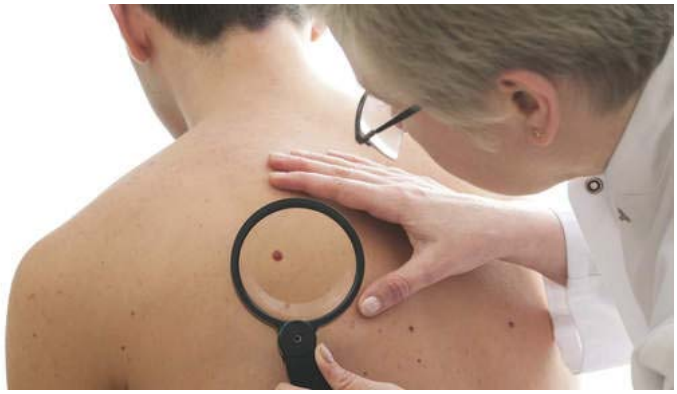
The impact of skin cancer in Belgium and the cost-effectiveness of prevention



A study by Ghent University in collaboration with the Foundation against Cancer

Drs. Lore Pil, Dr. Isabelle Hoorens, Dr. Katrien Vossaert, Prof. dr. Lieve Brochez, Prof. dr. Lieven Annemans

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Executive Summary

Skin cancer (melanoma- and non-melanoma skin cancer) is one of the most rapidly increasing cancers worldwide (1-4). Investing in population programs to prevent skin cancer is challenging for policy makers, since budget has to compete with other major health problems. Some studies have calculated the cost-effectiveness of prevention of melanoma, nonetheless few studies have been conducted concerning the cost-effectiveness of prevention of non-melanoma skin cancer (5). Skin cancer can be prevented by means of sun-protective behaviour or it can be detected at an early stage by means of screening, thereby intervening in the course of natural progression. This study analysed the current and future societal cost of skin cancer and the cost-effectiveness of primary and secondary prevention, in order to inform policy decision makers. The current societal cost of skin cancer in Belgium was calculated by means of a retrospective bottom-up cost-of-illness analysis, based on information from Belgian 287 patient questionnaires that were gathered from 1st March 2015 until 30th June. In order to calculate the future societal cost, a Markov model was composed (Microsoft Excel® 2013), with a time horizon of 20 years. This Markov model also simulated the health economic impact of a primary prevention campaign and a ban on sunbeds in reference no prevention, assuming an effect on the incidence of skin cancer, based on literature (6-8). Additionally, the Markov model compared the health economic impact of a total body screening (TBE) and a lesion directed screening (LDS) in reference to a situation without screening. Over a period of 20 years in case of screening and 50 years in case of primary prevention, assuming a societal perspective, costs and quality-adjusted life-years (QALYs) with and without the primary or secondary prevention program were calculated in order to determine the incremental cost-effectiveness ratio (ICER) of both types of prevention. These analyses showed that the total economic burden of skin cancer in 2014 in Belgium was estimated at €103.2 million, with direct costs being €76.8 million and indirect costs being €26.3 million. The majority of this total cost was due to MSC (62%). Costs were slightly higher for females than for males. Costs due to productivity loss were 10 times higher in melanoma patients than in non-melanoma skin cancer patients, whereas costs for the patient were higher in case of non-melanoma skin cancer. Both primary prevention programs (prevention campaign and ban on sunbed use), would lead to a gain in QALYs and cost-savings, making them both dominant prevention strategies. The budget impact analysis revealed that for every euro invested in the prevention campaign, €5.7 would be saved on the long term (over 50 years). Both screening strategies resulted in a gain in QALYs over a period of 20 years. Health effects and costs are in good balance, leading to cost-effective results. All ICERs are below

the willingness-to-pay threshold of €35,000/QALY (€19,575/QALY in males and €7,763/QALY in females for TBE and €21,865/QALY in males and €8,031/QALY in females for LDS). To conclude, this study provides the evidence that the societal cost of skin cancer has an important future impact on health care budget. Primary prevention and a ban on sunbed use in Belgium are both dominant prevention interventions, meaning that a benefit in health is attained and costs are saved. Skin cancer screening proved to be cost-effective at a willingness-to-pay threshold of €35.0000/QALY. A total-body examination in the general adult, especially in the females, is the most cost-effective screening strategy and projected to result in a significant reduction of mortality over 20 years. However currently no observational data support this reduction in mortality.

