma before the age of 75 years is currently 1.3% in males and 1.9% in females. The mean age at diagnosis is respectively 60 and 55 years. Melanoma represents almost 10% of all skin cancers in Belgium. MM results in an estimated 400 deaths per year.[13] BCC represents the majority of skin cancers (69.6%) and its cumulative incidence is estimated at 8.1% in Belgium. Although mortality is very low (metastasis is reported in 0,003%)[14] it can cause significant morbidity. SCC represents 20% of the skin cancer burden and has a cumulative incidence of 2.2% in males and exactly half in females.[13] The other forms of NMSC are rare and represent less than 1% of all skin cancers.[15] MM and NMSC together are by far the most frequent diagnosed cancers in Belgium in males and females, before prostate- and breast cancer (Figure 1). Figure 2 illustrates the evolution in incidence of melanoma in Belgium from 2005-2013. In the Netherlands mortality and the incidence of thick melanomas increased up to 2009.[16] In the rest of Europe melanoma mortality remained more or less stable over the last two decades.[17,18] In Belgium a small increase in melanoma mortality was seen the last years (Figure 3).

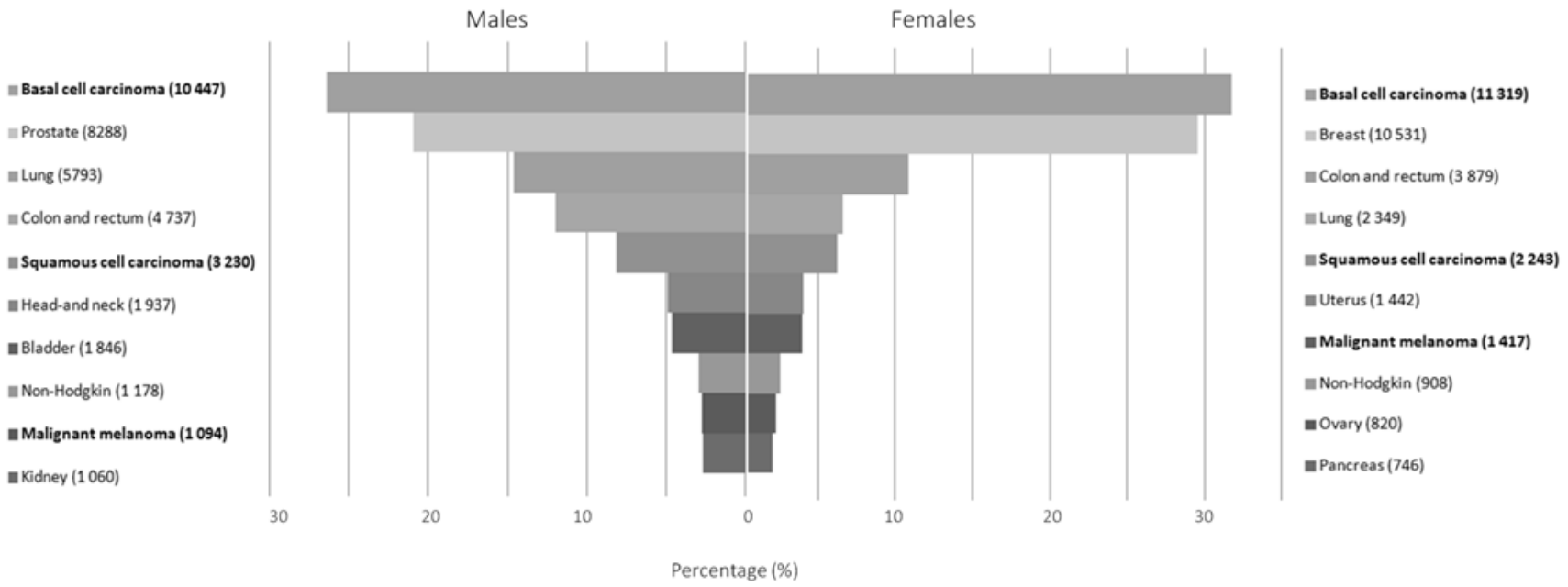

Figure 1. The ten most frequent occurring tumors in Belgium in 2012 (adapted from the Belgian Cancer registry[13]). BCC is the most frequent tumor in males and females. SCC is the 5th most frequent diagnosed cancer. Melanoma is for both males and females in the top ten of most commonly diagnosed cancers.

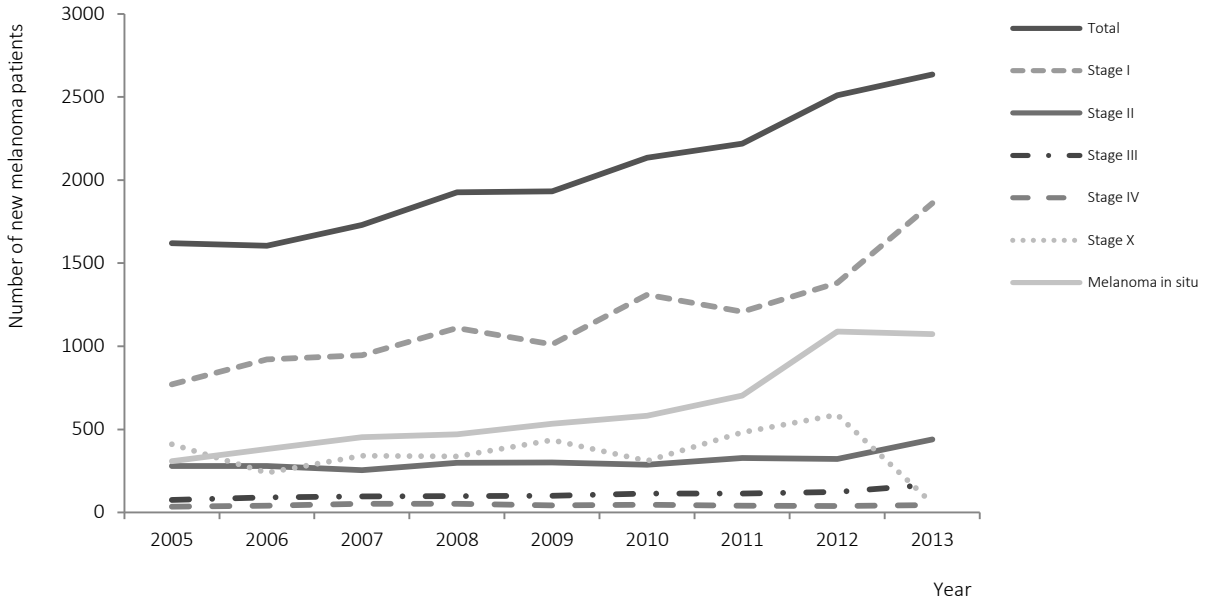

Figure 2. Total number of new melanoma diagnoses annually in males and females for all ages (adapted from the Belgian Cancer registry[13]). Stages according to the AJCC 2009 classification. Stage X: melanoma diagnosis without information concerning the stage.

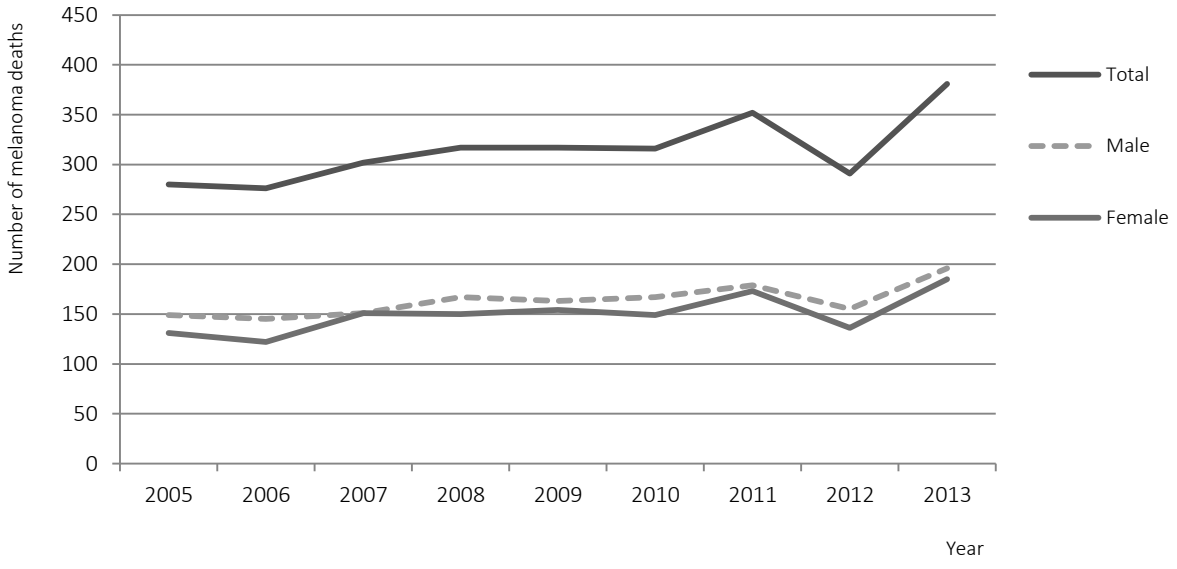

Figure 3. Annual number of melanoma deaths in Belgium (adapted from the Belgian Cancer registry[13]). Overall a stable or slightly increasing absolute mortality is seen the last years. More males than females are dying from melanoma in Belgium.

Ultraviolet radiation and carcinogenesis

Ultraviolet rays are the main environmental risk factor for the development of skin cancer. The International Agency for Research on Cancer defined solar UV as a group 1 carcinogen in 2009.[19] UV radiation is classified as UVA (400-315 nm), UVB (315-280 nm) or UVC (280-200 nm) based on their specific wavelengths.[20] The sun naturally emits the full UV spectrum, however no UVC reaches the earth surface since the atmosphere filters out wavelengths shorter than 280 nm. UVB absorption mainly depends on the thickness of the ozone layer. Other factors influencing the sun UV intensity are the season and time of day, latitude, altitude, presence of clouds and reflection of the radiation.

Sunbeds are artificial sources of UV radiation and emit relatively more UVA than UVB, some up to 5 times the dose of UVA compared to maximum exposition at midday.[21] Skin pigmentation following UV exposition is a result of pyrimidine dimers formation and increased activation of the *p53* protein. Consequently, transcription of the pro-opiomelanocortin, endotheline-1 and other pro-inflammatory genes is induced. In contrary to the protective effect of a high constitutional skin type by the presence of eumelanin, UV induced pigmentation protects in the range of sun protection factor (SPF) 2. UV induced pigmentation is only present following DNA damage (i.e. formation of pyrimidine dimers).[22]

A *p53* mutation has a key role in tumor initiation in the majority of sporadic BCC.[23] Loss-of-function mutations in the patched gene (*PTCH*) and smoothened genes are a cause of hereditary predisposition in patients with nevoid basal cell carcinoma (Gorlin's) syndrome and sporadic BCCs.[24] In cutaneous melanoma the *BRAF* gene is most frequently mutated (50–70%),[25] and part of the familial melanomas are characterized by a *CDKN2A* mutation.[26] The genetic predisposition accounts for 10% of melanoma cases.[27] Exposure to UV light is a well-established risk factor for the development of cutaneous melanoma by direct DNA damage or epigenetic events.[28] In SCC an UV induced *p53* mutation is also a key factor, in addition to a viral induced carcinogenesis caused by human papilloma virus (HPV).[29]

Risk factors

UVA and UVB exposure is associated with the development of skin cancer; however the pattern of exposure is different for the type of skin cancer. Based on epidemiological data, it seems that short intense periods of sun exposure early in life increases the risk for developing subsequent melanoma.[30] Some postulate that chronic UV exposure could have a protective effect.[31–33] In case of BCC the associated risk ratio for chronic UV is fairly low, and seems to be associated with acute sunburns and intermittent sun exposure.[33–36] SCC is related to chronic and cumulative UV exposure.[33,33,37] Table 1 summarizes the most important risk factors for the three most common types of skin cancer.

Awareness for UV radiation and carcinogenicity has increased exponentially the last 20 years. An exposure limit has been defined by the International Commission on Non-Ionizing Radiation Protection of maximum 30 J/m² or 0.3 of the standard erythemal dose daily.[38] Occupational UV radiation is acknowledged as a hazard for the development of NMSC (odds ratio (OR) SCC 1.77 (1.40–2.22) and OR BCC 1.43 (1.23-1.66)).[39,40] A French outdoor worker population has a yearly median exposure dose between 77 kJ/m² and 116 kJ/m², depending on the body site.[41] Road workers, construction workers and gardeners were most exposed. In Germany, SCC and multiple actinic keratoses (AK) of the skin caused by natural UV radiation was recently classified as an occupational disease.[42] In Denmark and France, skin cancer is acknowledged as work-related, though no financial compensation has been provided for these patients up to now.[43]

Table 1. Risk factors associated with the development of malignant melanoma, basal cell carcinoma and squamous cell carcinoma

		MM	BCC	SCC
Intrinsic	Male gender		++ [44,45]	+++ [24,25]
	Age	+	++ [44,45]	+++ [46,47]
	Fitzpatrick skin type (I-II)	+++ [48]	+++ [49]	+++ [50]
	Number of nevi	+++ [51]	+ [52]	
	Presence of atypical nevi	+++ [51]	+	
	Positive history of NMSC	++ [53]	+++ [53]	+++ [53]
	Positive history of MM	+++ [54,55]	+++ [55,56]	++ [55,56]
	Genetic predisposition	+++	+++ [57]	+++ [58]
External	Actinic keratoses	+ [59]	+++	+
	Smoking			++ [60]
	Ionizing radiation		++ [61,62]	++ [61,62]
	Human papilloma virus (HPV)			+ [63]
	Immunesupression	+ [64]	++ [65–67]	+++ [68–70]
UV exposure[33]	Total (cumulative)	+	+	+++
	Non-occupational or intermittent	++	++	+
	Acute	++	++	

Categorized relative risks; + relative risk of 1.0 -1.4, ++ relative risk of 1.5-5.0, +++ relative risk > 5.0. MM, malignant melanoma. BCC, basal cell carcinoma. SCC, squamous cell carcinoma.

Clinical examination

Melanoma frequently presents as a pigmented skin lesion with brown, red to grey color variation. On the other hand, some melanomas have complete absence of pigment. The ABCD rule (asymmetry, irregular border, color variation and diameter) can aid the diagnosis. BCC has no precursor lesion and presents as a small grayish or skin-colored nodule or induration with telangiectases. SCC develops mainly on chronically UV-exposed skin such as the face, ears, lower lip and back of the hand. They have a wide clinical variety and can present as indurated, hyperkeratotic papules, plaques, or nodules with or without ulceration.

Dermoscopy

This technique is used for the clinical diagnosis of skin cancer, and has shown to significantly increase the diagnostic accuracy for skin cancer detection in experienced users. A meta-analysis demonstrated an overall improvement in diagnostic accuracy for MM of 49% compared to naked-eye examination (NEE).[71] In case of NMSC, the diagnostic accuracy increased from 84% up to 91%, and from 58% to 84% for BCC in specific.[72,73] Dermoscopy is a non-invasive magnifying optical tool that visualizes several structures correlated to the histopathology of the lesion. Over 200 dermoscopic structures have currently been described. These are not visible to the naked eye, since dermoscopy inhibits the light reflection in the stratum corneum using liquid immersion (non-polarized dermoscopy) or light polarization (polarized dermoscopy, Figure 4).

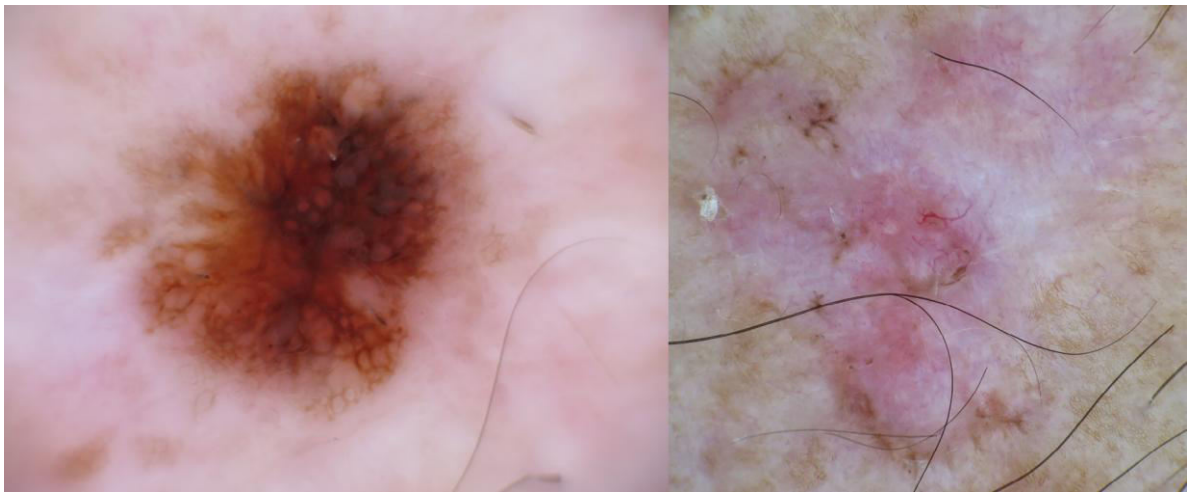

Figure 4. Polarized dermoscopic images of a melanoma *in situ* (left panel) and basal cell carcinoma (right panel).

Histology

Melanoma

A melanoma *in situ* is located intra-epidermal. In case atypical melanocytes are growing trough the basal membrane into the dermis the diagnosis of an invasive melanoma is made (Figure 5). A *radial* and *vertical* growth phase can be identified during this process. Breslow thickness is used to express the extend of invasion of atypical melanocytes. In addition, the presence of microscopic ulceration and the mitotic index are important prognostic factors (Table 2). Superficial spreading melanoma, nodular melanoma, lentigo maligna and acral lentiginous melanoma are the 4 major types.

Basal cell carcinoma

BCC is a slow growing tumor arising from the basal layer of the epidermis or the pilosebaceous adnexa (Figure 5). BCC is most frequently on sun exposed body areas such as the head, neck, lower arms and back, but can occur anywhere on the skin that contains hair follicles.[3] BCC has no clear clinical precursor lesion, in contrast to SCC. A range of variants have been identified according to the growth and pigmentation pattern. Histology most often shows large globules of basaloid cells confined to the dermis, or tumor cells infiltrating in to the subcutis in case of infiltrating BCC. The World Health Organization (WHO) proposed a histologic classification in 2006 consisting of 8 types [74]:

I. Superficial basal cell carcinoma,
II. Nodular basal cell carcinoma (solid, adenoid and cystic),
III. Micronodular basal cell carcinoma,
IV. Infiltrating basal cell carcinoma (non-sclerosing, sclerosing),
V. Fibroepithelial basal cell carcinoma,
VI. Basal cell carcinoma with adnexal differentiation (follicular, apocrine, eccrine),
VII. Basosquamous carcinoma,
VIII. Keratotic basal cell carcinoma.

Squamous cell carcinoma

Actinic keratoses are intraepithelial lesions that occur on chronic UV-exposed areas. Morbus Bowen and AK can be a precursor lesion of invasive SCC with a transition probabilities for AK ranging from 0.06% to 16%.[75–77] Actinic keratoses are seen as a marker of UV exposure and significantly increase the lifetime risk of developing a SCC, BCC and MM (Table 1).[78] The tumor cells in well-differentiated SCC, although atypical, resemble the normal keratinocytes from the stratum spinosum (Figure 5).

Keratinocytic skin tumors are classified according to the WHO in 6 histologic subtypes[74]:

I. Acantholytic squamous cell carcinoma,
II. Spindle-cell squamous cell carcinoma,
III. Verrucous squamous cell carcinoma,
IV. Pseudovascular squamous cell carcinoma,
V. Adenosquamous squamous cell carcinoma,
VI. Bowen disease.

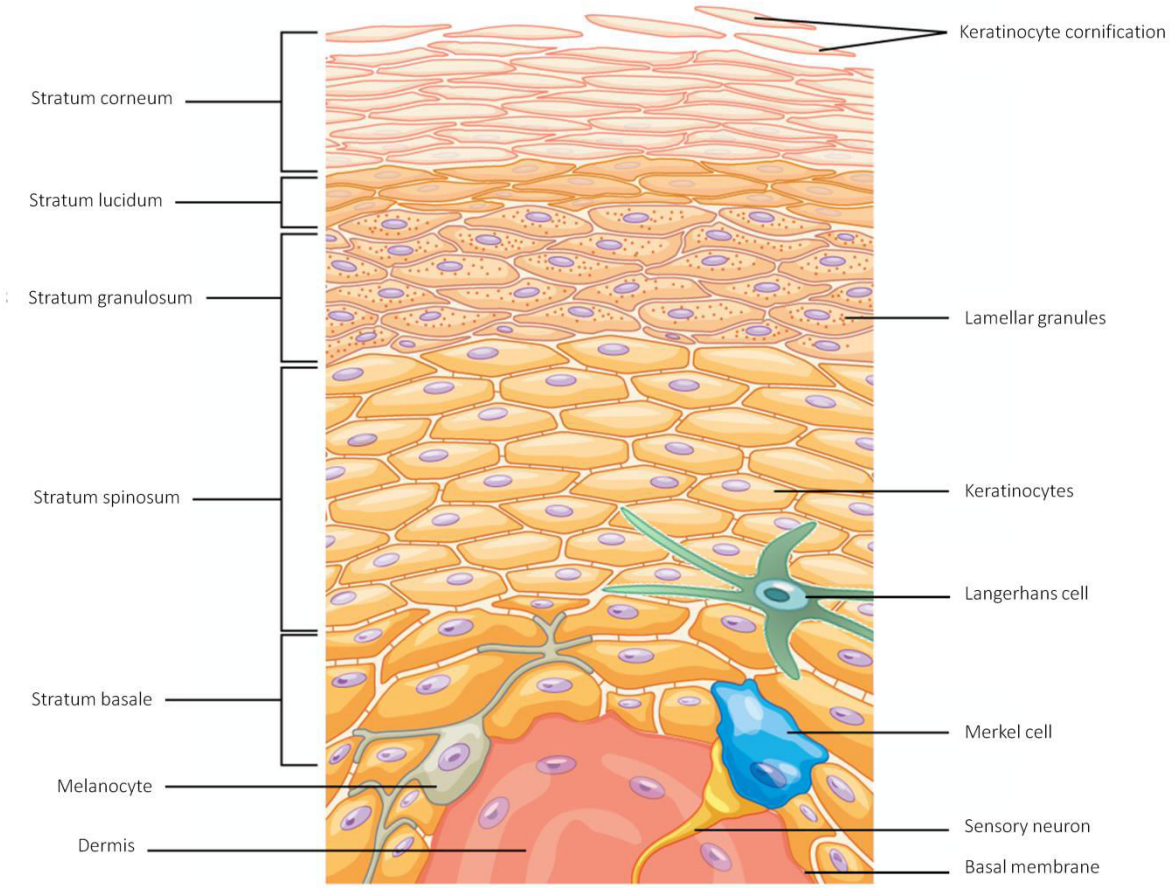

Figure 5. Illustration of the structure of the human epidermis with the different layers and specific cell types.

Staging

The staging of malignant melanoma and SCC is based on the TNM staging categories according to the American Joint Committee on Cancer (AJCC) classification. These comprise the main prognostic factors and are tabulated below. Because of the low metastatic potential of BCC the tumor-node-metastasis (TNM) classification is less applicable in daily practice to determine prognosis and treatment. The National Comprehensive Cancer Network proposed a clinically relevant classification to determine the risk for recurrence of BCC.[79] The factors described below comprise a lower risk. Lesions located on the central face, especially around the eyes, nose, lips and ears, are at higher risk of recurrence, this is also denoted as the H-zone.

Location and size:

I. < 6 mm in diameter in high-risk areas (facial H-zone)
II. < 10 mm in diameter in other areas of the head and neck
III. < 20 mm in diameter in all other areas (excluding hands and feet)

Histology:

I. Nodular or superficial histopathologic growth pattern
II. Absence of perineural invasion

Others:

I. Primary BCC
II. Well-defined clinical borders
III. No history of radiation therapy at site
IV. Immune competent patient

In the Netherlands, the Rotterdam criteria for high risk BCC proposed by Flohil et al. in 2012 include indistinct clinical margins, aggressive histopathological subtype (e.g. sclerosing and morpheaform), size > 2 cm, localized in the H-zone, previously incompletely excised, perineural invasion or recurrent tumors.[80]

Table 2. TNM staging categories for cutaneous melanoma according to the AJCC classification 2009

T	Tumor thickness	Other prognostic parameters
Tis	Melanoma in situ, no tumor invasion	Tis
T1	≤1.00 mm	a: without ulceration, mitotic rate < 1/mm^2 b: with ulceration or mitotic rate ≥ 1/mm^2
T2	1.01-2.00 mm	a: without ulceration b: with ulceration
T3	2.01-4.00 mm	a: without ulceration b: with ulceration
T4	> 4.00 mm	a: without ulceration b: with ulceration
N	**Number of metastatic nodes**	**Extent of lymph node metastases**
N0	0	NA
N1	1	a: micrometastasis[1] b: macrometastasis[2]
N2	2-3	a: nodal micrometastasis b: nodal macrometastasis c: satellites or in-transit metastases without metastatic regional lymph nodes
N3	> 4 LN, or matted lymph nodes or satellites or in-transit metastases with metastatic regional lymph nodes	
M	**Type of distant metastasis**	**Serum LDH**
M0	No distant metastasis	NA
M1a	Metastases in distant skin, subcutis or lymph nodes beyond the regional lymph nodes	Normal
M1b	Lung metastases	Normal
M1c	Distant metastases at other site or distant metastases at any site with elevated serum LDH levels	Normal Elevated

NA, not applicable. LDH, lactate dehydrogenase.[1] Diagnosed after sentinel lymph node biopsy.[2] Macrometastasis is defined as clinically detectable nodal metastasis with histologic confirmation.

Table 3. Clinical stages for cutaneous melanoma according to the AJCC classification 2009

Clinical stages	T	N	M	Pathological stages	T	N	M
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0	Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0	Stage IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	Stage IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	Stage IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	Stage IIC	T4b	N0	M0
Stage III	Any T	N > N0	M0	Stage IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				Stage IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				Stage IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	Stage IV	Any T	Any N	M1

Table 4. TNM staging categories for cutaneous SCC according to the AJCC classification 2010

Classification	
T	**Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension with < 2 high-risk features
T2	Tumor > 2 cm or any size with ≥ 2 high-risk features
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton or perineural invasion of skull base
High risk features	
Depth/invasion	> 2 mm thickness
	Clark level ≥ IV
	Perineural invasion
Anatomic location	Primary site ear
	Primary site hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated
N	**Lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis a single ipsilateral lymph node, ≤ 3 cm
N2	a: metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm; b: multiple ipsilateral lymph nodes ≤ 6 cm; c: bilateral or contralateral lymph nodes ≤ 6 cm
N3	Metastasis in a lymph node > 6 cm
M	**Distant metastasis**
MX	Distant metastasis cannot be assessed
M0	No distant metastasis present
M1	Distant metastasis present
MX	Distant metastasis cannot be assessed

Clark level ≥ IV: invasion into the reticular dermis (level IV) or beyond in the subcutis (level V).

Table 5. Clinical stages for cutaneous SCC according to the AJCC classification 2010

Clinical stages	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

Prognosis

Melanoma stage and gender influence the overall survival significantly. Men have a significant higher mortality rate than females. The 5-year survival rate is 90% in case of stage I disease but decreases to 40% in case of regional disease (stage III) and only around 10% when metastases are present. In that case the median survival is around 9 months.[81]

The relative survival rates of basal cell carcinoma are excellent since BCC grows slow and is mainly locally invasive. This however causes significant morbidity and disfigurement. Metastases are very rare and the prevalence ranges between 0.0028%-0.55% based on published cases.[14,82] The 5-year survival rate for a primary cutaneous SCC is over 90%,[83] and the yearly overall mortality rate is estimated to be less than 4%.[84,85] Rates of metastasis from primary SCC are reported to be around 2-5%, and the risk is significantly correlated to tumor size and depth.[85–87]

Treatment

Melanoma

The primary melanoma is excised with a 2 mm standard margin and the diagnosis is confirmed histologically. In addition a total body examination looking for a second primary melanoma and cutaneous or nodal metastases must be performed. The Belgian Association for Dermato-Oncology (BADO) recommends a local wide excision if there is no evidence for metastasis.[88] The margin is based on the Breslow thickness and ranges from 0.5 to 2cm, to avoid local recurrence. If ulceration or a

mitotic rate ≥ 1/mm^2 is present (pT1b or more) a sentinel node biopsy can be performed at the same time. If in-transit metastases are present or lymph nodes are invaded the patient is diagnosed with stage III melanoma and should be surgically treated with complete lymph node dissection. Adjuvant treatment with interferon-alpha has shown to improve relapse free survival.[89] Metastatic melanoma (stage IV) has a 5-year survival rate of around 10% and is still considered as incurable. Four main treatment approaches are currently available: chemotherapy (dacarbazine), radiation therapy, targeted therapies (*BRAF*, *MEK* and *c-KIT* inhibitors) and immune therapies targeting *CTLA4* and *PD-1*. Although some argue that dacarbazine has no clear role in treatment of metastatic melanoma since the development of the newer treatments. In addition it never achieved a significant survival benefit in stage IV melanoma patients.[90]

Basal cell carcinoma

A variety of treatment options are available for basal cell carcinoma, and these are reviewed in extend by Telfer et al.[91] The most important factors influencing treatment choice and efficacy are tumor size (>2 cm versus ≤2 cm), primary or recurrent BCC, histologic subtype, and the tumor location (low-risk or high-risk site for recurrence). Surgery is considered the main treatment option and standard excision has a 5-year recurrence rate of only 2-10% for primary BCC.[92–96] A margin of 3-5 mm is recommended depending on the presence of risk features (size > 10 mm, recurrent or infiltrative BCC).[97] Mohs micrographic surgery with microscopic margin control during surgery is only indicated for high risk BCC in the facial area, since it is labor intensive and has a higher cost. The 5-year cure rate is up to 100%.[98] Non-surgical treatments (imiquimod, 5-fluorouracil, photodynamic therapy (PDT)) are indicated for low-risk superficial BCC. Destructive techniques such as curettage and cautery, cryosurgery and carbon dioxide laser have varying effectiveness and only low quality evidence is available. Recurrent (non radiation induced) BCC or patients not indicated for surgery can be treated with radiation therapy. The small-molecule inhibitor of Smoothened *(SMO)* receptor, vismodegib is a new treatment option for metastatic or locally advanced disease not amenable to surgery or radiotherapy.

Squamous cell carcinoma

Several treatment options are available for SCC, depending on the risk factors of loco-regional recurrence or the risk for lymph node involvement of metastases. These include standard surgical excision or Mohs surgery, radiation therapy, topical therapy (5-fluorouracil or imiquimod) and PDT. However, systematic reviews could not retrieve enough high quality evidence for general conclusions about the comparative effectiveness of the available treatments.[99–101] In case of aggressive or nodal disease, surgery is the main approach. Adjuvant radiotherapy is mandatory in the management of

nodal disease.[102,103] Systemic chemotherapy or monoclonal antibodies that target the epidermal growth factor receptor *(EGFR)* are indicated for patients with distant metastases or locally advanced disease that cannot be managed with surgery or radiation.[104–109]

Follow-up

Follow-up is necessary for all types of skin cancer mainly for two reasons: to detect disease progression or recurrence early, and to detect subsequent primary lesions. For NMSC no international evidence-based consensus exists concerning their follow-up. The latest European guidelines propose that ideally all patients presenting with BCC should be offered a lifelong follow-up yearly. Since this is not feasible for all public health care systems, follow-up every 6-12 months for 3-5 years is recommended especially for patients at high risk for recurrences or had recurrent BCC, and patients with multiple BCC.[110] In Belgium, an initial 6 monthly follow-up the first 3-5 years and afterwards a yearly check-up is standard. The same schedule is followed for local SCC in healthy patients, however a recent study showed that patients with high risk for metastases (depending on tumor thickness, immunosuppression, localization at the ear and large horizontal size) should be evaluated every 3 or 4 months for 4 years by clinical investigation and ultrasound of the regional lymph nodes.[86] For melanoma the follow-up also differs between countries, and the Belgian Association of Dermato-Oncology proposed the guidelines below (Table 6).[88] In stage I and II melanoma the main purpose is to detect loco-regional recurrence, and depending on Breslow thickness, clinical examination or radiologic imaging is suggested. In stage III melanoma ultrasound and radiologic follow-up is suggested the first years to detect distant metastases. It is uncertain whether the intense follow-up schedule for stage I melanoma produces any survival benefit, in addition, it results in a significant cost.[111] Leiter et al. concluded that the follow-up visits for stage IA melanoma can be yearly, based on the hazard rates for recurrent and secondary melanoma of a large cohort of 33 384 melanoma patients.[112] These results were confirmed by a smaller study based on the survival benefits between asymptomatic and symptomatic recurrences.[113]

Table 6. Follow-up of melanoma according to the BADO guidelines

	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IIIC
Year 1-2							
Clinical	3 months	3 months	3 months	3 months	3 months	2 months	2 months
Imaging	clinical guidance	clinical guidance	clinical guidance	chest Rx, ultrasound abdomen and draining lymph node	chest Rx, ultrasound abdomen and draining lymph node	CT brain, chest and abdomen	CT brain, chest and abdomen
Year 3-5							
Clinical	6 months	6 months	6 months	6 months	6 months	4 months	4 months
Imaging	clinical guidance	clinical guidance	clinical guidance	clinical guidance	clinical guidance	chest Rx, ultrasound abdomen and draining lymph node	chest Rx, ultrasound abdomen and draining lymph node
Year > 5							
Clinical	12 months	12 months	12 months	12 months	12 months	12 months	12 months
Imaging	clinical guidance	clinical guidance	clinical guidance	clinical guidance	clinical guidance	clinical guidance	clinical guidance

PREVENTIVE LANDSCAPE

Preventive medicine can be organized at three levels (Figure 6). Primary prevention is addressed to healthy individuals with the goal of preventing or reducing the risk of skin cancer. Secondary prevention aims at individuals in preclinical or early stage with the goal of detecting lesions early and ameliorating the outcome of the disease. Secondary prevention involves screening and early detection methods. Primary and secondary prevention strategies can be aimed at the entire population, or specific risk groups. The individual often does not have any impairment at the time of the intervention, in contrary to tertiary prevention, that is addressed at diagnosed patients where therapy is given to prevent local relapses, invasion and metastasis.[114]

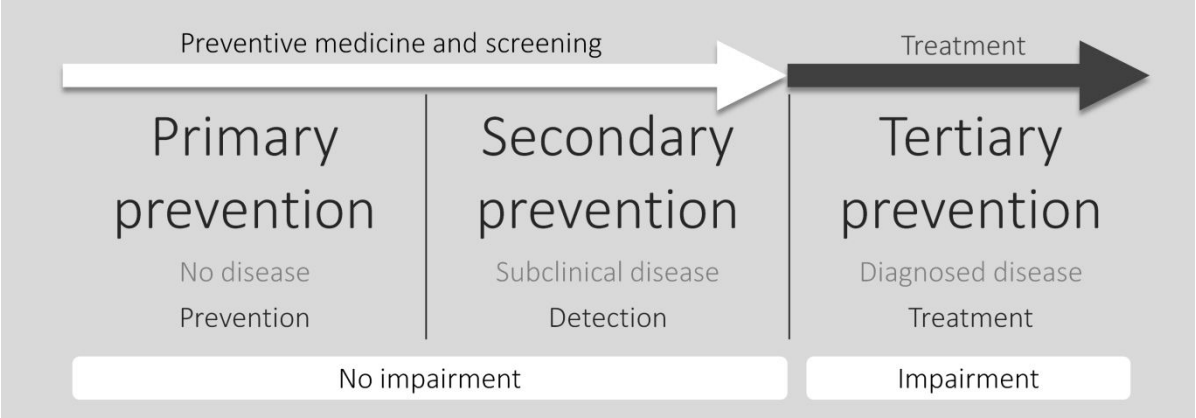

Figure 6. Different levels of preventive medicine, early detection and screening.

The WHO defined a set of criteria in 2008,[115] based on the criteria of Wilson and Jungner[116] to address the question whether a healthcare problem is amenable for early detection. These are summarized below. First of all the disease has to be an important health care problem, its natural history is known and there has to be a safe, simple and inexpensive screening test that is acceptable to the population. In addition there should be a treatment for early disease that is more effective than treatment for later disease and all means for diagnosis and treatment should be available. In Flanders, a specific committee named 'Vlaamse Werkgroep Bevolkingsonderzoek', authorizes population-based screening and advises on this subject based on a set of criteria.[117] These state that the expected health benefits to the target group as a result of the screening should be scientifically substantiated, the effectiveness of the screening is justified in a context that is relevant for Flanders, the screening should reach all individuals of the target group and provide them the opportunity to participate, and that it is shown that participants experience more benefits than harms referring to the diagnostic work-up, treatment

or other actions resulting from the screening. In addition, the committee advises in name of the Flemish government on the choice of the screening tool and the definition of the target group.

The ten WHO criteria for early detection and screening:

I. The disease should be an important health problem
II. A generally acceptable method of treatment must be available
III. The policy for treatment must be clear
IV. Provision for diagnosis and treatment must be available
V. The disease must have a detectable latent stage
VI. A suitable screening method must be available
VII. The screening method must be accepted by the target population
VIII. The natural course of the disease must be known
IX. The program is cost-effective
X. The treatment of early disease should favor the prognosis of the patients

HEALTH ECONOMICS

For any health care intervention it is crucial to examine not only the efficacy (=produce beneficial effect under ideal circumstances) and effectiveness (=produce beneficial effect in daily practice) but also the cost-effectiveness: measuring the effect of the intervention in relation to its costs.[118] Health economic research and cost-effectiveness studies have the main objective to *adequately allocate* the available financial means in order to gain as much health as possible.[119] The benefit that is produced can be expressed as quality of life (QOL) by influencing morbidity and mortality in individuals and also the population as a whole.

Health costs

The perspective that will be applied in an economic study is important since it will determine which costs and effects of the intervention will be taken in account. It is recommended to analyze from the societal perspective, which is the most comprehensive. This includes the direct health care costs to the government and patients, as well as direct non-health care costs and costs due to productivity loss (= indirect non-health care costs). The KCE report for Belgian health economic (HE) evaluations states that "direct medical costs paid by the federal government's and the communities' health care budget, as well as the patients' co-payments need to be included in the basic analyses". This is the perspective of the health care payer.[120] A broader perspective can be applied, but needs to be differentiated from the reference case. Table 7 summarizes the different types of costs to include in HE assessments (non-exhaustive list of examples).

Table 7. Health care costs in HE assessments (adapted from the KCE report[120])

	Health care costs	Non-health care costs
Direct	Medications Hospitalizations Medical services, including procedures Diagnostic, investigational and screening services	Travel expenses Informal care Invalidity/incapacity allowances
Indirect	Health care costs in life years gained	Productivity losses

QALY

To have an indicator for the health gain of a specific intervention or health state, several units have been proposed: number of life years gained (LYG), number of adverse effects avoided, number of

years in responder group. However these units focus on numeric life years or days gained, not on the life quality added to the years. In other words a unit combining quantity of the years gained with the QOL experienced in these years is more accurate. For this reason the disability-adjusted life years (DALY) and quality-adjusted life years (QALY) measures were developed. The KCE recommends reporting all outcomes using the QALY measure,[121] for this reason the following text focuses solely on the latter.

The QALY, developed in 1976 is frequently used in HE assessments since it combines QOL of life and the quantity in one concept. To determine the QALYs, an index to determine the health related QOL (HRQOL) needs to be calculated (Y-axis, between 0 and 1). One would mean perfect health and 0 represents death. This number, ranging from 0 to 1 is called the utility. The x-axis would represent the time (in years) that a person spent at that level of QOL (or utility). The area under the curve would then represent the number of QALYs. For example, a patient receiving standard care lives 10 years at an HRQOL index of 0.7. This would mean a total of 7 QALYs are achieved. In contrast a new treatment that ameliorates the patients QOL to an index of 0.8 during those same 10 years, would produce 8 QALYs. A gain of health effect corresponding to 1 QALY could thus be produced. One could however also gain health by increasing the life expectancy of the patients, or both HRQOL and life expectancy. In reality however the level of the index value is not constant. Figure 7 represents a situation that is closer to daily practice.

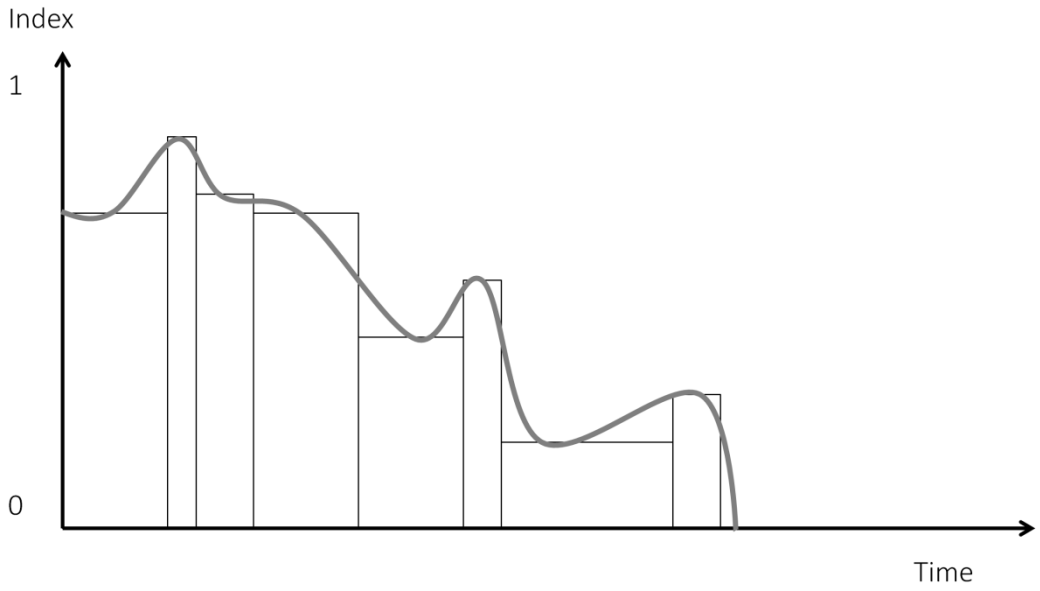

Figure 7. QALY concept explained, an index 1 value indicates perfect health and 0 represents death. The x-axis represents the time in years that a person spent at that level of utility index. The area under the curve represents the number of QALYs.

Utilities

To generate these HRQOL indexes or utilities, different techniques and tools can be used. The EuroQOL 5 dimensions questionnaire (EQ-5D) and health utilities index are the most frequently used generic instruments that provide utilities. Some other methods are: the short form health health survey (SF-36), the WHO quality of life assessment, short form-6 dimension questionnaire or visual analogue scales. The international and Belgian guidelines encourage the use of the EQ-5D since this is a useful instrument in a broad range of health problems.[120,122] In addition an EQ-5D valuation set is available for Belgium.[59] Although it has to be noted that the EQ-5D may sometimes be less sensitive to pick up certain subtle changes in contrast to a disease-specific instrument. In the case of skin cancer however no validated disease specific instrument is available.

The EQ-5D is a European questionnaire asking patients about five domains; mobility, self-care, daily activities, pain or discomfort and anxiety or depression.[124] A 3 and 5 level multiple choice answer is available, respectively EQ-5D-3L and EQ-5D-5L. Based on the answer profile of the patient the utility can be designated according to the value sets provided by the EuroQOL. It is important to realize that these value sets are dependent on the patients' country, since the relative weight given to certain life dimensions (for example mobility) is culturally determined. A VAS can be incorporated at the end of the questionnaire, in order to score their general wellbeing. This is a scale from 0 (meaning the worst possible health one can imagine) to 100 (best possible health one can imagine). This can be used in addition to the time trade-off or standard gamble method for valuing HRQOL weights.[125]

Incremental cost-effectiveness ratio and threshold

Cost-effectiveness analyses produce a central outcome that is called the incremental cost-effectiveness ratio (ICER). It expresses a cost per QALY gained, and is calculated as follow:

$$\text{ICER} = \frac{\text{Total costs (new intervention)} - \text{Total costs (current standard)}}{\text{QALY (new intervention)} - \text{QALY (current standard)}}$$

When comparing two medical interventions based on the costs and effects 4 possible scenarios can occur. These are illustrated according to the cost-effectiveness plane (Figure 8). The current standard (or comparator) is located in the center, the x-axis denotes the incremental effect and the y-axis the incremental cost. In case the new intervention is more effective and less costly (situation A), this intervention is called dominant. A new intervention that is found to be less effective and more costly

(situation D) than the current standard, is not cost-effective and will be excluded. When the new intervention however is less costly and less effective (situation C) one could debate about its acceptance, especially when the new intervention is only a bit less effective and costs significantly less. In most cases the new intervention will be located in plane B of this figure and a threshold for cost-effectiveness needs to be determined (dotted line). Above this line the new intervention is not cost-effective.

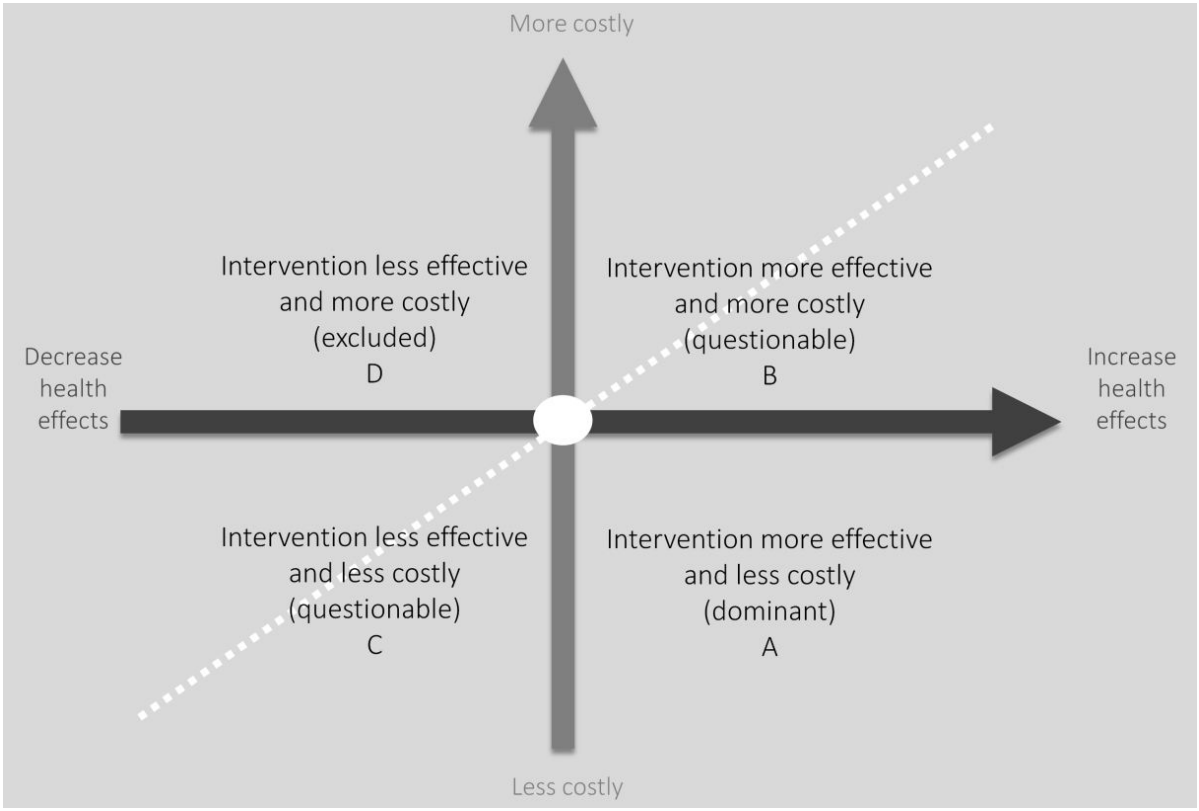

Figure 8. The cost-effectiveness plane. When comparing two medical interventions based on the costs and effects 4 scenarios can occur (A, B, C or D). The current standard (or comparator) is located in the center (white dot).

The threshold at which an intervention should be considered as cost-effective is dependent on the *gross domestic product* (GDP) per capita according to the WHO.[126] If the ICER is below the GDP per capita, it is assumed to be very cost-effective; in case of 1-3 x GDP per capita, it is cost-effective; and in case it exceeds 3 x GDP per capita the new intervention is considered not to be cost-effective. The gross domestic product at current prices per head of population for Belgium in 2014 was €35 909.[127] However in a recent KCE report it clearly states that no country uses one single ICER threshold value for acceptance of a new intervention.[128] In the UK the National Institute for Health and Clinical

Excellence state two threshold values of £20 000 to £30 000 per QALY, and for other countries thresholds are deducted from previous positive or negative recommendations. ICER threshold values or ranges were proposed for the United States (US) ($50 000/QALY), New Zeeland (NZ$20 000/QALY), the Netherlands (€80 000/QALY) and Canada (CAN$20 000 - $100 000/QALY).[129–132] In general one could say that the probability of a new intervention being accepted is higher when having a lower ICER, but no exact cut-off is available to date. The reimbursement process is not seldom an interactive decision making process evaluating on a case-by-case basis. In addition to the ICER the budget impact analyses are indispensable.

Markov modeling

The ICER is calculated using a Markov model. This is a decision-analytic model that consists of different disease states.[120] These are in fact all possible disease events that are representative both clinically and economically for the disease that need to be modeled. When defining the states one basic assumption is important: the patient can only be in one health state or the other. Figure 9 illustrates a simplified Markov model for melanoma skin cancer. The circles represent the disease states and arrows the different transitions with their associated probabilities (tp). At all states it is possible to die from a natural cause (tpND), but in case of patients diagnosed with melanoma stage IV this is added up to the probability of dying from melanoma stage V disease (tpDM). In addition there are different probabilities for melanoma progression (tpPMI, tpPMII, tpPMIII, tpPMIV). Patients can stay in the same health state during different cycles of the model (arrows returning), and death is called to be an absorbing state, of which patients are unable to leave. This figure does not completely represent clinical practice, and in reality the Markov Model will be more complex. For example, adding different health states for undetected, diagnosed melanoma (I to IV), treatment and follow-up would resemble current knowledge more closely, since it is possible for a patient to be diagnosed as stage II melanoma and previously feeling healthy.

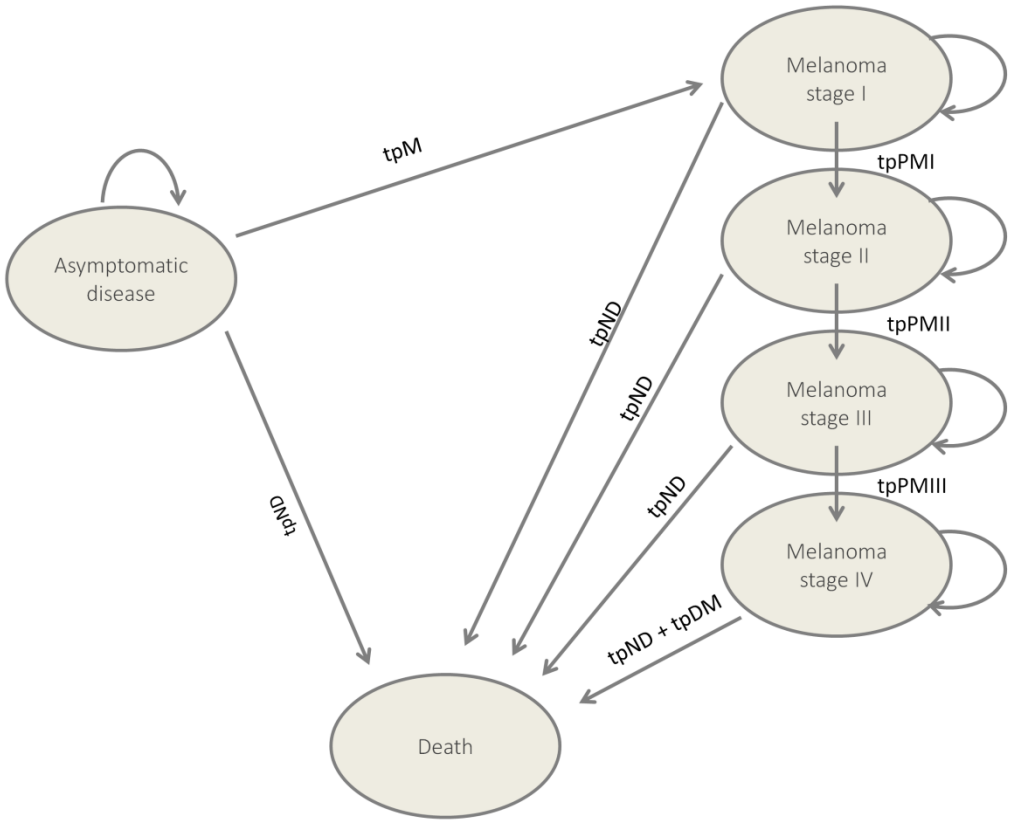

Figure 9. Simplified Markov model disease state for malignant melanoma. TpND: transition probability to natural death state; tpMD: transition probability to death as a direct result of melanoma stage IV; tpPMI: transition probability from stage I to II; tpPMII: transition probability from stage II to III; tpPMIII transition probability from stage III to IV.

For every health state a utility (0-1) and cost is assigned. Depending on the patients in the state and the runtime of the model an ICER can be calculated when the costs and QALYs are summed over a large number of model cycles. Other parameters required for running the Markov model are cycle length (for example 6 months), time horizon (total runtime of the model), age of patients entering the model and of course the effect of the new intervention. In addition several general adjustments need to be considered. First of all it is important to include discount rates in the model for utilities and costs. The KCE states that costs need to be discounted at 3% and health effects at 1.5%.[44,45]

Discounting means recalculating future values to values at current time. In this way a net present value can be calculated for cost of outcomes that are adjusted for different timings of occurrence. The following formula is used:

$$\text{Net present value} = \frac{\text{Value}_{\text{time}}}{(1 + \text{discount rate})^{\text{time}}}$$

Since there is uncertainty around almost all variables sensitivity analyses are essential.[133,134] There are several statistical techniques to assess the sensitivity of the ICER. *Probabilistic sensitivity analysis* or PSA is performed by running the model a large number of times, each time selecting a random value in the confidence interval (CI) of the specific distribution of the input variable (for example cost, utility, transition probability or effect of new intervention). A scatter plot of all these Monte Carlo simulations is then presented in the cost-effectiveness plane around the base case ICER. Cost-effectiveness acceptability curves are a graphic way to illustrate the probability that a certain intervention is cost-effective, or in other words a statistical alternative to calculate the CIs for the ICER. These probabilities (y-axis) are plotted for a range of λ (x-axis, which is the maximum acceptable threshold for the decision-maker). In fact this probability is simply the proportion of scatter plot points that will fall below the slope of λ (dotted line, Figure 8) in the B quadrant of the cost-effectiveness plane.[135] *One-way sensitivity analyses* are less complex, and illustrate the effect of variance around a single input variable, when all other variables remain constant. A tornado graph is used to illustrate this.

Budget impact analyses (BIA) are important for policy makers since they estimate the net cumulative cost of the new intervention (including consequent care, follow-up and examinations). This outcome can be obtained using the disease specific Markov model.[136]

Cost of illness studies

Cost of illness studies are health economic studies only taking the cost of a specific disease in account. These studies give information, depending on the applied perspective, on the total cost society is spending on a certain disease and can demonstrate the different cost components (direct versus indirect, health care versus non-health care related). In addition the percentages of costs that are paid by the government versus these by patients are identified. Two prevalence based methods are described; a bottom-up and top-down protocol to calculate the total annual cost of a disease. The bottom-up approach estimates costs by calculating the average cost of disease state and multiplying it by the prevalence. In a top-down cost of illness studies the health expenditures serve as a fixed starting point and cost attributed to the disease of interest are deducted.[137] It has to be noted that

cost of illness studies are mainly performed to indicate areas of high expenditure, but fail to provide information on possible inadequate allocation of resources.[138]

REFERENCES

1. Global Burden of Disease Cancer Collaboration et al. The Global Burden of Cancer 2013. JAMA Oncol. 1, 505–527 (2015).

2. Lomas, A., Leonardi-Bee, J. & Bath-Hextall, F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br. J. Dermatol. 166, 1069–1080 (2012).

3. Flohil, S. C., de Vries, E., Neumann, H. A., Coebergh, J. W. & Nijsten, T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol 91, 24–30 (2011).

4. Black, R. J., Bray, F., Ferlay, J. & Parkin, D. M. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur. J. Cancer Oxf. Engl. 1990 33, 1075–1107 (1997).

5. Garbe, C. & Blum, A. Epidemiology of cutaneous melanoma in Germany and worldwide. Skin Pharmacol. Appl. Skin Physiol. 14, 280–290 (2001).

6. Lipsker, D. Growth rate, early detection, and prevention of melanoma: melanoma epidemiology revisited and future challenges. Arch. Dermatol. 142, 1638–1640 (2006).

7. Levell, N. J., Beattie, C. C., Shuster, S. & Greenberg, D. C. Melanoma epidemic: a midsummer night's dream? Br. J. Dermatol. 161, 630–634 (2009).

8. Welch, H. G. & Black, W. C. Overdiagnosis in cancer. J. Natl. Cancer Inst. 102, 605–613 (2010).

9. Bristow, B. N., Casil, J., Sorvillo, F., Basurto-Dávila, R. & Kuo, T. Melanoma-related mortality and productivity losses in the USA, 1990-2008. Melanoma Res. 23, 331–335 (2013).

10. Flohil, S. C. et al. Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. J. Invest. Dermatol. 133, 913–918 (2013).

11. Birch-Johansen, F., Jensen, A., Mortensen, L., Olesen, A. B. & Kjær, S. K. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. Int. J. Cancer 127, 2190–2198 (2010).

12. Christenson, L. J. et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA 294, 681–690 (2005).

13. Stichting Kankerregister. Incidence melanoma, basal cell carcinoma and squamous cell carcinoma in Belgium, 2013. (2016).

14. Wysong, A., Aasi, S. Z. & Tang, J. Y. Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. JAMA Dermatol 149, 615–6 (2013).

15. Holterhues, C., Vries, E., Louwman, M. W., Koljenovic, S. & Nijsten, T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 130, 1807–12 (2010).

16. Hollestein, L. M. et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 23, 524–30 (2012).

17. Barbaric, J. et al. Disparities in melanoma incidence and mortality in South-Eastern Europe: Increasing incidence and divergent mortality patterns. Is progress around the corner? Eur. J. Cancer Oxf. Engl. 1990 55, 47–55 (2016).

18. Bosetti, C. et al. Mortality from cutaneous malignant melanoma in Europe. Has the epidemic levelled off? Melanoma Res. 14, 301–309 (2004).

19. El Ghissassi, F. et al. A review of human carcinogens--part D: radiation. Lancet Oncol. 10, 751–752 (2009).

20. Grether-Beck, S., Marini, A., Jaenicke, T. & Krutmann, J. Photoprotection of human skin beyond ultraviolet radiation. Photodermatol. Photoimmunol. Photomed. 30, 167–174 (2014).

21. Nilsen, L. T. N., Aalerud, T. N., Hannevik, M. & Veierød, M. B. High UV-A exposure from sunbeds. Pigment Cell Melanoma Res. 25, 639–640 (2012).

22. Chen, H., Weng, Q. Y. & Fisher, D. E. UV signaling pathways within the skin. J. Invest. Dermatol. 134, 2080–2085 (2014).

23. Kim, M. Y., Park, H. J., Baek, S. C., Byun, D. G. & Houh, D. Mutations of the p53 and PTCH gene in basal cell carcinomas: UV mutation signature and strand bias. J Dermatol Sci 29, 1–9 (2002).

24. Hahn, H. et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 85, 841–51 (1996).

25. Hou, P., Liu, D., Dong, J. & Xing, M. The BRAF(V600E) causes widespread alterations in gene methylation in the genome of melanoma cells. Cell Cycle 11, 286–95 (2012).

26. Sharpless, E. & Chin, L. The INK4a/ARF locus and melanoma. Oncogene 22, 3092–8 (2003).

27. Pho, L. N. & Leachman, S. A. Genetics of pigmentation and melanoma predisposition. G Ital Dermatol Venereol 145, 37–45 (2010).

28. Sarkar, D., Leung, E. Y., Baguley, B. C., Finlay, G. J. & Askarian-Amiri, M. E. Epigenetic regulation in human melanoma: past and future. Epigenetics 10, 103–21 (2015).

29. Loeb, K. R. et al. Analysis of Tp53 codon 72 polymorphisms, Tp53 mutations, and HPV infection in cutaneous squamous cell carcinomas. PLoS One 7, e34422 (2012).

30. Autier, P. & Doré, J. F. Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. Int. J. Cancer 77, 533–537 (1998).

31. Kaskel, P. et al. Outdoor activities in childhood: a protective factor for cutaneous melanoma? Results of a case–control study in 271 matched pairs. Br. J. Dermatol. 145, 602–609 (2001).

32. Gandini, S. et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur. J. Cancer Oxf. Engl. 1990 41, 2040–2059 (2005).

33. Armstrong, B. K. & Kricker, A. The epidemiology of UV induced skin cancer. J. Photochem. Photobiol. B 63, 8–18 (2001).

34. van Dam, R. M. et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. Am. J. Epidemiol. 150, 459–468 (1999).

35. Rosso, S. et al. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Br. J. Cancer 73, 1447–1454 (1996).

36. Kricker, A., Armstrong, B. K., English, D. R. & Heenan, P. J. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. Int. J. Cancer 60, 489–494 (1995).

37. Leiter, U. & Garbe, C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv. Exp. Med. Biol. 624, 89–103 (2008).

38. International Commission on Non-Ionizing Radiation Protection. Guidelines on limits of exposure to ultraviolet radiation of wavelengths between 180 nm and 400 nm (incoherent optical radiation). Health Phys. 87, 171–186 (2004).

39. Schmitt, J., Seidler, A., Diepgen, T. L. & Bauer, A. Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. Br. J. Dermatol. 164, 291–307 (2011).

40. Bauer, A., Diepgen, T. L. & Schmitt, J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. Br. J. Dermatol. 165, 612–625 (2011).

41. Vernez, D. et al. Anatomical UV Exposure in French Outdoor Workers. J. Occup. Environ. Med. Am. Coll. Occup. Environ. Med. 57, 1192–1196 (2015).

42. Diepgen, T. L. et al. Skin cancer induced by natural UV-radiation as an occupational disease—requirements for its notification and recognition. J. Dtsch. Dermatol. Ges. J. Ger. Soc. Dermatol. JDDG 12, 1102–1106 (2014).

43. Ulrich, C. et al. The European Status Quo in legal recognition and patient-care services of occupational skin cancer. J. Eur. Acad. Dermatol. Venereol. JEADV 30 Suppl 3, 46–51 (2016).

44. Karagas, M. R. et al. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. JAMA 267, 3305–3310 (1992).

45. Kiiski, V. et al. Risk factors for single and multiple basal cell carcinomas. Arch. Dermatol. 146, 848–855 (2010).

46. Gray, D. T. et al. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Arch. Dermatol. 133, 735–740 (1997).

47. Karagas, M. R., Greenberg, E. R., Spencer, S. K., Stukel, T. A. & Mott, L. A. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int. J. Cancer 81, 555–559 (1999).

48. Gandini, S. et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur. J. Cancer Oxf. Engl. 1990 41, 2040–2059 (2005).

49. Gallagher, R. P. et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. Arch. Dermatol. 131, 157–163 (1995).

50. Gallagher, R. P. et al. Sunlight exposure, pigmentation factors, and risk of nonmelanocytic skin cancer. II. Squamous cell carcinoma. Arch. Dermatol. 131, 164–169 (1995).

51. Gandini, S. et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur. J. Cancer 41, 28–44 (2005).

52. Wu, S., Han, J., Li, W.-Q., Li, T. & Qureshi, A. A. Basal-Cell Carcinoma Incidence and Associated Risk Factors in US Women and Men. Am. J. Epidemiol. 178, 890–897 (2013).

53. Flohil, S. C., van der Leest, R. J. T., Arends, L. R., de Vries, E. & Nijsten, T. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. Eur. J. Cancer Oxf. Engl. 1990 49, 2365–2375 (2013).

54. Spanogle, J. P., Clarke, C. A., Aroner, S. & Swetter, S. M. Risk of second primary malignancies following cutaneous melanoma diagnosis: a population-based study. J. Am. Acad. Dermatol. 62, 757–767 (2010).

55. Levi, F., La Vecchia, C., Randimbison, L., Te, V.-C. & Erler, G. Incidence of invasive cancers following cutaneous malignant melanoma. Int. J. Cancer 72, 776–779 (1997).

56. van der Leest, R. j. t., Flohil, S. c., Arends, L. r., de Vries, E. & Nijsten, T. Risk of subsequent cutaneous malignancy in patients with prior melanoma: a systematic review and meta-analysis. J. Eur. Acad. Dermatol. Venereol. 29, 1053–1062 (2015).

57. Parren, L. j. m. t. & Frank, J. Hereditary tumour syndromes featuring basal cell carcinomas. Br. J. Dermatol. 165, 30–34 (2011).

58. Kraemer, K. H., Lee, M. M., Andrews, A. D. & Lambert, W. C. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. Arch. Dermatol. 130, 1018–1021 (1994).

59. Gandini, S. et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur. J. Cancer 41, 2040–2059 (2005).

60. De Hertog SA, null et al. Relation between smoking and skin cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 19, 231–238 (2001).

61. Karagas, M. R. et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. For The Skin Cancer Prevention Study Group. J. Natl. Cancer Inst. 88, 1848–1853 (1996).

62. Karagas, M. R. et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. Epidemiol. Camb. Mass 18, 776–784 (2007).

63. Karagas, M. R. et al. Genus beta human papillomaviruses and incidence of basal cell and squamous cell carcinomas of skin: population based case-control study. BMJ 341, c2986 (2010).

64. Green, A. C. & Olsen, C. M. Increased risk of melanoma in organ transplant recipients: systematic review and meta-analysis of cohort studies. Acta Derm. Venereol. 95, 923–927 (2015).

65. Jemec, G. B. E. & Holm, E. A. Nonmelanoma skin cancer in organ transplant patients. Transplantation 75, 253–257 (2003).

66. Berg, D. & Otley, C. C. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J. Am. Acad. Dermatol. 47, 1-17-20 (2002).

67. Jensen, A. O. et al. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. Acta Derm. Venereol. 90, 474–479 (2010).

68. Hartevelt, M., Bavinck, J., Kootte, A., Vermeer, B. & Vandenbroucke, J. Incidence of Skin-Cancer After Renal-Transplantation in the Netherlands. Transplantation 49, 506–509 (1990).

69. Jensen, P. et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J. Am. Acad. Dermatol. 40, 177–186 (1999).

70. Lindelof, B., Sigurgeirsson, B., Gabel, H. & Stern, R. S. Incidence of skin cancer in 5356 patients following organ transplantation. Br. J. Dermatol. 143, 513–519 (2000).

71. Kittler, H., Pehamberger, H., Wolff, K. & Binder, M. Diagnostic accuracy of dermoscopy. Lancet Oncol. 3, 159–165 (2002).

72. Pehamberger, H., Binder, M., Steiner, A. & Wolff, K. In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma. J. Invest. Dermatol. 100, 356S–362S (1993).

73. Rosendahl, C., Tschandl, P., Cameron, A. & Kittler, H. Diagnostic accuracy of dermatoscopy for melanocytic and nonmelanocytic pigmented lesions. J. Am. Acad. Dermatol. 64, 1068–1073 (2011).

74. Le Boit, P. World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumours. IARC Lyon, (2006).

75. Criscione, V. D. et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 115, 2523–30 (2009).

76. Glogau, R. G. The risk of progression to invasive disease. J Am Acad Dermatol 42, 23–4 (2000).

77. Marks, R., Rennie, G. & Selwood, T. S. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1, 795–7 (1988).

78. Chen, G. J. et al. Clinical diagnosis of actinic keratosis identifies an elderly population at high risk of developing skin cancer. Dermatol Surg 31, 43–7 (2005).

79. Miller, S. J. et al. Basal cell and squamous cell skin cancers. J. Natl. Compr. Cancer Netw. JNCCN 8, 836–864 (2010).

80. Flohil, S. C., van Dorst, A. M. J. M., Nijsten, T., Martino Neumann, H. A. & Munte, K. Mohs micrographic surgery for basal cell carcinomas: appropriateness of 'Rotterdam' criteria and predictive factors for three or more stages. J. Eur. Acad. Dermatol. Venereol. JEADV 27, 1228–1235 (2013).

81. Balch, C. M. et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 19, 3635–48 (2001).

82. von Domarus, H. & Stevens, P. J. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. J Am Acad Dermatol 10, 1043–60 (1984).

83. Rowe, D. E., Carroll, R. J. & Day, C. L. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J. Am. Acad. Dermatol. 26, 976–990 (1992).

84. Osterlind, A., Hjalgrim, H., Kulinsky, B. & Frentz, G. Skin cancer as a cause of death in Denmark. Br. J. Dermatol. 125, 580–582 (1991).

85. Joseph, M. G., Zulueta, W. P. & Kennedy, P. J. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. Aust. N. Z. J. Surg. 62, 697–701 (1992).

86. Brantsch, K. D. et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 9, 713–720 (2008).

87. Brougham, N. D. L. S., Dennett, E. R., Cameron, R. & Tan, S. T. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J. Surg. Oncol. 106, 811–815 (2012).

88. Brochez, L., Chevolet, I. & Hoorens, I. Verslag van de BADO launch meeting. OncoHemato 74–81 (2014).

89. Ascierto, P. A. et al. Interferon alpha for the adjuvant treatment of melanoma: review of international literature and practical recommendations from an expert panel on the use of interferon. J. Chemother. Florence Italy 26, 193–201 (2014).

90. Serrone, L., Zeuli, M., Sega, F. M. & Cognetti, F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J. Exp. Clin. Cancer Res. CR 19, 21–34 (2000).

91. Telfer, N. R., Colver, G. B., Morton, C. A. & British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. Br. J. Dermatol. 159, 35–48 (2008).

92. Walker, P. & Hill, D. Surgical treatment of basal cell carcinomas using standard postoperative histological assessment. Australas. J. Dermatol. 47, 1–12 (2006).

93. Griffiths, R. W., Suvarna, S. K. & Stone, J. Do basal cell carcinomas recur after complete conventional surgical excision? Br. J. Plast. Surg. 58, 795–805 (2005).

94. Chren, M.-M. et al. Recurrence after treatment of nonmelanoma skin cancer: a prospective cohort study. Arch. Dermatol. 147, 540–546 (2011).

95. Chren, M.-M. et al. Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. J. Invest. Dermatol. 133, 1188–1196 (2013).

96. Rhodes, L. E. et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch. Dermatol. 143, 1131–1136 (2007).

97. Gulleth, Y., Goldberg, N., Silverman, R. P. & Gastman, B. R. What is the best surgical margin for a Basal cell carcinoma: a meta-analysis of the literature. Plast. Reconstr. Surg. 126, 1222–1231 (2010).

98. Malhotra, R., Huilgol, S. C., Huynh, N. T. & Selva, D. The Australian Mohs database, part II: periocular basal cell carcinoma outcome at 5-year follow-up. Ophthalmology 111, 631–636 (2004).

99. Lansbury, L. et al. Interventions for non-metastatic squamous cell carcinoma of the skin. Cochrane Database Syst. Rev. CD007869 (2010). doi:10.1002/14651858.CD007869.pub2

100. Lansbury, L., Bath-Hextall, F., Perkins, W., Stanton, W. & Leonardi-Bee, J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ 347, f6153 (2013).

101. Bath-Hextall, F. J., Matin, R. N., Wilkinson, D. & Leonardi-Bee, J. Interventions for cutaneous Bowen's disease. Cochrane Database Syst. Rev. 6, CD007281 (2013).

102. Veness, M. J., Morgan, G. J., Palme, C. E. & Gebski, V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. The Laryngoscope 115, 870–875 (2005).

103. Bumpous, J. Metastatic cutaneous squamous cell carcinoma to the parotid and cervical lymph nodes: treatment and outcomes. Curr. Opin. Otolaryngol. Head Neck Surg. 17, 122–125 (2009).

104. Denic, S. Preoperative treatment of advanced skin carcinoma with cisplatin and bleomycin. Am. J. Clin. Oncol. 22, 32–34 (1999).

105. Sadek, H. et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer 66, 1692–1696 (1990).

106. Foote, M. C. et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. ESMO 25, 2047–2052 (2014).

107. Reigneau, M. et al. Efficacy of neoadjuvant cetuximab alone or with platinum salt for the treatment of unresectable advanced nonmetastatic cutaneous squamous cell carcinomas. Br. J. Dermatol. 173, 527–534 (2015).

108. Maubec, E. et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 29, 3419–3426 (2011).

109. Suen, J. K., Bressler, L., Shord, S. S., Warso, M. & Villano, J. L. Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab. Anticancer. Drugs 18, 827–829 (2007).

110. Trakatelli, M. et al. Update of the European guidelines for basal cell carcinoma management. Eur. J. Dermatol. EJD 24, 312–329 (2014).

111. Hengge, U. R., Wallerand, A., Stutzki, A. & Kockel, N. Cost-effectiveness of reduced follow-up in malignant melanoma. J. Dtsch. Dermatol. Ges. J. Ger. Soc. Dermatol. JDDG 5, 898–907 (2007).

112. Leiter, U. et al. Hazard rates for recurrent and secondary cutaneous melanoma: an analysis of 33,384 patients in the German Central Malignant Melanoma Registry. J. Am. Acad. Dermatol. 66, 37–45 (2012).

113. Poo-Hwu, W.-J. et al. Follow-up recommendations for patients with American Joint Committee on Cancer Stages I–III malignant melanoma. Cancer 86, 2252–2258 (1999).

114. David Alberts, L. M. H. Fundamentals of Cancer Prevention. 3, (Springer-Verlag, 2014).

115. Andermann, A., Blancquaert, I., Beauchamp, S. & Dery, V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ 86, 317–9 (2008).

116. Wilson, J. M. & Jungner, Y. G. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam 65, 281–393 (1968).

117. Besluit van de Vlaamse Regering betreffende bevolkingsonderzoek in het kader van ziektepreventie. (2008).

118. Cochrane, A. Effectiveness and efficiency: random reflection on health services. Nuffield Prov. Hosp. Trust (1972).

119. Sassi, F., Archard, L. & Le Grand, J. Equity and the economic evaluation of healthcare. Health Technol Assess 5, 1–138 (2001).

120. KCE. Belgische richtlijn voor economische evaluaties en budget impact analyses. Rep. 183A (2012).

121. Gold, M. R., Stevenson, D. & Fryback, D. G. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. Annu Rev Public Health 23, 115–34 (2002).

122. Neyt, M. Towards more consistent use of generic quality-of-life instruments. Pharmacoeconomics 28, 345–6 (2010).

123. Cleemput, I., Neyt, M., Thiry, N., De Laet, C. & Leys, M. Using threshold values for cost per quality-adjusted life-year gained in healthcare decisions. Int J Technol Assess Health Care 27, 71–6 (2011).

124. EuroQol, G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 16, 199–208 (1990).

125. Whitehead, S. J. & Ali, S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull 96, 5–21 (2010).

126. WHO. Threshold values for intervention cost-effectiveness by Region. (2016).

127. Bruto nationaal product België. (2016).

128. KCE. Threshold values for cost-effectiveness in health care. Rep. 100 C (2008).

129. Zorg., Zinnige en duurzame zorg. (2006). Available at http://www.rvz.net/data/download/advies_Zinnige_zorg.pdf.

130. Laupacis, A., Feeny, D., Detsky, A. S. & Tugwell, P. X. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 146, 473–81 (1992).

131. Pritchard, C. Overseas approaches to decision making. In: Towse A, Pritchard C, Devlin N, editors. Cost-Effectiveness Thresholds. Economic and Ethical Issues. King's Fund Off. Health Econ. (2002).

132. Braithwaite, R. S., Meltzer, D. O., King, J. T., Jr., Leslie, D. & Roberts, M. S. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care 46, 349–56 (2008).

133. Briggs, A. H. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 17, 479–500 (2000).

134. Briggs, A. Economics notes: handling uncertainty in economic evaluation. BMJ 319, 120 (1999).

135. Fenwick, E., O'Brien, B. J. & Briggs, A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ 13, 405–15 (2004).

136. Marshall, D. A. et al. Guidelines for conducting pharmaceutical budget impact analyses for submission to public drug plans in Canada. Pharmacoeconomics 26, 477–95 (2008).

137. Jo, C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol 20, 327–37 (2014).

138. Byford, S., Torgerson, D. J. & Raftery, J. Economic note: cost of illness studies. BMJ 320, 1335 (2000).

Chapter 2

Research aims

AIMS

The alarming global increase in incidence of MM and NMSC, partly due to the aging of the population and altered sun seeking behavior, obliges us to investigate preventive measures in this domain. Due to the consequent growing epidemic, the related health care costs are rising significantly. In addition to the augmenting direct costs, recent studies showed that young females are increasingly affected by skin cancer, resulting in important societal indirect costs due to productivity loss.[5–7] Current opinion states that the health care spending is not sustainable in future, so studies with a focus on estimating current expenditures and innovative ways to improve cost-effective health care are needed.[8] Despite the growing awareness of the magnitude of the skin cancer burden, the detection by visual inspection, and its known relation to either natural or artificial UV radiation, studies as such are rare.

OUTLINES

I. Evaluation of the current and future burden of skin cancer in Belgium

Starting with knowledge on the exact magnitude of the health problem in terms of prevalence and economic burden was needed. Several studies in Australia and the United States mapped the expenses directed towards skin cancer, most however focusing on MM and the direct costs only.[9–13] Few European studies estimated the costs of both MM and NMSC, but were performed in Sweden, Germany, Denmark and the UK, and only up to 2010.[14–17] No data on the current and future epidemiology, nor cost of skin cancer were available for Belgium.

II. Evaluation of the cost-effectiveness of primary prevention strategies

Primary prevention is assumed to reduce the burden of skin cancer. All cost-effectiveness studies on a *SunSmart* campaign or sunbed regulation have been performed in Australia, resulting in considerable cost-savings.[18–21] Because of the substantial epidemiological and environmental disparities, we simulated the cost-effectiveness and budget impact of primary prevention, being a hypothetical UV protection campaign and a total ban on sunbed use in the Belgian setting.

III. Clinical and cost-effectiveness of two skin cancer screening methods

At this point, no evidence exists that mass population-based screening by means of whole body examination in asymptomatic persons is cost-effective[22], although the experience in Germany suggests that such screening is feasible.[23] Several early detection initiatives focus on MM and/or specific high risk groups, with the disadvantage that a larger number of skin cancers occur outside this high risk

group setting.[24] The current cost-effectiveness studies performed in the United States and Australia, only focused on MM screening and were aimed at individuals at risk because of a positive family history, skin type and/or age.[25,26] We examined the feasibility and effectiveness of a secondary prevention strategy for skin cancer in Belgium. We evaluated the clinical, as well as cost-effectiveness of a new lesion-directed screening method compared to a general standard total body examination.

IV. The early detection of BCC

Most early detection efforts focus on MM, in view of its mortality and the deduction that earlier detection would lead to a reduction in melanoma deaths. We questioned whether it is worthwhile to include BCC in a skin cancer screening in healthy individuals. In other words, whether early detection of BCC has a beneficial effect in terms non-survival endpoints. This matter was reviewed using the WHO criteria.[27]

V. Effectiveness and clinical utility of dermoscopy in early detection of skin cancer

A reliable and acceptable screening test is important when evaluating screening methods. Dermoscopy has been proven to increase diagnostic accuracy for melanoma over naked-eye-examination in experienced users.[28–30] On the other hand, dermoscopy is also known to be helpful in detecting NMSC,[31–33] and in this way dermoscopy could reduce the number of unnecessary excisions. Although broadly used by dermatologists, the benefit of using dermoscopy in skin cancer screening, including NMSC has not been investigated. In addition, most of the studies examining the accuracy of dermoscopy are performed in a high prevalent setting with highly trained experts, which is known to influence accuracy of the technique.[34] We examined the sensitivity, specificity and the number needed to excise using dermoscopy in the hands of the screening physician in a setting resembling screening practice.

STRUCTURE OF THE DISSERTATION

We addressed these aims systematically in the following chapters. In chapter 3, the direct and indirect cost of skin cancer in Belgium is described to indicate the magnitude of the problem. In addition the future prevalence and cost due to aging of the population were estimated. The evaluation of a primary prevention strategy and a ban on sunbed use is also presented in this chapter. Chapter 4 describes the clinical results of two skin cancer screening methods. The results concerning the cost-effectiveness of these secondary prevention methods, including the budget impact analyses can be found in chapter 5. In addition, we investigated whether the early detection of BCC could potentially be useful. We have

addressed this question in chapter 6. Chapter 7 describes the diagnostic accuracy of the main technique used for the early detection and diagnosis of skin cancer daily practice, dermoscopy. Chapter 8 consists of a general discussion and conclusion on the results and we end this thesis with some future research perspectives.

REFERENCES

1. Flohil, S. C. et al. Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. J. Invest. Dermatol. 133, 913–918 (2013).

2. Flohil, S. C., de Vries, E., Neumann, H. A., Coebergh, J. W. & Nijsten, T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol 91, 24–30 (2011).

3. Holterhues, C., Vries, E., Louwman, M. W., Koljenovic, S. & Nijsten, T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 130, 1807–12 (2010).

4. Hollestein, L. M. et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 23, 524–30 (2012).

5. Bristow, B. N., Casil, J., Sorvillo, F., Basurto-Dávila, R. & Kuo, T. Melanoma-related mortality and productivity losses in the USA, 1990-2008. Melanoma Res. 23, 331–335 (2013).

6. Global Burden of Disease Cancer Collaboration et al. The Global Burden of Cancer 2013. JAMA Oncol. 1, 505–527 (2015).

7. Christenson, L. J. et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA 294, 681–690 (2005).

8. OECD. Health at a Glance: Europe 2012. (OECD Publishing, 2012).

9. Fransen, M. et al. Non-melanoma skin cancer in Australia. Med. J. Aust. 197, 565–568 (2012).

10. Chen, J. G. et al. Cost of nonmelanoma skin cancer treatment in the United States. Dermatol. Surg. Off. Publ. Am. Soc. Dermatol. Surg. Al 27, 1035–1038 (2001).

11. Housman, T. S. et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J. Am. Acad. Dermatol. 48, 425–429 (2003).

12. Seidler, A. M., Pennie, M. L., Veledar, E., Culler, S. D. & Chen, S. C. Economic burden of melanoma in the elderly population: population-based analysis of the Surveillance, Epidemiology, and End Results (SEER)--Medicare data. Arch. Dermatol. 146, 249–256 (2010).

13. Rogers, H. W. & Coldiron, B. M. Analysis of skin cancer treatment and costs in the United States Medicare population, 1996-2008. Dermatol. Surg. Off. Publ. Am. Soc. Dermatol. Surg. Al 39, 35–42 (2013).

14. Tinghög, G., Carlsson, P., Synnerstad, I. & Rosdahl, I. Societal cost of skin cancer in Sweden in 2005. Acta Derm. Venereol. 88, 467–473 (2008).

15. Stang, A., Stausberg, J., Boedeker, W., Kerek-Bodden, H. & Jöckel, K.-H. Nationwide hospitalization costs of skin melanoma and non-melanoma skin cancer in Germany. J. Eur. Acad. Dermatol. Venereol. JEADV 22, 65–72 (2008).

16. Bentzen, J. et al. Costs of illness for melanoma and nonmelanoma skin cancer in Denmark. Eur. J. Cancer Prev. Off. J. Eur. Cancer Prev. Organ. ECP 22, 569–576 (2013).

17. Vallejo-Torres, L., Morris, S., Kinge, J. M., Poirier, V. & Verne, J. Measuring current and future cost of skin cancer in England. J. Public Health Oxf. Engl. 36, 140–148 (2014).

18. Hirst, N., Gordon, L., Gies, P. & Green, A. C. Estimation of avoidable skin cancers and cost-savings to government associated with regulation of the solarium industry in Australia. Health Policy Amst. Neth. 89, 303–311 (2009).

19. Shih, S. T.-F., Carter, R., Sinclair, C., Mihalopoulos, C. & Vos, T. Economic evaluation of skin cancer prevention in Australia. Prev. Med. 49, 449–453 (2009).

20. Gordon, L. G. et al. Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. J. Invest. Dermatol. 129, 2766–2771 (2009).

21. Hirst, N. G., Gordon, L. G., Scuffham, P. A. & Green, A. C. Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res. 15, 261–268 (2012).

22. Bigby, M. Why the evidence for skin cancer screening is insufficient: lessons from prostate cancer screening. Arch. Dermatol. 146, 322–324 (2010).

23. Breitbart, E. W. et al. Systematic skin cancer screening in Northern Germany. J. Am. Acad. Dermatol. 66, 201–211 (2012).

24. Vuong, K. et al. Development and External Validation of a Melanoma Risk Prediction Model Based on Self-assessed Risk Factors. JAMA Dermatol. (2016). doi:10.1001/jamadermatol.2016.0939

25. Watts, C. G. et al. Specialized surveillance for individuals at high risk for melanoma: a cost analysis of a high-risk clinic. JAMA Dermatol. 151, 178–186 (2015).

26. Losina, E. et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch. Dermatol. 143, 21–28 (2007).

27. Andermann, A., Blancquaert, I., Beauchamp, S. & Dery, V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ 86, 317–9 (2008).

28. Bafounta, M. L., Beauchet, A., Aegerter, P. & Saiag, P. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch. Dermatol. 137, 1343–1350 (2001).

29. Pehamberger, H., Binder, M., Steiner, A. & Wolff, K. In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma. J. Invest. Dermatol. 100, 356S–362S (1993).

30. Vestergaard, M. E., Macaskill, P., Holt, P. E. & Menzies, S. W. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol 159, 669–76 (2008).