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Background

Skin cancer affects nearly 1 out of 5 persons in Belgium (1-4) and is highly related to ultraviolet exposure, either naturally from the sun or artificially through solarium use. These risk factors are the strongest for non-melanoma skin cancer (NMSC) –i.e. basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)-, however meta-analyses also confirm the influence in development of melanoma skin cancer (MSC) (8-10). Several epidemiologic studies show an alarming increase in incidence of MSC and NMSC, due to the increasing age of the population, but also to altered risk seeking behavior (1;11-13). Although NMSC is less aggressive than MSC, it has an important impact on the health expenditures because of the high prevalence (14). Consequently to this epidemic, the related health care costs are rising significantly. In addition to the more obvious direct medical costs, recent studies show that young females are increasingly affected resulting in important societal indirect costs due to productivity loss (15;16). Current opinion in Europe states that the healthcare spending is not sustainable in the future, so studies with a focus on estimating the current expenditures on skin cancer and innovative ways to improve cost-effective health care and prevention are needed. However, despite the growing awareness of the magnitude of the skin cancer burden, studies on this subject are scarce. Besides, current studies on primary or secondary prevention programs –such as prevention campaigns on the one hand and screening on the other hand- focus mainly on MSC (11-15).

For this reason the first objective of this study was to calculate the current and future health and economic burden of MSC and NMSC in Belgium. Estimating the total cost of skin cancer is particularly useful for measuring the potential cost savings from averting a case, emphasizing the importance of skin cancer prevention. As such, in this study we also simulated the cost-effectiveness and budget impact of primary prevention of skin cancer, being a hypothetical prevention campaign or a total ban on sunbed use, and of secondary prevention of skin cancer, being a total-body examination (TBE) or a lesion-directed screening (LDS). These two population-based screening strategies were organized as a pilot study in Belgium in 2014 (17).

Methods

1. Burden of skin cancer

The current prevalence of skin cancer (MSC, BCC, SCC) was estimated based on undiagnosed - calculated as the yield of the screening study (17) divided by the sensitivity of the dermoscopy- and diagnosed skin cancer (Table A1). This current prevalence was projected to 2034, taking into account the ageing of the population and other skin-cancer related trends such as going on holiday more often, getting a check-up more frequently etcetera, based on the estimated annual increase of skin cancer incidence (3;18;19). In order to estimate the economic burden, we performed a bottom-up cost-of-illness study (20) based on retrospective information from Belgian patient questionnaires that were gathered from 1st March 2015 until 30th June 2015. The current cost of skin cancer was calculated by multiplying the unit costs with the prevalence of detected skin cancer (defined as patients in treatment as well as patients in follow-up). In order to calculate the future cost of skin cancer in Belgium, a Markov model was composed (Microsoft Excel® 2013), with a time horizon of 20 years (cf. infra). All costs were computed at the 2014 EURO price level.

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 questionnaire to the patients. Eligible patients were those who 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 health-related 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.

Based on the resource utilization patterns for individuals with MSC, BCC or SCC and official Belgian unit costs (RIZIV), we calculated the cost per skin cancer stage per six months, separately for diagnosis and treatment, intense follow-up and long-term follow-up. For some patient groups (all stages of SCC and the more severe lesions of melanoma) a low sample of completed questionnaires was obtained. In order to increase power, we calculated the direct cost based on guidelines produced by EURODERM and dermatologist and oncologist expert opinion. For these groups we constructed a care pathway that reflected current management patterns as accurate as possible. Also for large and aggressive BCC

not enough questionnaires had been returned, so the cost of larger and aggressive BCCs was deduced from the cost of small BCC (<1cm), based on the ratios reported by Rogers et al. (21). The cost due to productivity loss was also based on the patient questionnaires and calculated by multiplying the number of days of absenteeism due to skin cancer (caused by sick leave, dismissal, early retirement or premature death) with the average cost per working day, weighted for employment rate (22). This cost was applied to persons younger than 65 years.