31. Menzies, S. W. et al. Surface microscopy of pigmented basal cell carcinoma. Arch. Dermatol. 136, 1012–1016 (2000).

32. Pan, Y. et al. Dermatoscopy aids in the diagnosis of the solitary red scaly patch or plaque-features distinguishing superficial basal cell carcinoma, intraepidermal carcinoma, and psoriasis. J. Am. Acad. Dermatol. 59, 268–274 (2008).

33. Altamura, D. et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. J Am Acad Dermatol 62, 67–75 (2010).

34. Chevolet, I. et al. A short dermoscopy training increases diagnostic performance in both inexperienced and experienced dermatologists. Australas. J. Dermatol. 56, 52–55 (2015).

Chapter 3

Burden of skin cancer in Belgium and cost-effectiveness of primary prevention

Submitted as journal article:

Pil L*, Hoorens I*, Vossaert K, Kruse V, Tromme I, Speybroeck N, Annemans L, Brochez L. Economic burden of skin cancer in Belgium and cost-effectiveness of primary prevention by reducing ultraviolet exposure (submitted to Preventive Medicine, 2016). *Both authors equally contributed.

ABSTRACT

Background: Skin cancer is one of the most rapidly increasing cancers worldwide. In order to inform policy decision makers, this study analyzed the current and future economic burden and cost-effectiveness of primary prevention of skin cancer in Belgium.

Methods: A retrospective bottom-up cost-of-illness study was performed, based on patient questionnaires with questions on the consumption of care, quality of life and absenteeism. Patients were included from 1st March 2015 until 30th June 2015 when visiting dermatologists and oncologists working in general and university hospitals, small (< 200 beds), medium (200-400 beds) or big (> 400 beds) hospitals, as well as private practices. At the end of the patient recruiting period, 287 completed questionnaires from Belgian skin cancer patients were received. A Markov model with a latent period of 20 years and a time horizon of 50 years analyzed the cost-effectiveness and the budget impact analysis of a nation-wide population-based strategy promoting UV protective behavior and a national ban on sunbed use.

Results: Information from these questionnaires was used in the Markov model, analyzing the health economic impact of skin cancer prevention in the Belgian adult population (about 8.8 million people). The total economic burden of skin cancer in 2014 in Belgium was estimated at €107 million, with a cumulative cost of €3 billion in 2034. The majority of this total cost was due to melanoma (65%). Over a period of 50 years, both prevention programs would lead to a gain in quality-adjusted life-years and cost-savings, making them dominant strategies. The budget impact analysis revealed that for every euro invested in the prevention campaign, €3.6 would be saved on the long-term for the health care payer.

Conclusion: A nation-wide population-based strategy promoting UV protective behavior and a national ban on sunbed use can lead to a positive health and economical benefit from a health care payer as well as societal point of view. The results from this study can aid policy makers and clinicians to promote UV protection strategies

INTRODUCTION

Skin cancer is increasing globally[1–4], and affects nearly one out of five persons in Belgium. It is related to ultraviolet exposure, either naturally from the sun or artificially through solarium use.[5–7] Several epidemiologic studies show an alarming global increase in incidence of melanoma skin cancer (MM) and non-melanoma skin cancer (NMSC) - defined as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)-, due to the increasing age of the population, but also to altered risk seeking behavior.[1,8–11] Although NMSC is less aggressive than MM, it has an important impact on the health expenditures because of the high prevalence.[12] Consequently to this epidemic, the related health care costs are rising significantly. The first objective of this study was to calculate the current and future health and economic burden of MM and NMSC in Belgium. The second objective was to assess the cost-effectiveness and budget impact of primary prevention of skin cancer, being a hypothetical prevention campaign and a total ban on sunbed use.

METHODS

Burden of skin cancer

The health-related burden of skin cancer was estimated based on the registered prevalence of skin cancer lesions being in treatment, in intense follow-up or in long-term follow-up.[13,14] The prevalence of undiagnosed skin cancer was calculated based on the yield of a screening trial performed in Belgium in 2014[15], divided by the sensitivity of the dermoscopy.[16] In order to estimate the total economic burden of skin cancer on society, we conducted a bottom-up cost-of-illness study based on retrospective information from Belgian patient questionnaires being gathered from 1st March 2015 until 30th June 2015. Dermatologists and oncologists working in general and university hospitals, small (< 200 beds), medium (200-400 beds) or big (> 400 beds) hospitals, as well as private practices were recruited in December 2014. These physicians were asked to give skin cancer patients the information about the study and to hand out the questionnaires to the patients. Eligible patients were those who were 18+, had a diagnosis of MSC, BCC and SCC maximum ten years ago and who presented to a participating physician. Patients were asked questions about their medical consumption for their skin disease during the last six months, as well as productivity loss and quality of life. Questions concerned the number of consultations, hospitalizations, transportation, number and type of examinations, drug use, number of days absent from work, informal care and health-related quality of life (based on the EQ-5D-5L questionnaire). Based on the resource utilization patterns derived from these patient questionnaires for patients with MM, BCC or SCC and official Belgian unit costs[17], we calculated the cost per skin cancer type per 6 months,

separately for the phases diagnosis and treatment, intense follow-up and long-term follow-up. The current total societal cost was calculated by multiplying the medical cost per cancer stage with prevalence of detected skin cancer (defined as patients in treatment as well as patients in follow-up) and by multiplying the cost per day absenteeism[18] with the number of days absent from work due to skin cancer (based on the patient questionnaires). In order to calculate the future health and economic burden of skin cancer in Belgium, a Markov model was composed (Microsoft Excel® 2013), with a time horizon of 20 years. The model projected the current prevalence to 2034, taking into account the rising trend in incidence[3,11,19]. All costs were computed at the 2014 EURO price level and expressed separately as costs for the health care payer (i.e. government), costs for the patient (co-payment) and costs due to productivity loss.

Health economic evaluation of primary prevention

A Markov state-transition cohort model was developed, examining the economic impact and the cost-effectiveness of a sensitizing prevention campaign and a total ban on sunbed use in reference to the current situation. A Markov model is a type of decision model based on a series of states that a person can occupy at a given point in time.[20] MM as well as NMSC were included in the model, consisting of a lesion-free state and several disease states: undiagnosed skin cancer, diagnosis & treatment, intense follow-up, long-term follow-up and death (Figure A1). All states were separated according to skin cancer stage. All cohort members started the model in one of the model states, according to the current prevalence of BCC, SCC and MM. Transitions between the disease states were possible every six months. Health effects and costs of a cohort of Belgian adult males and females were simulated from a societal perspective, during a time horizon of 50 years. This time horizon included an induction period (i.e. the period between risk factor exposure – being UV exposure or sunbed use - and the onset of skin cancer) of 20 years (based on expert opinion). Main outcomes of the health economic evaluation included the incremental cost-effectiveness ratio (ICER), the total economic societal impact as well as the impact on the health care budget, and the mortality reduction. The ICER was calculated by dividing the net costs by the net health benefits of the prevention program. In order to calculate the total economic burden and the budget impact over 50 years, the model allowed for annual new entrance of 18-year olds each cycle in the lesion-free state, who were subjected to the natural skin cancer progression. The same model design has been used before to estimate the cost-effectiveness of skin cancer screening. More information on the design of the model can be found in Pil et al.[21]

Intervention strategies

Prevention campaign reducing risk of sunburn

The hypothetical prevention campaign was defined as a comprehensive program such as the *SunSmart* campaign in Australia. *SunSmart* is a public education program which has been running in Australia (especially in the state Victoria) since 1987. The impact of a campaign on skin cancer was modeled through an effect on being sunburned. Published literature has shown the impact of ever being sunburned on the risk of MM to be preventable by means of comprehensive prevention campaigns. Hill et al.[22] evaluated the *SunSmart* campaign in Australia two years after its implementation and found an effect on reducing sunburns by 41% (RR 0.59). The risk on developing MM was estimated to be 59% higher for persons ever being sunburned during lifetime in reference to those never being sunburned (RR 1.59; 95%CI 1.37-1.83; Table 1).[23] No evidence was found for the impact of sunburns on SCC[24] or BCC. As there is no evidence on the duration of the effect, in our analysis the prevention campaign was implemented annually. Based on these relative risks, a comprehensive prevention campaign would result in a relative risk reduction in MM of 14.2%.

Table 1. Input parameters related to the impact of primary prevention on health

Parameter	Mean (SE)	Source
Prevalence of ever sunburned, Belgium	90%	Expert opinion
RR on sunburn if prevention campaign	0.59 (0.11)	[22]
RR on skin cancer if ever sunburned		
MM	1.59 (0.12)	[23]
SCC	1	[25]
BCC	1	
Prevalence of ever used sunbed, Belgium	47%	[26]
RR on skin cancer if ever used sunbed		
MM	1.25 (0.09)	[27]
SCC	1.93 (0.43)	[24]
BCC	1	[28]

RR: Relative risk.

Ban on sunbed use

Boniol et al. found in their meta-analysis –based on 18 cohort studies- a relative risk on MM of 1.25 (95%CI 1.09-1.43) for people who have ever versus those who have never used sunbeds (Table 1).[5] The relative risk on SCC was 1.93 and for BCC no evidence on excess risk was found.[24,28,29] In this way, a ban on sunbed use would result in a relative risk reduction of 9.6% in MM and 27.8% in SCC.

Comparator

The comparator strategy is the situation without such a comprehensive prevention campaign and without a total ban on sunbed use. As our cost-effectiveness analysis is an incremental analysis, it is assumed that only the extra costs of the strategies evaluated are considered in the analysis. It is assumed that the current local fragmented initiatives would still exist in case of a national comprehensive prevention campaign.

Input data

Prevalence of diagnosed MM (excl. in situ) was derived from the Belgian cancer registry[13] and of NMSC from the Dutch cancer registry[14], since NMSC is more accurately registered in the Netherlands. A correction factor was applied to adapt the NMSC figures to Belgium, based on the ratio between the MM incidences of both countries. Prevalence of undiagnosed skin cancer derived from the screening trial.[15] Information on the probability of natural progression can be found in Appendix I. All-cause mortality risk was applied to all persons in the model (based on Belgian life tables), whereas mortality from skin cancer was possible only for MM and SCC skin cancer patients stage III and IV.[30] All epidemiologic and clinical input data are depicted in Table A1. The study was performed from the societal perspective, including direct medical costs as well as costs related to productivity loss because of morbidity and early mortality. Travel costs of patients were not included. The cost for the prevention campaign was calculated according to the study of Shih et al.[31] who estimated the annual future cost for the *SunSmart* intervention to be €0.17 per capita. Applied to the Belgian population, this would imply a total cost for the prevention campaign of €1 525 998 per year. The possible associated costs of implementing a sunbed ban and financial consequences for the industry are not taken into account. Health effects of the primary prevention were defined as the impact on quality-adjusted life-years (QALYs) and skin-cancer related deaths. Stage-specific QALYs were based on EQ-5D utilities derived from the Belgian patient questionnaires in combination with literature data (Appendix I + Table A2). Following Belgian guidelines, health effects were discounted at 1.5% and costs at 3%.[18]

Scenario and sensitivity analysis

In base case we assumed an induction period of 20 years. However, since the duration of this period is not well documented, we varied it between 10 and 30 years. A second scenario consisted of a combination of both a prevention campaign and a ban on public sunbed use. A one-way sensitivity analysis assessed the impact of variation in the key parameters one by one (according to the CI), or increased or decreased by 30% of their original value in case the CI was not available) in order to take into account uncertainty in the input variables. A probabilistic sensitivity analysis (PSA) created credibility intervals around the deterministic ICER by running 5 000 (Monte Carlo) simulations

according to the distribution of the parameters. Utilities and probabilities were varied according to beta-distributions and costs according to a gamma-distribution.

RESULTS

Burden of skin cancer

Sample characteristics

In total 16 dermatologists, nine oncologists and one general practitioner, employed in 10 different hospitals and six private practices participated in the study. In total, we received 287 completed patient questionnaires in a time span of four months. Response rates were 82.8% in dermatology patients and 71.9% in oncology patients. The sample consisted of 56% women and 44% men. The median age-category was 61-70 years old. Table 2 displays the stage distribution per cancer type.

Table 2. Stage distribution of study population

	D&T	Intense FU	Longterm FU	Total
BCC <1cm	19	17	15	51
BCC 1-2cm	26	10	3	39
BCC>2cm	8	1	0	9
BCC agressive histology	6	4	3	13
SCC 0-I-II	7	11	10	28
SCC III	0	2	0	2
SCC IV	0	0	0	0
MM 0-I	15	43	42	100
MM II	5	7	3	15
MM III	8	8	3	19
MM IV	2	8	1	11
Total	96	111	80	287

D&T: Diagnosis and treatment, FU: follow-up. Duration D&T: BCC, SCC0-II, MM 0-I-II: 6 months (1 cycle) SSC III-IV, MM III-IV: 1 years (2 cycles), Duration intense FU:BCC, SCC0-II, MM 0-I-II: 1.5 year (3 cycles) SSC III-IV, MM III-IV: 4 year (8 cycles), Duration long-term FU: lifetime.

Epidemiology of skin cancer

The model estimated the total number of skin cancers in 2014 in Belgium to be 137 117, of which the greatest part (70%) were BCC cases (95 871), 18.5% were SCC cases (25 345) and 11.5% were MM cases (15 902). There were more female than male skin cancer patients, with a ratio of 1.13 to 1. This current prevalence is estimated to have tripled by 2034, to 397 213 skin cancer cases, of which 66% BCC, 21.2% SCC and 12.8% MM.

Cost of skin cancer

Table 3 shows the cost per skin cancer stage, expressed per six months. As already stated in previously published studies[32,33], it is clear from the table that costs increase with tumour stage. There were almost no costs due to productivity loss in NMSC patients. The total economic burden of skin cancer on society in 2014 in Belgium was estimated at €107 million, with direct costs being €78 million and indirect costs being €29 million (Table 4). The majority of this total cost was due to MM (65%). Total cumulative cost over a period of 20 years (up to 2034) was estimated at €3.2 billion and over 50 years €8 billion. The Markov model simulation over 50 years showed that of the total cumulative societal burden (including direct and indirect costs) of €8 billion, €228 million could be saved by a prevention campaign and €238 million by a total ban on sunbeds, which is respectively 2.8% and 2.9% of the total societal burden (Table 5). The budget impact analysis demonstrated that a prevention campaign could save €142 million (or 0.36%) of the health care budget (initial investment cost taken into account) and in case of a ban on sunbed use €167 million (or 0.42%). Every euro invested in the prevention campaign would save €3.6 to the health care payer on the long term.

Table 3. Cost per stage per six months, separated according to phase

	Diagnosis & treatment			Intense FU			Longterm FU		
	HC payer	patient	prod. loss	HC payer	patient	prod. loss	HC payer	patient	prod. loss
BCC <1cm	€ 196	€ 34	€ 0	€ 119	€ 22	€ 0	€ 82	€ 46	€ 0
BCC 1-2cm	€ 211	€ 37	€ 0	€ 128	€ 24	€ 0	€ 89	€ 49	€ 0
BCC>2cm	€ 227	€ 40	€ 0	€ 137	€ 26	€ 0	€ 95	€ 53	€ 0
BCC agressive hist.	€ 227	€ 40	€ 0	€ 137	€ 26	€ 0	€ 95	€ 53	€ 0
SCC 0-I-II	€ 243	€ 17	€ 0	€ 18	€ 13	€ 13	€ 9	€ 7	€ 0
SCC III	€ 1 396	€ 217	€ 0	€ 91	€ 24	€ 24	€ 45	€ 12	€ 0
SCC IV	€ 1 659	€ 262	€ 0	€ 91	€ 24	€ 24	€ 45	€ 12	€ 0
MM 0-I	€ 1 891	€ 161	€ 2 663	€ 385	€ 71	€ 1 872	€ 231	€ 41	€ 26
MM II	€ 2 119	€ 244	€ 1 213	€ 318	€ 60	€ 1 872	€ 258	€ 43	€ 26
MM III	€ 4 737	€ 200	€ 6 591	€ 1 082	€ 72	€ 11 864	€ 822	€ 72	€ 3 401
MM IV	€ 51 034	€ 344	€ 6 591	€ 6 758	€ 147	€ 16 688	€ 1 401	€ 141	€ 3 401
Death*	-	-	-	-	-	-	-	-	€ 43 200

Hist: histology, HC: Health care, FU: follow-up, prod: productivity, * Source: [18,34]

Table 4. Total current and future societal cost of skin cancer in Belgium (calculated with annual inflow)

Total cost 2014								Total cumulative cost 2014-2034	Total cumulative cost 2014-2064
	MALES		FEMALES		TOTAL (incl. death)				
	MM	NMSC	MM	NMSC	MM	NMSC	TOTAL	TOTAL	TOTAL
Health care payer	€ 17 574 784	€ 12 791 731	€ 20 289 465	€ 13 983 486	€ 37 864 249	€ 26 775 217	€ 64 639 466	€ 1 909 776 064	€ 5 243 814 688
Patient	€ 893 220	€ 5 102 829	€ 1 293 760	€ 5 683 730	€ 2 186 979	€ 10 786 559	€ 12 973 539	€ 341 834 700	€ 993 608 874
Productivity	€ 12 769 907	€ 9 191	€ 16 496 350	€ 16 841	€ 29 266 257	€ 26 032	€ 29 292 288	€ 931 099 033	€ 1 878 309 125
Total	**€ 31 237 910**	**€ 17 903 750**	**€ 38 079 575**	**€ 19 684 057**	**€ 69 317 485**	**€ 37 587 808**	**€ 106 905 293**	**€ 3 182 709 797**	**€ 8 115 732 687**

Table 5. Results from the economic impact analysis showing cumulative costs over 50 years (calculated with inflow)

	Cost of intervention	Cost for health care payer	Cost for patient	Cost productivity loss	Total cost	Total extra cost from societal perspective	Total extra cost from health care payer perspective
Control	€ 0	€ 5 243 814 688	€ 993 608 874	€ 1 878 309 125	€ 8 115 732 687		
Prevention campaign	€ 39 219 386	€ 5 062 395 121	€ 987 492 778	€ 1 798 897 062	€ 7 888 004 347	-€ 227 728 340	-€ 142 200 181
Ban on sunbed use	€ 0	€ 5 076 473 226	€ 981 978 239	€ 1 819 282 111	€ 7 877 733 575	-€ 237 999 112	-€ 167 341 463

Table 6. Results from the cost-effectiveness analysis of primary prevention for skin cancer expressed per 1 000 persons (calculated without inflow)

	QALYs		COSTS		INCREMENTAL QALYs (95% CI)		INCREMENTAL COSTS (95% CI)		ICER	
	males	females	males	females	males	females	males	females	males	females
No prevention strategy	18 876	20 856	€ 669 861	€ 977 368						
Prevention campaign	18 877	20 857	€ 654 587	€ 959 957	1.39 (0.56-3.75)	1.39 (0.33-4.25)	-€ 15 273 (-44 506-[-4209])	-€ 17 411 (-54 403 -[-2905])		
Ban on sunbed use	18 881	20 862	€ 649 975	€ 956 984	4.81 (1.90 - 7.78)	5.94 (2.63-8.49)	-€ 19 886 (-49837 -[-6970])	-€ 20 384 (-57751 -[-4403])	cost-saving	
Interventions simultaneously	18 882	20 863	€ 641 858	€ 942 074	5.65	7.21	-€ 28 002	-€ 35 294		

Health economic evaluation of primary prevention

Impact on skin cancer mortality

Based on the relative risks on skin cancer found in published literature (cf. supra), primary prevention of skin cancer would lead to a relative risk reduction in the prevalence of diagnosed SCC and MSC, by affecting the transition from 'free of events' to 'undiagnosed lesion'. Our analysis showed that after 50 years, the sensitizing campaign and the ban on sunbed use would lead to a reduction in the prevalence of diagnosed MSC stage I of 11.3% (absolute numbers: 10 954 in males and 15 053 in females) and 8.6% (absolute numbers: 9 491 in males and 11 335 in females) respectively. The ban on sunbed reduced the prevalence of SCC with 22.7% (absolute numbers: 35 934 in males and 52 565 in females). Due to this decrease in the prevalence of SCC and MSC, less tumors would progress to later stages, because of which a reduction in skin cancer mortality is to be expected. In our model, over a period of 50 years, 3 991 deaths were predicted to be avoided by means of an annual prevention campaign (1 593 in males and 2 398 in females) and 3 927 by means of a ban on public sunbed use (1 602 in males and 2 329 in females).

Cost-effectiveness and economic impact of primary prevention

Table 6 shows the results of the cost-effectiveness analysis of both primary prevention programs. Both programs would lead to a gain in QALYs and cost-savings, making them dominant prevention strategies. The effect of a shorter or longer induction period was tested and showed that the strategy of a ban on sunbed use remained cost-saving in case of a 10 year or 30 year period. A one-way sensitivity analysis of both primary prevention strategies showed the most influencing parameters to be the utility of MM and SCC patients, the discount rate of costs and health effects, the direct cost of diagnosis and treatment of MM stage III-IV, the relative risk on sunburn in case of a prevention campaign, the relative risk on MM and SCC if sunbed use, the risk of dying from MM IV, the incidence of MM and the natural progression of MM (Figure A2). However, in all cases, the results remained cost-saving. The cost-effectiveness planes drawn based on the PSA represent all simulations (Figure A3). These planes show that all simulations are located in the south-east quadrant and hence are cost-saving, showing the robustness of the results.

DISCUSSION

The analysis on the burden of skin cancer showed that if the rising incidence trend continues, the skin cancer health and economic burden in Belgium will triple in 20 years. In comparison, a recent study in the U.S. estimated MM incidence rates to double from 2011 to 2030.[35] Tromme et al. have previously assessed the cost of MM treatment by means of 145 hospital bills and 253 patient questionnaires from one hospital (Cliniques Universitaires St-Luc).[32] The cost they calculated for treatment of MM stage IV was lower than our result. Most probably, this has to do with the high cost of new treatment drugs for the management of melanoma stage IV, which were not yet used in the time Tromme et al. did their research. The current annual total cost for skin cancer in Belgium was estimated to be €107 million in this study (for a population of 8.8 million Belgian adults), of which almost €65 million is to be paid by the health care payer (government), resulting in about 0.19% of the total health care budget in Belgium. The result is comparable to other European studies. A Danish study found that in 2010 direct skin cancer cost accounted for €33.3 million or 0.2% of the Danish health care budget.[36] However, this study was performed some years ago, not yet taking into account the recent more expensive therapies to treat metastatic MM. According to our results, MM was responsible for 65% of the medical costs, in contrast to a study examining the hospitalization costs of skin cancer in Germany.[12] The latter study concluded that NMSC-related costs for hospitalizations are about twice the rates of MM. Nonetheless, in other studies the proportion of cost due to MM was similar to the Belgian proportion (resp. 68.7% and 59%, although the latter only included direct costs).[36,37] However, since only the first NMSC is registered in the epidemiologic data from the Dutch cancer registry (IKNL), it is expected that the estimated total economic burden of skin cancer is an underestimation of the real cost of skin cancer. Projections to 2034 showed an estimated cumulative cost of €3.2 billion. To compare, in England a projection from 2008 to 2020 showed almost a doubling in the annual cost of skin cancer (106.4 pound to 190.5 pound).[38]

The results at hand showed that an on average €155 million of the health care budget could be redirected to other diseases by implementing a skin cancer prevention campaign or a ban on sun beds in Belgium. Although a total ban on sunbed use would gain more health benefits, both interventions are cost-saving on the long term and thus dominant. A major challenge is to create the desired altered behavior by implementing a prevention campaign. Consequently, a total ban on sunbed use could be a relatively more easy way to achieve a specific behavior. The extra costs for the individuals as a consequence of the prevention campaign, such as extra sunscreen and sun-protecting clothing was not included in our model, since we do not have accurate information on these costs in the control group (i.e. without intervention). The sensitivity analysis revealed that the higher the medical costs of treating metastatic MM, the more cost-effective prevention would be, since the financial benefit of

prevention would be higher. Recently, new expensive treatments for metastatic MM were introduced and it is expected that in the future treatment costs will continue to rise, which further favors preventive strategies for MM.

Gordon & Rowell included seven studies in their review of the cost-effectiveness of primary prevention.[39] Although all studies had different designs and context, they concluded that skin cancer primary prevention programs or policies are consistently cost-effective and may even be cost-saving for governments in the near future. A cost-effectiveness evaluation of the Australian *SunSmart* program demonstrated to reduce the burden of disease and to be highly cost-effective. Shih et al.[31] calculated a return of 2.3 AUD (= €1.5) for every dollar (AUD) invested in the campaign. In our study we estimated the return on investment to be €3.6.

Some limitations of our analysis should be acknowledged. First, since for some skin cancer stages the sample of returned patient questionnaires was too small, we had to rely on expert opinions and literature data to calculate the medical costs for these groups. In addition, we cannot exclude a degree of selection bias, since sampling of the skin cancer patients was performed by the participating physicians. The indirect costs were derived from the small sample data and could therefore be partly biased. However, the prevention strategies remained cost-saving even without inclusion of productivity loss. Second, the simulation of the primary prevention programs is hypothetical; a trial-based analysis may be beneficial. Therefore, we deduced the effect of a prevention campaign from the Australian *SunSmart* program. However, it is not known if such a campaign would have a similar effect on reduction of the relative risk of sunburn in Belgium. A German study evaluating the effectiveness of skin cancer information campaigns during the last 16 years found a relative risk of 0.68 for the risk on sunburn, which is lower than the relative risk in case of the *SunSmart* campaign in Australia.[40] However, the sensitivity analysis acknowledged this uncertainty and showed that the intervention would still be cost-saving in case of a lower effectiveness. Third, in Belgium there is no accurate registration of NMSC. Therefore, we relied on epidemiologic figures of the Dutch cancer registry, adjusted to Belgium. Lastly, knowledge on the natural history and progression of MM and NMSC is limited. Therefore, in our model, the natural progression was estimated based on calibration. For methodological reasons transition probabilities were assumed to be equal for all ages and gender, although for MM these are known to be gender and age-specific.[41–43]

CONCLUSIONS

This analysis provides an accurate estimation of the current and future impact of skin cancer in Belgium and demonstrates that a nation-wide population-based strategy promoting UV protective behavior and a national ban on the use of sunbeds can lead to a positive health and economical benefit from a health care payer as well as societal point of view. The results from this study can aid policy makers and clinicians to promote UV protection strategies.

REFERENCES

1. Flohil, S. C., de Vries, E., Neumann, H. A., Coebergh, J. W. & Nijsten, T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol 91, 24–30 (2011).

2. Nikolaou, V. & Stratigos, A. J. Emerging trends in the epidemiology of melanoma. Br. J. Dermatol. 170, 11–19 (2014).

3. Flohil, S. C. et al. Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. J. Invest. Dermatol. 133, 913–918 (2013).

4. Arits, A. H. M. M., Schlangen, M. H. J., Nelemans, P. J. & Kelleners-Smeets, N. W. J. Trends in the incidence of basal cell carcinoma by histopathological subtype. J. Eur. Acad. Dermatol. Venereol. JEADV 25, 565–569 (2011).

5. Boniol, M., Autier, P., Boyle, P. & Gandini, S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 345, e4757 (2012).

6. Elwood, J. M. & Jopson, J. Melanoma and sun exposure: an overview of published studies. Int. J. Cancer 73, 198–203 (1997).

7. Gandini, S. et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur. J. Cancer Oxf. Engl. 1990 41, 2040–2059 (2005).

8. Diffey, B. L. The future incidence of cutaneous melanoma within the UK. Br. J. Dermatol. 151, 868–872 (2004).

9. de Vries, E., van de Poll-Franse, L. V., Louwman, W. J., de Gruijl, F. R. & Coebergh, J. W. W. Predictions of skin cancer incidence in the Netherlands up to 2015. Br. J. Dermatol. 152, 481–488 (2005).

10. Marcos-Gragera, R. et al. Rising trends in incidence of cutaneous malignant melanoma and their future projections in Catalonia, Spain: increasing impact or future epidemic? J. Eur. Acad. Dermatol. Venereol. JEADV 24, 1083–1088 (2010).

11. Hollestein, L. M. et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 23, 524–30 (2012).

12. Stang, A., Stausberg, J., Boedeker, W., Kerek-Bodden, H. & Jöckel, K.-H. Nationwide hospitalization costs of skin melanoma and non-melanoma skin cancer in Germany. J. Eur. Acad. Dermatol. Venereol. JEADV 22, 65–72 (2008).

13. Stichting Kankerregister. Incidence melanoma, basal cell carcinoma and squamous cell carcinoma in Belgium, 2013. (2016).

14. Integraal Kankercentrum Nederland. Incidence of basal en squamous cell carcinoma. (2011).

15. Hoorens, I. et al. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol. 152, 27–34 (2016).

16. Chevolet, I. et al. A short dermoscopy training increases diagnostic performance in both inexperienced and experienced dermatologists. Australas. J. Dermatol. 56, 52–55 (2015).

17.Rijksinstituut voor Ziekte- en Invaliditeitsverzekering. Nomenclatuur van de geneeskundige verstrekkingen. (2015).

18. KCE. Belgische richtlijn voor economische evaluaties en budget impact analyses. Rep. 183A (2012).

19. Hollestein, L. M., de Vries, E. & Nijsten, T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur. J. Cancer Oxf. Engl. 1990 48, 2046–2053 (2012).

20. Adamiak, G. Methods for the economic evaluation of health care programmes, 3rd ed. J. Epidemiol. Community Health 60, 822–823 (2006).

21. Pil, L. et al. Cost-effectiveness and budget impact of two population-based skin cancer screening methods. JAMA Dermatol (2016).

22. Hill, D., White, V., Marks, R. & Borland, R. Changes in sun-related attitudes and behaviours, and reduced sunburn prevalence in a population at high risk of melanoma. Eur. J. Cancer Prev. Off. J. Eur. Cancer Prev. Organ. ECP 2, 447–456 (1993).

23. Dennis, L. K. et al. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. Ann. Epidemiol. 18, 614–627 (2008).

24. Veierød, M. B., Couto, E., Lund, E., Adami, H.-O. & Weiderpass, E. Host characteristics, sun exposure, indoor tanning and risk of squamous cell carcinoma of the skin. Int. J. Cancer 135, 413–422 (2014).

25. Vuong, K. et al. Development and External Validation of a Melanoma Risk Prediction Model Based on Self-assessed Risk Factors. JAMA Dermatol. (2016). doi:10.1001/jamadermatol.2016.0939

26. IPSOS. Kankerbarometer: steekproef in de belgische papulatie in 2015.

27. Boniol, M., Autier, P., Boyle, P. & Gandini, S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 345, e4757 (2012).

28. Hirst, N., Gordon, L., Gies, P. & Green, A. C. Estimation of avoidable skin cancers and cost-savings to government associated with regulation of the solarium industry in Australia. Health Policy Amst. Neth. 89, 303–311 (2009).

29. International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. Int. J. Cancer 120, 1116–1122 (2007).

30. Stichting Kankerregister. Belgian mortality rates, 2004-2011. (2013).

31. Shih, S. T.-F., Carter, R., Sinclair, C., Mihalopoulos, C. & Vos, T. Economic evaluation of skin cancer prevention in Australia. Prev. Med. 49, 449–453 (2009).

32. Tromme, I. & Speybroeck, N. Cost-effectiveness analyis of dermoscopy: a pilot study. (2016).

33. Alexandrescu, D. T. Melanoma costs: a dynamic model comparing estimated overall costs of various clinical stages. Dermatol. Online J. 15, 1 (2009).

34. Swan Tan, S., Bouwmans-Frijters, C. A. M. & Hakkaart-van Roijen, L. Handleiding voor kostenonderzoek: methoden en referentieprijzen voor economische evaluaties in de gezondheidszorg. Tijdschr. Voor Gezondheidswetenschappen 90, 367–372 (2012).

35. Guy, G. P. et al. Vital signs: melanoma incidence and mortality trends and projections - United States, 1982-2030. MMWR Morb. Mortal. Wkly. Rep. 64, 591–596 (2015).

36. Bentzen, J. et al. Costs of illness for melanoma and nonmelanoma skin cancer in Denmark. Eur. J. Cancer Prev. Off. J. Eur. Cancer Prev. Organ. ECP 22, 569–576 (2013).

37. Tinghög, G., Carlsson, P., Synnerstad, I. & Rosdahl, I. Societal cost of skin cancer in Sweden in 2005. Acta Derm. Venereol. 88, 467–473 (2008).

38. Vallejo-Torres, L., Morris, S., Kinge, J. M., Poirier, V. & Verne, J. Measuring current and future cost of skin cancer in England. J. Public Health Oxf. Engl. 36, 140–148 (2014).

39. Gordon, L. G. & Rowell, D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur. J. Cancer Prev. Off. J. Eur. Cancer Prev. Organ. ECP 24, 141–149 (2015).

40. Breitbart, E. W., Greinert, R. & Volkmer, B. Effectiveness of information campaigns. Prog. Biophys. Mol. Biol. 92, 167–172 (2006).

41. Joosse, A. et al. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. J. Invest. Dermatol. 131, 719–726 (2011).

42. Joosse, A. et al. Sex is an independent prognostic indicator for survival and relapse/progression-free survival in metastasized stage III to IV melanoma: a pooled analysis of five European organisation for research and treatment of cancer randomized controlled trials. J. Clin. Oncol. 31, 2337–2346 (2013).

43. Balch, C. M. et al. Age as a predictor of sentinel node metastasis among patients with localized melanoma: an inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. Ann. Surg. Oncol. 21, 1075–1081 (2014).

Chapter 4

Clinical effectiveness of skin cancer screening

Published as journal article:

Hoorens I, Vossaert K, Pil L, Boone B, De Schepper S, Ongenae K, Annemans L, Chevolet I, Brochez L. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol. 2016; 152(1):27-34.

ABSTRACT

Background: Skin cancer is at present the most frequent cancer type. The question remains if and how screening programs can be organized in a cost-effective manner. Two screening strategies (systematic total body examination (TBE) and lesion-directed screening (LDS)) were compared as to their participation rate, effectiveness, adverse effects and costs.

Methods: Population-based cross-sectional screenings by a team of 6 dermatologists were organized in two socio-demographically similar regions. The first population received a personal invitation for a standard TBE. In the second population people were invited for a LDS, if they had a lesion meeting one or more of the criteria listed: ABCD rule, ugly duckling sign, new lesion since more than 4 weeks, red non-healing lesions. The TBE was organized in a community of 9325 inhabitants older than 18 years (Wichelen, East Flanders, Belgium) during a five-day screening (March 2014). The LDS was organized in a socio-demographically comparable community (Nevele, East Flanders, Belgium) of 9484 adult inhabitants during a four-day screening (April 2014).

Results: In total 1982 persons were screened and 47 (2.4%) skin cancers were confirmed histologically (0.45% melanoma, 1.9% basal cell carcinoma, 0.05% squamous cell or Bowen). The positive predictive value for all suspicious lesions was 56.6%. Participation rate was higher in the TBE group compared to the LDS group (17.9% versus 3.3%, P=<0.01). Detection rate did not differ significantly between the two groups per 100 participants (2.3 TBE versus 3.2 LDS, P=0.40). The diagnostic yield per 100 invitees for TBE was 0.42 and 0.08 for the LDS method (P<0.01). LDS was 5.6 times less time-consuming than TBE. Participants in the LDS group had a significant higher baseline anxiety compared to the TBE group (3.7 versus 3.3 points, P<0.01). In screenees without a suspicious lesion anxiety significantly declined after screening.

Conclusion: TBE yielded a higher absolute number of skin cancers, LDS has similar detection rate (3.2%) but was 5.6 times less time consuming. LDS by dermatologists can be an alternative screening method in health care systems with limited budget and/or long waiting lists.

INTRODUCTION

The incidence of melanoma and non-melanoma skin cancer (NMSC) has been rising dramatically worldwide, and this increase is expected to continue with aging of the population.[1 2] The cumulative lifetime risk of developing a basal cell carcinoma (BCC) is being estimated as high as 1 in 5 to 6 in the Netherlands.[3] In the United Kingdom (UK), the lifetime risk of developing malignant melanoma is 1 in 55 for men and 1 in 56 for women (UK cancer registry, Statistical Information Team at Cancer Research UK, 2012). Early detection is assumed to result in better cure rates and subsequently a more cost-effective treatment.[4 5] Since skin examination is a simple, non-invasive technique, several early detection initiatives exist of which most focus on melanoma only. However, the majority of skin cancers are NMSC and these constitute the most important direct cost to public health.[6-8] Mass population-based screening by means of total-body examination (TBE) in asymptomatic persons has not been proven cost-effective at this point,[9 10] although a recent experience in Germany suggests that such screening is feasible and can reduce skin cancer burden.[4 11] Most of the screening initiatives focus on specific high-risk groups,[12-14] missing the great deal of skin cancers that occur outside this high-risk group setting. A reliable and acceptable test is an important tool in screening. Dermoscopy has been proven to increase diagnostic accuracy for melanoma over naked eye examination in experienced users.[15 16]

As to date evidence for the cost-effectiveness of skin cancer screening by TBE is lacking, we conceived the idea to test a lesion-directed screening approach. As screenees can present with only a specific lesion of concern meeting certain pre-set criteria, we hypothesized that this technique could lower the threshold for screenees, increase the a priori probability of skin cancer and could be time-saving for the physician.

In a pilot study evaluating lesion-directed screening (LDS) in 199 persons, a total of 25 suspicious lesions (12.6%) was detected and referred to the general practitioner (GP) or dermatologist for further care. When only the detected BCC, which can reliably be diagnosed clinically, and two histologically confirmed melanomas were included, this pilot study gave a detection rate of at least 8.5%. This is 10-fold higher than the detection rate of the systematic population-based skin cancer screening program in the German state Schleswig-Holstein, in which 0.8% skin cancers were detected (0.5% BCC, 0.1% squamous cell carcinoma (SCC) and 0.2% melanoma).[4] Based on estimated incidence rates in Belgium, the expected skin cancer yield would be less than 0.2% of the population. So screening people for selected lesions, meeting pre-defined criteria, could give a higher yield of relevant lesions than promoting a systematic whole body screening. This concept is new in the skin cancer screening world. Based on these data, we decided to perform a comparative effectiveness study.[17]

We compared dermatologist-conducted LDS screening to a standard TBE screening in 2 socio-demographically similar regions with focus on participation rate, effectiveness, time and costs. As screening may induce unnecessary anxiety and depression,[18 19] a visual analogue scale (VAS) to measure anxiety was included in the protocol. This is an accepted tool used in dental practice and for measuring fear perioperative.[20 21] The VAS corresponds well to the STAI (Spielberger State-Trait Anxiety Inventory), a validated test quantifying anxiety.[21]

MATERIALS AND METHODS

Patients and screening

Population-based cross-sectional skin cancer screenings were performed without randomization. The TBE was organized in a community of 9325 inhabitants (Wichelen, East Flanders, Belgium) during a five-day screening (March 2014). All inhabitants of 18 years and older received a personal invitation 5 weeks in advance for a free of charge TBE, with the message that skin cancer incidence is an increasing health care problem.

The LDS was organized in a comparable community in terms of genetic background, socio-economic status, culture and geographical area (Nevele, East Flanders, Belgium) during a four-day screening (April 2014). The 9484 inhabitants where also invited by a personal letter 5 weeks in advance for a free of charge skin cancer check, if they had a lesion meeting one or more of the criteria listed: ABCD rule, ugly duckling sign, new lesion since more than 4 weeks, red non-healing lesions. A TBE was offered to all LDS participants at the end of the lesion screening.

People were asked to pre-register in order to have an estimate on the number of participants and to organize the screening team. All aspects of the sensitization campaign and registration process were similar; only the specific messages given to the populations differed.

The screenings were organized in a public place of the municipality. All participants were randomly allocated to one of the six dermatologists (LB, KV, KO, SDS, BB, SL) with similar expertise in skin cancer and dermoscopy. The screening was performed using both naked eye inspection and dermoscopy. In case of a suspicious lesion, a second opinion was asked to reduce inter-observer variability. Suspicious lesions were photographed and the patient received a referral letter for his GP or dermatologist. The study was approved by the Flemish government and by the medical ethical committee of the University Hospital Ghent. All participants provided written informed consent.

Data collection

The participants were interviewed using a standard questionnaire to collect information on demographics and risk factors. Anxiety for skin cancer was evaluated using a visual analogue scale from 0 (no fear) to 10 (highest possible fear) before and immediately after screening irrespective of the outcome.

During clinical examination, the following features were recorded; skin type according to Fitzpatrick,[22] solar lentigines, actinic keratosis (AK), number of nevi and presence of atypical nevi. All melanocytic lesions on exposed skin (except genitalia) were counted, and atypical melanocytic nevi were defined as previously described by Garbe et al.[23 24] The duration of the clinical examination was registered. This was defined as the time needed for the patient to get fully undressed (TBE) or to show the specific lesion (LDS), added up to the time needed for the dermatologist to examine the body (TBE) or the lesion (LDS) with naked eye and dermoscopy.

When a suspicious lesion was detected during one of the screenings, the patient was referred to their GP or dermatologist for biopsy/excision and treatment. The clinical suspicion rate was defined as the number of referrals divided by the number of participants. The pathological outcome of the lesion was retrieved and considered to be the final diagnosis and yield.

Outcomes

Four primary outcomes were evaluated. First, the participation rate, defined as the total number of participants divided by the total number of invited inhabitants. Secondly, the detection rate, defined as the number of histological confirmed skin cancers on the total number of participants and the operational effectiveness, defined as the overall yield in the invited population. Thirdly, the impact of the screening on anxiety was evaluated by comparison of the VAS score before and after the screening. Finally, the cost, expressed as the direct costs per detected lesion, was calculated for the two methods. For calculation of the costs, the measurement and valuation of the costs was consistent with the perspective of the Belgian health care budget and in accordance with the 2014 National Institute for Health reimbursement guidelines. For these costs of the screening program, the subsequent treatment- and indirect cost were not taken into account. In addition, time spent per screening was also assessed in order to better understand the screening capacity of both methods. Mortality was not included as an endpoint.

Statistical analysis

All categorical variables were compared using Pearson's chi-squared test or Fisher's exact test in case the conditions for Pearson's chi-squared test were not met. The independent or paired sample T-test

was used for continuous variables. Differences are expressed with a 95% confidence interval (CI). All statistical tests were two-tailed and P-values <0.05 were considered statistically significant. The analyses were conducted in SPSS version 21.0 (IBM, Armonk, NY, U.S.A). Sample size calculation of the number of invitees was based on participation rate and effect size of published data and the pilot study. Power analysis was conducted in SPSS SamplePower version 3.0 (IBM, Armonk, NY, U.S.A).

RESULTS

Participation

A total of 1982 persons were screened in this study. Participation rate was significantly higher in the TBE group (17.9%) compared to the LDS group (3.3%, P<0.01) (Table 1). Gender distribution was comparable, with a modest female predominance of 56%. There was no difference in median age. Educational level was higher in the LDS group; there were more participants with a university degree (16% versus 9.9%, P<0.01).

As expected, the main reason for people participating in the TBE screening was to have a total skin check (77.3%) whereas in the LDS group 75.8% consulted for a specific lesion. However 6.6% of the screenees in the TBE group consulted because of concern about a specific lesion, and 17.8% (n=56) of the screenees in the LDS group had no specific lesion of concern but consulted for a total skin examination. In total 283 participants (90.1%) of the 314 participants in the LDS group agreed to a total skin check.

Table 1. Demographics of participants, participation rate, motivations to participate, and previous skin checks

	Overall	TBE	LDS	P-value[a]
Sex				
Females	1113 (56.2)	936 (56.1)	177 (56.4)	
Males	869 (43.8)	732 (43.9)	137 (43.6)	0.93
Total	1982	1668	314	-
Participation rate, %		17.9	3.3	<0.01
Educational level				
Primary school		208 (12.6)	37 (12.1)	
High school		757 (45.8)	119 (38.9)	
Higher education		526 (31.8)	101 (33.0)	
University degree		163 (9.9)	49 (16.0)	<0.01
Personal history of skin cancer		40 (2.4)	6 (2.0)	0.84
Familial history of skin cancer		179 (11.2)	41 (14.0)	0.17
Motivation to participate				
"I just wanted to be checked"		1280 (77.3)	56 (17.8)	<0.01
"I have many moles"		131 (7.9)	1 (0.3)	<0.01
"I have one/ more suspicious skin lesions"		109 (6.6)	238 (75.8)	<0.01
"A family member/friend advised me"		5 (0.3)	4 (1.3)	0.06
"A doctor advised me"		59 (3.6)	2 (0.6)	0.01
"Other"		71 (4.3)	13 (4.1)	0.99
At least one previous skin check		634 (38.3)	123 (40.2)	0.29

N (%) presented unless otherwise stated. Numbers do not always add up to the total due to missing data. SD, standard deviation; TBE, Total body examination; LDS, lesion directed screening; IQR, interquartile range. [a] Pearson's chi-squared test unless otherwise stated. [b] Wilcoxon Rank Sum Test.

Clinical findings

The clinical findings are illustrated in Table 2. Participants in the two groups did not differ significantly with regard to Fitzpatrick skin type, total nevus count, presence of AK or atypical nevi. A positive personal or family history of skin cancer and the number of participants who received at least 1 previous skin check was similar in both groups (38.3% in the TBE - and 40.2% in the LDS group).

The clinical suspicion rate was 4.4% (n=73) in the TBE group and 3.2% (n=10) in the LDS group (P=0.66). BCC was the most frequent clinical diagnosis. Several screenees had more than one clinically suspicious lesion especially multiple BCCs (10 (n=1), 9 (n=1), 3 (n=1), 2 (n=6)) and more than one Bowen's disease (3 (n=1), 2 (n=3)).

Table 2. Clinical findings and risk factors in the participants

	Overall	TBE	LDS	P-value[a]
Number of participants	1982	1668	314	-
Skin type				
I	123 (6.4)	107 (6.5)	16 (5.7)	
II	1143 (59.0)	965 (58.4)	178(62.9)	
III	637 (32.9)	551 (33.3)	86 (30.4)	
IV	26 (1.3)	24 (1.5)	2 (0.7)	
V	6 (0.3)	6 (0.4)	0 (0.0)	
VI	1 (0.1)	0 (0.0)	1 (0.4)	0.23[b]
Nevus count				
<25	1108 (57.3)	944 (57.1)	164 (58.0)	
25-50	567 (29.3)	483 (29.2)	84 (29.7)	
50-100	194 (10.0)	168 (10.2)	26 (9.2)	
>100	66 (3.4)	57 (3.4)	9 (3.2)	0.96
Presence of AK	152 (7.8)	130 (7.9)	22 (7.6)	0.90
Presence of solar lentigines	1264 (65.3)	1051 (63.6)	213 (75.0)	<0.01
Presence of atypical nevi	298 (15.4)	249 (15.1)	49 (17.3)	0.33
Screenees with suspected skin cancer of any type	83 (4.2)	73 (4.4)	10 (3.2)	0.66
Screenees with suspected melanoma	10 (0.5)	9 (0.5)	1 (0.3)	
Screenees with atypical nevi referred for excision	17 (0.8)	17 (1.0)	0 (0)	
Screenees with suspected BCC	47 (2.4)	40 (2.4)	7 (2.2)	
Screenees with suspected SCC/Bowen	8 (0.4)	6 (0.4)	2 (0.6)	
Screenees with other suspected skin cancer [c]	1 (0.05)	1 (0.1)	0 (0)	

n (%) presented unless otherwise stated. Numbers do not always add up to the total due to missing data. TBE, Total body examination; LDS, lesion directed screening; AK, actinic keratosis; BCC, basal cell carcinoma; SCC, squamous cell carcinoma. [a] Pearson's chi-squared test unless otherwise stated. [b] Fisher's exact test has been used because conditions for Pearson's chi-squared test have not been met. [c] Merkel cell carcinoma.

Skin cancer detection rate

The histological diagnosis of one participant in the LDS group and 12 participants in the TBE group could not be retrieved. In the LDS group a lesion suspicious for Bowen's disease had disappeared spontaneously when the participant presented for biopsy at the dermatology office. In the TBE group one participant died before referral, 4 persons have chosen not to have an excision or biopsy and 7 have postponed the excision or biopsy because of other health problems.

In total 1982 persons were screened and 47 (2.4%) skin cancers were confirmed histologically. No suspicious lesions were found in screenees younger than 35 and the calculated skin cancer detection

rate in the age group >35 was 3.0%. Melanoma was detected in 9 (0.45%) screenees, 37 (1.9%) had confirmed BCC and 1 (0.05%) SCC or Bowen. Of the pathologically confirmed melanomas, 3 were in situ and 6 melanomas were invasive. The predictive value of a positive screening test for melanoma was 50% (95% CI 0.24 - 0.76), compared to a positive predictive value (PPV) of 72.3% (95% CI 0.58 - 0.83) for BCC. The PPV of a positive screening test for SCC or Bowen was only 12.5% (95% CI 0.01 - 0.49). The overall predictive value of a positive screening test for skin cancer was 56.6% (95% CI 0.46 - 0.67) (Table 3).

Detection rates between the two screening methods did not differ significantly (TBE 2.3% versus LDS 3.2%, P=0.40), but in the population invited for TBE significantly more skin cancers were detected given the higher participation rate (TBE 0.42% versus LDS 0.08%, P=<0.01) (Table 4).

In total 283 (90.1%) participants in the LDS group agreed to have a total skin check. Only 1 skin cancer at a non-examined site was detected if the initial index lesion was not suspicious. In the subgroup of 10 participants where the presented lesion was suspicious, additional malignant lesions were revealed by total skin check in 3 persons (confirmed BCC in two, confirmed Bowen in one). In the 66 participants in the LDS group that did not consulted for a specific lesion, only one skin cancer was detected in het total body check (confirmed BCC).

Table 3. Histological findings

	Overall	TBE	LDS	P-value[a]	Difference TBE-LDS % (95% CI)
Number of participants	1982	1668	248[g]	-	-
Skin cancer detection rate	47 (2.4)	39 (2.3)	8 (3.2)	0.40	-0.89 (-3.96,0.90)
Melanoma detection rate	9 (0.45)	8 (0.5)[b]	1 (0.4)	0.87[f]	0.08 (-1.78, 0.65)
Positive predictive value for melanoma	5/10 (50)	4/9 (44.4)[b]	1/1 (100)	0.99[f]	
BCC detection rate	37 (1.9)	30 (1.8)[c, e]	7 (2.8)[d]	0.28	-1.02 (-3.96,0.61)
Positive predictive value for BCC	34/47 (72.3)	28/40 (70.0)[c,e]	6/7 (85.7)[d]	0.69	
SCC/Bowen detection rate	1 (0.05)	1 (0.06) [e]	0 (0)	0.99[f]	0.06 (-1.47, 0.34)
Positive predictive value for SCC/Bowen	1/8 (12.5)	1/6 (16) [e]	0/2 (-)	-	-
Missing histology reports	13	12	1	-	-

n (%) presented unless otherwise stated. Numbers do not always add up to the total due to missing data. TBE, total body examination; LDS, lesion directed screening; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; CI confidence interval. [a] Pearson's chi-squared test unless otherwise stated. [b] Four melanomas were detected in participants referred for excision of an atypical nevus, four melanomas were detected in participants referred for excision of a lesion suspicious for melanoma. [c] Two BCCs were detected in participants with suspicion of Bowen's disease. [d] One BCC was detected in a patient with a lesion suspicious for SCC. [e] For calculation of the detection rate and positive predictive value (PPV) only the first BCC and Bowen were taken in account. [f] Fisher's exact test has been used because conditions for Pearson's chi-squared test have not been met. [g] A total of 248 participants in the LDS group presented with a specific lesion, participants presenting for a standard skin check were not included in the total number.

Table 4. Detection rate and operational effectiveness

	Detection rate (per 100 participants)			
	TBE (n=1668)	LDS (n=248)	P-value[a]	Difference TBE-LDS % (95% CI)
Skin cancer	2.3 (39)	3.2 (8)	0.40	-0.89 (-3.96,0.90)
Melanoma	0.48 (8)	0.4 (1)	0.87[b]	0.08 (-1.78, 0.65)
BCC	1.8 (30)	2.8 (7)	0.28	-1.02 (-3.96,0.61)
SCC/Bowen	0.06 (1)	0 (0)	0.99[b]	0.06 (-1.47, 0.34)
	Operational effectiveness (per 100 invitees)			
	TBE (n=9325)	LDS (n=9484)	P-value[a]	Difference TBE-LDS % (95% CI)
Skin cancer	0.42 (39)	0.08 (8)	<0.01	0.33 (0.19, 0.49)
Melanoma	0.08 (8)	0.01 (1)	0.02[b]	0.08 (0.01, 0.16)
BCC	0.32(30)	0.07(7)	<0.01	0.25 (0.12, 0.39)
SCC/Bowen	0.01 (1)	0 (0)	0.99[b]	0.01 (-0.03, 0.06)

Number in brackets are the actual numbers of individuals. Numbers do not always add up to the total due to missing data. TBE, total body examination; LDS, lesion directed screening; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; CI confidence interval. [a] Pearson's chi-squared test unless otherwise stated. [b] Fisher's exact test has been used because conditions for Pearson's chi-squared test have not been met.

Anxiety

Participants in the LDS group had a significant higher baseline anxiety (3.7 points) compared to the TBE group (3.3 points, P<0.01). In screenees in whom no suspicious lesion was detected by screening a similar reduction in anxiety using the VAS was observed in both groups (reduction with 1.3 points, P<0.01). In screenees who were diagnosed with a suspicious lesion, a small rise in anxiety (0.3 points) was seen, but this was not statistically significant (Table 5).

Table 5. Anxiety

	TBE	LDS	P-value[a]
Anxiety rate before screening, mean (SD)	3.3 (2.5)	3.7 (2.8)	<0.01[b]
Anxiety rate after diagnosis, mean (SD)	2.1 (2.2)	2.5 (2.6)	0.01[b]
Difference in anxiety before and after screening, mean (SD)	- 1.2 (2.2)	- 1.2 (2.4)	0.69[b]
Paired anxiety difference, mean (SD)			
No suspicious lesion	- 1.3 (2.1)	-	<0.01
Diagnosis of AK	- 0.1 (2.8)	-	0.57
Diagnosis of suspicious lesion	0.3 (2.5)	-	0.28
Paired anxiety difference, mean (SD)			
No suspicious lesion	-	- 1.3 (2.2)	<0.01
Diagnosis of AK	-	- 0.2 (3.1)	0.80
Diagnosis of suspicious lesion	-	- 0.45 (3.4)	0.57

Mean (SD) presented unless otherwise stated, Difference = VAS after minus VAS before screening. Numbers do not always add up to the total due to missing data. TBE, total body examination; LDS, lesion directed screening [a] Paired sample T-test unless otherwise stated. [b] Independent sample-T test.

Time and costs

The mean duration of the complete TBE examination was 3 minutes 52 seconds compared to 40.9 seconds in the LDS group (SD 70.1 and SD 67.1 resp., P<0.01). In this way LDS is 5.6 times less time-consuming than TBE. Analysis of the time needed to perform only the clinical examination, without taking the time to undress in consideration, revealed similar results (TBE 2 minutes 51.6 seconds (SD 62.7), LDS 24.2 seconds (SD 31.8)).

Reimbursement for clinical examination, excision and pathology are in accordance with the 2014 National Institute for Health guidelines. The total estimated cost of screening per detected skin cancer was €931 for the LDS method and €1012 for the TBE method. A Markov model will be designed to determine the incremental cost-effectiveness ratio comparing the TBE and LDS method versus no screening.

DISCUSSION

We present in this paper the results of a study comparing two different screening methods for skin cancer by dermatologists in 2 similar populations as to participation rate, effectiveness and cost. The effect of screening at decreasing advanced skin cancer stage was not included as an endpoint and no conclusions can be drawned based on the current study design. However, 1982 persons were screened by this initiative and 47 (2.4%) skin cancers were histologically confirmed (0.45% melanoma, 1.9% BCC, 0.05% SCC or Bowen). No skin cancers were detected in the age group <35 (n=434), hence for the subgroup aged >35 detection rate was 3.0%. In addition the positive predictive value was at least 56.6%. In 13 lesions definitive histological diagnosis was missing, meaning that the number of false positives, an important side effect of screening, ranged between 27.7 and 44.6%.

These detection rates and PPV were high compared to other screening initiatives. The largest European study to date is the screening in Schleswig-Holstein (Germany) reporting a histological yield of 0.8% malignant lesions (0.5% BCC, 0.1% SCC and 0.2% melanoma) and a false positive rate of 74.3%.[4 25] The use of/and experience in dermoscopy could have led to a higher diagnostic accuracy in the current study. It has been demonstrated that the odds for detecting melanoma increases by at least nine times over naked eye examination.[16] The difference in overall yield could also be explained by study design. In this screening, a team of dermatologists highly experienced in skin cancer and dermoscopy were involved, whereas in Germany non-dermatologists could also participate in the screening after an 8-hour course. As a result it is possible that the false negative rate was higher in the German study because some patients with suspicious lesions may not have been referred correctly to the dermatologist resulting in an overall lower yield.

Data from the Euromelanoma campaigns rarely report complete histologic follow-up for NMSC. The yield for histological confirmed melanoma varies in different European countries; in the 2009 and 2010 campaigns the total detection rate was 0.35% among all participating countries. Only one campaign in Switzerland included NMSC histology, resulting in a detection rate of 0.38% for BCC and 0.15% for SCC.[26-28] During the 2009 Euromelanoma campaign in Belgium, 2652 participants were screened and 12 melanomas were found resulting in a detection rate of 0.45% similar to our findings.[28] The PPV for melanoma in this setting was 22.2% compared to 50% in our study, although dermoscopy was used in 94.4% of the examinations.

LDS has a lower operational effectiveness, since TBE detects five times more skin cancers present in the population. The detection rate within the participant groups was not significantly different between the two screening methods (2.3% TBE versus 3.2% LDS, P=0.40). LDS was 5.6 times less time-consuming and resulted in a lower cost per detected skin cancer. The effectiveness of LDS can be

increased if a whole body screening is offered in case of a suspicious index lesion that was the reason for participation. A large two-step screening study, offering a TBE after dermatologists performed inspection of problem and uncovered area, found that if a skin tumor is a reason for consultation (OR 3.8 (95% CI 2.0 - 4.8)) or the presence of a suspicious lesion on the problem or uncovered area (OR 6.8 (95% CI 5.2 – 9.0)) the risk of missing a skin cancer significantly increased when no additional total skin examination was performed.[29] It is also known that a large proportion of patients with BCC develop multiple BCCs over time, and a proportion of these patients present with multiple BCCs synchronously.[30] In our study 3 out of 10 patients had a second confirmed BCC or Bowen after presenting with a confirmed malignant lesion on LDS screening. TBE seems to be the most complete skin cancer screening that can be offered to a population, but health care systems today are faced to specific challenges of scarcity in budget and medical staff resulting in waiting lists, the LDS method might be an viable alternative.

Participation rate in the TBE group is comparable to the participation rate of 19.1% in the German SCREEN project.[31] The almost 5 times lower participation rate in the LDS group can only be explained by the specific message on the invitation or the stated conditions to participate, since all other aspects of the sensitization were similar and the 2 areas that were socio-economically comparable according to the official statistics. In the TBE group, 109 participants (6.6%) attended the screening because they were worried about one or more lesions, in contrast to 238 persons in the LDS group (75.8%). The message was thus correctly interpreted by the majority of participants in the LDS group, probably resulting in a general lower participation rate. In screening, higher education levels lead to higher participation. Our data showed a significantly higher level of education in the LDS group: 49.0% of the participants had higher education or university degree compared to 41.7% in the TBE group. This finding could be related to the more complex and selective message in LDS group and deserves attention since lower socio-economic class is an important risk factor for non-participation in health care programs and more advanced cancers at diagnosis.[32 33] The effect of increasing the participation rate in the LDS group by means of sensitization using TV, social media and extra reminders should be examined to fully exploit the benefits of the LDS method and increase its overall yield. Introduction of a preventive health care pathway managed by the GP could benefit the current socio-economic discrimination in screening campaigns.

Although melanoma is one of the most aggressive of all skin cancers, the screening cost per melanoma detected in our study is high, raising the question whether it can be cost-effective to focus only on melanoma. In this study the screening cost per melanoma detected varied between €4631 and €7449. NMSCs have a higher direct cost on the health care budget. Their early detection can help to reduce

this cost since the different treatment options, when applied to early stage disease, are less costly and more effective.[34]

To our knowledge, no studies evaluating anxiety in skin cancer screening have been published so far and this adverse effect is frequently used as an argument contra skin cancer screening. The literature suggests defining the high-anxiety state at 1 standard deviation above the normative mean, or a STAI >45.[35] This correlates to a cut-off in VAS of >2 with a sensitivity of 76,7% and specificity of 64.9%.[21] Our results show that the mean anxiety significantly drops after a negative screening in both groups with 1.2 points (P<0.01). In case of a positive screening anxiety did not increase significantly. It is possible that anxiety was induced by the personal invitations send out 5 weeks in advance, resulting in a return to baseline afterwards. A measurement before sending out the invitation would give a more accurate effect from the intervention. Anxiety pre-screening was 0.4 points higher in the LDS group (P<0.01). This effect is most probably due to the information about lesions alarming for skin cancer on the LDS invitation. The mean anxiety of 109 participants presenting with a specific lesion of concern in the TBE group was comparable to pre-screening LDS anxiety (mean 3.7, P=0.95). Overall, it is thus not only the specific message on the invitation, but also the invitee's reason for participation that influences their anxiety of having skin cancer.

CONCLUSIONS

In general this study reached a high skin cancer detection rate and PPV compared to other screening initiatives. There was also high male participation compared to other screenings. Community-based sensitization and personal invitation for screening, as well as a screening team with experienced dermatologists using dermoscopy could be important factors in establishing this.

TBE yielded a higher absolute number of skin cancers in the invited population, LDS has similar detection rate of 3.2% and is 5.6 times less time consuming. LDS by dermatologists can be an alternative screening method especially in health care systems with limited budget and/or waiting lists. However the effectiveness of this method by non-dermatologists warrants further study. It is important to increase participation rate in LDS and thus the absolute number of skin cancer detected, paying attention to any differences in educational level and skin cancer awareness. Only one skin cancer was found by total skin examination in the LDS group if the lesion of concern was not malignant. This suggests that a total skin examination would mainly be indicated in case the participant presents with a suspicious lesion.

REFERENCES

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. The British journal of dermatology 2012;166(5):1069-80.

2. de Vries E, van de Poll-Franse LV, Louwman WJ, et al. Predictions of skin cancer incidence in the Netherlands up to 2015. The British journal of dermatology 2005;152(3):481-8.

3. Flohil SC, de Vries E, Neumann HA, et al. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta dermato-venereologica 2011;91(1):24-30.

4. Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. Journal of the American Academy of Dermatology 2012;66(2):201-11.

5. Katalinic A, Waldmann A, Weinstock MA, et al. Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. Cancer 2012;118(21):5395-402.

6. Tinghog G, Carlsson P, Synnerstad I, et al. Societal cost of skin cancer in Sweden in 2005. Acta dermato-venereologica 2008;88(5):467-73.

7. Stang A, Stausberg J, Boedeker W, et al. Nationwide hospitalization costs of skin melanoma and non-melanoma skin cancer in Germany. Journal of the European Academy of Dermatology and Venereology : JEADV 2008;22(1):65-72.

8. Vallejo-Torres L, Morris S, Kinge JM, et al. Measuring current and future cost of skin cancer in England. Journal of public health 2014;36(1):140-8.

9. Bigby M. Why the evidence for skin cancer screening is insufficient: lessons from prostate cancer screening. Archives of dermatology 2010;146(3):322-4.

10. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation 2014.

11. Waldmann A, Nolte S, Weinstock MA, et al. Skin cancer screening participation and impact on melanoma incidence in Germany--an observational study on incidence trends in regions with and without population-based screening. British journal of cancer 2012;106(5):970-4.

12. Osborne JE. Skin cancer screening and surveillance. The British journal of dermatology 2002;146(5):745-54.

13. Girgis A, Clarke P, Burton RC, et al. Screening for melanoma by primary health care physicians: a cost-effectiveness analysis. Journal of medical screening 1996;3(1):47-53.

14. Losina E, Walensky RP, Geller A, et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Archives of dermatology 2007;143(1):21-8.

15. Kittler H, Pehamberger H, Wolff K, et al. Diagnostic accuracy of dermoscopy. The Lancet Oncology 2002;3(3):159-65.

16. Vestergaard ME, Macaskill P, Holt PE, et al. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. The British journal of dermatology 2008;159(3):669-76.

17. Peppercorn J, Zafar SY, Houck K, et al. Does comparative effectiveness research promote rationing of cancer care? The Lancet Oncology 2014;15(3):e132-8.

18. Korfage IJ, Essink-Bot ML, Westenberg SM, et al. How distressing is referral to colposcopy in cervical cancer screening?: a prospective quality of life study. Gynecologic oncology 2014;132(1):142-8.

19. Keyzer-Dekker CM, De Vries J, van Esch L, et al. Anxiety after an abnormal screening mammogram is a serious problem. Breast 2012;21(1):83-8.

20. Facco E, Zanette G, Favero L, et al. Toward the validation of visual analogue scale for anxiety. Anesthesia progress 2011;58(1):8-13.

21. Kindler CH, Harms C, Amsler F, et al. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. Anesthesia and analgesia 2000;90(3):706-12.

22. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Archives of dermatology 1988;124(6):869-71.

23. Garbe C, Buttner P, Weiss J, et al. Associated factors in the prevalence of more than 50 common melanocytic nevi, atypical melanocytic nevi, and actinic lentigines: multicenter case-control study

of the Central Malignant Melanoma Registry of the German Dermatological Society. The Journal of investigative dermatology 1994;102(5):700-5.

24. Garbe C, Buttner P, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. The Journal of investigative dermatology 1994;102(5):695-9.

25. Waldmann A, Nolte S, Geller AC, et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. Archives of dermatology 2012;148(8):903-10.

26. Bulliard JL, Maspoli M, Panizzon RG, et al. Evaluation of the Euromelanoma skin cancer screening campaign: the Swiss experience. Journal of the European Academy of Dermatology and Venereology : JEADV 2008;22(3):365-6.

27. Stratigos A, Nikolaou V, Kedicoglou S, et al. Melanoma/skin cancer screening in a Mediterranean country: results of the Euromelanoma Screening Day Campaign in Greece. Journal of the European Academy of Dermatology and Venereology : JEADV 2007;21(1):56-62.

28. van der Leest RJ, de Vries E, Bulliard JL, et al. The Euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010. Journal of the European Academy of Dermatology and Venereology : JEADV 2011;25(12):1455-65.

29. Argenziano G, Zalaudek I, Hofmann-Wellenhof R, et al. Total body skin examination for skin cancer screening in patients with focused symptoms. Journal of the American Academy of Dermatology 2012;66(2):212-9.

30. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple basal cell carcinomas. Archives of dermatology 2010;146(8):848-55.

31. Anders MP, Nolte S, Waldmann A, et al. The German SCREEN project - design and evaluation of the communication strategy. European journal of public health 2014.

32. Kristensson JH, Sander BB, von Euler-Chelpin M, et al. Predictors of non-participation in cervical screening in Denmark. Cancer epidemiology 2014;38(2):174-80.

33. von Euler-Chelpin M, Olsen AH, Njor S, et al. Does educational level determine screening participation? European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation 2008;17(3):273-8.

34. Rogers HW, Coldiron BM. A relative value unit-based cost comparison of treatment modalities for nonmelanoma skin cancer: effect of the loss of the Mohs multiple surgery reduction exemption. Journal of the American Academy of Dermatology 2009;61(1):96-103.

35. Millar K, Jelicic M, Bonke B, et al. Assessment of preoperative anxiety: comparison of measures in patients awaiting surgery for breast cancer. British journal of anaesthesia 1995;74(2):180-3.

Chapter 5

Cost-effectiveness of skin cancer screening

Submitted as journal article:

Pil L*, Hoorens I*, Vossaert K, Kruse V, Tromme I, Speybroeck N, Annemans L, Brochez L. Cost-effectiveness of population-based skin cancer screening (submitted to JAMA dermatology, 2016). *Both authors equally contributed.

ABSTRACT

Background: Several epidemiologic studies show an alarming global increase in incidence of melanoma and non-melanoma skin cancer. Consequently to this epidemic, the related health care costs are rising significantly. Two strategies (systematic total body examination (TBE) and lesion-directed screening (LDS)) were compared as to their participation rate, effectiveness, adverse effects and costs.

Methods: A Markov model with a latent period of 20 years and a time horizon of 50 years analysed their cost-effectiveness and budget impact in Belgium. In total 1982 persons were screened and 47 (2.4%) skin cancers were confirmed histologically (0.45% melanoma, 1.9% basal cell carcinoma, 0.05% squamous cell or Bowen). TBE yielded a higher absolute number of skin cancers, LDS had a similar detection rate but was 5.6 times less time consuming. The cost per quality-adjusted life-year of the two strategies, and the net costs for the health care payer over 50 years was measured.

Results: Both screening strategies produced a gain in QALYs, resulting in incremental cost-effectiveness ratios of €33 072/QALY in males and €18 687/QALY in females for TBE and €34 836/QALY in males and €19 470/QALY in females for LDS. The budget impact analysis demonstrated that over a period of 20 years a one-time screening would induce an extra cost for the health care payer of €36 million in case of TBE or €6 million in case of LDS, respectively €4.1 or €0.7 per adult.

Conclusion: These results can be interpreted as cost-effective at a willingness-to-pay threshold in Belgium of €35 000/QALY. Based on these results a TBE in general adult population (especially in the females, in males the results were less explicit) is the most cost-effective strategy and is predicted to result in a reduction of mortality over 20 years.

INTRODUCTION

Although the worldwide incidence, prevalence, and economic burden of skin cancer is substantial[1-7] and despite the idea that early detection can lead to better cure rates and reduce the costs of disease, few clinical studies have assessed the cost-effectiveness of secondary prevention strategies.[8] Investing in population-based prevention programs is challenging for policy makers, since the budget is challenged by many other major health challenges. Screening is a prevention strategy by which early detection changes the prognosis by a shift in stage distribution to earlier stages. However, few studies have analysed the cost-effectiveness of skin cancer screening up to now. Currently available studies mainly addressed melanoma skin cancer (MM)[8-12], while non-melanoma skin cancer (NMSC) is also responsible for a large part of the direct medical health care costs of skin cancer[5], In addition, some of these early detection campaigns specifically focused on high-risk groups[13], but it is known that most skin cancers develop outside these groups. Moreover, most published cost-effectiveness models on skin cancer screening predict mortality reduction, while this had not yet been proved in observational studies. At this point, no evidence exists that population-based screening by means of whole body examination in asymptomatic persons is cost-effective.[14] In this study we compared the cost-effectiveness of two population-based screening strategies organized as a pilot study in Belgium: a standard total body examination (TBE) versus a lesion-directed approach (LDS).[15] The LDS approach, in which screenees are seen with only a specific lesion of concern meeting certain pre-set criteria, was shown to result in lower participation rates but similar skin cancer detection rates. In reference to TBE, LDS was time-saving for the physician. As most of the cost-effectiveness studies of skin cancer screening up to now do not provide information on the financial impact of a skin cancer screening intervention on the health care budget[8], we also performed a budget impact analysis.

METHODS

A decision-analytic Markov model was developed, examining the economic impact of a single TBE and a single LDS compared to the current situation (i.e. no screening program). Health effects and costs of a cohort of adult males and females were simulated from a societal perspective, over a time horizon of 20 years, with six-monthly cycles. Main outcomes included the incremental cost-effectiveness ratio (calculated as the net costs divided by the net health effects), the budget impact and the estimated mortality reduction. In order to calculate the budget impact, the model allowed new entrance of 18-year olds each cycle in the lesion-free state, who were subjected to the natural progression of skin cancer. The budget impact analysis estimated the net cumulative cost of the screening program (and consequent examinations, treatment and follow-up) for the health care payer (i.e. government) over a

period of 20 years. Ethics committee approval for this study and patient informed consents were obtained for the clinical screening trial.

Screening strategies

The modelled screening strategies were based on a skin cancer screening trial which has been organised in Belgium in 2014, comparing TBE to LDS in two socio-demographically comparable regions.[15] The TBE was organized in a community of 9325 inhabitants during a 5-day screening (March 14-18, 2014). All inhabitants 18 years and older received a personal invitation. The LDS was organized in a comparable community (April 22 and 25-27, 2014), of which the inhabitants were invited for a free-of-charge skin cancer check of a specific lesion meeting one or more of the following listed criteria: ABCD rule (A, asymmetry; B, borders; C, colours; and D, differential structures), ugly duckling sign, new lesion lasting longer than 4 weeks, or red non-healing lesions. All participants (1668 TBE and 248 LDS) were screened by a team of six dermatologists. As expected, the participation rate was higher in the TBE region compared to the LDS region (17.9% versus 3.3%, P = < 0.01). Skin cancer yield did not differ significantly between both groups (2.3% TBE versus 3.2% LDS, P = 0.40). Further details on the design of this trial can be found in Hoorens et al.[15] In the health economic model all Belgian adult males and females, except those who have had skin cancer before, were assumed to be invited for the single screening program. Modelled clinical outcomes of the screening were pathologically confirmed skin cancer, a (false) positive result or a (false) negative result. It was assumed that persons with an undiagnosed lesion who chose not to participate in the screening program or persons with a false negative result could have their lesion diagnosed by spontaneous clinical detection in the same cycle. Spontaneous clinical detection was also possible in the comparator (i.e. current situation).

Model structure

The Markov model was developed in Microsoft Excel® 2013 and incorporated MM as well as BCC and SCC. It consisted of different disease states: undiagnosed skin cancer, diagnosis & treatment, follow-up and death (Appendix II), separated per skin cancer stage. The duration of the diagnosis & treatment phase was 6 months (= 1 cycle) for patients with BCC, SCC 0-II or MM I-II and 1 year for patients with SSC III-IV or MM III-IV. To assign a higher probability of skin cancer death in the first years after diagnosis in case of SCC IV and MM IV, the follow-up phase was divided into intense- and long-term follow-up, which lasted for 4 years, after which one moved into long-term follow-up. Patients in follow-up remained in this state until the end of the model's time horizon, or until they died. MM and SCC stages were determined according to the 7th edition of the Tumor-Nodes-Metastases-classification for malignant tumours.[16] Stages for BCC were defined as <1cm, 1-2cm, >2cm and aggressive histology. BCC and SCC patients were assigned higher risk to develop an MM lesion. Risk of

a recurrent or subsequent similar lesion (for all cancer types) was only accounted for in the costs, since the effect of a subsequent lesion on the quality of life has not yet been described in current literature. All cohort members started the model in one of the model states, according to the baseline prevalence of BCC, SCC and MM.[17;18] More information on the age- and gender-specific transitions, the epidemiological, economical and clinical data inputs and sensitivity- and scenario analyses can be found in appendix II.

RESULTS

Impact on skin cancer epidemiology

Over a period of 20 years, the model estimated the one-time screening to result in a 4% decrease in the incidence rates of stage III&IV MM at population level. Moreover, both single screening programs were estimated to have a positive, although modest, impact on mortality from skin cancer, with an absolute reduction of 628 deaths in case of TBE (273 in males and 355 in females) and 118 in case of LDS (57 in males and 61 in females). This corresponds to a relative mortality reduction of about 5.6% in case of TBE and 1% in case of LDS (in reference to mortality if the one-time screening would not take place).

Cost-effectiveness

Base case

Both screening strategies resulted in a gain in QALYs over a period of 20 years (Table 1). Health effects and costs are in good balance, leading to incremental cost-effectiveness ratios of €33 072/QALY in males and €18 687/QALY in females for TBE and €34 836/QALY in males and €19 470/QALY in females for LDS which can be interpreted as a moderate cost-effective result regarding a willingness-to-pay threshold in Belgium of €35 000.[19;20] The budget impact analysis presented in table 2, showed that over a period of 20 years a one-time screening would induce an extra cost for the health care payer of €36 million in case of TBE or €6 million in case of LDS, respectively €4.1 or €0.7 per adult.

Table 1. Results of the cost-effectiveness analysis, over a period of 20 years, per 1 000 persons

	Incremental QALYs (95% CI)		Incremental Costs (95% CI)		ICER	
	males	females	males	females	males	females
TBE	0.20 (0.16-0.25)	0.34 (0.30-0.39)	€ 6 465 (5521-7517)	€ 6 383 (5143-7450)	€ 33 072	€ 18 687
LDS	0.04 (0.03-0.05)	0.05 (0.04-0.06)	€ 1 391 (1101-1502)	€ 977 (750-1117)	€ 34 836	€ 19 470

TBE: total body examination; LDS: lesion-directed screening; QALY: Quality adjusted life year; ICER: incremental cost-effectiveness ratio.

Table 2. Results of the budget impact analysis, over a period of 20 years

	Cost of intervention	Health care payer	Total cost	Total extra cost
Control	€ 0	€ 1 909 776 064	€ 1 909 776 064	
TBE	€ 7 308 319	€ 1 938 193 177	€ 1 945 501 496	€ 35 725 432
LDS	€ 463 275	€ 1 915 431 360	€ 1 915 894 635	€ 6 118 570

TBE: total body examination; LDS: lesion-directed screening.

Scenario- and sensitivity analysis

Results from the scenario-analysis are displayed in Table 3. A one-time screening from the age of 18 remained the most cost-effective strategy. Screening every two or five years had a lower cost-effectiveness ratio, but since the time horizon was set at 50 years for this scenario -as 20-year time horizon would not capture the effect of screening in e.g. year 18 - it should be compared to the scenario of a one-time screening with a time horizon of 50 years. To evaluate the effect of possible overdiagnosis, a worst-case scenario analysis with the hypothetical presumption that 25% of all melanomas detected and treated during the screening would not have progressed, was performed on the base case scenario. The one-way sensitivity analysis showed the most influencing parameters to be the natural progression of MM, the utility related to MM, the direct cost of follow-up of BCC, the indirect as well as direct cost of MM III and IV, the direct follow-up cost of MM I-II, the discount ratio, the prevalence of BCC and the sensitivity of dermoscopy for MM, (Figure 1, tornado diagram shown for TBE). A higher value on these parameters led to a more cost-effective result, except for the cost of BCC (long-term follow-up), the discount ratio and the direct follow-up cost of MM I-II in which the effect was the opposite. In case of a worse value on the parameter (bars on the right side of the figure), ratios were higher than the €35 000 threshold, leading to a worse result. The cost of screening (TBE) in males remains cost-effective up to an increase of the screening cost of 50%, whereas

screening (TBE) in females remains cost-effective up to a screening cost of 7 times higher. The probabilistic sensitivity analysis created credibility intervals around the deterministic result, which are depicted in Figure 2. The cost-effectiveness planes show that most simulations are located in the north-east quadrant and are below the willingness-to-pay threshold of €35 000/QALY, although for the simulation in males part of the values are situated above the threshold. The cost-effectiveness acceptability curves in appendix II show that regarding willingness-to-pay threshold of €35 000/QALY, the probability of screening being cost-effective is 79.7% and 59.9% for TBE and LDS in males and 100% and 99.9% in females.

Table 3. Results of the scenario analysis

	TBE (cost/QALY)		LDS (cost/QALY)	
	males	females	males	females
ICER base case	€ 33 072	€ 18 687	€ 34 836	€ 19 470
Screening from 40 years	€ 35 622	€ 21 841	€ 36 348	€ 23 485
Time horizon 50 years	€ 9 253	€ 5 722	€ 10 262	€ 5 549
Screening every 5 years*	€ 11 811	€ 6 060	€ 12 758	€ 5 671
Screening every 2 years*	€ 12 180	€ 6 021	€ 12 404	€ 5 436
Base case overdiagnosis	€ 58 388	€ 29 897	€ 59 948	€ 32 561
ICER probabilistic	€ 31 360	€ 18 051	€ 34 170	€ 18 999
(95% CI)	(€ 23 251 – € 41 468)	(€ 13 493-€ 23 019)	(€ 25 586-€ 44 831)	(€ 13 725-€ 25 139)

TBE: total body examination; LDS: lesion-directed screening; QALY: Quality adjusted life year; ICER: incremental cost-effectiveness ratio* during 20 years, but with a time-horizon of 50 years; CI: confidence interval.

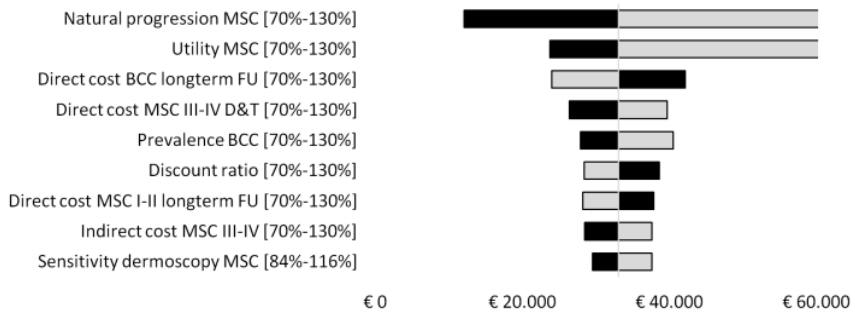

Figure 1a. Tornado diagrams with results of the one-way sensitivity analysis (for TBE in males); MSC: melanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; D&T: Diagnosis and treatment; FU: follow-up; Light grey bars: minimum value of parameter; Dark grey bars: maximum value of parameter.

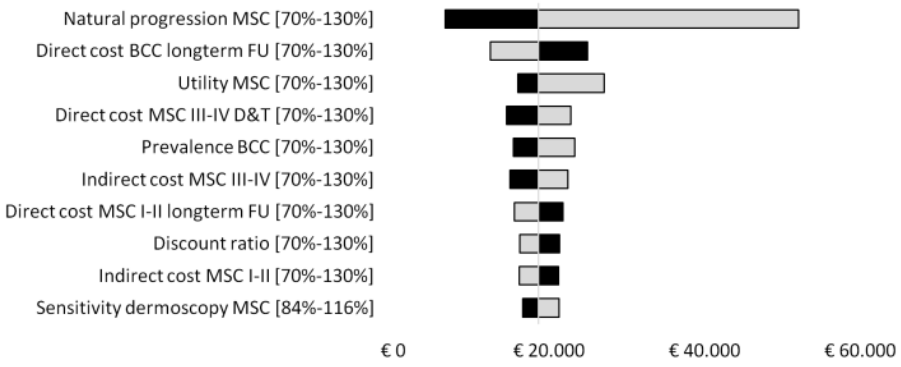

Figure 1b. Tornado diagrams with results of the one-way sensitivity analysis (for TBE in females); MSC: melanoma skin cancer; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; D&T: Diagnosis and treatment; FU: follow-up; Light grey bars: minimum value of parameter; Dark grey bars: maximum value of parameter.

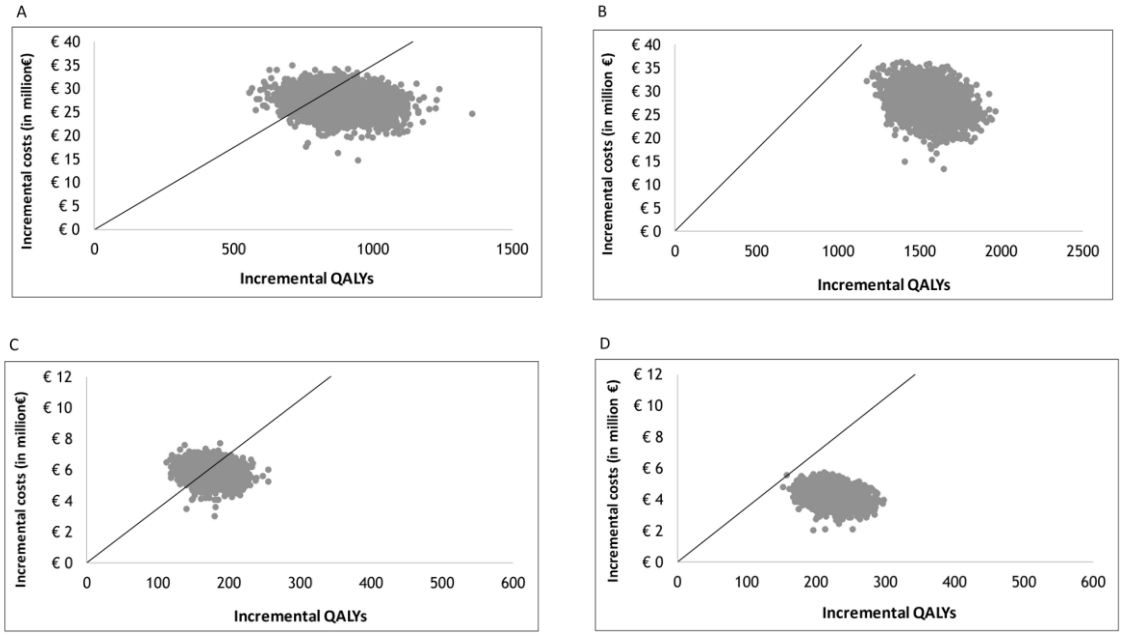

Figure 2. Cost-effectiveness planes displaying the 5 000 simulations. Each point depicted in represents the value of one simulation performed from the distribution around each of the key variables in the model. Willingness-to-pay threshold of €35,000/QALY is displayed in the graphs. Figure 2A: Total body examination in males; Figure 2B: Total body examination in females; Figure 2C: Lesion-directed screening in males; Figure 2D: Lesion-directed screening in females.