2. Health economic evaluation of primary and secondary prevention

General

A decision-analytic Markov model was developed, examining the cost-effectiveness and economic impact of a sensitizing prevention campaign and a total ban on sunbed use on the one hand, and of a single TBE and a single LDS on the other hand, compared to the current situation (i.e. no prevention program). 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 in case of primary prevention and 20 years in case of screening, with six-monthly cycles. The time horizon was longer in case of primary prevention, since a latent period (i.e. the period between risk factor exposure (UV exposure or sunbed use) and the clinical appearance of the lesion) of 20 years was taken into account. Main outcomes included the incremental cost-effectiveness ratio (ICER), the total economic societal burden of skin cancer, the budget impact and the mortality reduction. The ICER was calculated by dividing the net costs by the net health benefits. In order to calculate the total economic burden and 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 analysis of the total economic burden is performed from a societal perspective, including costs for the healthcare payer, patient and costs due to productivity loss. The budget impact analysis (BIA) calculated the net cumulative cost of the primary as well as secondary prevention strategies (and consequent examinations, treatment and follow-up) for the healthcare payer (i.e. government) over a period of 50 years in case of primary prevention and 20 years in case of screening.

Model structure

The Markov model included MSC, BCC and SCC and consisted of different disease states: undiagnosed skin cancer, diagnosis & treatment, intense follow-up, long-term follow-up and death (Figure A1). All

states were separated per skin cancer stage. MSC and SCC stages were determined according to the 7th edition of the Tumor-Nodes-Metastases (TNM)-classification for malignant tumors (23). Stages for BCC were defined as <1cm, 1-2cm, >2cm and aggressive histology. Some tunnel states were incorporated in the model, i.e. intense follow-up and long-term follow-up, to assign a higher probability of recurrence and death in the first years after diagnosis compared to subsequent years. All cohort members started the model in one of the model states, according to the baseline prevalence of BCC, SCC and MSC.

Intervention strategies

1) *Prevention campaign reducing risk of sunburn*

The impact of a hypothetical prevention campaign on skin cancer has been modelled through an effect on being sunburned. Sunburn is an indicator of acute high sun exposure but no dose response for the number of sunburns leading to MSC has been clearly established (24). The risk on developing MSC in case of ever being sunburned during lifetime was estimated to be 59% higher than persons who have never experienced sunburn (RR 1.59, 95%CI (1.37-1.83); Table 1) (6). No evidence was found for the impact of sunburns on SCC (24)or BCC. Published literature has shown the impact of ever being sunburned on the risk of MSC to be preventable by means of comprehensive prevention campaigns. Hill et al. (25) evaluated the SunSmart campaign in Australia two years after its implementation and found an effect on reducing sunburns by 41% (RR 0.59).

2) *Ban on sunbed use*

In this analysis, a ban on public sunbed use was defined as a total ban. Boniol et al. (8) found in their meta-analysis –based on 18 cohort studies- a relative risk on MSC of 1.25 (95%CI: 1.09-1.43) for people who have ever used sunbeds versus never used (Table 1). The risk on SCC was 1.93 (7) and for BCC no evidence on excess risk was found (26;27).

3) *Screening strategies*

The modelled screening strategies were based on a skin cancer screening trial which has been organised in 2014, comparing TBE to LDS in two socio-demographically comparable regions (17). The TBE was organized in a Flemish 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 9484 inhabitants were also invited by a personal for a free-of-charge skin cancer check if they had a lesion meeting 1 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 group compared to the LDS group (17.9% versus 3.3%, P = < 0.01) but 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 and results of this trial can be found in Hoorens et al. (17). 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. The screening was performed in the first year of the model. Clinical outcomes of the screening incorporated in the model were pathologically confirmed skin cancer, a (false) positive result or a (false) negative result. It was assumed in the model that persons with an undetected lesion who chose not to participate in the screening program or persons with a false negative result could have their lesion detected by spontaneous clinical detection in the same cycle, which was included in both screening interventions and comparator.

Table 1: input parameters related to the impact of primary prevention on health

RR: Relative risk

Parameter	Mean (SE)	Source
Prevalence of ever sunburned in	90%	*Expert opinion*
RR on sunburn if prevention	0.59 (0.11)	*(25)*
RR on skin cancer if ever sunburned		
MSC	1.59 (0.12)	*(6)*
SCC	1	*(7)*
BCC	1	
Prevalence of ever used sunbed in	47%	*(28)*
RR on skin cancer if ever used		
MSC	1.25 (0.09)	*(8)*
SCC	1.93 (0.43)	*(7)*
BCC	1	*(26)*

Table 2: Screening-related input parameters

Parameter	Input value (95%CI)							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%	*(17)*
TBE females	14.5%	20.1%	20.3%	24.0%	27.1%	18.6%	4.6%	*(17)*
LDS males	1.5%	2.1%	2.2%	3.8%	5.9%	3.7%	2.6%	*(17)*
LDS females	1.8%	3.3%	3.7%	2.7%	5.5%	2.7%	0.9%	*(17)*
TEST CHARACTERISTICS								
sensitivity dermoscopy BCC	83% (73%-93%)							*(29)*
SCC	83% (73%-93%)							*(29)*
MSC	74% (62%-86%)							*(29)*
specificity dermoscopy BCC	86.5% (85%-88%)							*(29)*
SCC	86.5% (85%-88%)							*(29)*
MSC	89% (87%-91%)							*(29)*

Input data

1) *Epidemiological and clinical data*

Prevalence of detected MSC was derived from the Belgian cancer registry (30) and of NMSC from the Dutch cancer registry (31), 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 MSC incidence of both countries. Prevalence of undetected skin cancer was –as explained before- derived from the TBE and LDS screening trial. Since skin cancer yield was not different between both screening groups, TBE results were used in the model because of the greater sample. Information on the probability of natural progression can be found in the appendix. Risk of recurrence in a treated lesion and risk of developing a subsequent lesion was obtained from published literature (32-39). Risk of a subsequent lesion (for all cancer types) was only accounted for in the costs. The probability of spontaneous clinical detection was defined as the average prevalence of detected skin cancer divided by the total prevalence (detected and undetected). All-cause mortality risk was applied to all persons in the model (based on Belgian life tables), whereas mortality from skin cancer was only possible for melanoma and SCC skin cancer patients stage III and IV (40). All risks were applied age- and gender-specific where possible. All epidemiologic and clinical input data are depicted in Table A1.

2) *Costs and health effects*

Costs included the cost of the intervention, direct medical costs and costs due to productivity loss, expressed separately for the healthcare payer and for the patient. The cost for the prevention campaign was assessed according to the study of Shih et al. (24) who estimated the annual future cost for the SunSmart intervention to be €0.17 per capita. Applied to Belgian population figures, 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. The total cost of the screening per screenee was calculated at €4.9 in the TBE group and €1.8 in the LDS group. This included the costs for the invitation, poster and flyers, the cost for renting a public place for screening, the cost for using medical equipment, and the cost of total time spent by the dermatologists. Productivity loss due to attending the screening was also taken into account. The difference in cost was mainly due to the difference in duration of the two screening methods (TBE 5 times longer than LDS). Direct costs for treatment and follow-up and indirect costs due to productivity loss (because of early mortality and morbidity) were calculated

from the 287 Belgian skin cancer patients questionnaires. Costs per stage, per six months, are depicted in Table A2 (expressed in 2014 EURO values).

Health effects of the prevention programs 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 287 Belgian patient questionnaires in combination with literature data (Table A3). More information on the utilities can be found in the appendix. Following the Belgian guidelines, health effects were discounted at 1.5% and costs at 3% (22).

Scenario and sensitivity analysis

In a scenario-analysis, the impact of several scenarios on the ICER were tested. In the base case analysis of primary prevention, we assumed a latency period of 20 years. However, since the duration of this period is not well documented, we varied it between 10 years and 30 years. A second scenario consisted of implementing both a both a prevention campaign and a ban on public sunbed use simultaneously. Also several screening-scenarios were tested: screening from the age of 40 years instead of 18 -since skin cancer tumours usually do not arise frequently in younger persons-, assuming a time horizon of 50 years instead of 20 years and screening every 5 or 2 years during 20 years (when assuming a time horizon of 50 years and with constant screening uptake rates, not linked to disease incidence or progression), instead of only once.

A one-way sensitivity analysis was performed in order to take into account uncertainty in some variables. This analysis varied these parameters one by one (according to the confidence interval (CI), or increased or decreased by 30% of their original value in case the CI was not available) and reflected the influence of this variation on the cost-effectiveness result. A probabilistic sensitivity analysis (PSA) is a second way to explore the effect of uncertainty in the parameters. A PSA creates a credibility interval around the ICER by running 5,000 (Monte Carlo) simulations according to the distribution of the parameters. Utilities and probabilities were varied according to a beta-distribution and costs according to a gamma-distribution. The credibility interval demonstrates whether the findings of the cost-effectiveness analysis are robust.