DISCUSSION

Given the health impact and economic burden of MM and NMSC[21], developing and implementing cost-effective strategies for its early diagnosis and treatment is crucial. Over a period of 20 years, a one-time TBE leads to a gain of 2,380 healthy life-years in the total population (8.8 million) and LDS gains 397 healthy life-years. In addition, TBE was projected to reduce skin cancer mortality by 5% over 20 years. However, currently no prospective studies support a reduction in skin cancer mortality due to screening. According to Boniol et al., the transient decrease in mortality in Schleswig-Holstein followed by return to pre-screening levels could reflect a temporal modification in the reporting of death causes.[22,23] In addition, no decrease in MM mortality has been documented since the nation-wide skin cancer screening was introduced in Germany in 2013.[24] Due to the screening cost, and the extra costs for treatment and follow-up, implementing a one-time screening costs extra money for the health care payer. Nevertheless, the balance between costs and health effects is shown to be beneficial, both for TBE and LDS (ratio below the accepted threshold of €35 000), although in the case of males both screening strategies tend to this threshold limit. However, most simulations in the probabilistic sensitivity analysis for males were below the threshold (80% TBE and 60% LDS). The incremental cost-effectiveness ratio for TBE was better than for LDS, and LDS did not seem to have a high impact on increasing healthy life years and reducing deaths, which can be explained by the low participation rate in the LDS screening arm. Since the skin cancer detection rates were comparable in both screening arms and since LDS screening was time-saving, it could be worthwhile to investigate how participation in this type of screening could be increased. If the same participation rates of TBE would be attained in LDS, then LDS would be more cost-effective than TBE. Screening in females was clearly more cost-effective than in males, because of the higher prevalence and incidence of skin cancer in females in Belgium. Screening from the age of 40 instead of 18 only slightly deteriorated the cost-effectiveness result, probably because younger persons have a higher quality of life, which means that screening could gain more health benefits in younger persons, and because older persons have a higher risk to die from other causes than skin cancer, which disadvantages the beneficial effect of screening. Suppose the time horizon of the model would be extended to 50 years, then the cost-effectiveness ratio would be better than with a 20-year time horizon, because the effect of the screening is estimated to still continue for an extra 30 years. The choice to implement the screening program repeatedly would be cost-effective, but a one-time screening would still be the most cost-effective strategy.

The model found that the ICER is just below the Belgian willingness-to-pay threshold. However, the PSA suggests that, given the parameter uncertainty modeled, the ICER is likely to be between € 23 251 - € 41 468 per QALY gained for TBE in males. In addition, the one-way sensitivity analyses demonstrate

that natural progression is the most detrimental parameter in the overall uncertainty around the outcome. When a variation is applied of 30% the ICER exceeds € 60 000 per QALY gained. And since, the transitions and melanoma pathway are methodological assumptions, we need to underline the need for long term observational data to accurately evaluate these health and economic effects. Other important influencing parameters were the cost of MM III and IV (for diagnosis and treatment), and the sensitivity of the dermoscopy for MM. It is possible that the cost for treating MM III and IV will keep on rising due to new (combinations of) drugs and other technologies, which would result in screening becoming more cost-effective. Furthermore, since a better sensitivity of dermoscopy leads to a better cost-effectiveness result, training initiatives for dermoscopy are strongly recommended. Incidence of MM did not affect the result to a great extent, which shows that even in case of good primary prevention programs for skin cancer, screening would still be cost-effective. Other studies on the cost-effectiveness of skin cancer screening have been conducted especially in the U.S. and Australia and only included MM. Most of these studies expressed the cost-effectiveness of MM screening to no screening in cost per life-year saved. These studies showed that screening men over 50 years biennially by general practitioners resulted in an ratio of $12 137/life-year saved (AUD).[9] A one-time screening by dermatologists in a self-selected population resulted in $51 481/life-year saved (USD)[25] and in a high-risk population in $39.600/life-year saved (USD).[11] One study calculated the cost per QALY of a visual one-time screening from the age of 50 to be $10 100/QALY (USD) (~ €9 256/QALY).[10] When implemented biennially the ratio rose to $80 700/QALY (~ €73 882/QALY) and if annually to $586 800/QALY (~ €537 220/QALY). Our results supports this latter result of better cost-effectiveness in case of one-time screening. However, it is difficult to compare studies because of different screening setting (visual screening versus dermoscopy screening, composition of the screening team), different epidemiological backgrounds (cf. incidence of MM higher in United States and in Australia than in Belgium) and different model design.

The major strength of this study is that it is based on a large population-based screening trial. This is the first time that the costs and benefits of a skin cancer screening program have been analyzed in detail. Not only the benefits of screening were captured in the model, but the impact of a false-positive screening result on quality of life in terms of psychological harms was included as well. However, in our model, the screening examination itself did not have an impact on the quality-of-life. The study of Collins et al.[26] showed that screening (in general) does not appear to have an adverse emotional impact in the longer term and they stated that up to now too few studies have assessed the short-term emotional impact of screening. The study of Hoorens et al. [27] questioned the anxiety of the screenees right after the screening, but baseline levels were not available so no conclusions on the quality-of-life right before and after the screening could be deducted from this study.

Some limitations of our analysis should be addressed. Firstly, in Belgium there is no accurate registration of NMSC. Therefore, we relied on epidemiologic results of the Dutch cancer registry, since they have a more systematic registration of NMSC. Secondly, accurate information on the natural progression of skin cancer is not available. Therefore, in our model, the natural progression was estimated based on calibration. This is generally a more reliable approach than making assumptions on parameters based on limited studies. In addition, the transition probabilities were assumed to be equal for all ages and gender, although for MM these are known to be gender and age-specific. Traditionally, a 95% CI is recommended to capture the uncertainty. Since the current study used several deducted estimations and calculations the 95% CI was not known; and for several input parameters a 30% interval was applied which is determined by convention. Lastly, it may be noted that screening parameters such as participation rate, diagnostic performance of the screening team as well as unit costs of detection, treatment and follow-up are context-specific limiting the generalization and transferability of the results across different countries. However, we believe that our results can inform policymakers worldwide about the potential efficiency of skin cancer screening.

CONCLUSIONS

In terms of policy implications skin cancer screening proved to be cost-effective at a willingness-to-pay threshold of €35 000/QALY. Based on these results a total-body examination in the general adult population (especially in the females, in males the results were less explicit) is the most cost-effective strategy and projected to result in a significant reduction of mortality over 20 years. The study indicates an important opportunity to collect observational data in support of the mortality reduction.

REFERENCES

1. Flohil SC, de VE, Neumann HA, Coebergh JW, Nijsten T. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol 2011;91:24-30.

2. Flohil SC, Seubring I, van Rossum MM, Coebergh JW, de VE, Nijsten T. Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. J Invest Dermatol 2013;133:913-918.

3. Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. Br J Dermatol 2014;170:11-19.

4. Connolly SM, Baker DR, Coldiron BM et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. J Am Acad Dermatol 2012;67:531-550.

5. Stang A, Stausberg J, Boedeker W, Kerek-Bodden H, Jockel KH. Nationwide hospitalization costs of skin melanoma and non-melanoma skin cancer in Germany. J Eur Acad Dermatol Venereol 2008;22:65-72.

6. Tinghog G, Carlsson P, Synnerstad I, Rosdahl I. Societal cost of skin cancer in Sweden in 2005. Acta Derm Venereol 2008;88:467-473.

7. Brochez L, Myny K, Bleyen L, De BG, Naeyaert JM. The melanoma burden in Belgium; premature morbidity and mortality make melanoma a considerable health problem. Melanoma Res 1999;9:614-618.

8. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. Eur J Cancer Prev 2015;24:141-149.

9. Girgis A, Clarke P, Burton RC, Sanson-Fisher RW. Screening for melanoma by primary health care physicians: a cost-effectiveness analysis. J Med Screen 1996;3:47-53.

10. Losina E, Walensky RP, Geller A et al. Visual screening for malignant melanoma: a cost-effectiveness analysis. Arch Dermatol 2007;143:21-28.

11. Freedberg KA, Geller AC, Miller DR, Lew RA, Koh HK. Screening for malignant melanoma: A cost-effectiveness analysis. J Am Acad Dermatol 1999;41:738-745.

12. Beddingfield FC. A Decision analysis to estimate the effectiveness and cost-effectiveness of screening and an analysis of the relevant epidemiology of the disease 2002.

13. Okafor PN, Stallwood CG, Nguyen L et al. Cost-effectiveness of nonmelanoma skin cancer screening in Crohn's disease patients. Inflamm Bowel Dis 2013;19:2787-2795.

14. Bigby M. Why the evidence for skin cancer screening is insufficient: lessons from prostate cancer screening. Arch Dermatol 2010;146:322-324.

15. Hoorens I, Vossaert K, Pil L et al. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol 2015.

16. L.H.Sobin, M.K.Gospodarowicz, Ch.Wittekind. TNM Classification of Malignant Tumours, 7th edition. 2009. UICC.

17. Belgian Cancer Registry. Incidence Melanoma in Belgium, 2013.

18. Integraal Kankercentrum Nederland. Incidence of basal and squamous cell carcinoma, 2011.

19. Williams A. What could be nicer than NICE?. Office for Health Economics , 2004.

20. World Health Organization. Threshold values for intervention cost-effectiveness by Region. http://www.who.int/choice/costs/CER_levels/en/. Accessed April 7, 2016.

21. Pil L, Hoorens I, Vossaert K et al. Economic burden of skin cancer in Belgium and cost-effectiveness of primary prevention by reducing ultraviolet exposure. 2016. [in submission]

22. Boniol M, Autier P, Gandini S. Melanoma mortality following skin cancer screening in Germany. BMJ Open 2015;5:e008158.

23. Katalinic A, Waldmann A, Weinstock MA et al. Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. Cancer 2012;118:5395-5402.

24. Katalinic A, Eisemann N, Waldmann A. Skin Cancer Screening in Germany. Documenting Melanoma Incidence and Mortality From 2008 to 2013. Dtsch Arztebl Int 2015;112:629-634.

25. Beddingfield FC. A decision analysis to estimate the effectiveness and cost-effectiveness of screening and an anaysis of the relevant epidemiology of the disease 2002.

26. Collins RE, Lopez LM, Marteau TM. Emotional impact of screening: a systematic review and meta-analysis. BMC Public Health 2011;11:603.

27. Hoorens I, Vossaert K, Pil L et al. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol 2015.

Chapter 6

Screening for basal cell carcinoma

Published as journal article:

Hoorens I, Vossaert K, Ongenae K, Brochez L. Is early detection of basal cell carcinoma worthwhile? Systematic review based on the WHO criteria for screening. Br J Dermatol. 2016; 74(6):1258-65.

ABSTRACT

Background: The incidence of BCC has been rising 3- to 4-fold, and is expected to increase with aging of the population. Although BCC has a good prognosis, it causes significant morbidity for the patient and has an important impact on the public health budget due to direct costs related to the treatment.

Methods: Based on the existing data we systematically checked the WHO criteria on screening whether earlier detection of BCC could reduce morbidity and cost of disease.

Results: BCC slowly increases in size with time with a median increase in diameter of 0.5 mm over 10 weeks. There seem to be important delays in diagnosis with a mean time from appearance of the skin lesion to seeking medical attention ranging from 19.79 to 25 months. In several studies size of BCC is an important determinant for cost of treatment, surgical complexity influencing defect size, reconstruction technique and the exact surgical procedure followed such as MMS for BCC located in the face and more specifically around peri-orificial areas (H-zone). One study estimated that size also seems to affect the cost per treatment for other non-surgical options. The use of vismodegib, an inhibitor of the hedgehog pathway, is confined to unresectable or metastatic BCC. Delay in diagnosis and appropriate treatment are the most important underlying causes in the occurrence of giant BCC and/or BCC with metastasis. Although the latter represent only a very small fraction of all BCCs, the majority of them is located in the face region.

Conclusions: The available data point to a slow increase in size of BCC over time. This size is one of the major determinants in the choice of an effective treatment and the associated cost especially for facial BCC. Therefore current data supports early detection and adequate management of BCCs mainly located on the face.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in humans and represents 80% of all NMSC. The incidence rates increased from 40 to 165/100.000 for males and from 34 to 157/100.000 for females in the last 30 years in the Netherlands.[1] This approximately fourfold increase is similar in other European countries. [2] The lifetime risk of developing BCC is currently 1 in 5. The overall prevalence is 5.4% for people older than 65 years, compared to 1.3% in patients aged 35-64 years and 0.06% in patients younger than 34 years.[1] Although BCC is typically a disease of the elderly, the highest relative increase in incidence rates of BCC were found in woman below the age of 40 years.[1 3 4]

The main risk factor for BCC development is UV-radiation, however the risk ratio observed in epidemiological studies is relative low (2 for 8000-10 000 cumulated hours in a lifetime, 1.8 for 3-10 sunburns in a lifetime and 1.5 for 11+ sunburns in a lifetime)[5-8] Evidence for the primary prevention of BCC by regular use of sunscreens is missing,[9] in contrast to the effect in preventing melanoma, actinic keratoses and squamous cell carcinoma (SCC).[10-15] Interventions reducing ultraviolet exposure are assumed to only result in small changes in BCC incidence.[16] Chemoprevention with topical tretinoin 0.1 % has not been successful for BCC, systemic retinoids and nicotinamide have only been examined in high-risk patients.[17-22] Primary BCC is associated with an important delay in diagnosis ranging from 19 to 25 months.[23-26] Factors attributing to this late presentation are the patients age, denial and the important fact that BCC in early disease stage has little to no impact on the quality of life.[23 25 26] In addition, the initial rather benign appearance of BCC to the patient can lead to treatment delay.[27] Information delivered to the population to promote cancer awareness and early presentation in routine health care does not seem to affect the delay.[28]

The World Health Organization (WHO) criteria defined a health care problem amenable for screening if the disease is an important health care problem, its natural history of the disease is known and there is a safe, simple and inexpensive screening test that is acceptable to the population. In addition there should be a treatment for early disease that is more effective than treatment for later disease and the facilities for diagnosis and treatment should be available.[29] Table 1 summarizes the more extensive WHO principles, these have only partially been reviewed for BCC. The main objective is to discuss the current evidence in which early detection and treatment of BCC could reduce the important morbidity and costs by means of the WHO principles, and to address critical areas where knowledge is still insufficient.

Table 1. WHO criteria for screening

The ten WHO criteria for screening:
1. The disease should be an important health problem
2. A generally acceptable method of treatment must be available
3. The policy for treatment must be clear
4. Provision for diagnosis and treatment must be available
5. The disease must have a detectable latent stage
6. A suitable screening method must be available
7. The screening method must be accepted by the target population
8. The natural course of the disease must be known
9. The program is cost-effective
10. The treatment of early disease should favour the prognosis of the patients

METHODS

All applicable studies on the topic of the natural history of BCC, treatment, cost of treatment, cost-effectiveness and cost-of illness have been included in this review. Studies were recovered from PUBMED, Cochrane and Medline database. The following (Medical Subject Headings (MeSH)) term combinations were used: skin cancer, non-melanoma skin cancer, basal cell carcinoma, growth, natural course, treatment, treatment cost, cost-of illness, societal cost, burden of illness, cost-effectiveness. All English language abstracts were evaluated for inclusion in the review. A manual search of the bibliographies of retrieved articles was performed to ensure a comprehensive review. The study design, setting, intervention, data collection and patient population were evaluated.

RESULTS

BCC is an important health problem

BCC is by far the most common cancer in Caucasians, and the incidence rates are rising worldwide.[1 2] The impact of BCC diagnosis, treatment and follow-up on the health care system and budget is becoming an increasingly important. Several factors influence this epidemic rise namely the aging of the population, altered sun seeking behavior and efforts to increase registration in cancer registries.. Furthermore, in contrary to other cancer types, BCC is known for its high risk of multiple primary lesions. The relative risk of developing a second BCC with a positive history is 17.4, and 40% of patients will develop a second BCC in the following 5 years.[30 31] The large majority of the lesions are located in the head and neck area.[1] Because of the high visibility of this region, as well as its anatomic complexity as to innervation, vasculature and delicate anatomic structures such as the lacrimal system, the orbit

and its direct connection to the brain, BCCs in this area may cause important functional and esthetical morbidity.

Mortality of BCC is low (less than 0.1%) but morbidity causes a great burden for health care systems in Europe.[32-35] The main cost drivers for NMSC are the direct treatment costs, in contrast to melanoma where an important indirect cost is related to sick leave and premature mortality.[36] The total costs for NMSC are estimated to be twice the cost for melanoma in Germany.[37] In addition to the costs, this growing group of BCC patients will represent an important burden on the limited specialized dermatological care in most European countries in terms of number of patients needing treatment and follow-up.

The natural course of BCC must be known

Ultraviolet induced p53 mutation is an acquired genetic change and has a key role in tumor initiation in 30 -70% of all BCC.[38 39] Mutations in the patched gene and smoothened genes are a cause of hereditary predisposition in patients with nevoid BCC syndrome and sporadic BCCs.[38 40-42]

Growth rate

BCCs are normally characterized by slow clinical growth as opposed to a fast cell cycle of 217 hours, which is comparable to normal epidermal cells.[43] This discrepancy is explained by the fact that (1) only the external layer of BCC mass is actively proliferating (small growth fraction), and there is predominant cell death in BCC tumors (high rate of cell death). (2) Tumor regression may occur in response to host immune factors.[44-47]

Few studies examined the effect of treatment delay on the natural evolution and size of BCC. Two small prospective studies show a median change in largest diameter of 0.5 mm over 10 weeks in facial BCCs and 0.7 mm over 8.7 weeks for head and neck tumors.[48 49] Although it is generally stated that BCCs grow slowly, clinically some tumors have surprisingly fast growth. One study examining 115 peri-orbital BCCs shows a mean growth of 0.75 mm per 4.2 weeks after shave or punch biopsy. In tumors that increased in size after biopsy a worrisome 1.46 mm increase in size was seen after one month. Factors positively associated with a growth rate were large initial size, male sex and recurrent tumors.[50]

Several retrospective studies support these results. Delay of one year between initial diagnosis and surgical removal by MMS was associated with twice the size of a surgical defect.[51] The largest retrospective study evaluating the size of 889 BCCs in relation to time confirms an increase in largest diameter of 10% at 2-8 months, and 21% at 8-12 months. Independent factors found to be related to

BCC size or delay were male sex, having no physician checks, initial misdiagnosis, morpheaform or micronodular tumor histology, ulceration and scar tissue around the lesion.[51 52]

A recent review on giant tumors (BCC of more than 5 cm that represent 2.27% of all BCC), showed that time between the first appearance of the lesion to diagnosis of giant BCC is directly correlated with tumor dimension.[53] Most of these giant BCCs were located in the head and neck region (68.2%).

Histology and aggressiveness

BCCs may be categorized in several histological subtypes, and this is an important element in treatment options. Up to 66 BCC subtypes are described in the scientific literature. A recent study suggested a simplified classification to aid clinical decision-making in superficial, fibro-epithelial, nodular and infiltrative subtypes.[54] Superficial BCC (sBCC) is considered to be the least aggressive subtype since they do not tend to invade deeply in the dermis. Although, when large and located in the facial area, treatment can be challenging and recurrences occur.[55-57] Aggressiveness is mainly related to the risk of recurrence, being highest for the aggressive growth variants (e.g. 26.5% in infiltrative BCCs) and lowest in the indolent growth variants (e.g. 6.4% and 3.6% for nodular and superficial BCC, respectively).[56] Nodular BCC, also known as solid BCC is the most common histologic pattern. Some rare variants such as basosquamous, keratotic, infundibulo-cystic and adenoid BCC are also described.[58] In addition, 17.8% of BCC consist of a mixed histology, most often a combination of superficial and nodular histology.[59]

A recent study hypothesized that BCC represents a histologic continuum and progresses in a multistep model from superficial to nodular to infiltrative.[60] This hypothesis was based on the finding of specific epithelial, stromal and inflammatory patterns that correlate with individual tumor progression. Decreasing host response and gain of permissive tissue environment was seen when infiltrative BCCs compared to superficial BCC. This finding is supported by the increased incidence of BCC at young age only for the superficial subtype, and by the observed median age according to the histological subtype of 65 years for sBCC, 68 years for nBCC and 71 years for infiltrative BCC (iBCC).[4]

Metastasis

Metastatic BCC is extremely rare, with an estimated incidence of 0.0028% to 0.55% based on published cases from 1894-1980.[61] A recent update of the literature reported 194 cases during the period of 1981 through 2011.[62] The majority (64%) of these metastatic BCCs were located in the head and neck area. To date no clear evidence exists for increased rates of metastasis in certain histologic subtypes.[63 64] Currently size and delay in appropriate treatment seem to be the only independent risk factors for metastasis, with a median interval between onset of tumor to metastasis of 9 years.[61 62]

Furthermore risk of metastasis is estimated to be 1–2% in lesions > 3cm, 20–25% in lesions greater than 5 cm, increasing up to 50% in lesions greater than 10 cm in diameter.[65]

BCC has a detectable latent stage

BCCs grow slowly with an estimated growth rate of 0.5 mm over 10 weeks in facial BCCs and 0.7 mm over 8.7 weeks for head and neck tumors as discussed earlier.[48 49] In case of a linear growth pattern this would mean that a BCC would take 2.4-3.8 years to reach a size of 10 mm. Metastatic disease is rare, and several years precede the metastatic or giant stage.

A suitable screening method is available and the method is accepted by the target population

Naked-eye inspection and dermoscopy are safe, simple, non-invasive and inexpensive tests.[66 67] Dermoscopy has been a well established tool for diagnosis of BCC, regardless of its size.[68-70] Dermoscopy increases the diagnostic accuracy for BCC diagnosis from 58 to 84% over naked-eye examination.[71] Currently, sensitivity ranges from 95%-97% and specificity 87%-96% for expert observers.[68] Dermoscopy thus not only improves the diagnostic accuracy, but also reduces the number of unnecessary referrals, excisions or biopsies, an important side effect of screening.

There is an acceptable method of treatment available for BCC, the policy for treatment is clear and the treatment of early disease favours the prognosis of the patients

The major objective of screening is to reduce morbidity and mortality by detecting disease and implementing an effective treatment earlier in order to favor the outcome. Without this objective the early detection of BCC would be meaningless.

Treatment options for BCC are evaluated in a large number of studies, and a Cochrane review was published in 2007.[72] The British guidelines of 2008, defining the treatment of choice according to different factors are still applicable today.[73] Tumor size (>20 mm versus <20 mm) is the most important determinant to select treatment. Others include: primary or recurrent BCC, histologic subtype, and the tumor location (low-risk or high-risk for recurrence). Lesions located on the central face, especially around the eyes, nose, lips and ears, are at higher risk of recurrence.

Surgery is still considered first line treatment and is by far the most frequent treatment option in different European countries.[35 74-76] Standard excision (SE) is an effective treatment for all primary BCC with a 5-year recurrence rate of 2-10%.[77-82] The best safety margins in terms of relative recurrence range from 3 to 5 mm.[83] A 5 mm margin is advised in larger BCCs (> 10 mm), recurrent BCC or infiltrative BCC.

Mohs micrographic surgery (MMS) has the highest 5-year cure rate for primary BCC in the range from 94 to 99%,[84-89] but is an expensive technique.[90] The absolute direct cost for treatment of one BCC in an outpatient setting with direct closure for SE versus MMS is estimated to be 1:3.[91] Although MMS has proven to be cost-effective in high-risk tumors, in which the additional benefits of MMS outweigh its higher cost, earlier detection and adequate treatment of primary BCC might result in even more cost-effective surgery.[90] Flohil et al. concluded that size of the BCC larger than 20 mm and recurrent lesions were the strongest predictor for one versus multiple stages in facial lesions.[92] MMS for primary BCC in the non-facial area is only appropriate for nodular lesions larger than 20 mm and aggressive lesions based on their histology of 6 mm in size or more.[93] Non-surgical treatments including 5-fluorouracil, imiquimod and photodynamic therapy (PDT) can be indicated for low-risk superficial BCC. Topical 5-fluorouracil and imiquimod creams are available in various concentrations. A recent RCT concluded that imiquimod is the first line local treatment of choice for primary superficial BCC (sBCC) in a non-facial area compared to 5-fluorouracil and PDT in terms of effectiveness.[94] However a large 3 year follow-up RCT, comparing imiquimod with SE for superficial and nodular BCC at low-risk sites still showed inferiority of imiquimod (84% versus 98% clearance).[95] And no clear difference was noted between groups in patient-assessed cosmetic outcomes. Furthermore, tumor thickness influences therapeutic efficacy of imiquimod. The median tumor thickness is 0.26 mm for non-recurrent lesions, while for recurrent cases the median tumor thickness is 0.57 mm. The cut-off value is 0.4 mm, where no recurrence occurred in contrast to a recurrence rate of 58% for lesions thicker than 0.4 mm.[96] One small study examining the cost of treatment of sBCC smaller then 20 mm with imiquimod (with efficacy of 82%) versus surgical excision (efficacy of 97%) suggested that the savings per patient cured with topical imiquimod is 55 euro.[97] Two RCT's have shown 5- to 10-fold higher cure rate with excision of nodular BCC (nBCC) than treatment by PDT. Nodular BCC clearance is half of that seen for sBCC.[77 98-100] Guidelines recommend if PDT is used it should also be limited to sBCC less than 1 mm to 2 mm thick. When comparing the cost-effectiveness of all non-surgical treatments together imiquimod and topical fluorouracil cream are more cost-effective than PDT for treatment of sBCC. [101] Destructive techniques for treatment of BCCs include curettage and cautery, cryosurgery and carbon dioxide laser, but quality of the current evidence is low and results vary.[102-107] For this reason these techniques are not recommended as a first line treatment.[73] One RCT compared radiotherapy to SE for primary BCC and the 4-years recurrence rates where 10 times lower for SE (0.7%) versus radiotherapy (7.5%). Radiotherapy is indicated in the treatment of (non-radiation) recurrent BCC or patients unwilling or unable to undergo surgery.

Recently a new treatment option for metastatic or locally advanced disease not amenable to surgery or radiotherapy became available with vismodegib, a small-molecule inhibitor of SMO.[108] Most BCC

contain a genetic alteration in the hedgehog signaling pathway, resulting in aberrant pathway activation and uncontrolled proliferation of basal cells. These alterations cause loss of function of patched homologue 1 (PTCH1), which normally acts to inhibit the signaling activity of smoothened homologue (SMO), a seven-transmembrane protein.[109 110] In patients with metastases treatment with vismodegib showed 30% of partial response and no complete responses. Forty-three percent of patients with locally advanced BCC had complete or partial response during treatment.[111] Frequent adverse effects, including muscle spasms, fatigue and severe hyponatraemia have been reported. In some patients severe weight loss, ocular disorders alopecia, anemia or SCC developed. A 12 month follow-up study showed that 72.1% of patients discontinued treatment mainly for other reasons than disease progression.[111 112] In case of control of extensive local disease there is discussion how long the treatment should be continued.

Provision for diagnosis and treatment of BCC must be available

Diagnosis by means of naked-eye examination aided by dermoscopy and the different treatment options are available in most European countries. In some countries MMS is however not available (Greece, Malta, Poland and Romania).[74-76 113] Table 2 gives an overview of the therapeutic options used for treating BCC in the Netherlands, Scotland, Finland and England.

Table 2. BCC treatment in different European countries

Treatment	Netherlands [114]	Scotland [114]	Finland [114]	England [74 75 115]
Surgical excision	83.6	87.2	57.1	86.0
Mohs	1	1.5	2.4	0.4
Cryotherapy	6.1	2.3	28.4	3.1
Photodynamic	2.8	-	11.8	0.8
5-fluorouracil	0.5	1.5	-	0.5
Imiquimod	0.4	4.9	-	-
Diclofenac	-	0.3	-	-
Curettage	0.7	-	-	-
Tretinoin	-	-	-	-
Radiotherapy	-	0.3	-	1.7
Expectative	0.2	-	-	-
Missing	4.6	-	0.3	-

Numbers stated in percent.

The screening program is cost-effective

To our knowledge no studies examined the cost-effectiveness of screening programs for BCC. However, since the current screening method would detect all skin cancers, including melanoma and SCC, its cost-effectiveness can only be argued by an overall assessment for all skin cancers. Indirect evidence suggests that treatment of larger BCCs in the face is more costly and that the risk of recurrence is higher, which in turn increases treatment cost. Evidence for non-facial lesions is scarce.

Rogers et al. calculated that the cost per primary treatment modality (MMS, SE, imiquimod, radiotherapy) increases with increasing lesional size for a hypothetical BCC lesion on the cheek of 6 mm, 11 mm, 21 mm and 31 mm. [116] Size of the lesions can indirectly influence cost by its impact on different surgery setting (outpatient or inpatient basis) and complexity of the reconstruction technique. For excision of BCC on the ear a strong correlation between size and reconstruction technique has been demonstrated. Defects smaller than one fourth the vertical auricular size (15 to 20 mm) can be treated by primary closure, larger defects required more complex reconstruction.[117] Comparison of cost for NMSC showed that tumor size >10 mm, tumors on the head and neck and MMS were independently related to higher cost of treatment.[118]

DISCUSSION

In view of the high incidence of BCC, its predicted increase in the future and in the absence of mortality due to this type of skin cancer, this review addresses the question whether including BCC in skin cancer prevention campaigns could be worthwhile. In this respect we evaluated the WHO criteria for screening specifically adapted to BCC. Epidemiological data show that most BCCs develop in the head and neck area of older patients (> 65 years). Detection of BCC by visual inspection is a relatively simple, safe and non-invasive examination. Dermoscopy can increase diagnostic accuracy. On the other hand appropriate treatment strategies are available. Surgery remains the most effective treatment but some other non-surgical strategies have also proved to be effective and are currently used in daily practice.

Size of BCC and the specific growth pattern seem to be very important determinants in treatment complexity and related cost, especially for the facial location. Data on the natural progression of BCC and the main drivers for histology are scarce. Available data point to a rather slow increase in size of BCC, creating a large time frame where BCC is amenable for early detection and treatment. Current evidence supports delay as the main underlying cause for a more aggressive clinical behavior, and no specific intrinsic biological factor has been identified so far.

We conclude that it may be worthwhile for skin cancer screening initiatives to include BCC especially of the face region. Studies point out that complexity, effectiveness and cost of surgical procedures in this area is highly influenced by size of the lesion. A small increase in size might therefore lead to more extensive or complex surgery which may affect outcome of the patient (surgical defect), the risk of side effects due to the procedure, the frequency of follow-up visits and hence total cost in an important way.

The appropriate selection of an adequate initial treatment seems to be of equal importance, since treatment failure will lead to disease recurrence, necessitating a second treatment with increased complexity and cost.

CONCLUSIONS

We conclude that BCC in the facial area fulfills the majority of WHO criteria for screening. Early detection and adequate treatment of BCC could reduce treatment complexity and cost, and offers a chance for control.

REFERENCES

1. Flohil SC, de Vries E, Neumann HA, et al. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta dermato-venereologica 2011;91(1):24-30.

2. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. The British journal of dermatology 2012;166(5):1069-80.

3. Flohil SC, Seubring I, van Rossum MM, et al. Trends in Basal cell carcinoma incidence rates: a 37-year Dutch observational study. The Journal of investigative dermatology 2013;133(4):913-8.

4. Arits AH, Schlangen MH, Nelemans PJ, et al. Trends in the incidence of basal cell carcinoma by histopathological subtype. Journal of the European Academy of Dermatology and Venereology : JEADV 2011;25(5):565-9.

5. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple basal cell carcinomas. Archives of dermatology 2010;146(8):848-55.

6. Rosso S, Zanetti R, Martinez C, et al. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. British journal of cancer 1996;73(11):1447-54.

7. van Dam RM, Huang Z, Rimm EB, et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. American journal of epidemiology 1999;150(5):459-68.

8. Kricker A, Armstrong BK, English DR, et al. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. International journal of cancer Journal international du cancer 1995;60(4):489-94.

9. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 1999;354(9180):723-9.

10. Darlington S, Williams G, Neale R, et al. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Archives of dermatology 2003;139(4):451-5.

11. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. Archives of dermatology 1995;131(2):170-5.

12. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. The New England journal of medicine 1993;329(16):1147-51.

13. van der Pols JC, Williams GM, Pandeya N, et al. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2006;15(12):2546-8.

14. Mittelbronn MA, Mullins DL, Ramos-Caro FA, et al. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. International journal of dermatology 1998;37(9):677-81.

15. Green AC, Williams GM, Logan V, et al. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol 2011;29(3):257-63

16. de Vries E, Arnold M, Altsitsiadis E, et al. Potential impact of interventions resulting in reduced exposure to ultraviolet (UV) radiation (UVA and UVB) on skin cancer incidence in four European countries, 2010-2050. The British journal of dermatology 2012;167 Suppl 2:53-62.

17. Weinstock MA, Bingham SF, Digiovanna JJ, et al. Tretinoin and the prevention of keratinocyte carcinoma (Basal and squamous cell carcinoma of the skin): a veterans affairs randomized chemoprevention trial. The Journal of investigative dermatology 2012;132(6):1583-90.

18. Zhang XB, Zhang SQ, Li CX, et al. Acitretin systemic and retinoic acid 0.1% cream supression of basal cell carcinoma. Dermatology reports 2010;2(1):e4.

19. Clouser MC, Roe DJ, Foote JA, et al. Dose response of retinol and isotretinoin in the prevention of nonmelanoma skin cancer recurrence. Nutrition and cancer 2010;62(8):1058-66.

20. Levine N, Moon TE, Cartmel B, et al. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Southwest Skin Cancer Prevention Study Group. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 1997;6(11):957-61.

21. Tangrea J, Edwards B, Hartman A, et al. Isotretinoin-basal cell carcinoma prevention trial. Design, recruitment results, and baseline characteristics of the trial participants. The ISO-BCC Study Group. Controlled clinical trials 1990;11(6):433-50.

22. Chen AC, Martin AJ, Choy B, et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. The New England journal of medicine 2015;373(17):1618-26.

23. Alam M, Goldberg LH, Silapunt S, et al. Delayed treatment and continued growth of nonmelanoma skin cancer. Journal of the American Academy of Dermatology 2011;64(5):839-48.

24. Antoszewski B, Kasielska A, Fijalkowska M. Face skin neoplasms--reasons for delayed treatment. Polski przeglad chirurgiczny 2011;83(7):361-6.

25. Blackford S, Roberts D, Salek MS, et al. Basal cell carcinomas cause little handicap. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 1996;5(2):191-4.

26. Husein-Elahmed H, Gutierrez-Salmeron MT, Naranjo-Sintes R, et al. Factors related to delay in the diagnosis of basal cell carcinoma. Journal of cutaneous medicine and surgery 2013;17(1):27-32.

27. Yancovitz M, Rizzo C, Julian P, et al. Patient perceptions of nonmelanoma skin cancer before diagnosis. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2013;39(10):1496-501.

28. Austoker J, Bankhead C, Forbes LJ, et al. Interventions to promote cancer awareness and early presentation: systematic review. British journal of cancer 2009;101 Suppl 2:S31-9.

29. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Boletin de la Oficina Sanitaria Panamericana Pan American Sanitary Bureau 1968;65(4):281-393.

30. Flohil SC, van der Leest RJ, Arends LR, et al. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. European journal of cancer 2013;49(10):2365-75.

31. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Archives of dermatology 2000;136(12):1524-30.

32. Tinghog G, Carlsson P, Synnerstad I, et al. Societal cost of skin cancer in Sweden in 2005. Acta dermato-venereologica 2008;88(5):467-73.

33. Bentzen J, Kjellberg J, Thorgaard C, et al. Costs of illness for melanoma and nonmelanoma skin cancer in Denmark. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation 2013;22(6):569-76.

34. Morris S, Cox B, Bosanquet N. Cost of skin cancer in England. The European journal of health economics : HEPAC : health economics in prevention and care 2009;10(3):267-73.

35. Vallejo-Torres L, Morris S, Kinge JM, et al. Measuring current and future cost of skin cancer in England. Journal of public health 2014;36(1):140-8.

36. Brochez L, Myny K, Bleyen L, et al. The melanoma burden in Belgium; premature morbidity and mortality make melanoma a considerable health problem. Melanoma research 1999;9(6):614-8.

37. Stang A, Stausberg J, Boedeker W, et al. Nationwide hospitalization costs of skin melanoma and non-melanoma skin cancer in Germany. Journal of the European Academy of Dermatology and Venereology : JEADV 2008;22(1):65-72.

38. Kim MY, Park HJ, Baek SC, et al. Mutations of the p53 and PTCH gene in basal cell carcinomas: UV mutation signature and strand bias. Journal of dermatological science 2002;29(1):1-9.

39. Bolshakov S, Walker CM, Strom SS, et al. p53 mutations in human aggressive and nonaggressive basal and squamous cell carcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research 2003;9(1):228-34.

40. Bale AE. Hedgehog signaling and human disease. Annual review of genomics and human genetics 2002;3:47-65.

41. Hahn H, Wicking C, Zaphiropoulous PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 1996;85(6):841-51.

42. Bodak N, Queille S, Avril MF, et al. High levels of patched gene mutations in basal-cell carcinomas from patients with xeroderma pigmentosum. Proceedings of the National Academy of Sciences of the United States of America 1999;96(9):5117-22.

43. Weinstein GD, Frost P. Cell proliferation in human basal cell carcinoma. Cancer research 1970;30(3):724-8.

44. Grimwood RE, Ferris CF, Mercill DB, et al. Proliferating cells of human basal cell carcinoma are located on the periphery of tumor nodules. The Journal of investigative dermatology 1986;86(2):191-4.

45. Kerr JF, Searle J. A suggested explanation for the paradoxically slow growth rate of basal-cell carcinomas that contain numerous mitotic figures. The Journal of pathology 1972;107(1):41-4.

46. Mooney EE, Ruis Peris JM, O'Neill A, et al. Apoptotic and mitotic indices in malignant melanoma and basal cell carcinoma. Journal of clinical pathology 1995;48(3):242-4.

47. Curson C, Weedon D. Spontaneous regression in basal cell carcinomas. Journal of cutaneous pathology 1979;6(5):432-7.

48. Kirkup ME, De Berker DA. Clinical measurement of dimensions of basal cell carcinoma: effect of waiting for elective surgery. The British journal of dermatology 1999;141(5):876-9.

49. Gordon PM, Cox NH, Paterson WD, et al. Basal cell carcinoma: are early appointments justifiable? The British journal of dermatology 2000;142(3):446-8.

50. Tan E, Lin FP, Sheck LH, et al. Growth of Periocular Basal Cell Carcinoma. The British journal of dermatology 2014.

51. Eide MJ, Weinstock MA, Dufresne RG, Jr., et al. Relationship of treatment delay with surgical defect size from keratinocyte carcinoma (basal cell carcinoma and squamous cell carcinoma of the skin). The Journal of investigative dermatology 2005;124(2):308-14.

52. Kricker A, Armstrong B, Hansen V, et al. Basal cell carcinoma and squamous cell carcinoma growth rates and determinants of size in community patients. Journal of the American Academy of Dermatology 2014;70(3):456-64.

53. Horlock NM, Wilson GD, Daley FM, et al. Cellular proliferation characteristics of basal cell carcinoma: relationship to clinical subtype and histopathology. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 1997;23(3):247-52.

54. Nedved D, Tonkovic-Capin V, Hunt E, et al. Diagnostic concordance rates in the subtyping of basal cell carcinoma by different dermatopathologists. Journal of cutaneous pathology 2014;41(1):9-13.

55. Miller SJ. Biology of basal cell carcinoma (Part I). Journal of the American Academy of Dermatology 1991;24(1):1-13.

56. Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. Journal of the American Academy of Dermatology 1990;23(6 Pt 1):1118-26.

57. Jacobs GH, Rippey JJ, Altini M. Prediction of aggressive behavior in basal cell carcinoma. Cancer 1982;49(3):533-7.

58. LeBoit PE BG, Weedon D, Sarasin A. Pathology and genetics of skin tumors. . In: (WHO) WHOCot, ed., 2006:13-25.

59. Betti R, Radaelli G, Crosti C, et al. Margin involvement and clinical pattern of basal cell carcinoma with mixed histology. Journal of the European Academy of Dermatology and Venereology : JEADV 2012;26(4):483-7.

60. Kaur P, Mulvaney M, Carlson JA. Basal cell carcinoma progression correlates with host immune response and stromal alterations: a histologic analysis. The American Journal of dermatopathology 2006;28(4):293-307.

61. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. Journal of the American Academy of Dermatology 1984;10(6):1043-60.

62. Wysong A, Aasi SZ, Tang JY. Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. JAMA dermatology 2013;149(5):615-6.

63. Lo JS, Snow SN, Reizner GT, et al. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. Journal of the American Academy of Dermatology 1991;24(5 Pt 1):715-9.

64. Bowman PH, Ratz JL, Knoepp TG, et al. Basosquamous carcinoma. Dermatologic surgery : official publication for American Society for Dermatologic Surgery 2003;29(8):830-2; discussion 33.

65. Snow SN, Sahl W, Lo JS, et al. Metastatic basal cell carcinoma. Report of five cases. Cancer 1994;73(2):328-35.

66. Kittler H, Pehamberger H, Wolff K, et al. Diagnostic accuracy of dermoscopy. The Lancet Oncology 2002;3(3):159-65.

67. Vestergaard ME, Macaskill P, Holt PE, et al. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. The British journal of dermatology 2008;159(3):669-76.

68. Altamura D, Menzies SW, Argenziano G, et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. Journal of the American Academy of Dermatology 2010;62(1):67-75.

69. Popadic M. Dermoscopic Features in Different Morphologic Types of Basal Cell Carcinoma. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2014.

70. Popadic M, Vukicevic J. What is the impact of tumour size on dermoscopic diagnosis of BCC? Journal of the European Academy of Dermatology and Venereology : JEADV 2014.

71. Pehamberger H, Binder M, Steiner A, et al. In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma. The Journal of investigative dermatology 1993;100(3):356S-62S.

72. Bath-Hextall FJ, Perkins W, Bong J, et al. Interventions for basal cell carcinoma of the skin. The Cochrane database of systematic reviews 2007(1):CD003412.

73. Telfer NR, Colver GB, Morton CA, et al. Guidelines for the management of basal cell carcinoma. The British journal of dermatology 2008;159(1):35-48.

74. Gudi V, Ormerod AD, Dawn G, et al. Management of basal cell carcinoma by surveyed dermatologists in Scotland. Clinical and experimental dermatology 2006;31(5):648-52.

75. Goulding JM, Levine S, Blizard RA, et al. Dermatological surgery: a comparison of activity and outcomes in primary and secondary care. The British journal of dermatology 2009;161(1):110-4.

76. Flohil SC, Proby CM, Forrest AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. The British journal of dermatology 2012;167 Suppl 2:22-8.

77. Rhodes LE, de Rie MA, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Archives of dermatology 2007;143(9):1131-6.

78. Chren MM, Linos E, Torres JS, et al. Tumor recurrence 5 years after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. The Journal of investigative dermatology 2013;133(5):1188-96.

79. Chren MM, Torres JS, Stuart SE, et al. Recurrence after treatment of nonmelanoma skin cancer: a prospective cohort study. Archives of dermatology 2011;147(5):540-6.

80. Walker P, Hill D. Surgical treatment of basal cell carcinomas using standard postoperative histological assessment. The Australasian journal of dermatology 2006;47(1):1-12.

81. Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? British journal of plastic surgery 2005;58(6):795-805.

82. Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. The Journal of dermatologic surgery and oncology 1992;18(6):471-6.

83. Gulleth Y, Goldberg N, Silverman RP, et al. What is the best surgical margin for a Basal cell carcinoma: a meta-analysis of the literature. Plastic and reconstructive surgery 2010;126(4):1222-31.

84. Do D. Mohs micrographic surgery for Basal cell carcinoma of the face. Archives of dermatology 2009;145(12):1428-30.

85. Feldman S, Pearce DJ, Williford PM. Surgical decision making for basal-cell carcinoma of the face. The Lancet Oncology 2008;9(12):1119-20.

86. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery for primary and recurrent basal-cell carcinoma of the face: a prospective randomised controlled trial with 5-years' follow-up. The Lancet Oncology 2008;9(12):1149-56.

87. Smeets NW, Kuijpers DI, Nelemans P, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face--results of a retrospective study and review of the literature. The British journal of dermatology 2004;151(1):141-7.