Results

1. 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 3 displays the stage distribution per cancer type. From the table it is clear that returned questionnaires reflect the stage distribution of skin cancer prevalence, as the majority of patients had small BCC or MSC stage 0-I.

Epidemiology of skin cancer

In 2014 there were an estimated 137,117 skin cancer cases in Belgium, of which the greatest part (70%) were BCC cases (95,870), 18.5% were SCC cases (25,345) and 11.5% were MSC cases (15,902) (Table 4). There were more female than male skin cancer patients, with a ratio of 1.13 to 1. This current prevalence is estimated to triple by 2034, to 402,565 skin cancer cases, of which 65.1% BCC, 21% SCC and 13.8% MSC. The ratio of increase for MSC, SCC and BCC was respectively 3.5, 3.3 and 2.7.

Cost of skin cancer

Table A2 shows the cost per skin cancer stage, expressed per six months. As already stated in previously published studies (41;42), it is clear from the table that costs increase with tumour stage. The total economic burden of skin cancer in 2014 in Belgium was estimated at €103.2 million, with direct costs being €76.8 million and indirect costs being €26.3 million (Table 5). The majority of this total cost was due to MSC (62%). Costs were slightly higher for females than for males. Costs due to productivity loss were 10 times higher in MSC patients than in NMSC patients, whereas costs for the patient were higher in case of NMSC. Total discounted cost in 2034 amounted to €153 million. Total societal cumulative cost over a period of 20 years (up to 2034) were estimated at €3.2 billion and over 50 years almost €9 billion. The Markov model simulation over 50 years showed that of the total cumulative societal burden (including direct and indirect

costs) of €9 billion, €345 million could be saved by a prevention campaign and €325 million by a total ban on sunbeds, which is respectively 3.9% and 3.6% of the total societal burden.

Table 3: Stage distribution of study population

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

D&T: Diagnosis and treatment; hist.: histology

Table 4: Epidemiology of skin cancer in Belgium

	BCC	**SCC**	**MEL**	**TOTAL**
Prevalence 2014				
males	45,480	12,278	6,239	**137,117**
females	50,390	13,066	9,663	
Prevalence 2034				
males	101,980	39,340	18,961	**402,565**
females	160,276	45,314	36,694	

Table 5: Total current and future cost of skin cancer in Belgium (calculated with annual inflow)

	TOTAL COST 2014						
	MALES		FEMALES		TOTAL (incl death)		
	MSC	NMSC	MSC	NMSC	MSC	NMSC	TOTAL
HEALTHCARE PAYER	€ 16,925,086	€ 12,781,836	€ 20,187,840	€ 13,987,812	€ 37,112,926	€ 26,769,648	€ 63,882,574
PATIENT	€ 888,664	€ 5,101,267	€ 1,295,471	€ 5,684,613	€ 2,184,135	€ 10,785,880	€ 12,970,016
PRODUCTIVITY	€ 11,433,258	€ 9,152	€ 14,882,598	€ 16,834	€ 26,315,856	€ 25,985	€ 26,341,842
TOTAL	***€ 29,247,009***	***€ 17,892,255***	***€ 36,365,910***	***€ 19,689,258***	***€ 65,612,918***	***€ 37,581,513***	***€ 103,194,431***

	TOTAL CUMULATIVE COST OVER 20 YEARS (2014-2034)						
	MALES		FEMALES		TOTAL (incl death)		
	MSC	NMSC	MSC	NMSC	MSC	NMSC	TOTAL
RIZIV/INAMI	€ 555,710,595	€ 264,429,725	€ 766,039,212	€ 350,116,361	€ 1,321,749,807	€ 614,546,086	€ 1,936,295,893
PATIENT	€ 25,633,652	€ 118,693,787	€ 41,503,216	€ 159,465,879	€ 67,136,868	€ 278,159,666	€ 345,296,533
PRODUCTIVITY	€ 363,932,151	€ 191,743	€ 578,231,642	€ 220,015	€ 942,163,793	€ 411,758	€ 942,575,551
TOTAL	***€ 945,276,398***	***€ 383,315,255***	***€ 1,385,774,070***	***€ 509,802,255***	***€ 2,331,050,468***	***€ 893,117,509***	***€ 3,224,167,977***

2. Health economic evaluation of primary and secondary prevention

Impact on skin cancer mortality

Over a period of 50 years, 5944 deaths could be avoided by means of an annual prevention campaign (2368 in males and 3576 in females) and 5692 by means of a ban on public sunbed use (2198 in males and 3494 in females).