88. Wang L, Lei D, Zhao Y. Removal of basal-cell carcinoma of the face. The Lancet Oncology 2009;10(1):9-10; author reply 10.

89. Wennberg AM, Larko O, Stenquist B. Five-year results of Mohs' micrographic surgery for aggressive facial basal cell carcinoma in Sweden. Acta dermato-venereologica 1999;79(5):370-2.

90. Essers BA, Dirksen CD, Nieman FH, et al. Cost-effectiveness of Mohs Micrographic Surgery vs Surgical Excision for Basal Cell Carcinoma of the Face. Archives of dermatology 2006;142(2):187-94.

91. Aguilar-Bernier M, Gonzalez-Carrascosa M, Padilla-Espana L, et al. Five-year economic evaluation of non-melanoma skin cancer surgery at the Costa del Sol Hospital (2006-2010). Journal of the European Academy of Dermatology and Venereology : JEADV 2014;28(3):320-6.

92. Flohil SC, van Dorst AM, Nijsten T, et al. Mohs micrographic surgery for basal cell carcinomas: appropriateness of 'Rotterdam' criteria and predictive factors for three or more stages. Journal of the European Academy of Dermatology and Venereology : JEADV 2013;27(10):1228-35.

93. American Academy of D, American College of Mohs S, American Society for Dermatologic Surgery A, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2012;38(10):1582-603.

94. Arits AH, Mosterd K, Essers BA, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. The Lancet Oncology 2013;14(7):647-54.

95. Bath-Hextall F, Ozolins M, Armstrong SJ, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. The Lancet Oncology 2014;15(1):96-105.

96. McKay KM, Sambrano BL, Fox PS, et al. Thickness of superficial basal cell carcinoma (sBCC) predicts imiquimod efficacy: a proposal for a thickness-based definition of sBCC. The British journal of dermatology 2013;169(3):549-54.

97. Vanaclocha F, Dauden E, Badia X, et al. Cost-effectiveness of treatment of superficial basal cell carcinoma: surgical excision vs. imiquimod 5% cream. The British journal of dermatology 2007;156(4):769-71.

98. Mosterd K, Thissen MR, Nelemans P, et al. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. The British journal of dermatology 2008;159(4):864-70.

99. Baptista J, Martinez C, Leite L, et al. Our PDT experience in the treatment of non-melanoma skin cancer over the last 7 years. Journal of the European Academy of Dermatology and Venereology : JEADV 2006;20(6):693-7.

100. Lindberg-Larsen R, Solvsten H, Kragballe K. Evaluation of recurrence after photodynamic therapy with topical methylaminolaevulinate for 157 basal cell carcinomas in 90 patients. Acta dermato-venereologica 2012;92(2):144-7.

101. Arits AH, Spoorenberg E, Mosterd K, et al. Cost-effectiveness of topical imiquimod and fluorouracil vs. photodynamic therapy for treatment of superficial basal-cell carcinoma. The British journal of dermatology 2014.

102. Kokoszka A, Scheinfeld N. Evidence-based review of the use of cryosurgery in treatment of basal cell carcinoma. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2003;29(6):566-71.

103. Kuflik EG, Gage AA. The five-year cure rate achieved by cryosurgery for skin cancer. Journal of the American Academy of Dermatology 1991;24(6 Pt 1):1002-4.

104. Nouri K, Chang A, Trent JT, et al. Ultrapulse CO2 used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2002;28(3):287-90.

105. Barlow JO, Zalla MJ, Kyle A, et al. Treatment of basal cell carcinoma with curettage alone. Journal of the American Academy of Dermatology 2006;54(6):1039-45.

106. Silverman MK, Kopf AW, Grin CM, et al. Recurrence rates of treated basal cell carcinomas. Part 2: Curettage-electrodesiccation. The Journal of dermatologic surgery and oncology 1991;17(9):720-6.

107. Suhge d'Aubermont PC, Bennett RG. Failure of curettage and electrodesiccation for removal of basal cell carcinoma. Archives of dermatology 1984;120(11):1456-60.

108. Poggi L, Kolesar JM. Vismodegib for the treatment of basal cell skin cancer. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2013;70(12):1033-8.

109. Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. The Journal of investigative dermatology 1998;110(6):885-8.

110. Gailani MR, Stahle-Backdahl M, Leffell DJ, et al. The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas. Nature genetics 1996;14(1):78-81.

111. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. The New England journal of medicine 2012;366(23):2171-9.

112. Sekulic A, Migden MR, Lewis K, et al. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. Journal of the American Academy of Dermatology 2015;72(6):1021-6 e8.

113. Paoli J, Danielsson M, Wennberg AM. Results of the 'Euromelanoma Day' screening campaign in Sweden 2008. Journal of the European Academy of Dermatology and Venereology : JEADV 2009;23(11):1304-10.

114. Flohil SC, Proby CM, Forrest AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br J Dermatol;167 Suppl 2:22-8.

115. Vallejo-Torres L, Morris S, Kinge JM, et al. Measuring current and future cost of skin cancer in England. J Public Health (Oxf).

116. Rogers HW, Coldiron BM. A relative value unit-based cost comparison of treatment modalities for nonmelanoma skin cancer: effect of the loss of the Mohs multiple surgery reduction exemption. Journal of the American Academy of Dermatology 2009;61(1):96-103.

117. Ghassemi A, Modabber A, Talebzadeh M, et al. Surgical management of auricular defect depending on the size, location, and tissue involved. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2013;71(8):e232-42.

118. Wilson LS, Pregenzer M, Basu R, et al. Fee comparisons of treatments for nonmelanoma skin cancer in a private practice academic setting. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al] 2012;38(4):570-84.

Chapter 7

Dermoscopy for detecting skin cancer in a population-based sample

Submitted as journal article:

Hoorens I, Vossaert K, Argenziano G, Brochez L. Dermoscopy for detecting skin cancer in a population-based sample (submitted to JEADV, 2016).

ABSTRACT

Background: The use of dermoscopy has benefit the diagnosis of skin cancer significantly in well-trained dermatologists. However to evaluate its cost-effectiveness in daily practice, not only sensitivity but the excision rate is crucial. For this purpose we examined the diagnostic accuracy of cases derived from a population-based sample scored by Flemish dermatologists.

Methods: 126 dermatologists were randomly assigned to 145 digital cases of patients presented with a lesion to a skin cancer screening. This resulted in 4655 case-evaluations using a web application. Accuracy of diagnosis and treatment was correlated to the histological diagnosis or expert opinion.

Results: The larger part (89.7%) of dermatologists uses their dermatoscope daily. Dermoscopy dramatically increased sensitivity for skin cancer diagnosis from 70.6% to 84.6%, but this was associated with a small but significant decrease in specificity of 3.6%. To detect one skin cancer 5.23 lesions with suspicion had to be excised. Dermoscopy significantly increased the certainty about making a correct diagnosis, and this was most the case for seborrheic keratosis, Bowen's disease and melanoma.

Conclusion: No significant reduction in the number of excisions could be demonstrated in this sample, the use of dermoscopy by Flemish dermatologists in daily practice significantly improves the sensitivity of skin cancer detection and certainty in diagnosing melanoma.

INTRODUCTION

The skin cancer epidemic has an important impact on health care budget in Europe. Early detection and treatment is assumed to give better cure rates and subsequently a more cost-effective treatment. Dermoscopy is a well-established tool for diagnosis of melanoma and non-melanoma skin cancer (NMSC). Several meta-analyses have shown that dermoscopy, in the hands of experienced dermatologists, is superior to naked-eye examination (NEE) to detect melanoma.[1-3] Dermoscopy also significantly increases the diagnostic accuracy of NMSC diagnosis.[4] For basal cell carcinoma (BCC) the diagnostic accuracy obtained by dermoscopy is up to 95-99%.[5-7] It is known that the diagnostic accuracy of dermoscopy depends significantly on training of the examiners.[8] In the hands of untrained practitioners, dermoscopy provides no better diagnostic accuracy for melanoma than NEE.[1] Most of the studies on the additional diagnostic value of dermoscopy have been performed in a well-selected set of lesions, in which MM and other malignant lesions are usually overrepresented. Since skin cancer prevalence in real life setting is usually much lower, this can influence the number of false positives and their related cost in an important way (Bayes' theorem). For this reason we examined diagnostic accuracy of NEE alone and of additional dermoscopy among dermatologists in a population-based sample in Belgium.

METHODS

Study design

Cases and determination of reference diagnosis

The cases were collected during a population-based lesion-directed skin cancer screening. Screenees could register for a free of charge skin cancer check, if they had a lesion meeting one or more of the criteria listed: ABCD rule, ugly duckling sign, and new lesion since more than 4 weeks, red non-healing lesions. All lesions presented by the screenees were photographed both clinically and dermoscopically (respectively Canon EOS 1200 D and DermLite Photo System). In total 248 lesions were presented for screening and 8 out of them were histologically proven to be skin cancers (3.2%). Further details on this screening initiative have been published elsewhere.[9] In total 145 of the 248 cases (58%) were selected for a web application. Exclusion of cases was due to sub-optimal quality of the photographs or a missing clinical or dermoscopy photo. This study was approved by the Flemish government and by the medical ethical committee of the University Hospital Ghent. All screenees provided written informed consent.

As a histological diagnosis was not available for most of the lesions the following surrogate reference diagnosis was used in a hierarchical order: diagnosis of the pathologist in case of excision or biopsy of

the lesion (n = 6, 4.1%), concordant diagnosis by 2 expert dermoscopists (KV, LB (n = 100, 67.0%)); in case of discordance in diagnosis by these 2 experts, a third independent expert dermoscopist (GA) was asked and the most concordant diagnosis was chosen (n = 39, 26.9%). The gold standard diagnosis of all cases are listed in Table 1.

Table 1. Specific diagnosis lesions of the 145 cases

Diagnosis	Number	Percent
Melanoma	1	0.7
BCC	4	2.8
SCC/Bowen	1	0.7
Actinic keratosis	3	2.1
Angioma	5	3.4
Dermatofibroma	4	2.8
Atypical nevus	6	4.1
Blue nevus	3	2.1
Congenital nevus	6	4.1
Benign nevus	53	36.6
Solar lentigo	12	8.3
Seborrhoic keratosis	40	27.6
Other	7	4.8
Total	145	100

Recruitment of dermatologists

A personal invitation to participate in this study was sent out to all 384 Flemish dermatologists. Only certified dermatologists could participate. Participating dermatologists were asked to register online, and to evaluate 1 or more series of 25 cases each. Case series were presented randomly to each registered dermatologist. Upon registration, information concerning their practice, previous training in dermoscopy and the frequency of use of dermoscopy in routine practice was asked.

Case evaluation

Each online case mentioned a brief clinical information (age, gender and location of the lesion). First dermatologists were shown the clinical photo and were asked to select a clinical diagnosis (multiple choice), to score the certainty of their diagnosis on a visual analogue scale (VAS) from 0 - 100%, and to choose the best treatment action (no treatment, biopsy, surgical excision, curettage, cryotherapy and

other); after registration of these answers they were shown the dermoscopy photo and were asked to complete the exact same questions.

Sample size calculation and statistical analysis

A sample size of 1630 case-evaluations was required to achieve a power of 80% to detect a difference in specificity of 5% in the group of clinical evaluation compared to the group of additional dermoscopy evaluation with a significance level of 5%. A specificity of 85.4% for the clinical diagnosis was expected and an interclass correlation of 0.81 was assumed (based on pilot data). Sample size calculation was adjusted for the clustered nature of the design by applying the method described by Killip (2004).[10] Descriptive statistics were used to describe the cases and dermatologists participating. The related samples wilcoxon signed rank test was used for continuous variables. Due to the clustered nature of the data mixed logistic regression models were used to calculate sensitivity, specificity and number needed to excise (NNE) and their relation to experience and training of the dermatologist. All statistical tests were two-tailed and P-values <0.05 were considered statistically significant. The analyses were conducted in SPSS version 21.0 (IBM, Armonk, NY, U.S.A).

Outcomes

The primary outcome of this study was to evaluate the diagnostic accuracy of dermoscopy compared to NEE in a population-based setting. Furthermore we wanted to evaluate if dermoscopy can increase certainty of the correct diagnosis.

RESULTS

Characteristics dermatologists

In total 126 dermatologists randomly evaluated 1 or more series of cases with a mean of 32.1 evaluations per case. This resulted in 4655 case-evaluations. The majority of the participating dermatologists were female (80.2%). The median age was 45 (interquartile range (IQR) 38-52). The majority of dermatologists worked in a private practice (54.8%), 38.9% in a university center and 6.3% in a hospital setting. The reported median number of patients seen in their practice or hospital was 100 per week (IQR 70-130). Dermoscopy was used at least once a day in 89.7%, once a week but not daily in 7.9%, once a week up to once a month 1.6% and not at all in 0.8%. Thirty-seven dermatologists (29.4%) use a non-polarized dermatosope. Training in dermoscopy varied among the participating dermatologists: only 3 dermatologists (2.4%) had no training in dermoscopy; whereas 25 (19.8%) had 1-5 hours, 42 (33.3%) had 5-10 hours and 56 or 44.4% had more than 10 hours of training.

Diagnostic accuracy and certainty of diagnosis

Dermoscopy dramatically increased sensitivity for skin cancer diagnosis significantly from 70.6% to 84.6% (Binomial generalized linear mixed model, P<0.01; Table 2), and was associated with a small but significant decrease in specificity (96.9% for NEE versus 93.5% for dermoscopy, Binomial generalized linear mixed model, P<0.01; Table 2) (Figure 1). The sensitivity for the diagnosis of melanoma in specific increased from 76.0% to 94.3% (Binomial generalized linear mixed model, P=0.03). The odds for making a correct diagnosis of melanoma using dermoscopy was 5.38 (95%CI 1.22-23.81) compared to NEE. Dermoscopy also increased sensitivity for diagnosis of BCC and SCC/Bowen from 71.5% to 74.6%, and 58.9% to 71.0% respectively, but this failed to reach statistical significance.

Table 2. Diagnostic performance of dermoscopy according to level of training of the dermatologist

		Clinical			Dermoscopy			P-value[a]
		Sens	Spec	1-Spec	Sens	Spec	1-Spec	
All		0.706[b]	0.969[c]	0.031	0.846[b]	0.935[c]	0.065	[b,c]<0.01
Training	< 5 hours	0.645	0.915	0.085	0.774	0.861	0.139	-
	5- 10 hours	0.702	0.921	0.079	0.829	0.885	0.115	-
	>10 hours	0.704	0.940	0.060	0.852	0.887	0.113	-
P- value[a]		0.49	0.61	-	0.42	0.53	-	

Sens, sensitivity; Spec, specificity; [a] Binomial generalized linear mixed models.

A trend to increasing sensitivity/specificity was observed with increasing training level (figure 2). The confidence about a correct diagnosis significantly increased from a median of 70% (IQR 60-80) using NEE to 83.7% (IQR 70-90) with dermoscopy (Related samples wilxocon signed rank test, P<0.01). The increase was most pronounced for seborrheic keratosis, Bowen's disease and melanoma.

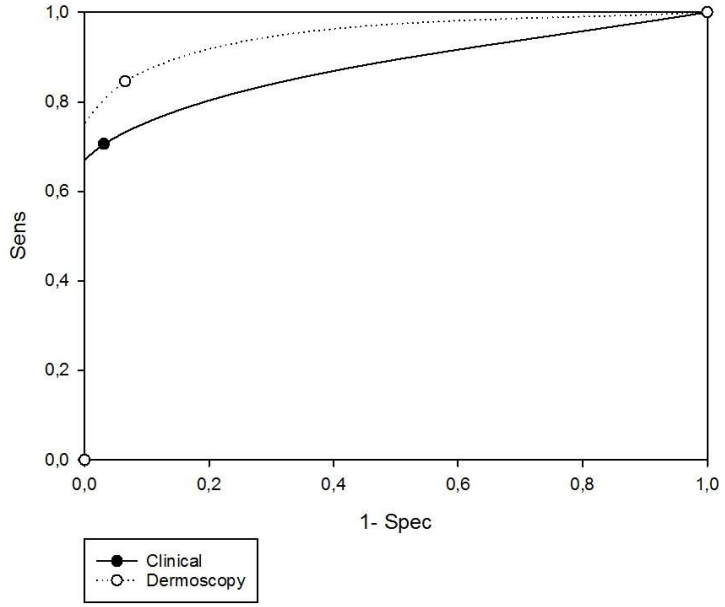

Figure 1. Sensitivity and and 1 minus specificity for a malignant diagnosis made clinically and using dermoscopy. Dermoscopy increased sensitivity for skin cancer diagnosis significantly from 70.6% to 84.6%, but this was associated with a small but significant decrease in specificity (96.9% for NEE versus 93.5% for dermoscopy).

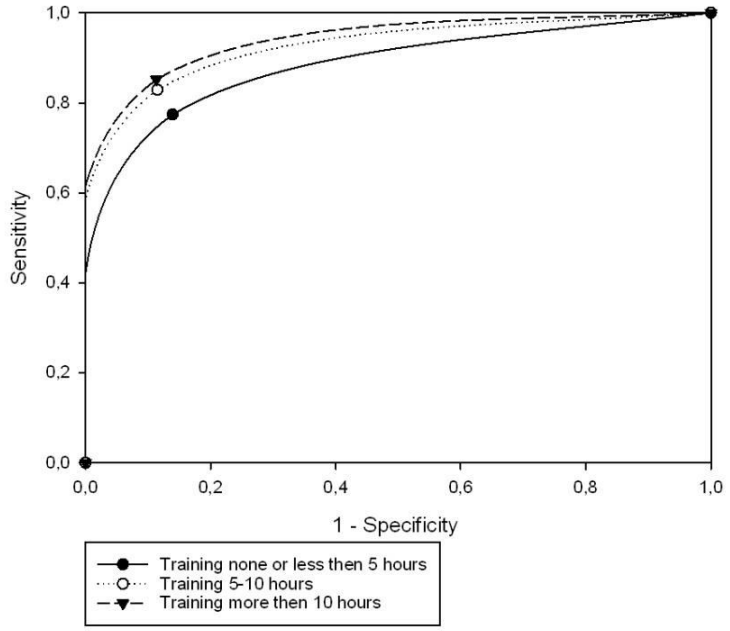

Figure 2. Sensitivity and 1 minus specificity for a malignant diagnosis according to level of training of the dermatologist. Sensitivity and specificity for skin cancer diagnosis raised with advanced level of training, although this failed to reach statistical significance.

Number needed to excise

Dermoscopy resulted in 43 additional excisions for skin cancer and 252 extra excisions for benign lesions (on a total of 1765 excisions or biopsies performed) compared to the clinical evaluation without dermoscopy. This resulted in a NNE of 4.77 for clinical evaluation alone and 5.23 when using dermoscopy (Binomial generalized linear mixed model, P=ns). NNE did not seem to be influenced by training level (0-5 hours NNE 5.15, 5-10 hours NNE 4.89 and > 10 hours NNE 5.62, Binomial generalized linear mixed model, P=ns). Regarding to specific diagnoses (melanocytic lesions and BCC) the NNE also did not change significantly between clinical diagnosis and dermoscopy diagnosis. In addition, no significant difference in NNE using dermoscopy could be demonstrated associated with characteristics of the dermatologist (age, number of patients per week, work environment or the frequency of use).

DISCUSSION

In this study the additional value of dermoscopy use over clinical diagnosis by 126 dermatologists was evaluated in a population-based series of 145 cases. In the past a lot of similar studies have used very selected case series in which skin cancer is usually overrepresented. As the aim is to not miss skin cancer (high sensitivity), which is especially important in melanoma, the importance of not over-diagnosing skin cancer (high specificity) may become more and more important in populations where skin cancer prevalence is low. In this study we therefore included a case series based on a skin cancer screening program, in which the skin cancer prevalence was 6/145 (4.1%). One hundred twenty six (32.8%) of all Flemish dermatologists evaluated at least 25 of the 145 cases. Cases were randomly presented to the dermatologists leading to a total of 4655 case-evaluations. In this way this study reflects the additional value of dermoscopy in the hands of Flemish dermatologists in a population-based series. In this regard, the possibility that lesions with more clear visual and clinical features were included, owing to the design of the screening study must be mentioned. On the other hand, since the screening was an early detection initiative, it could have rendered relative smaller lesions more difficult to diagnose.

The results of our study demonstrate that dermoscopy is frequently used in Belgian dermatology practice: almost 90% of the dermatologists use the dermatoscope daily. This is comparable to large studies performed in France and Australia (94.6-98%).[11 12] We noted, in accordance with other studies, that dermoscopy significantly increases sensitivity for malignant lesions.[1-4 6] However this results also in a small but significant decrease in specificity, thus increasing the number of false positives. In this study dermoscopy resulted in 43 additional excisions for skin cancer and 252 extra excisions for benign

lesions over clinical diagnosis. The sensitivity/specificity tended to increase with increased level of training, confirming previous studies.[1-4 6] Confidence about making a correct diagnosis was significantly higher using dermoscopy, and most important in melanoma, seborrheic keratosis and Bowen's disease. However this did not end up in a reduction of unnecessary excisions as the NNE did not significantly differ between clinical diagnosis and dermoscopy nor did it seem to be influenced by training. However the NNE of the experts in the real life setting on the screening (KV, LB) was clearly lower than the NNE reached in the online case evaluation.[9]

The use of both clinical and dermoscopical photographs with the added information of gender, age and lesion location to evaluate pigmented skin lesions remains somewhat artificial. In the absence of a total body inspection individual lesions may be interpreted in a different way, as it is for example known that one individual with multiple nevi usually displays similar lesions (signature nevi) and that there should be caution about lesions with a different pattern (ugly duckling sign). This was illustrated by 2 prominent nevi, that were considered non-suspicious by the 2 experts (KV, LB) on the screening and were scored as potential melanoma in the online case series by at least 2 of 3 experts. Digital follow-up of these lesions by means of new clinical and dermoscopy photographs about 20 months after screening demonstrated stability, suggesting that these lesions have a benign behavior. This illustrates that part of the false positive skin cancer diagnoses may be due to the artificial conditions in which the lesions are evaluated.

Compared to previous studies the NNE of 1 out 6 is more effective than dermoscopy use by general practitioners. Evaluation of the large SCREEN campaign in Germany in a partially non specialized setting resulted 17 excisions of suspicious melanocytic lesions for the detection of one melanoma.[13] Our data is comparable to a large multi-centric study examining excision rates over a period of 10 years in a specialized clinical settings, with a NNE of 6.8.[14]

There was a trend towards increased sensitivity and specificity with increased training, however training of >10 hours did not reach statistically significant superior results. In the current guidelines the use of/and training in dermoscopy regarding melanoma has a grade A recommendation, however the NNE in this study is not influenced by the hours of training in dermoscopy.[15] The required amount of training however is debated. It has been shown that despite the frequent use of dermoscopy training seems to be insufficient and that even among dermatologists who consider themselves experienced in dermoscopy, repeated training moments can increase diagnostic accuracy.[11,8] In addition currently a lot of training courses in dermoscopy mainly focus on red flags (increase of sensitivity for melanoma). However when used in low prevalence populations it could be interesting to

put more focus on green flags (recognition of harmless lesions), thereby reducing the number of false positive diagnoses and hence unnecessary excisions.

CONCLUSIONS

The current study evaluated the additional value of dermoscopy in the hands of Flemish dermatologists in a population-based setting using a series of photos in a web application. These results demonstrate that dermoscopy clearly increases sensitivity for malignant lesions in a population based setting, at the expense of a small but significant decrease in specificity. Although dermoscopy significantly increased confidence about a diagnosis, especially in melanoma, seborrheic keratosis and Bowen's disease, this did not result in a reduction of NNE. There was a trend towards higher sensitivity and specificity according to training level (<5 hours, 5-10 hours or > 10 hours). We suggest that continuous training for dermoscopy may be needed and that training courses should also pay enough attention to the recognition of benign lesions to avoid unnecessary excisions.

REFERENCES

1. Kittler H, Pehamberger H, Wolff K, et al. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002;3(3):159-65.

2. Bafounta ML, Beauchet A, Aegerter P, et al. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol 2001;137(10):1343-50.

3. Vestergaard ME, Macaskill P, Holt PE, et al. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol 2008;159(3):669-76.

4. Pehamberger H, Binder M, Steiner A, et al. In vivo epiluminescence microscopy: improvement of early diagnosis of melanoma. J Invest Dermatol 1993;100(3):356S-62S.

5. Altamura D, Menzies SW, Argenziano G, et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. J Am Acad Dermatol 2010;62(1):67-75.

6. Menzies SW, Westerhoff K, Rabinovitz H, et al. Surface microscopy of pigmented basal cell carcinoma. Arch Dermatol 2000;136(8):1012-6.

7. Pan Y, Chamberlain AJ, Bailey M, et al. Dermatoscopy aids in the diagnosis of the solitary red scaly patch or plaque-features distinguishing superficial basal cell carcinoma, intraepidermal carcinoma, and psoriasis. J Am Acad Dermatol 2008;59(2):268-74.

8. Chevolet I, Hoorens I, Janssens A, et al. A short dermoscopy training increases diagnostic performance in both inexperienced and experienced dermatologists. Australas J Dermatol 2015;56(1):52-5.

9. Hoorens I, Vossaert K, Pil L, et al. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol 2015.

10. Killip S, Mahfoud Z, Pearce K. What is an intracluster correlation coefficient? Crucial concepts for primary care researchers. Ann Fam Med 2004;2(3):204-8.

11. Breton AL, Amini-Adle M, Duru G, et al. Overview of the use of dermoscopy in academic and non-academic hospital centres in France: a nationwide survey. J Eur Acad Dermatol Venereol 2014;28(9):1207-13.

12. Venugopal SS, Soyer HP, Menzies SW. Results of a nationwide dermoscopy survey investigating the prevalence, advantages and disadvantages of dermoscopy use among Australian dermatologists. Australas J Dermatol 2011;52(1):14-8.

13. Waldmann A, Nolte S, Geller AC, et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. Arch Dermatol 2012;148(8):903-10.

14. Argenziano G, Cerroni L, Zalaudek I, et al. Accuracy in melanoma detection: a 10-year multicenter survey. J Am Acad Dermatol 2012;67(1):54-9.

15. Clinical Practice Guidelines in Australia and New Zealand for the Management of Melanoma. The Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington 2008.

Chapter 8

General discussion and future perspectives

EPIDEMIOLOGY AND SKIN CANCER COST

In chapter 3, we estimated the current and future prevalence, and economic burden of MM and NMSC in Belgium. These results indicated that the prevalence of skin cancer will triple in the next 20 years. In 2034, the total number of persons affected by skin cancer will be 397 213, of which 66% BCC, 21.2% SCC and 12.8% MM. The rate of increment for MM, SCC and BCC was calculated respectively at 3.2, 3.3 and 2.7. The total economic burden of skin cancer in 2014 was estimated at €107 million (direct costs €78 million; indirect costs €29 million), with a cumulative cost of €3.2 billion in 2034. The majority of the total cost is due to MM (65%). The indirect costs due to productivity losses are mainly (>90%) due to MM. Melanoma and NMSC are both responsible for about half of the direct costs. To summarize, we found that MM is responsible for the majority of the costs; and NMSC affects the majority of patients.

A limitation of the current epidemiological and economic studies, including ours, is that these future prevalence and costs are presumably underestimated, since few cancer registries collect correct data on NMSC. As most national registries are pathology based, tumors without histological confirmation will not be captured. The EPIDERM audit, performed in 4 European countries (Netherlands, Scotland, Finland and Malta), demonstrated that up to 24.1% of BCCs are diagnosed without histological confirmation.[1] In addition, most registries only document the first NMSC per patient and do not differentiate SCC from BCC. For the current study, we had to rely on the Dutch cancer registry, likewise not including BCC without histological confirmation, nor multiple NMSCs. The latter also impacting the results significantly, since it is generally acknowledged that over a period of 10 years up to 30% of BCC patients develop a second or even third BCC.[2]

Cost calculations were based on patient questionnaires gathered in different clinical settings; private practices, private hospitals and university setting. In contrast to the relatively large amount of physicians (16 dermatologists, nine oncologists and one general practitioner), only 287 patients were included using consecutive sampling. We tried to minimize recall bias by only questioning disease related costs and QOL over the last 6 months. Even under these circumstances, the bottom-up nature of our study has several advantages compared to top-down methods. Since the latter are more predisposed to misallocate direct and indirect categories of the costs. In addition, the design does not include informal costs, such as transport, informal care or other indirect costs which were included in our questionnaires. And given that elderly skin cancer patients have multiple pathologies, it can be difficult to attribute the exact part of, for example a hospitalization, to the disease of interest in a top-down design.[3]

PRIMARY PREVENTION

UV prevention campaign and a total ban on sunbed use

The impact of a *SunSmart* campaign was modeled in chapter 3. The effects of the intervention were expressed as a reduction in sunburns, since the risk of developing MM is 59% higher compared to those who have never been sunburned. We did not model an impact of reduced sunburn on SCC or BCC incidence.[4] In addition, the effect of a total ban on sunbeds was modeled. Over a period of 50 years, both prevention programs would lead to a gain in QALYs and cost-savings, being dominant strategies. It is clear that a ban on sunbed use would be the most cost-effective solution, because intervention costs are absent, and the strategy achieves a higher incremental QALY than a UV protection campaign. The budget impact analysis revealed that for every euro invested in the prevention campaign, €3.6 would be saved in the long-term for the health care payer.

In the absence of clear data on the tumor biology, lag-time of UV exposure and tumor initiation and promotion, an induction period of 20 years was applied.[5] Repeated analyses with 10 and 30 years induction periods also resulted in dominant ICERs. Based on migration studies, it is shown that exposure to high levels of sunlight in childhood is a strong determinant of MM incidence and even mortality.[6] In addition, a large meta-analysis demonstrated that the risk for developing MM is 1.91 when ever being sunburned during childhood, compared to 1.44 during adult life.[7] Our cohort included the adult Belgian population, and to appropriately capture the positive impact of the intervention in children, a longer induction period would be required. Nevertheless, a prevention campaign should focus on sun avoidance and wearing of protective clothing, especially in children based on the epidemiologic evidence.[7] Additionally, the campaign teaches children responsible sun behavior, having an educational effect. For parts of the body not protected by clothing, the use of sunscreens with SPF in the range of 30 to 50 should be advised. These results indicate that policy makers are obliged to critically review the topic of a national UV prevention campaign and a sunbed ban. In Brazil and Australia, a national sunbed ban is currently in place.[8,9] At present the Belgian Superior Health Council is preparing a report supporting a restriction on sunbed use in Belgium.

Some methodological assumptions concerning the disease models are imperative to discuss. Since knowledge on the natural history of skin cancer is limited, generic progression rates were applied irrespective of age and gender, based on the large dataset of Leiter et al.[10] and calibration for the natural progression of MM. It is known, however that females have a lower risk of melanoma progression (hazard ratio (HR) 0.68).[11–13] In addition, age is an independent prognostic factor for melanoma survival and progression. Patients under the age of 20 years have better survival, and older age (> 70 years) is a negative prognostic factor.[14,15] Because of the large amount of calculations

needed for validation and fitting the data, making a full age- and gender specific model would be impossible. On the other hand, the most important effect, namely the female advantage in survival was adopted in the disease model. Secondly, the model assumed that the effect of the *SunSmart* campaign would only affect sunburn and MM. A reduction of cumulative UV exposure was not incorporated because of the lack of data on this effect. In the ideal situation, a difference in incidence of MM and NMSC between to nearby regions, with one having a *SunSmart* campaign would be needed to model the true impact. No such data is available at the moment for Europe, and the only study performed in Australia showed that the incidence of only BCC had decreased (in age groups less than 50 years old). These findings were based on surveys, and partly as a result of the primary prevention initiative. There was no impact on SCC incidence observed.[16] Therefore, the effectiveness of the *SunSmart* program was measured by reduction in sunburn only, knowing that the overall UV exposure and risk for development of BCC and SCC would also decrease,[17] benefiting the cost-effectiveness ratio.

Challenges for primary prevention

Effective primary prevention is faced with some important challenges; below we provide a non-exhaustive overview. Behavioral changes, needed for successful primary prevention, are difficult to implement in the general population as shown by the Australian example. Its well known '*Slip, slop, slap!'* campaign advises people to spend time in the shade between 11am and 3pm, cover up with a t-shirt, hat and sunglasses and to use a sunscreen generously. Since 1980 there have been enormous efforts to promote sun safe behavior in Australia using multi-component and community-wide programs.[18] Unfortunately, people enjoy being in the sun and tanned skin is still considered as a sign of beauty. And the visible negative effects of UV radiation, such as solar aging and development of skin cancer develop with a significant delay. Research on sun protection in schools and families in Australia indicates that despite the programs, the rates of sun protection remain unsatisfactory.[19,20] More recently, however, a positive trend was seen with an increase in sunscreen use and a consistently high use of sunglasses; however seeking shade, staying inside and wearing protective clothing remained low.[21] And exactly those measurements are known to be most protective; as some studies actually show that sunscreen use is associated with increased intentional tanning and a moderate increased MM risk.[22,23]

Likewise, a change in mentality concerning the use of sunbeds is needed. In Belgium, 16% of the population stated to have had at least 1 tanning session in the past 12 months, with 8% stating that they use indoor tanning devices at least 5 times a year.[24] The users are predominantly young females. The Belgian government recently introduced regulations banning those with a history of skin cancer,

skin type 1 and minors, from using indoor tanning facilities.[25] Unfortunately, more than 90% of the indoor tanning centers ignored these regulations, with half surpassing the intensity of 0.3 W/m^2 UV radiation.[26] Moreover, the industry makes false claims concerning possible positive effects of indoor tanning. These profess that indoor tanning will 'increase vitamin D production, improve bone structure, benefit the immune system and cure various skin diseases'. Because of the failed self-control by the industry and the carcinogenic effects, the Belgian government acknowledged the importance of this matter and gave it a prominent place on the policy agenda.

A last factor interfering with effective primary prevention is, as mentioned above, the relation between UVB radiation and vitamin D metabolism. This vitamin is essential for calcium homeostasis and bone development, and vitamin D3 is synthesized in the skin under the influence of UVB radiation. Because serum 25-hydroxyvitamin D levels are sensitive to amounts of vitamin D consumption and UVB exposure, the measurement of serum 25-hydroxyvitamin D levels is commonly used as a marker of individual vitamin D status. Several recent meta-analyses could not confirm the health benefits supposedly associated with increased 25-hydroxyvitamin D. Despite high doses of supplementation of ≥50 μg per day, administered to individuals with low vitamin D status before randomization, even on endpoints as osteoporosis, fractures or falls.[27–29] The exposure to artificial or natural UV for increasing vitamin D is not more efficient than taking oral supplements of vitamin D, while it increases the risk for skin cancer. In the current climate of attention for vitamin D status and sunbed use or sun exposure, the general population, and even clinicians should be informed about the lack of evidence.

SECONDARY PREVENTION

BCC screening

Because skin examination and dermoscopy is a simple non-invasive technique, several early detection initiatives exist, of which most focus on MM. However the majority of skin cancers patients suffer from NMSC, resulting in 35% of the total cost of skin cancer in Belgium. Based on the WHO criteria, we questioned the role for simultaneous early detection of BCC - in which the main outcome of mortality is absent - as an answer to the growing economic burden. In chapter 7, we found that BCC grows slowly and increases with a median diameter of 0.5 mm over 10 weeks. Delay in diagnosis and appropriate treatment are the most important underlying causes in the occurrence of giant BCC or metastasis. The early detection and initial adequate treatment of BCC seems to be crucial for BCC located on the face, more specifically in the H-zone, as small changes in size on this location can dramatically affect treatment options, their effectiveness and associated costs. Despite the above, it needs to be recognized that, the effectiveness of BCC screening can only be justified by the overall

benefit of skin cancer screening, since no method exists to date to solely detect facial BCC. On the other hand, our findings support the inclusion of BCC in screening initiatives, a topic in the prevention of skin cancer that was, to our knowledge, not addressed earlier.

Clinical effectiveness of skin cancer screening

Mass population-based screening by means of whole body examination in asymptomatic persons has not been proven cost-effective, although the experience in Germany seems to suggest that such screening is feasible and could reduce skin cancer burden.[30] We proposed a new technique and compared it to the standard screening method in two socio-economical similar populations; these results are described in chapter 4. The novel lesion-directed approach implied that screenees were invited to present with a specific lesion meeting criteria listed on the invitation (ABCD rule, ugly duckling sign, new lesion since more than 4 weeks and/or red non-healing lesions). Based on a smaller pilot study we hypothesized that the lesion-directed screening (LDS) would increase the a priori chance of skin cancer and could be more efficient than a total body examination (TBE).

Our work showed that a systematic screening initiative seems achievable in Belgium, and that participation rate is remarkably higher in TBE than in LDS (17.9% versus 3.3%). The TBE participation was comparable to the participation rate of 19.1% in the German state where the SCREEN project was organized.[31] We observed a high male participation; 43.8% compared to 26.4% in Germany. Since our studies were conducted in Belgium we cannot exclude an effect of awareness resulting from the Euromelanoma initiative. This is an opportunistic early detection campaign that has been conducted annually in Belgium since 1999. The Euromelanoma day is now also organized in 31 European countries with the main objective to offer free screenings by dermatologists and inform on skin cancer and its prevention.[32] In our study, 38.2% of the screening participants previously received a skin check. This high number could be explained by a combination of several factors; the rising awareness for skin cancer in general, healthy subject bias and effects of the Euromelanoma campaigns. In order to have as minimal contamination as possible, the longest duration feasible between the Euromelanoma campaign (launched in May) and our screening study was established (March/April).

The two screening methods yielded the same number of skin cancer per 100 participants, though the diagnostic yield per 100 invitees was 5 times higher for the TBE method due to the significant difference in participation. As for the negative consequences, i.e. false positives or unnecessary excisions and anxiety; we reached a high positive predictive value of 56.6% compared to other screening initiatives (22.2% in the 2009 Euromelanoma campaign and 25.7% in the SCREEN project).[33,34] In addition, participant's anxiety measured before and immediately after screening did not change significantly, which is a criticized undesired side effect of all screening initiatives. Since LDS

had a similar detection rate of 3.2% as TBE, though 5.6 times less time-consuming, we hypothesized that LDS by dermatologists could be an alternative screening method, especially in health care systems with limited budget and, or waiting lists. In addition, only one skin cancer was found by total skin examination in the LDS group if the lesion of concern was not malignant. This suggests that a total skin examination is mainly indicated in case the participant presented with a suspicious lesion.

Cost-effectiveness of skin cancer screening

In contrast to our main hypothesis, we could not demonstrate an economic benefit from a lesion-directed technique. This was mainly due to the significantly lower participation rate (17.9% versus 3.3%) (chapter 5). Both screening methods ranged below the Belgian willingness-to-pay threshold. Our research findings did however demonstrate a clear benefit, in terms of cost-effectiveness for females over males for both methods (ICER females € 18 687 - 19 470 versus € 33 072 - 34 836 for males). Presumably, this finding can be attributed to the higher incidence of MM in females, and especially in the age group of 35 - 64 years (male/female ratio is 0.6).[35]

The base case scenario (i.e. one time screening in the adult population) is most cost-effective. Screening from 18 years on seems to be more cost-effective than from 40 years. An argument for the latter is the more important gain in QOL and productivity in case of early detection in younger age groups. However, several scientific findings argue the opposite; in Germany the nation-wide screening is organized every 2-years from the age of 35 years, though this decision was solely based on observational results and a micro-simulation model examining MM mortality, not QOL; nor comparing different age-scenarios.[36] To date no cost-effectiveness study using QALY as an outcome measurement, published different age-scenarios.[37–40] The only study that included QOL, examined only a one-time screening scenario from the age of 50 years, and the result was clearly more cost-effective than our screening strategy ($ 10 100/QALY).[38] In this discussion, several methodological issues should be taken in account, and could explain the relative benefit of inviting the population from the age of 18 years old, observed in our study. To the best of our knowledge, the Markov model presented is the *first* to include NMSC, the indirect costs due to productivity losses, the cost of death *and* QOL. On the contrary, several studies demonstrate that in case the cost per life-years gained (LYG) is the only outcome of interest,[39] prevalence of disease in participants is pivotal in the cost-effectiveness ratio per LYG.[37]

In accordance with the study of Losina et al., our research demonstrated that repeated screenings would be less cost-effective, presumed as a result of the rising intervention costs.[38] When comparing two screening intervals during a period of 20 years with a time horizon of 50 years, the TBE strategy is most cost-effective for males every 5-years and females every 2-years. When organizing repeated

lesion directed screenings, this would be most cost-effective every 2-years compared to screening intervals of 5-years for both sexes, but differences are minimal (Table 1). Nevertheless, with the background knowledge that defining the interval and target population for cervix-, colorectal- and breast cancer screening in Belgium was a continuous process, the aforementioned findings need to be confirmed and corroborated in order to determine the most optimal target group and screening interval.[41–43]

Table 1. Cost-effectiveness ratio of different preventive strategies and scenarios

Intervention	Level	Cost-effectiveness (cost/QALY)	
		Males	Females
Ban on sunbed use	Primary	Cost-saving	Cost-saving
Prevention campaign	Primary	Cost-saving	Cost-saving
Screening time horizon 20 years			
TBE 18 years one time	Secondary	€ 33 072	€ 18 687
LDS 18 years one time	Secondary	€ 34 836	€ 19 470
TBE 40 years one time	Secondary	€ 35 622	€ 21 841
LDS 40 years one time	Secondary	€ 36 348	€ 23 485
Screening time horizon 50 years			
TBE 18 years one time	Secondary	€ 9 253	€ 5 722
LDS 18 years one time	Secondary	€ 10 262	€ 5 549
TBE every 2 years	Secondary	€ 12 180	€ 6 021
LDS every 2 years	Secondary	€ 12 404	€ 5 436
TBE every 5 years	Secondary	€ 11 811	€ 6 060
LDS every 5 years	Secondary	€ 12 758	€ 5 671

Patient specific data gathered in the prospective clinical trial, was inputted in the Markov model and was subjected to the corresponding uncertainty around each parameter. In practice, even for economic evaluations performed parallel to clinical trials, several input data needs to be synthesized from other studies in order to evaluate the cost-effectiveness with the best knowledge at hand. The one-way and probabilistic sensitivity analyses are, because of the above, as important as the main outcome since it allows to systematically investigate all influencing factors. The 95% CI for each input parameter is necessary to quantify the uncertainty. In deducted estimations and calculations, the 95% CI is not at one's disposal; and by convention a 30% interval is applied.[44] This was the case for utilities and costs of skin cancer, as well as the progression rates. As mentioned earlier, we found an ICER just below the Belgian willingness-to-pay threshold, however the PSA suggests that, given the parameter uncertainty modeled, the ICER is likely to be between € 23 251 – € 41 468 per QALY gained for TBE in

males. In addition, the one-way sensitivity analyses demonstrate that natural progression is the most decisive parameter in the overall uncertainty around the outcome. In case a variation of 30% is applied around the progression, the ICER clearly exceeds the threshold at € 60 000 per QALY gained. As discussed above, these transitions and MM pathway are methodological assumptions, and long-term observational data is needed to accurately calculate these input parameters. The sensitivity analyses, in this way, underline the importance of gathering additional knowledge on this crucial determinant in the evaluation of skin cancer screening.

Challenges for secondary prevention

Several important challenges and controversies concerning skin cancer screening and early detection need to be discussed. Arguments supporting early detection are that significant lower melanoma Breslow thickness has been demonstrated when melanomas were detected (i) during physician clinical examination compared to by patients or their family members.[45–47] A mean reduction of 0.55 mm in thickness is seen when melanomas are detected by clinicians,[47] and a TBE in the last 3 years prior to MM diagnosis is inversely associated with MM thickness.[46] In the US, the incidence of all thickness MM is still increasing,[48,49] and among patients of lower SES with limited access to care, the highest increases were seen for melanomas of 2.01 mm up to more than 4.01 mm thickness.[50] (ii) by a dermatologist compared to other physicians,[51,52] and (iii) using dermoscopy instead of a NEE.[53] In addition to the above, the association between dying from MM and increasing tumor thickness has been demonstrated incontestable by several studies.[54–61] Hazard ratios up to 32.6 for melanoma-related mortality have been observed for Breslow thickness of 4.01 mm compared to 0.50 mm.[55] However, no prospective controlled studies could currently demonstrate a reduction in melanoma-specific mortality due to screening, nor are there studies proving the contrary.

Following the German SCREEN study in 2003-2004, including 360 288 adults, the proportion of thin melanomas increased significantly from 52 to 64% and a reduction in mortality was observed.[30] Boniol et al. argue that this transient mortality decrease was observed to close to the screening and possibly due to bias in registration of the cause of death.[62] To the present day, there is no consistent evidence that screening results in a decrease of disease-specific mortality; on the contrary some argue that early detection initiatives and awareness will induce *overdiagnosis* of lesions without malignant potential and only cause significant morbidity.[63] On the other hand, it has been shown in a retrospective study of 2000 individuals, that in case the melanoma was detected by a dermatologist, this lead to improved survival.[51] Older men (>60 years) living alone presented with more advanced stage at diagnosis and had a reduced MM specific survival.[64]

A limitation of the presented study is that the magnitude of overdiagnosis was not quantified, since knowledge on the exact proportion of patients diagnosed with a MM that will progress - or not - is missing. A worst-case scenario analysis, with the hypothetical presumption that 25% of all melanomas detected and treated during the screening would not progress, increased the ICER for the base-case screening scenario significantly up to € 29 897 – € 32 561 for females and € 58 388 – € 59 948 for males. In the above assumption of overdiagnosis, the ICER would thus exceed the willingness-to-pay threshold for males.

An argument contrasting the above criticism of overdiagnosis, is the development of melanoma, which involves successive biologic phenomena, with cell cycle dysregulation, invasion of the dermis, which can ultimately lead to distant metastases. Some melanomas behave more aggressively and demonstrate events early that usually occur later in the process. As a consequence the concept of different subtypes of *MM kinetics* (slow-growing, medium-growing versus rapid-growing) is postulated by several authors.[65–67] Presence of a BRAF mutation is not necessarily associated with rapid tumor growth,[68] yet on the other hand melanomas that show initial fast growth seem to be prognostically less favorable, and a high mitotic index predicts a short-term relapse.[69] Some believe that these rapid-growing melanomas are the true killers, and therefore, without diagnosing these, early detection will not result in any survival benefit, but mainly overdiagnosis. The difficulty is also identifying risk factors associated with thick, fast-growing melanomas. Since this subtype does not develop in the typical high-risk groups, but often in older male patients with few solar lentigines and nevi. Clinically, these fast growing melanomas are often amelanotic symmetrical lesions, lacking typical clinical and dermoscopic features, which makes them more difficult to diagnose in an early phase.[65] Such lesions would be missed by one-time or routine screenings, inherent to their fast growth in a number of weeks. However, the awareness and early detection of slow- or medium growing lesions may impact survival in a positive way. The most common histological subtype of MM, namely the superficial spreading melanoma, also develops a nodular and aggressive component, since more than 50% of metastatic patients had initially a superficial spreading MM.[70] The authors conclude that “as superficial spreading melanomas are growing over a longer period to become invasive and potentially metastatic, there might be a chance to focus prevention programs not only on fast growing tumors but also on slowly changing tumors.”

It is argued that the increasing incidence of thin melanomas and the stable mortality are actually a result of a steady improvement in our ability to diagnose MM early, with a resulting continuous decline in the average thickness of melanoma at diagnosis. Following the aforementioned argument, the proportion of thick melanomas should also steadily decrease. Unfortunately, this is not the case and the absolute number of thick melanomas is not declining up to now.[71] A combination of factors

may explain the observed trend; increased awareness, diagnostic drift and overdiagnosis of *in situ* and thin melanomas as mentioned before, or as a third argument, the fact that thick melanomas are a continually smaller proportion of a continually increasing number of melanomas and lastly a changing tumor biology as suggested by the group of Autier et al. The authors studied cohort effects of melanoma mortality that support the drastic effect of UV exposure at young age in the MM biology. The group hypothesizes that melanomas will become gradually less aggressive and deadly since the importance of UV protection in children became highly recognized.[72] Nevertheless, the beneficial effect of early detection of MM and NMSC must also be seen in the light of alternative non-survival outcomes, including reduced morbidity and enhanced QOL as suggested by Lewandrowski et al.[73] Our research focused on the intermediary outcome of cost-effectiveness, taking all these alternative non-survival benefits into account. We believe that in the current health economic climate such endpoints are of great importance to support the decision makers in their assessment of screening initiatives.

Participation in screening is an important concern in all cancer screenings, and especially in individuals of lower socio-economic backgrounds. In Belgium, the health care system is organized around primary care by a general practitioner, holding a global medical record of the majority of his patients. Because of the latter, patients are encouraged to have a primary care physician that is the first contact in case of medical problems. Currently, a fee-for-service applies in Belgium for primary care, although it is known that this encourages over-servicing.[74–76] A mixed payment incentive such as fee-for-service and specific payments to meet population health targets is known to effect providers behavior and increase quality, especially for chronic pathologies (such as diabetes and hypertension).[77,78] In addition target-based prevention modules (i.e. screening for colon cancer, vaccination and other preventive measures) including for skin cancer, could increase the effectiveness and participation of population-based prevention strategies significantly.

Screening physicians and dermoscopy

The presented clinical screening study was performed by dermatologists highly trained in dermoscopy. Because of the known interaction between the observer's training and accuracy of the technique, the diagnostic performance by Flemish dermatologists was examined. In chapter 7 we described our results based on the image analyses in a web-based application, demonstrating respectively clinical and dermoscopic photographs of the lesions presented at the LDS screening. A high sensitivity and specificity was observed of respectively 84.6 and 93.5%. Surprisingly, we could not demonstrate additional benefit of using dermoscopy in terms of NNE, the most important side effect of screening. Due to the method of case collection, we cannot exclude the possible inclusion of lesions with more clear visual and clinical features. On the other hand one could argue, because based on an early

detection initiative, relative smaller lesions, more difficult to diagnose were included. Dermoscopy however significantly increased the certainty about making a correct diagnosis, and this was mainly the case for seborrheic keratosis, Bowen's disease and MM.

Our findings suggest it would be interesting to repeat this study among trained general practitioners to evaluate the diagnostic accuracy and its impact on the early detection of skin cancer in general practice, where according to some a need for diagnostic tools exists.[79,80] In our opinion, the most representative study is performed in a real-life setting, since it is known that a digital evaluation and paucity of clinical information can influence performance in a negative way, namely improved sensitivity with decreased specificity. In addition, the adequate amount of training should be investigated, since significant differences are reported in literature, and it is acknowledged that the level of training needed to ameliorate sensitivity is relatively less than for improving specificity.[81,82]

RECOMMENDATIONS FOR FURTHER RESEARCH

Our findings inevitably led to several additional questions that are important to address in future research. Below, we provide a non-limitative overview of these questions and lacunas that arose in the setting of our analyses.

Mortality as a result of NMSC is rare, though the disease influences QOL in a distinct way. The current generic instruments to measure the QOL are lacking in sensitivity to correctly calculate the impact. Since these tumors are frequently located in important esthetic units and demand surgery, BCC and SCC result in distinct functional limitations and cosmetic concerns not captured in the classical generic instruments such as the EQ-5D. Several dermatology-specific or disease-specific instruments have been studied in this respect; the dermatology life quality index (DLQI), Skindex-16 and skin cancer index (SCI).[83–87] It seems that the SCI is the most sensitive and captured significant changes in all subscales as compared to the DLQI.[88] Efforts should be made to generate utility weightings for these instruments to develop more robust cost-effectiveness analyses. In addition to more accurate QOL data, the main hazard remains the poor registration of NMSC in most countries, including Belgium. As only the first histological NMSC is registered, subsequent tumors are not included, and multiple tumors are not differentiated, we are continuously underestimating the true burden of NMSC. Flohil et al. performed an appreciable audit in Europe, demonstrating that up to 24.1% of the BCCs in Europe are not histologically confirmed.[89] Registration of NMSC should be improved and consensus standards need to be developed.

Unraveling the biology and natural progression of the different types of skin cancer would benefit preventive studies in a significant way. As mentioned before, the progression of BCC was determined

as 1 cm per 3.8 years or 1.2 mm per 6 months, based on the results of Kirkup et al.[90] The transition risk from SCC stage 0-II to stage III or IV was estimated as 0.5% per 6 months based on the estimation of Smoller et al. (1-2% per year).[91] For MM we used a calibration method based on the total number of deaths annually, in the absence of accurate measurements. The one-way sensitivity analyses show that for skin cancer screening, natural progression and utilities of MM are the most important variables influencing the ICER. To more adequately assess the effect of prevention, efforts should be made to examine these parameters more thoroughly. In addition to the growth rate, identifying patients who are at risk for developing a more aggressive or deadly course of skin cancers by predictive risk factors or biomarkers would benefit the research field.[92–94]

Knowledge about suitable interventions for permanently changing the population's behavior is needed. Several interventions use a multi-component approach that combines strategies aimed at individuals, mass-media campaigns, environment and policy. The yearly Euromelanoma campaign, a well-organized opportunistic early detection initiative, its main objective is to inform and raise awareness in the general population using varied media. Research and surveillance is needed to determine the contribution of individual components to help prioritize and maximize the use of limited resources. Current evidence suggests that intentional tanning is strongly associated with a preference for tanned skin and other appearance-focused behaviors; future messages could focus on the appearance-related harms of excessive UV exposure.[95] To reduce harms from indoor tanning one could examine the use of topical, sunless tanning products, although the effect of dihydroxyacetone inhalation is unknown and the promotion of sunless tanning products does not address the underlying social norms that drive tanning behaviors.

Randomized controlled trials documenting the effect of screening on mortality are absent. Studies with sufficient power and long-term follow-up are needed, though due to the relatively low incidence of MM and mortality such trials would take a long time and are costly.[73] The first large European pilot study examining an organized population based screening was an ecological study organized in 2003-2004 with a 19% participation rate.[96] A reduction in mortality was observed in 2008-2009 for the entire state,[97] however criticized to be too close to the intervention.[62] Indeed, one could assume that since the lag-time for breast- and prostate cancer is respectively 10.7 years and 10.3 years before one death can be prevented per 1000 patients screened,[96] definite consensus on the presence - or absence - of a reduction in mortality is still some years ahead. Especially, since the aforementioned estimations were estimated in a *controlled* group setting at higher incidence of disease. A feasibility study published in 2000, calculated that 560 000 adults should be randomized in an intervention and control group, to find a mortality reduction of 20% in 15 years.[98] Overdiagnosis and increased treatment of clinically insignificant cancers should be a major focus, in order to accurately assess all

key aspects of skin cancer screening. Further research should be designed comparing screened versus unscreened individuals head-to-head. In addition, new techniques, that are less operator dependent such as digital image analysis systems, could offer interesting novel perspectives in the setting of skin cancer screening.

As mentioned at the start of this dissertation, skin cancer prevention is currently a major subject of interest. The presented research was designed to examine the highly discussed interventions from a clinical and health-economical point of view. It is our firm hope that the presented results will help researchers in future studies to determine the most opportune and cost-effective strategy in addressing the skin cancer epidemic.

REFERENCES

1. Flohil, S. C. et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br. J. Dermatol. 167 Suppl 2, 22–28 (2012).
2. Kiiski, V. et al. Risk factors for single and multiple basal cell carcinomas. Arch. Dermatol. 146, 848–855 (2010).
3. Tarricone, R. Cost-of-illness analysis: What room in health economics? Health Policy 77, 51–63 (2006).
4. Veierød, M. B., Couto, E., Lund, E., Adami, H.-O. & Weiderpass, E. Host characteristics, sun exposure, indoor tanning and risk of squamous cell carcinoma of the skin. Int. J. Cancer 135, 413–422 (2014).
5. Yeh, I. Recent advances in molecular genetics of MM progression: implications for diagnosis and treatment. F1000Research 5, (2016).
6. Whiteman, D. C., Whiteman, C. A. & Green, A. C. Childhood sun exposure as a risk factor for MM: a systematic review of epidemiologic studies. Cancer Causes Control CCC 12, 69–82 (2001).
7. Dennis, L. K. et al. Sunburns and risk of cutaneous MM: does age matter? A comprehensive meta-analysis. Ann. Epidemiol. 18, 614–627 (2008).
8. Tripp, M. K., Watson, M., Balk, S. J., Swetter, S. M. & Gershenwald, J. E. State of the science on prevention and screening to reduce MM incidence and mortality: The time is now. CA. Cancer J. Clin. (2016). doi:10.3322/caac.21352
9. Pawlak, M. T. et al. Legislation restricting access to indoor tanning throughout the world. Arch. Dermatol. 148, 1006–1012 (2012).
10. Leiter, U. et al. Hazard rates for recurrent and secondary cutaneous MM: an analysis of 33,384 patients in the German Central Malignant MM Registry. J. Am. Acad. Dermatol. 66, 37–45 (2012).
11. Joosse, A. et al. Gender differences in MM survival: female patients have a decreased risk of metastasis. J. Invest. Dermatol. 131, 719–726 (2011).
12. Joosse, A. et al. Sex is an independent prognostic indicator for survival and relapse/progression-free survival in metastasized stage III to IV MM: a pooled analysis of five European organisation for research and treatment of cancer randomized controlled trials. J. Clin. Oncol. 31, 2337–2346 (2013).

13. Joosse, A. et al. Sex differences in MM survival are not related to mitotic rate of the primary tumor. Ann. Surg. Oncol. 22, 1598–1603 (2015).

14. Balch, C. M. et al. Age as a predictor of sentinel node metastasis among patients with localized MM: an inverse correlation of MM mortality and incidence of sentinel node metastasis among young and old patients. Ann. Surg. Oncol. 21, 1075–1081 (2014).

15. Balch, C. M. et al. Age as a prognostic factor in patients with localized MM and regional metastases. Ann. Surg. Oncol. 20, 3961–3968 (2013).

16. Staples, M., Marks, R. & Giles, G. Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985-1995: are primary prevention programs starting to have an effect? Int. J. Cancer 78, 144–148 (1998).

17. Greinert, R. et al. European Code against Cancer 4th Edition: Ultraviolet radiation and cancer. Cancer Epidemiol. 39 Suppl 1, S75-83 (2015).

18. Montague, M., Borland, R. & Sinclair, C. Slip! Slop! Slap! and SunSmart, 1980-2000: Skin cancer control and 20 years of population-based campaigning. Health Educ. Behav. Off. Publ. Soc. Public Health Educ. 28, 290–305 (2001).

19. Montague, M., Borland, R. & Sinclair, C. Slip! Slop! Slap! and SunSmart, 1980-2000: Skin cancer control and 20 years of population-based campaigning. Health Educ. Behav. Off. Publ. Soc. Public Health Educ. 28, 290–305 (2001).

20. Jones, S. B. W., Beckmann, K. & Rayner, J. Australian primary schools' sun protection policy and practice: evaluating the impact of the National SunSmart Schools Program. Health Promot. J. Aust. Off. J. Aust. Assoc. Health Promot. Prof. 19, 86–90 (2008).

21. Koch, S. et al. Trends in sun-protection behaviour in Australian adults 2007-2012. Australas. J. Dermatol. (2016). doi:10.1111/ajd.12433

22. Autier, P., Boniol, M. & Doré, J.-F. Sunscreen use and increased duration of intentional sun exposure: still a burning issue. Int. J. Cancer 121, 1–5 (2007).

23. Autier, P. Sunscreen abuse for intentional sun exposure. Br. J. Dermatol. 161 Suppl 3, 40–45 (2009).

24. IPSOS. Kankerbarometer: steekproef in de belgische papulatie in 2015.

25. FOD Economie. Reglementering veiligheid van zonnecentra. (2016). Available at: http://economie.fgov.be/nl/ondernemingen/securite_produits_et_services/Zonnecentra/#.VvJdV9LhDcs. (Accessed: 23rd March 2016)

26. Prosafe. Joint action on sunbeds 2008-2009 and 2010-2011. (2012).

27. Theodoratou, E., Tzoulaki, I., Zgaga, L. & Ioannidis, J. P. A. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 348, g2035 (2014).

28. Bolland, M. J., Grey, A. & Reid, I. R. Differences in overlapping meta-analyses of vitamin D supplements and falls. J. Clin. Endocrinol. Metab. 99, 4265–4272 (2014).

29. Autier, P., Boniol, M., Pizot, C. & Mullie, P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2, 76–89 (2014).

30. Breitbart, E. W. et al. Systematic skin cancer screening in Northern Germany. J. Am. Acad. Dermatol. 66, 201–211 (2012).

31. Breitbart, E. W. et al. Systematic skin cancer screening in Northern Germany. J. Am. Acad. Dermatol. 66, 201–211 (2012).

32. Forsea, A. M., Euromelanoma Working Group & del Marmol, V. Impact, challenges and perspectives of Euromelanoma, a pan-European campaign of skin cancer prevention. J. Eur. Acad. Dermatol. Venereol. JEADV 27, 1317–1319 (2013).

33. Waldmann, A. et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. Arch. Dermatol. 148, 903–910 (2012).

34. van der Leest, R. J. T. et al. The Euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010. J. Eur. Acad. Dermatol. Venereol. JEADV 25, 1455–1465 (2011).

35. Stichting Kankerregister. Incidence MM, basal cell carcinoma and squamouis cell carcinoma in Belgium, 2011. (2016).

36. Eisemann, N., Waldmann, A., Garbe, C. & Katalinic, A. Development of a microsimulation of MM mortality for evaluating the effectiveness of population-based skin cancer screening. Med. Decis. Mak. Int. J. Soc. Med. Decis. Mak. 35, 243–254 (2015).

37. Girgis, A., Clarke, P., Burton, R. C. & Sanson-Fisher, R. W. Screening for MM by primary health care physicians: a cost-effectiveness analysis. J. Med. Screen. 3, 47–53 (1996).

38. Losina, E. et al. Visual screening for malignant MM: a cost-effectiveness analysis. Arch. Dermatol. 143, 21–28 (2007).

39. Freedberg, K. A., Geller, A. C., Miller, D. R., Lew, R. A. & Koh, H. K. Screening for malignant MM: A cost-effectiveness analysis. J. Am. Acad. Dermatol. 41, 738–745 (1999).

40. Beddingfield, F. C. The MM epidemic: res ipsa loquitur. The Oncologist 8, 459–465 (2003).

41. Pil, L., Fobelets, M., Putman, K., Trybou, J. & Annemans, L. Cost-effectiveness and budget impact analysis of a population-based screening program for colorectal cancer. Eur. J. Intern. Med. 32, 72–78 (2016).

42. Demarteau, N., Van Kriekinge, G. & Simon, P. Incremental cost-effectiveness evaluation of vaccinating girls against cervical cancer pre- and post-sexual debut in Belgium. Vaccine 31, 3962–3971 (2013).

43. Heijnsdijk, E. a. M. et al. Cost-effectiveness of prostate cancer screening: a simulation study based on ERSPC data. J. Natl. Cancer Inst. 107, 366 (2015).

44. KCE. Belgische richtlijn voor economische evaluaties en budget impact analyses. Rep. 183A (2012).

45. Swetter, S. M., Pollitt, R. A., Johnson, T. M., Brooks, D. R. & Geller, A. C. Behavioral determinants of successful early MM detection: role of self and physician skin examination. Cancer 118, 3725–3734 (2012).

46. Aitken, J. F., Elwood, M., Baade, P. D., Youl, P. & English, D. Clinical whole-body skin examination reduces the incidence of thick MMs. Int. J. Cancer 126, 450–458 (2010).

47. Terushkin, V. & Halpern, A. C. MM early detection. Hematol. Oncol. Clin. North Am. 23, 481–500, viii (2009).

48. Jemal, A. et al. Recent trends in cutaneous MM incidence and death rates in the United States, 1992-2006. J. Am. Acad. Dermatol. 65, S17-25–3 (2011).

49. Shaikh, W. R. et al. MM Thickness and Survival Trends in the United States, 1989 to 2009. J. Natl. Cancer Inst. 108, (2016).

50. Linos, E., Swetter, S. M., Cockburn, M. G., Colditz, G. A. & Clarke, C. A. Increasing burden of MM in the United States. J. Invest. Dermatol. 129, 1666–1674 (2009).

51. Pennie, M. L. et al. MM outcomes for Medicare patients: association of stage and survival with detection by a dermatologist vs a nondermatologist. Arch. Dermatol. 143, 488–494 (2007).

52. Carli, P. et al. Dermatologist detection and skin self-examination are associated with thinner MMs: results from a survey of the Italian Multidisciplinary Group on MM. Arch. Dermatol. 139, 607–612 (2003).

53. Haenssle, H. A. et al. MM thickness: the role of patients' characteristics, risk indicators and patterns of diagnosis. J. Eur. Acad. Dermatol. Venereol. JEADV 29, 102–108 (2015).

54. Owen, S. A. et al. Identification of higher risk thin MMs should be based on Breslow depth not Clark level IV. Cancer 91, 983–991 (2001).

55. Luke, C. G., Coventry, B. J., Foster-Smith, E. J. & Roder, D. M. A critical analysis of reasons for improved survival from invasive cutaneous MM. Cancer Causes Control CCC 14, 871–878 (2003).

56. Leiter, U., Buettner, P. G., Eigentler, T. K. & Garbe, C. Prognostic factors of thin cutaneous MM: an analysis of the central malignant MM registry of the german dermatological society. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 22, 3660–3667 (2004).

57. Reyes-Ortiz, C. A., Goodwin, J. S., Freeman, J. L. & Kuo, Y.-F. Socioeconomic status and survival in older patients with MM. J. Am. Geriatr. Soc. 54, 1758–1764 (2006).

58. Zell, J. A. et al. Survival for patients with invasive cutaneous MM among ethnic groups: the effects of socioeconomic status and treatment. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 26, 66–75 (2008).

59. Pollack, L. A. et al. MM survival in the United States, 1992 to 2005. J. Am. Acad. Dermatol. 65, S78-86 (2011).

60. Green, A. C., Baade, P., Coory, M., Aitken, J. F. & Smithers, M. Population-based 20-year survival among people diagnosed with thin MMs in Queensland, Australia. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 30, 1462–1467 (2012).

61. Marashi-Pour, S., Morrell, S., Cooke-Yarborough, C., Arcorace, M. & Baker, D. Competing risk analysis of mortality from invasive cutaneous MM in New South Wales: a population-based study, 1988-2007. Aust. N. Z. J. Public Health 36, 441–445 (2012).

62. Boniol, M., Autier, P. & Gandini, S. MM mortality following skin cancer screening in Germany. BMJ Open 5, e008158 (2015).

63. Bigby, M. Why the evidence for skin cancer screening is insufficient: lessons from prostate cancer screening. Arch. Dermatol. 146, 322–324 (2010).

64. Eriksson, H. et al. Later stage at diagnosis and worse survival in cutaneous malignant MM among men living alone: a nationwide population-based study from Sweden. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 32, 1356–1364 (2014).

65. Liu, W. et al. Rate of growth in MMs: characteristics and associations of rapidly growing MMs. Arch. Dermatol. 142, 1551–1558 (2006).

66. Argenziano, G., Zalaudek, I. & Ferrara, G. Fast-growing and slow-growing MMs. Arch. Dermatol. 143, 802-803-804 (2007).

67. Lipsker, D. Growth rate, early detection, and prevention of MM: MM epidemiology revisited and future challenges. Arch. Dermatol. 142, 1638–1640 (2006).

68. Mar, V. J. et al. The role of BRAF mutations in primary MM growth rate and survival. Br. J. Dermatol. 173, 76–82 (2015).

69. Grob, J. J. et al. The kinetics of the visible growth of a primary MM reflects the tumor aggressiveness and is an independent prognostic marker: a prospective study. Int. J. Cancer 102, 34–38 (2002).

70. Richtig, G., Richtig, E., Massone, C. & Hofmann-Wellenhof, R. Analysis of clinical, dermoscopic and histopathological features of primary MMs of patients with metastatic disease--a retrospective study at the Department of Dermatology, Medical University of Graz, 2000-2010. J. Eur. Acad. Dermatol. Venereol. JEADV 28, 1776–1781 (2014).

71. van der Leest, R. J. T. et al. Increasing time trends of thin MMs in The Netherlands: What are the explanations of recent accelerations? Eur. J. Cancer Oxf. Engl. 1990 51, 2833–2841 (2015).

72. Autier, P., Koechlin, A. & Boniol, M. The forthcoming inexorable decline of cutaneous MM mortality in light-skinned populations. Eur. J. Cancer Oxf. Engl. 1990 51, 869–878 (2015).

73. Curiel-Lewandrowski, C. et al. Survival is not the only valuable end point in MM screening. J. Invest. Dermatol. 132, 1332–1337 (2012).

74. Gosden, T. et al. Capitation, salary, fee-for-service and mixed systems of payment: effects on the behaviour of primary care physicians. Cochrane Database Syst. Rev. CD002215 (2000). doi:10.1002/14651858.CD002215

75. Robinson, J. C. Theory and practice in the design of physician payment incentives. Milbank Q. 79, 149–177, III (2001).

76. Devlin, R. A. & Sarma, S. Do physician remuneration schemes matter? The case of Canadian family physicians. J. Health Econ. 27, 1168–1181 (2008).

77. Giuffrida, A. et al. Target payments in primary care: effects on professional practice and health care outcomes. Cochrane Database Syst. Rev. CD000531 (2000). doi:10.1002/14651858.CD000531

78. Mcguire, T. G. in Handbook of Health Economics (ed. Newhouse, A. J. C. and J. P.) 1, Part A, 461–536 (Elsevier, 2000).

79. Koelink, C. J. L. et al. Diagnostic accuracy and cost-effectiveness of dermoscopy in primary care: a cluster randomized clinical trial. J. Eur. Acad. Dermatol. Venereol. JEADV 28, 1442–1449 (2014).

80. Koelink, C. J. L., Jonkman, M. F., Van Der Meer, K. & Van Der Heide, W. K. Examination of skin lesions for cancer: which clinical decision aids and tools are available in general practice? Eur. J. Dermatol. EJD 24, 297–304 (2014).

81. Vestergaard, M. E., Macaskill, P., Holt, P. E. & Menzies, S. W. Dermoscopy compared with naked eye examination for the diagnosis of primary MM: a meta-analysis of studies performed in a clinical setting. Br J Dermatol 159, 669–76 (2008).

82. Argenziano, G. et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 24, 1877–1882 (2006).

83. Shah, M. & Coates, M. An assessment of the quality of life in older patients with skin disease. Br. J. Dermatol. 154, 150–153 (2006).

84. Rhee, J. S. et al. Skin cancer and quality of life: assessment with the Dermatology Life Quality Index. Dermatol. Surg. Off. Publ. Am. Soc. Dermatol. Surg. Al 30, 525–529 (2004).

85. Chren, M.-M., Sahay, A. P., Bertenthal, D. S., Sen, S. & Landefeld, C. S. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. J. Invest. Dermatol. 127, 1351–1357 (2007).

86. Chen, T., Bertenthal, D., Sahay, A., Sen, S. & Chren, M.-M. Predictors of skin-related quality of life after treatment of cutaneous basal cell carcinoma and squamous cell carcinoma. Arch. Dermatol. 143, 1386–1392 (2007).

87. Steinbauer, J. et al. Quality of life in health care of non-MM skin cancer - results of a pilot study. J. Dtsch. Dermatol. Ges. J. Ger. Soc. Dermatol. JDDG 9, 129–135 (2011).

88. Rhee, J. S. et al. The skin cancer index: clinical responsiveness and predictors of quality of life. The Laryngoscope 117, 399–405 (2007).

89. Flohil, S. C. et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. Br. J. Dermatol. 167 Suppl 2, 22–28 (2012).

90. Kirkup, M. E. & De Berker, D. A. Clinical measurement of dimensions of basal cell carcinoma: effect of waiting for elective surgery. Br. J. Dermatol. 141, 876–879 (1999).

91. Smoller, B. R. Squamous cell carcinoma: from precursor lesions to high-risk variants. Mod. Pathol. Off. J. U. S. Can. Acad. Pathol. Inc 19 Suppl 2, S88-92 (2006).

92. Lugowska, I. et al. Serum markers in early-stage and locally advanced MM. Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med. 36, 8277–8285 (2015).

93. de Souza, C. F. et al. Mining gene expression signature for the detection of pre-malignant melanocytes and early MMs with risk for metastasis. PloS One 7, e44800 (2012).

94. Weber, J. et al. Expression of the MAGE-1 tumor antigen is up-regulated by the demethylating agent 5-aza-2'-deoxycytidine. Cancer Res. 54, 1766–1771 (1994).

95. Lin, J. S., Eder, M. & Weinmann, S. Behavioral counseling to prevent skin cancer: a systematic review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 154, 190–201 (2011).

96. Lee, S. J. et al. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. BMJ 346, e8441 (2013).

97. Katalinic, A. et al. Does skin cancer screening save lives?: an observational study comparing trends in MM mortality in regions with and without screening. Cancer 118, 5395–5402 (2012).

98. Aitken, J. F. et al. A randomised trial of population screening for MM. J. Med. Screen. 9, 33–37 (2002).

Appendix I

Cost-of-illness study based on patient questionnaires

In order to estimate the total economic burden of skin cancer on society, we conducted a bottom-up cost-of-illness study, based on retrospective information from Belgian patient questionnaires being gathered from 1st March 2015 until 30th June 2015. Dermatologists and oncologists working in general and university hospitals, small (< 200 beds), medium (200-400 beds) or big (> 400 beds) hospitals, as well as private practices were recruited in December 2014. These physicians were asked to give skin cancer patients the information about the study and to hand out the questionnaires to the patients. Eligible patients were those who were 18+, had a diagnosis of MSC, BCC and SCC maximum ten years ago and who presented to a participating physician between 1st March 2015 and 30th June 2015. Patients were asked questions about their medical consumption for their skin disease during the last six months, as well as productivity loss and quality of life. Questions concerned the number of consultations, number and type of examinations, drug use, number of days absent from work and health-related quality of life (based on the EQ-5D-5L questionnaire). Ethics committee approval and patient informed consents were obtained.

For some patient groups (all stages of SCC and the more severe lesions of MSC) the response rate was low. To increase the power of the study, we calculated the direct cost based on guidelines produced by EURODERM as well as dermatologist and oncologist expert opinions. For these groups with low sample, we constructed a care pathway that reflected current management patterns as accurate as possible. Also for large and aggressive BCCs, there was a low response rate, so from the cost of small BCC (<1cm) we calculated the cost of larger and aggressive BCCs based on the ratios reported by Rogers et al. [1]

Table A1. Epidemiologic input parameters

Parameter	Input value 18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	Source
PREVALENCE UNDIAGNOSED LESIONS								
BCC <1cm M	0.015	0.135	0.377	0.699	1.528	3.022	3.809	[2]
BCC <1cm F	0.035	0.150	0.633	0.799	1.419	2.033	2.275	[2]
BCC 1-2cm M	0.008	0.075	0.209	0.387	0.846	1.674	2.109	[2]
BCC 1-2cm F	0.019	0.083	0.350	0.443	0.786	1.126	1.260	[2]
BCC >2cm M	0.002	0.021	0.059	0.109	0.238	0.470	0.592	[2]
BCC >2cm F	0.005	0.023	0.098	0.124	0.221	0.316	0.354	[2]
BCC agr. hist. M	0.011	0.101	0.282	0.522	1.141	2.257	2.844	[2]
BCC agr. hist. F	0.026	0.112	0.472	0.597	1.059	1.518	1.699	[2]
SCC stage 0-II M	0.000	0.001	0.002	0.013	0.048	0.268	0.967	[2]
SCC stage 0-II F	0.001	0.002	0.010	0.033	0.095	0.222	0.419	[2]
SCC stage III M	0.000	0.000	0.000	0.001	0.006	0.031	0.112	[2]
SCC stage III F	0.000	0.000	0.001	0.004	0.011	0.026	0.049	[2]
SCC stage IV M	0.000	0.000	0.000	0.000	0.001	0.007	0.026	[2]
SCC stage IV F	0.000	0.000	0.000	0.001	0.003	0.006	0.011	[2]
MSC stage I M	0.065	0.173	0.328	0.527	0.805	1.156	1.132	[2]
MSC stage I F	0.128	0.311	0.488	0.543	0.704	0.767	0.502	[2]
MSC stage II M	0.019	0.049	0.094	0.151	0.230	0.331	0.324	[2]
MSC stage II F	0.029	0.070	0.109	0.122	0.158	0.172	0.112	[2]
MSC stage III M	0.000	0.000	0.000	0.000	0.000	0.000	0.000	[2]
MSC stage III F	0.000	0.000	0.000	0.000	0.000	0.000	0.000	[2]
MSC stage IV M	0.000	0.000	0.000	0.000	0.000	0.000	0.000	[2]
MSC stage IV F	0.000	0.000	0.000	0.000	0.000	0.000	0.000	[2]
Correction factor IKNL prevalence BCC/SCC				0.51				Based on mortality (IARC) and incidence (2010) BE versus NDL

Table A1. Epidemiologic input parameters (contd)

Parameter	Input value							Source
	18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	
INCIDENCE								
BCC M	0.001%	0.004%	0.013%	0.024%	0.053%	0.101%	0.107%	[3]
BCC F	0.002%	0.006%	0.024%	0.029%	0.055%	0.075%	0.078%	[3]
SCC M	0.000%	0.000%	0.001%	0.005%	0.018%	0.053%	0.123%	[3]
SCC F	0.000%	0.000%	0.002%	0.006%	0.017%	0.038%	0.076%	[3]
MSC I M	0.002%	0.004%	0.007%	0.010%	0.013%	0.019%	0.017%	[4]
MSC I F	0.005%	0.011%	0.017%	0.016%	0.015%	0.017%	0.009%	[4]
NATURAL PROGRESSION								
BCC				12.5%				[5]
SCC stage 0-II => III				1.0%				[6]
SCC stage III => IV				7.0%				calibration
MSC I/II => II/III				0.8%				calibration
MSC I/II => IV				0.7%				calibration

Table A1. Epidemiologic input parameters (contd)

Parameter	Input value							Source
	18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	
PROGRESSION TO METASTASES, AFTER TREATMENT								
SCC				0.23%				[7]
MSC stage I => MSC stage III				0.07%				[8]
MSC stage I => MSC stage IV				0.07%				[8]
MSC stage II => MSC stage III				0.47%				[8]
MSC stage II => MSC stage IV				0.47%				[8]
MSC stage III => MSC stage IV				2.26%				[9]
RR OF DEVELOPING MSC AFTER DIAGNOSES OF NMSC								
MSC after BCC				3.28				[10]
MSC after SCC				3.62				[10]
MORTALITY RATES								
Mortality due to skin cancer (first year)								
MSC stage IV				26.66%				[11] corrected for new therapies
SCC stage IV				13.55%				[12]
Mortality due to skin cancer (follow-up)								
MSC stage IV				M: 12.45% F: 7.65%				[11] corrected for new therapies
SCC stage IV				M: 6.33% F: 9.71%				[13]
Mortality due to other causes								
M	0.04%	0.05%	0.12%	0.33%	0.76%	1.97%	3.85%	Belgian life tables 2012
F	0.01%	0.02%	0.04%	0.13%	0.30%	0.71%	2.46%	

Health-related quality of life: utilities

Undiagnosed BCC, SCC stage 0-II and MSC stage 0-I were assigned the same utility as the population norm, which is 0.81.[14] The utility for undiagnosed SCC stage III-IV and MSC stage III-IV was calculated as the average of the population norm and the utility for diagnosis and treatment. There were too few returned patient questionnaires for SCC and MSC stage II-III and IV to have sufficient sample power, so the utilities of these stages (diagnosed) were calculated based on the ratio of the utilities in these stages compared to stage I, as described by Tromme et al.[15] The utility for BCC patients, who are in treatment or intense follow-up is derived from the study of Gaulin et al.[16] The utility for patients in long-term follow-up for BCC, SCC 0-II and MSC 0-I and II was defined to be the same as the population norm, since we assume that once the lesion has been excised, the quality-of-life will return to baseline on the long-term.

Table A2. Utilities assigned to the model states

Parameter	Utility	Source
General population	0.812	[14]
BCC undiagnosed	0.812	
D&T BCC	0.790	[16]
intensive FU BCC	0.790	[16]
longterm FU BCC	0.812	General population (assumption)
SCC 0-II undiagnosed	0.812	General population (assumption)
SCC III undiagnosed	0.631	
SCC IV undiagnosed	0.651	
SCC 0-II D&T	0.532	patient questionnaires (n=7)
SCC III D&T	0.450	
SCC IV D&T	0.490	
SCC 0-II intense FU	0.707	patient questionnaires (n=11)[1]
SCC III intense FU	0.620	
SCC IV intense FU	0.702	
SCC 0-II longterm FU	0.812	General population (assumption)
SCC III longterm FU	0.617	
SCC IV longterm FU	0.699	
MSC 0-I undiagnosed	0.812	
MSC IIundiagnosed	0.812	
MSC III undiagnosed	0.672	
MSC IV undiagnosed	0.695	
MSC 0-I D&T	0.682	patient questionnaires (n=15)[1]
MSC II D&T	0.575	
MSC III D&T	0.531	
MSC IV D&T	0.579	
MSC 0-I intense FU	0.701	patient questionnaires (n=43)[1]
MSC II intense FU	0.695	
MSC III intense FU	0.609	
MSC IV intense FU	0.690	
MSC 0-I longterm FU	0.812	General population (assumption)
MSC II longterm FU	0.812	
MSC III longterm FU	0.665	
MSC IV longterm FU	0.753	
False positive result on screening	0.805	Assumption

Natural evolution of skin cancer

Information on the natural evolution of undiagnosed melanoma tumours is lacking. Therefore, we applied model calibration by manually searching for the best combination of parameter values, as to match the modelled outputs to the observed evidence on the outputs, in this case the number of melanoma deaths. In Belgium, every year about 450 people die from skin cancer. Over 20 year this would mean about 9,000 deaths (without taking the rising trend in incidence into account). Since SCC lesions are under registered in Belgium, the actual number of deaths is estimated to be higher. The output of the model, in terms of number of skin cancer deaths after 20 year, was matched to this expected 9,000 deaths based on estimation of the natural progression. When this natural progression to MSC stage II or III was set at 0.8% and to stage III at 0.7% per six months, the output of the model showed 11,100 deaths over 20 years, which is in line with the estimated number of deaths in reality. Natural progression of BCC was derived from the study of Kirkup et al.[5], showing an evolution of 1 cm per 3.8 years or 1.2 mm per 6 months. The transition risk from SCC stage 0-II to stage III or IV was estimated as 0.5% per 6 months based on the estimation of Smoller et al (1-2% per year).[6] The probability of spontaneous clinical detection was defined as the average prevalence of diagnosed skin cancer divided by the total prevalence (diagnosed and undiagnosed).

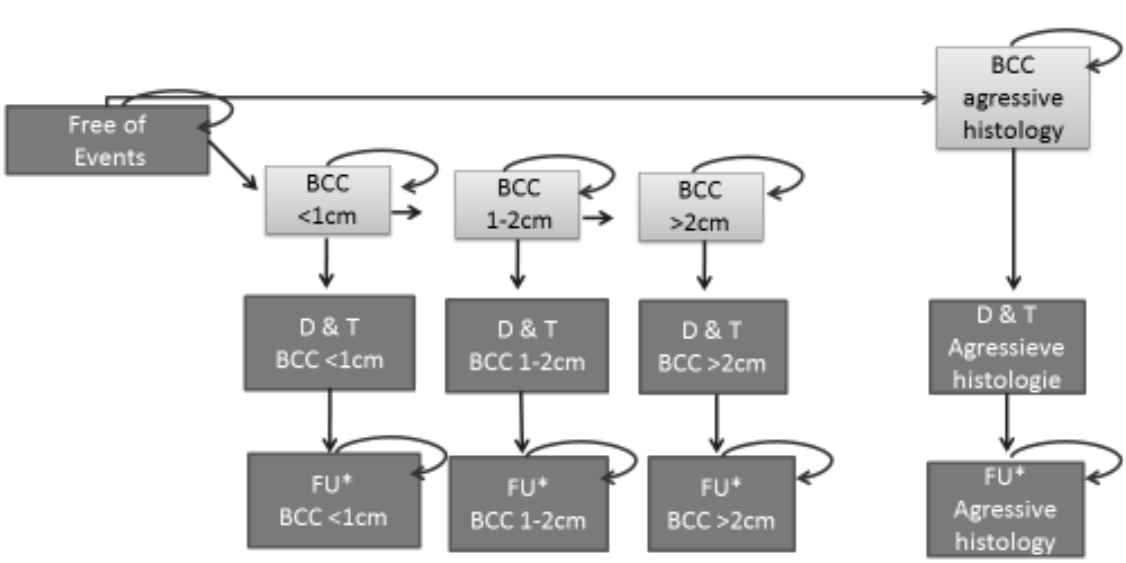

Figure A1a. visualization of the Markov model; BCC: Basal cell carcinoma; FU: Follow-up; D & T: Diagnosis and treatment. Light-colored states correspond to undiagnosed cancer *FU is divided in intense FU (3 cycles) and long-term FU; from state BCC one can also develop a Melanoma lesion.

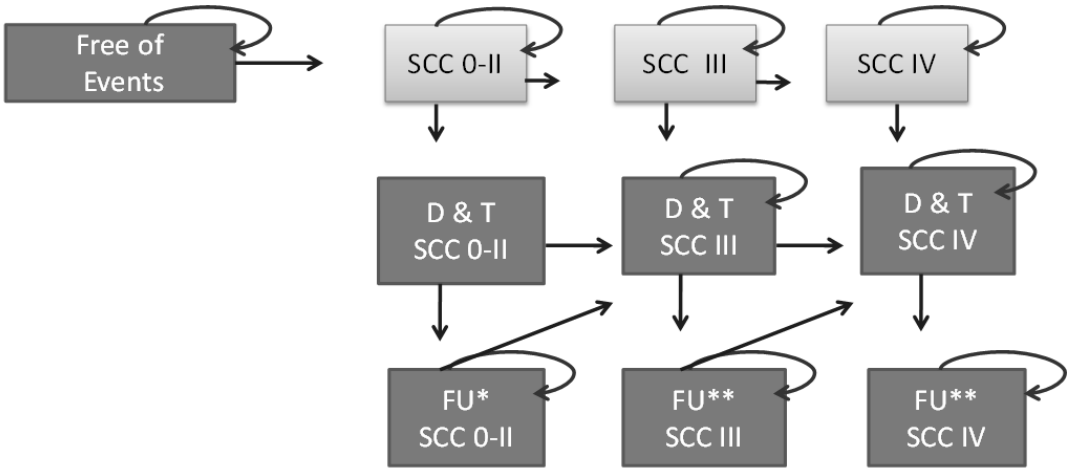

Figure A1b. visualization of the Markov model; SCC: Squamous cell carcinoma; FU: Follow-up; D & T: Diagnosis and treatment. Light-colored states correspond to undiagnosed cancer *FU is divided in intense FU (3 cycles) and long-term FU ** FU is divided in intense FU (8 cycles) and long-term FU From SCC one can also develop a MSC lesion

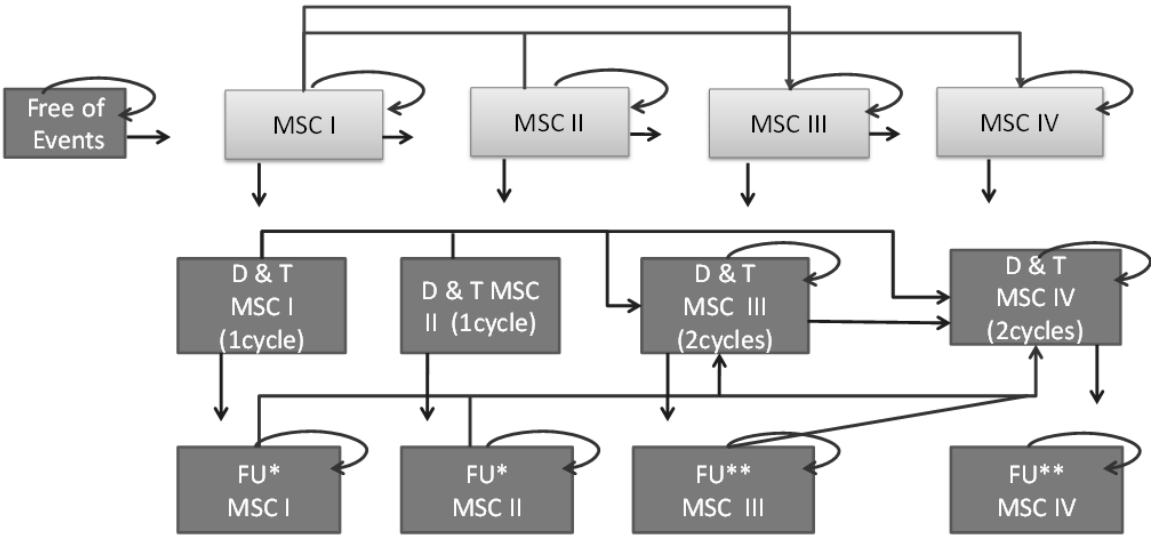

Figure A1c. visualization of the Markov model; MSC: melanoma skin cancer; FU: Follow-up; D & T: Diagnosis and treatment. Light-colored states correspond to undiagnosed cancer *FU is divided in intense FU (3 cycles) and longterm FU ** FU is divided in intense FU (8 cycles) and longterm FU

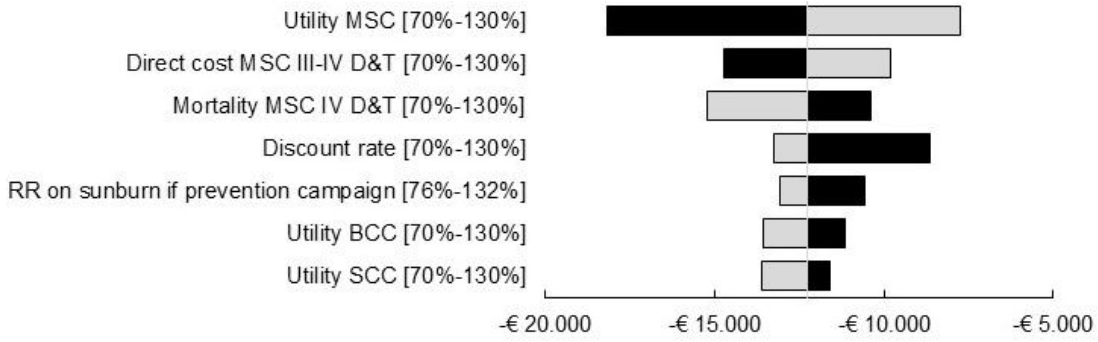

Figure A2a: One-way sensitivity analysis: tornado-diagram showing the most influencing parameters on the cost-effectiveness of a prevention campaign in females. Dark-colored bars = maximum parameter value; light-colored bars = minimum parameter value [range of variation in relative terms]; D&T: diagnosis & treatment; RR: relative risk.

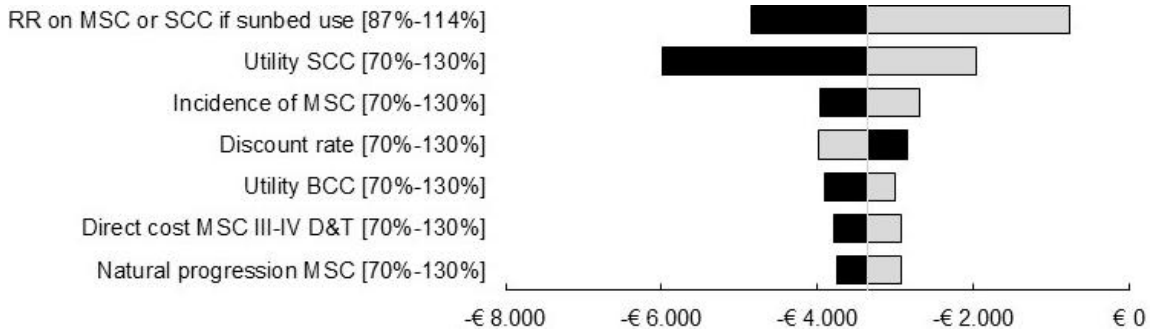

Figure A2b: One-way sensitivity analysis: tornado-diagram showing the 5 most influencing parameters on the cost-effectiveness of a total ban on sunbed use in females. Dark-colored bars = maximum parameter value; light-colored bars = minimum parameter value [range of variation in relative terms]; D&T: diagnosis & treatment; RR: relative risk.

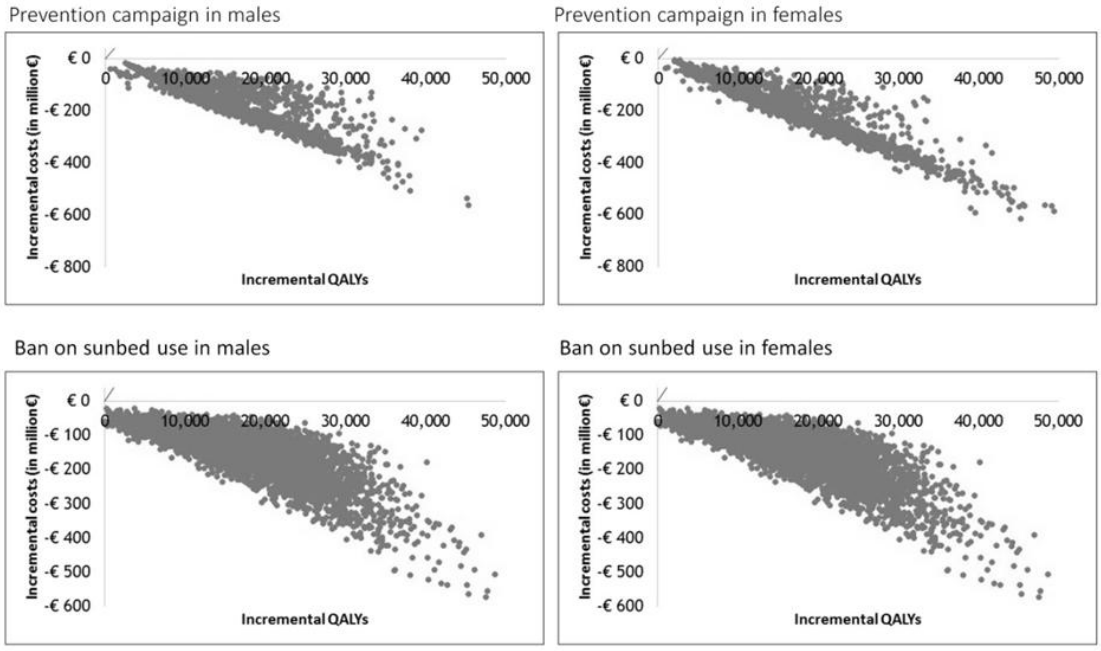

Figure A3: Cost-effectiveness planes displaying the results of the 5,000 simulations. Each point depicted in represents the value of one simulation performed from the distribution around each of the key variables in the model.

REFERENCES

1. Rogers HW, Coldiron BM. A relative value unit-based cost comparison of treatment modalities for nonmelanoma skin cancer: effect of the loss of the Mohs multiple surgery reduction exemption. J Am Acad Dermatol 2009 Jul;61(1):96-103.

2. Hoorens I, Vossaert K, Pil L, Boone B, De SS, Ongenae K, et al. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol 2015 Oct 14.

3. Integraal Kankercentrum Nederland. Incidence of skin cancer, 2012.

4. Belgian Cancer Registry. Incidence Melanoma in Belgium, 2013.

5. Kirkup ME, De Berker DA. Clinical measurement of dimensions of basal cell carcinoma: effect of waiting for elective surgery. Br J Dermatol 1999 Nov;141(5):876-9.

6. Smoller BR. Squamous cell carcinoma: from precursor lesions to high-risk variants. Mod Pathol 2006 Feb;19 Suppl 2:S88-S92.

7. Rowe DE, Carroll RJ, Day CL, Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 1992 Jun;26(6):976-90.

8. Leiter U, Buettner PG, Eigentler TK, Brocker EB, Voit C, Gollnick H, et al. Hazard rates for recurrent and secondary cutaneous melanoma: an analysis of 33,384 patients in the German Central Malignant Melanoma Registry. J Am Acad Dermatol 2012 Jan;66(1):37-45.

9. Eggermont AM, Suciu S, Testori A, Santinami M, Kruit WH, Marsden J, et al. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol 2012 Nov 1;30(31):3810-8.

10. Rees JR, Zens MS, Gui J, Celaya MO, Riddle BL, Karagas MR. Non melanoma skin cancer and subsequent cancer risk. PLoS One 2014;9(6):e99674.

11. Belgian Cancer Registry. Cancer Mortality Rates, 2004-2011.

12. Clayman GL, Lee JJ, Holsinger FC, Zhou X, Duvic M, El-Naggar AK, et al. Mortality risk from squamous cell skin cancer. J Clin Oncol 2005 Feb 1;23(4):759-65.

13. Hollestein LM, de VE, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012 Sep;48(13):2046-53.

14. Wetenschappelijk instituut voor Volksgezondheid. Gezondheidsenquête 2013. https://his.wiv-isp.be/NL/SitePages/Introductiepagina.aspx. Accessed March 23, 2015.

15. Tromme I, Devleesschauwer B, Beutels P, Richez P, Leroy A, Baurain JF, et al. Health-related quality of life in patients with melanoma expressed as utilities and disability weights. Br J Dermatol 2014 Dec;171(6):1443-50.

16. Gaulin C, Sebaratnam DF, Fernandez-Penas P. Quality of life in non-melanoma skin cancer. Australas J Dermatol 2015 Feb;56(1):70-6.

Appendix II

Natural evolution of skin cancer

Information on the natural evolution of undiagnosed melanoma tumours is lacking. Therefore, we applied model calibration by manually searching for the best combination of parameter values, as to match the modelled outputs to the observed evidence on the outputs, in this case the number of melanoma deaths. In Belgium, every year about 450 people die from skin cancer. Over 20 year this would mean about 9 000 deaths (without taking the rising trend in incidence into account). Since SCC lesions are underregistered in Belgium, the actual number of deaths is estimated to be higher. The output of the model, in terms of number of skin cancer deaths after 20 year, was matched to this expected 9,000 deaths based on estimation of the natural progression. When this natural progression to MSC stage II or III was set at 0.8% and to stage III at 0.7% per six months, the output of the model showed 11,100 deaths over 20 years, which is in line with the estimated number of deaths in reality. Natural progression of BCC was derived from the study of Kirkup et al.[1], showing an evolution of 1 cm per 3.8 years or 1.2 mm per 6 months. The transition risk from SCC stage 0-II to stage III or IV was estimated as 0.5% per 6 months based on the estimation of Smoller et al. (1-2% per year).[2]

Table A1. Screening related input parameters

Parameter	Input value							Source
	18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	
PARTICIPATION RATE								
TBE males	8.8%	13.6%	14.2%	20.5%	24.1%	18.3%	5.4%	[3]
TBE females	14.5%	20.1%	20.3%	24.0%	27.1%	18.6%	4.6%	[3]
LDS males	1.5%	2.1%	2.2%	3.8%	5.9%	3.7%	2.6%	[3]
LDS females	1.8%	3.3%	3.7%	2.7%	5.5%	2.7%	0.9%	[3]
TEST CHARACTERISTICS								
sensitivity dermoscopy BCC	83% (73%-93%)							[4]
SCC	83% (73%-93%)							[4]
MSC	74% (62%-86%)							[4]
specificity dermoscopy BCC	86.5% (85%-88%)							[4]
SCC	86.5% (85%-88%)							[4]
MSC	89% (87%-91%)							[4]

Table A2. Epidemiologic input parameters

Parameter	Input value							Source
	18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	
PREVALENCE UNDIAGNOSED LESIONS								
BCC <1cm M	0.015%	0.135%	0.377%	0.699%	1.528%	3.022%	3.809%	[3]
BCC <1cm F	0.035%	0.150%	0.633%	0.799%	1.419%	2.033%	2.275%	[3]
BCC 1-2cm M	0.008%	0.075%	0.209%	0.387%	0.846%	1.674%	2.109%	[3]
BCC 1-2cm F	0.019%	0.083%	0.350%	0.443%	0.786%	1.126%	1.260%	[3]
BCC >2cm M	0.002%	0.021%	0.059%	0.109%	0.238%	0.470%	0.592%	[3]
BCC >2cm F	0.005%	0.023%	0.098%	0.124%	0.221%	0.316%	0.354%	[3]
BCC agr. hist. M	0.011%	0.101%	0.282%	0.522%	1.141%	2.257%	2.844%	[3]
BCC agr. hist. F	0.026%	0.112%	0.472%	0.597%	1.059%	1.518%	1.699%	[3]
SCC stage 0-II M	0.000%	0.001%	0.002%	0.013%	0.048%	0.268%	0.967%	[3]
SCC stage 0-II F	0.001%	0.002%	0.010%	0.033%	0.095%	0.222%	0.419%	[3]
SCC stage III M	0.000%	0.000%	0.000%	0.001%	0.006%	0.031%	0.112%	[3]
SCC stage III F	0.000%	0.000%	0.001%	0.004%	0.011%	0.026%	0.049%	[3]
SCC stage IV M	0.000%	0.000%	0.000%	0.000%	0.001%	0.007%	0.026%	[3]
SCC stage IV F	0.000%	0.000%	0.000%	0.001%	0.003%	0.006%	0.011%	[3]
MSC stage I M	0.065%	0.173%	0.328%	0.527%	0.805%	1.156%	1.132%	[3]
MSC stage I F	0.128%	0.311%	0.488%	0.543%	0.704%	0.767%	0.502%	[3]
MSC stage II M	0.019%	0.049%	0.094%	0.151%	0.230%	0.331%	0.324%	[3]
MSC stage II F	0.029%	0.070%	0.109%	0.122%	0.158%	0.172%	0.112%	[3]
MSC stage III M	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	[3]
MSC stage III F	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	[3]
MSC stage IV M	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	[3]
MSC stage IV F	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	[3]
Correction factor IKNL prevalence BCC/SCC				0.51				Based on mortality (IARC) and incidence (2010) BE versus NDL

Table A2. Epidemiologic input parameters *(contd)*

Parameter	Input value							Source
	18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	
INCIDENCE								
BCC M	0.001%	0.004%	0.013%	0.024%	0.053%	0.101%	0.107%	[5]
BCC F	0.002%	0.006%	0.024%	0.029%	0.055%	0.075%	0.078%	[5]
SCC M	0.000%	0.000%	0.001%	0.005%	0.018%	0.053%	0.123%	[5]
SCC F	0.000%	0.000%	0.002%	0.006%	0.017%	0.038%	0.076%	[5]
MSC I M	0.002%	0.004%	0.007%	0.010%	0.013%	0.019%	0.017%	[6]
MSC I F	0.005%	0.011%	0.017%	0.016%	0.015%	0.017%	0.009%	[6]
NATURAL PROGRESSION								
BCC				12.5%				[1]
SCC stage 0-II => III				1.0%				[2]
SCC stage III => IV				7.0%				calibration
MSC I/II => II/III				0.8%				calibration
MSC I/II => IV				0.7%				calibration

Table A2. Epidemiologic input parameters *(contd)*

Parameter	Input value							Source
	18-29y	30-39y	40-49y	50-59y	60-69y	70-79y	79+y	
PROGRESSION TO METASTASES, FU								
SCC				0.23%				[7]
MSC stage I => MSC stage III				0.07%				[9]
MSC stage I => MSC stage IV				0.07%				[9]
MSC stage II => MSC stage III				0.47%				[9]
MSC stage II => MSC stage IV				0.47%				[9]
MSC stage III => MSC stage IV				2.26%				[9]
RR OF DEVELOPING MSC AFTER DIAGNOSES OF NMSC								
MSC after BCC				3.28				[11]
MSC after SCC				3.62				[11]
MORTALITY RATES								
Mortality due to skin cancer (first year)								
MSC stage IV				26.66%				[12], corrected for new therapies
SCC stage IV				13.55%				[13]
Mortality due to skin cancer (follow-up)								
MSC stage IV				M: 12.45% F: 7.65%				[12], corrected for new therapies
SCC stage IV				M: 6.33% F: 9.71%				[14]
Mortality due to other causes								
M	0.04%	0.05%	0.12%	0.33%	0.76%	1.97%	3.85%	Belgian life tables 2012
F	0.01%	0.02%	0.04%	0.13%	0.30%	0.71%	2.46%	

Table A3. Cost input parameters: Direct costs per 6 months, per stage and phase

DIRECT COSTS	diagnosis & treatment		intense FU		longterm FU	
	HC payer	patient	HC payer	patient	HC payer	patient
BCC <1cm	€ 196	€ 34	€ 119	€ 22	€ 82	€ 46
BCC 1-2cm	€ 211	€ 37	€ 128	€ 24	€ 89	€ 49
BCC>2cm	€ 227	€ 40	€ 137	€ 26	€ 95	€ 53
BCC agressive histology	€ 227	€ 40	€ 137	€ 26	€ 95	€ 53
SCC 0-II	€ 243	€ 17	€ 18	€ 13	€ 9	€ 7
SCC III	€ 1,396	€ 217	€ 91	€ 24	€ 45	€ 12
SCC IV	€ 1,659	€ 262	€ 91	€ 24	€ 45	€ 12
MSC I	€ 1,891	€ 161	€ 385	€ 71	€ 231	€ 41
MSC II	€ 2,119	€ 244	€ 318	€ 60	€ 258	€ 43
MSC III	€ 4,737	€ 200	€ 1,082	€ 72	€ 822	€ 72
MSC IV	€ 51,034	€ 344	€ 6,758	€ 147	€ 1,401	€ 141

Table A4. Cost input parameters: Indirect costs due to productivity loss per 6 months, per stage and phase

INDIRECT COSTS	diagnosis & treatment		intense FU		longterm FU	
	transport	prod. loss	transport	prod. loss	transport	prod. loss
BCC <1cm	€ 43	€ 0	€ 7	€ 0	€ 6	€ 0
BCC 1-2cm	€ 17	€ 0	€ 5	€ 0	€ 45	€ 0
BCC>2cm	€ 76	€ 0	€ 30	€ 0	€ 0	€ 0
BCC agressive histology	€ 21	€ 0	€ 18	€ 0	€ 38	€ 0
SCC 0-II	€ 55	€ 0	€ 8	€ 13	€ 42	€ 0
SCC III	€ 317	€ 0	€ 40	€ 24	€ 208	€ 0
SCC IV	€ 377	€ 0	€ 40	€ 24	€ 208	€ 0
MSC I	€ 102	€ 2 663	€ 30	€ 1 872	€ 33	€ 26
MSC II	€ 69	€ 1 213	€ 12	€ 1 872	€ 32	€ 26
MSC III	€ 98	€ 6 591	€ 34	€ 11 864	€ 81	€ 3 401
MSC IV	€ 274	€ 6 591	€ 152	€ 16 688	€ 106	€ 3 401
Death	-	-	-	-	€ 0	€ 16 200

REFERENCES

1. Kirkup ME, De Berker DA. Clinical measurement of dimensions of basal cell carcinoma: effect of waiting for elective surgery. Br J Dermatol 1999 Nov;141(5):876-9.

2. Smoller BR. Squamous cell carcinoma: from precursor lesions to high-risk variants. Mod Pathol 2006 Feb;19 Suppl 2:S88-S92.

3. Hoorens I, Vossaert K, Pil L, Boone B, De SS, Ongenae K, et al. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol 2015 Oct 14.

4. Chevolet I, Hoorens I, Janssens A, Speeckaert R, Van GN, Van MG, et al. A short dermoscopy training increases diagnostic performance in both inexperienced and experienced dermatologists. Australas J Dermatol 2015 Feb;56(1):52-5.

5. Integraal Kankercentrum Nederland. Incidence of basal and squamous cell carcinoma, 2011. 2015.

6. Belgian Cancer Registry. Incidence Melanoma in Belgium, 2013.

7. Rowe DE, Carroll RJ, Day CL, Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 1992 Jun;26(6):976-90.

8. Francken AB, Accortt NA, Shaw HM, Wiener M, Soong SJ, Hoekstra HJ, et al. Prognosis and determinants of outcome following locoregional or distant recurrence in patients with cutaneous melanoma. Ann Surg Oncol 2008 May;15(5):1476-84.

9. Leiter U, Buettner PG, Eigentler TK, Brocker EB, Voit C, Gollnick H, et al. Hazard rates for recurrent and secondary cutaneous melanoma: an analysis of 33,384 patients in the German Central Malignant Melanoma Registry. J Am Acad Dermatol 2012 Jan;66(1):37-45.

10. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg 2002 Mar;28(3):268-73.

11. Rees JR, Zens MS, Gui J, Celaya MO, Riddle BL, Karagas MR. Non melanoma skin cancer and subsequent cancer risk. PLoS One 2014;9(6):e99674.

12. Belgian Cancer Registry. Cancer Mortality Rates, 2004-2011.

13. Clayman GL, Lee JJ, Holsinger FC, Zhou X, Duvic M, El-Naggar AK, et al. Mortality risk from squamous cell skin cancer. J Clin Oncol 2005 Feb 1;23(4):759-65.

14. Hollestein LM, de VE, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012 Sep;48(13):2046-53.

15. Wetenschappelijk instituut voor Volksgezondheid. Gezondheidsenquête 2013.

16. Tromme I, Devleesschauwer B, Beutels P, Richez P, Leroy A, Baurain JF, et al. Health-related quality of life in patients with melanoma expressed as utilities and disability weights. Br J Dermatol 2014 Dec;171(6):1443-50.

17. Gaulin C, Sebaratnam DF, Fernandez-Penas P. Quality of life in non-melanoma skin cancer. Australas J Dermatol 2015 Feb;56(1):70-6.

Summary

SUMMARY

The main objective of this dissertation was to gain more insight in the preventive landscape of skin cancer in Belgium. We examined the 3 most common forms of skin cancer, malignant melanoma arising from the melanocytes, and non-melanoma skin cancer (NMSC) that originate from keratinocytes (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)). Prevention can be aimed at the healthy population resulting in primary prevention strategies, or trying to detect a disease at an earlier state, being secondary prevention. We started mapping the current health as economic burden of melanoma as well as NMSC in Belgium.

In Chapter 3 the results of the cost-of illness study are presented; the economic burden of skin cancer in 2014 in Belgium was estimated at €107 million (direct costs: €78 million; indirect costs: €29 million), with a cumulative cost of €3.2 billion in 2034. The majority of this total cost was due to melanoma (65%). We found that the prevalence of skin cancer in Belgium will triple in the next 20 years. A model examining the effects of a UV protection campaign and ban on sunbeds showed that both would lead to a gain in quality-adjusted life-years (QALY) and cost-savings, making them dominant strategies. The budget impact analysis revealed that for every euro invested in the prevention campaign, €3.6 would be saved on the long-term for the healthcare payer.

In addition to primary prevention, we examined the clinical effectiveness of two population based skin cancer screening methods in Chapter 4. We compared a lesion-directed screening method (LDS) to a standard total body examination (TBE). Participation rate was higher in the TBE group compared to the LDS group (17.9% versus 3.3%). Detection rate did not differ significantly between the two groups per 100 participants (2.3 TBE versus 3.2 LDS), but the diagnostic yield per 100 invitees for TBE was 0.42 and 0.08 for the LDS method. LDS was as hypothesized 5.6 times less time-consuming than TBE. For this reason we concluded that LDS by dermatologists could be an alternative screening method in health care systems with limited budget and/or long waiting lists.

In Chapter 5 we compared these two screening methods as to their cost-effectiveness using Markov Models. We found that both screening strategies produced a gain in QALYs, resulting in incremental cost-effectiveness ratios (ICERs) of €33 072/QALY in males and €18 687/QALY in females for TBE and €34 836/QALY in males and €19 470/QALY in females for LDS. These ICERs are moderately cost-effective at a Belgian willingness-to-pay threshold of €35 000/QALY. We concluded that a TBE in general adult population (especially in females) is the most cost-effective strategy and is predicted to result in a reduction of mortality over 20 years.

Several screening initiatives focus on melanoma, but as demonstrated in chapter 3, NMSC and especially BCC also produce a large cost and burden for the health care system. For this reason in Chapter 6 we addressed the question if it is useful in to screen for BCC – in which no effect of mortality is absent – in addition to melanoma and SCC. We examined this question based on the WHO criteria for screening and found that BCC slowly increases in size with time with a median increase in diameter of 0.5 mm over 10 weeks. There seem to be important delays in diagnosis with a mean time from appearance of the skin lesion to seeking medical attention ranging from 19.8 to 25 months and size is one of the major determinants in the choice of an effective treatment and the associated cost especially for facial BCC.

The final part of this thesis describes the results of an observational study examining the main diagnostic aid in detecting skin cancer being dermoscopy. We questioned all Flemish dermatologist about their use an examined the diagnostic accuracy. The majority (89.7%) of dermatologists uses their dermatoscope daily. The study showed that dermoscopy dramatically increased sensitivity for skin cancer diagnosis from 70.6% to 84.6%, but also with small but significant decrease in specificity of 3.5%. To detect one skin cancer 5.23 lesions with suspicion had to be excised. Dermoscopy significantly increased the certainty about making a correct diagnosis, and this was most the case for seborrheic keratosis, Bowen's disease and melanoma. However, surprisingly we could not demonstrate a significant reduction in the number of excisions in daily practice using dermoscopy.

In conclusion primary prevention is cost-saving and a missed opportunity to control the skin cancer epidemic. Secondary prevention offering a total body examination, including BCC screening is moderately cost-effective, and comparable to other Belgian screening initiatives.

Samenvatting

SAMENVATTING

De hoofddoelstelling van dit proefschrift is inzicht te verwerven in het preventieve landschap van huidkanker in België. We hebben hierbij de 3 meest voorkomende vormen van huidkanker onderzocht met name maligne melanoom, uitgaande van de melanocyten en de niet-melanome huidkanker die ontstaan uit de keratinocyten (basaalcel- en spinocellulaire carcinomen). Preventie kan gericht zijn naar gezonde individuen en wordt dan onder de noemer van primaire preventieve gedefinieerd, of preventieve interventies kunnen het doel hebben de ziekte vroegtijdig op te sporen en behandelen. Deze laatste interventies, zoals ook screening, vallen onder secundaire preventie.

In hoofdstuk 3 hebben we getracht de huidige impact van huidkanker in België in kaart te brengen. Deze kostenstudie heeft aangetoond dat de totale kost van huidkanker in 2014, €107 miljoen bedraagt (directe kosten: €78 miljoen; indirecte kosten: €29 miljoen), met een cumulatieve kost van €3.2 miljard in 2034. De meerderheid (65%) van deze kost werd veroorzaakt door melanomen. Verder zagen we dat de prevalentie van huidkanker in België zal verdrievoudigen over de volgende 20 jaar. Het modelleren van 2 primaire preventiecampagnes toonde aan dat zowel UV protectie maatregelen als een totaal verbod op zonnebanken een netto besparing zou opleveren. Voor iedere euro die geïnvesteerd wordt in de campagnes zal op lange termijn €3.6 uitgespaard worden.

Naast deze primaire preventiestrategieën hebben we de klinische effectiviteit van huidkankerscreening in België onderzocht. Hiervoor werden 2 screeningsmethoden in een populatiegebaseerde setting vergeleken, deze resultaten zijn terug te vinden in hoofdstuk 4. Een letselgerichte screening werd hiervoor vergeleken met een standaard totale huidinspectie. De participatie was duidelijk hoger in de totale huidinspectie groep (17.9% versus 3.3%), de detectie ratio was niet significant verschillend per 100 deelnemers (2.3 TBE versus 3.2 LDS). Wanneer de operationele effectiviteit vergeleken werd, is het duidelijk dat een totale huidinspectie de meeste maligne letsels detecteert in de uitgenodigde populatie (0.42 versus 0.08) per 100 genodigden. De letselgerichte screening was 5.6 maal meer efficiënt wat betreft tijdsbesteding, en op basis van deze resultaten konden we concluderen dat letselgerichte screening een alternatieve en meer kosten-effectieve screeningsmethode kan zijn, vooral in een gelimiteerde gespecialiseerde zorg.

In hoofdstuk 5 werd de kosteneffectiviteit van deze twee screeningsmethoden onderzocht en vergeleken aan de hand van Markov modellen. Beide screeningsstrategiën resulteerden in een winst aan ‘quality-adjusted life years’ (QALY) en een incrementele kosten-effectiviteitsratio (IKER) voor een totale huidinspectie van €33 072/QALY voor mannen en €18 687/QALY voor vrouwen. De IKER voor een letselgerichte screening is €34 836/QALY voor mannen en €19 470/QALY voor vrouwen. Deze

resultaten kunnen we interpreteren als matig kosteneffectief gezien de drempel voor aanvaardbaarheid in België €35 000/QALY is. Een totale huidinspectie in de algemene volwassen populatie (en voornamelijk vrouwen), lijkt de meest kosteneffectieve methode.

De huidige screeningsintitiatieven focussen voornamelijk op melanomen, maar zoals aangetoond in hoofdstuk 3 zijn de niet-melanome vormen van huidkanker, en vooral de basaalcel carcinomen verantwoordelijk voor een belangrijk deel van het gezondheidszorgbudget. In hoofdstuk 6 hebben we onderzocht of het nuttig is basaalcel carcinomen op te nemen in screeningsinitiatieven, gezien er geen effect op mortaliteit verwacht kan worden. Aan de hand de WHO criteria werd systematisch de huidige evidentie bestudeerd; deze toonde dat basaalcel carcinomen traag groeiende tumoren zijn met een mediane toename in diameter van 0.5 mm over 10 weken. Er is een belangrijke latentie tussen het verschijnen van het letsel en de diagnose, die varieert van 19.8 tot 25 maanden. De huidige literatuur toont ook aan dat tumordiameter een van de belangrijkste determinanten is in de keuze van de behandeling, de effectiviteit en geassocieerde kosten. Dit is voornamelijk zo voor tumoren gelokaliseerd in het gelaat, meer specifiek de H-zone. Het verband tussen tumor grootte en behandelingsoutcome voor basaalcel carcinomen gelokaliseerd op het lichaam is minder overtuigend.

In het laatste hoofdstuk beschrijven we de resultaten van een studie over de diagnostische accuraatheid van dermoscopie. Door middel van een webapplicatie werden alle Vlaamse dermatologen uitgenodigd om deel te nemen aan deze observationele studie. De meerderheid van de dermatologen (89.7%) gebruikt dermoscopie in hun dagelijkse praktijk. We vonden een significante stijging in sensitiviteit (70.6% naar 84.6%), bij het gebruik van dermoscopie tov. de klinische evaluatie van letsels verdacht voor huidkanker. Dit gaat gepaard met een kleine, maar significante daling in specificiteit van 3.5%. Om één huidkanker te detecteren moeten 5.23 letsels geëxciseerd worden. Dermoscopie verhoogt significant de zekerheid bij het maken van de correcte diagnose, en dit vooral de diagnose verruca seborrhoica, ziekte van Bowen en melanomen. We konden echter geen daling in het aantal excisies aantonen als gevolg van het gebruik van dermoscopie.

Als besluit kunnen we stellen dat op heden, primaire preventie de meest kosten-effectieve vorm van preventie is om de huidkankerepidemie te bestrijden. Screening door middel van totale huidinspectie, inclusief screenen voor basaalcel carcinomen heeft een aanvaardbare kosten-baten verhouding.

Dankwoord

Niets gebeurt tweemaal en niets zal tweemaal gebeuren.

Wislawa Szymborska (Roepen naar Yeti, 1957)

Het tot stand komen van een doctoraat is een lange weg waarop verschillende momenten bepalend zijn. Het afleggen en verdedigen van dit werk was enkel mogelijk door goede begeleiding en steun van naasten. Dit proefschrift zou dus niet compleet zijn zonder enkele woorden van dank.

Allereerst wil ik mijn promotor Professor Lieve Brochez bedanken voor haar kritische input, ondersteuning en aanmoediging tot op de laatste momenten van mijn doctoraatsperiode. Zij speelde een centrale rol in het tot stand komen van dit doctoraat, en ondanks haar immer drukke agenda was ze steeds bereid tijd te maken voor mij. Lieve, het was een groot plezier om met u te mogen samenwerken, bedankt voor deze kans en het vertrouwen.

Ik wil ook een woord van dank richten aan mijn copromotor Professor Lieven Annemans. Ik had het genoegen zeer veel van u te mogen leren over de complexe en wondere wereld van de gezondheidseconomie. Bedankt voor uw betrokkenheid, motivatie en inspiratie bij dit onderzoek.

Bij het opzetten van het onderzoek, de uitwerking van de klinische studies en schrijven van mijn doctoraat kon ik op steun van verschillende mensen in het onderzoeksgebouw rekenen. Ik wil Els, Marie-Chantal, Eline en Martine bedanken. Mireille en Reinhart moet ik in het bijzonder vermelden, de interessante gesprekken en discussies hebben mijn nieuwsgierigheid tijdens het onderzoek steeds aangewakkerd. Reinhart, uw wijsheid en spirit voor research verdient bewonderd te worden.

Ik had het geluk om de voorbije periode omringd te zijn geweest door zeer fijne collega's. De lijst is te lang om hier op te noemen maar ik wil in het bijzonder Inès, Stefanie en Ana-Karina bedanken. Door de jaren heen heb ik jullie beter leren kennen. Ik apprecieer jullie aanwezigheid, ideeën en bedenkingen zowel binnen het onderzoek als daarnaast. Lore, bedankt voor de leuke samenwerking en steeds enthousiast de gezondheidseconomie in al zijn facetten te willen verhelderen.

Professor Joris Delanghe en Elke Lecocq, die steeds bereid waren me te helpen bij de interpretatie en praktische uitvoering van het werk op de dienst klinische biologie. Bedankt Professor Delanghe voor uw tijd om mijn vragen te beantwoorden en vooral de fascinerende bedenkingen betreffende de klinische biologie en historische migratiestromen.

Voor de klinische studies kon ik op de buitengewone steun rekenen van de verschillende stafleden en assistenten van de dienst Dermatologie, waarvoor dank. Een bijzonder woord van dank aan de deelnemers en patiënten die bereid waren mee te werken aan dit onderzoeksproject is hier op zijn plaats. Verder wil ik ook de volledige DRU bedanken voor de kritische reflecties en opbouwende commentaren tijdens de onderzoeksvergaderingen.

Deze doctoraatsperiode was een bijzonder leerrijke periode, maar mijn eerste klinische stappen in de dermatologie werden gezet onder leiding van de stagemeesters Katrien Vossaert en Marianne Van de Kerckhove. Jullie hebben me met open armen ontvangen en me een onschatbare kennis meegegeven voor de start van dit doctoraat. Katrien, het is duidelijk dat zonder jou dit doctoraat niet tot stand zou zijn gekomen. Jouw bijdrage in het slagen van dit onderzoeksproject is te groot om op te noemen.

Bedankt aan mijn vrienden en familie voor de momenten van plezier, warmte en geborgenheid. Opa, jouw sereniteit is inspirerend, je interesse in alle aspecten van mijn leven aanmoedigend. Anouk, we gaan al ver terug en je animo blijft aanstekelijk. Elisabeth, ik wil je bedanken voor de vele glimlachen en ontelbare momenten van schaterlachen, maar vooral ook voor de troost wanneer het nodig was. Jessica, bedankt voor je zorg, openheid en spontaniteit. I owe special thanks to Aidan for the help in editing the final text. Michel, bedankt voor de steun en aanmoediging deze laatste maanden, maar vooral voor wie je bent.

In het bijzonder wil ik mijn zus bedanken. Je bent een bron van inspiratie voor velen zonder het te weten. Ik kijk op naar jouw enthousiasme voor het leven. Natuurlijk moet ik grote dank richten aan mijn ouders. Jullie onvoorwaardelijke steun en liefde maken mij tot wie ik nu ben. Lieve mama en papa, jullie warme nest heeft me vleugels voor het leven gegeven.

Isabelle

Curriculum Vitae

Personal information	Isabelle Hoorens Date & place of birth: 01-02-1988, Ghent Nationality: Belgian Phone: +32 (0)9 332 53 05 Mail: isabelle.hoorens@ugent.be Address: De Pintelaan 185, 9000 Ghent, Belgium
Education	2013-2016: PhD Fellow, Ghent University 2012-2018: Residency Dermatology, Ghent University Hospital 2005-2012: Medical Doctor, magna cum laude, Ghent University 1999-2005: Latin and Science-Mathematics, cum laude, Sint-Bavo Ghent
Postgraduate courses	2013-2015: Doctoral schools life sciences and medicine, Ghent University 2013: Statistical thinking and smart experimental design, VIB, Brussels 2013: Statistical analysis, advanced course, Ghent University 2013: Statistical analysis and SPSS, basic principles, Ghent University 2009: Basic principles of electrocardiography, Ghent University
A1 Publications	Hoorens I, Vossaert K, Ongenae K, Brochez L. Is early detection of basal cell carcinoma worthwhile? Systematic review based on the WHO criteria for screening. Br J Dermatol. 2016; doi: 10.1111/bjd.14477. Haspeslagh M, Vossaert K, Lanssens S, Noë M, Hoorens I, Chevolet I, De Wispelaere I, Degryse N, Facchetti F, Brochez L. Comparison of Ex Vivo and In Vivo Dermoscopy in Dermatopathologic Evaluation of Skin Tumors. JAMA Dermatol. 2016; 152(3):312-7. Hoorens I, Vossaert K, Pil L, Boone B, De Schepper S, Ongenae K, Annemans L, Chevolet I, Brochez L. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. JAMA Dermatol. 2016; 152(1):27-34.

Hoorens I, Batteauw A, Van Maele G, Lapiere K, Boone B, Ongenae K. Mohs micrographic surgery for basal cell carcinomas: evaluation of indication criteria and predictive factors of extensive subclinical spread. Br J Dermatol. 2015; doi: 10.1111/bjd.14308.

Hoorens I, van de Kerckhove M, Poppe B, Vossaert K. Nevoid Basal Cell Carcinoma Syndrome and dysgerminoma: an incidental association? J Eur Acad Dermatol Venereol. 2015; doi: 10.1111/jdv.13297.

Chevolet I, Schreuer M, Speeckaert R, Neyns B, Hoorens I, van Geel N, Krüse V, Hennart B, Allorge D, Van Gele M, Brochez L. Systemic immune changes associated with adjuvant interferon-α2b-therapy in stage III melanoma patients: failure at the effector phase? Melanoma Res. 2015; 25(4):357-61.

Chevolet I, Hoorens I, Janssens A, Speeckaert R, Van Geel N, Van Maele G, Vossaert K, Brochez L. A short dermoscopy training increases diagnostic performance in both inexperienced and experienced dermatologists. Australas J Dermatol. 2015; 56(1):52-5.

Hoorens I, Ongenae K. Primary focal hyperhidrosis: current treatment options and a step-by-step approach.J Eur Acad Dermatol Venereol. 2012; 26(1):1-8.

Abstracts/posters
Non-A1 publications

Hoorens I, Vossaert K, Ongenae K, Brochez L. Is early detection of basal cell carcinoma worthwhile? Systematic review based on the WHO criteria for screening. 3rd International UV and Skin Cancer Prevention Congress 2015; Melbourne, Australia.

Hoorens I, Vossaert K, Pil L, Boone B, De Schepper S, Ongenae K, Annemans L, Chevolet I, Brochez L. Skin cancer screening: participation rate, effectiveness and anxiety of standard total skin examination versus a lesion-directed screening. 3rd International UV and Skin Cancer Prevention Congress 2015; Melbourne, Australia.

Hoorens I, Speeckaert R, Vossaert K, Verhaeghe E, Ongenae K, Boone B, De Schepper S, Lanssens S, Temmerman L, De Bacquer D, Delanghe J, Brochez L. Haptoglobin polymorphism and the risk of actinic keratoses and cutaneous squamous cell carcinoma: a case-control study. 11th EADO Congress 2015; Marseille, France.

Brochez L, Chevolet I, De Munter S, Hoorens I, Vossaert K, Maselis T, Van Geel N. Yield of a lesion-directed screening initiative in Flanders, Belgium. Journal Der Deutchen Dermatologischen Gesellschaft 2013; 11(7): 29.

Brochez L, Chevolet I, Hoorens I. The Belgian Association of Dermato-Oncology launch meeting: verslag van de vergadering. OncoHemato 2014; 8 (2):74-81.

Oral presentations

Belgian dermatology Days 2016; Brussels, Belgium. Economic impact of skin cancer in Belgium and effect of prevention strategies. Hoorens I, Vossaert K, Pil L, Annemans L, Brochez L.

Belgian Federal Parlement 2015; Brussels, Belgium. Impact of skin cancer in Belgium. Hoorens I, Pil L, Boone B, Annemans L, Brochez L.

23th World congress of Dermatology 2015; Vancouver, Canada. Total-Body Examination vs Lesion-Directed Skin Cancer Screening. Hoorens I, Vossaert K, Pil L, Boone B, De Schepper S, Ongenae K, Annemans L, Chevolet I, Brochez L.

4th World Congress of Dermoscopy 2015; Vienna, Austria. Skin cancer screening: participation rate, effectiveness and anxiety of standard total skin examination versus a lesion-directed screening. Hoorens I, Vossaert K, Pil L, De Schepper S, Ongenae K, Annemans L, Chevolet I, Brochez L.

	Koninklijke Belgische Vereniging voor Dermatologie en Venerologie 2013; Ghent, Belgium. Multiple basal cell carcinomas in a young women: What's the story behind it? Hoorens I, Van De Kerckhove M, Vossaert K.
Funding	PhD aspirant, Clinical Research Fund, Ghent University Hospital Research Grant, Leo Foundation Denmark