Over a period of 20 years, both one-time screening programs were estimated to have a positive, although modest, impact on mortality from skin cancer, with an absolute reduction of 686 deaths in case of TBE (275 in males and 411 in females) and 124 in case of LDS (57 in males and 66 in females). This corresponds to a relative mortality reduction of 5.14% in case of TBE and 0.95% in case of LDS (in reference to mortality if the one-time screening would not take place). Besides, a one-time screening led to a shift in stage-specific incidence, showing an increase in the proportion of MSC stage I and II (by 4.3%) and a decrease in the proportion of MSC stage III and IV (by 4.4%).

Cost-effectiveness and budget impact of primary prevention

1) *Base case*

Table 6 shows the results of the cost-effectiveness analysis of both hypothetical primary prevention programs. Both programs would lead to a gain in QALYs and cost-savings, making them dominant prevention strategies. Almost €224 million (or 0.56%) of the healthcare budget could be saved due to a comprehensive prevention campaign and €230 million (or 0.58%) due to a total ban on sunbed use (initial investment cost taken into account) (Table 7). Every euro invested in the prevention campaign would save €5.7 to the healthcare budget on the long term.

Both screening strategies resulted in a gain in QALYs over a period of 20 years (Table 8). Health effects and costs are in good balance, leading to ICERs of €19,575/QALY in males and €7,763/QALY in females for TBE and €21,865/QALY in males and €8,031/QALY in females for LDS, which can be interpreted as a cost-effective result regarding a willingness-to-pay threshold in Belgium of €35,000 (35;36). The BIA showed that over a period of 20 years a one-time screening induces extra costs for the healthcare payer. The total extra cost was calculated at €29,5 million in case of TBE, and €4.9 million in case of LDS or respectively €3.3 and €0.6 per adult. (Table 9).

Table 6: Results of the cost-effectiveness analysis of primary prevention (over 50 years), expressed per 1,000 persons (calculated without inflow)

	Incremental QALYs		Incremental Costs		ICER	
	males	*females*	*males*	*females*	*males*	*females*
Prevention campaign	2.15	2.23	€ -24,317	€ -27,228	cost-saving	
Ban on sunbed use	5.36	6.26	€ -27,133	€ -27,706		
Both interventions simultaneously	6.78	8.27	€ -46,675	€ -55,817		

Table 7: Results from the budget impact analysis of primary prevention (over 50 years) (calculated with inflow)

	Cost of intervention	Cost for healthcare payer	Total cost	Total extra cost
Control	€ 0	€ 5,767,611,377	€ 5,767,611,377	
Prevention campaign	€ 39,219,386	€ 5,504,523,218	€ 5,543,742,604	€ -223,868,773
Ban on sunbed use	€ 0	€ 5,536,954,717	€ 5,536,954,717	€ -230,656,660

Table 8: Results of the cost-effectiveness analysis of secondary prevention (over 20 years), expressed per 1,000 persons (calculated without inflow)

	Incremental QALYs		Incremental Costs		ICER	
	males	*females*	*males*	*females*	*males*	*females*
TBE	0.23	0.41	€ 4,426	€ 3,192	€ 19,575	€ 7,763
LDS	0.05	0.06	€ 994	€ 470	€ 21,865	€ 8,031

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

Table 9: Results of the budget impact analysis, over a period of 20 years

	Cost of intervention	Healthcare payer	Total cost	Total extra cost
Control	€ 0	€ 1,936,255,253	€ 1,936,255,253	
TBE	€ 7,308,319	€ 1,958,382,523	€ 1,965,690,842	€ 29,435,589
LDS	€ 463,275	€ 1,940,781,939	€ 1,941,245,214	€ 4,989,961

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

2) *Scenario- and sensitivity analysis*

When both primary prevention interventions would be implemented simultaneously, more QALYs could be gained and more costs could be saved than implementing only one of them (Table 6). The effect of a shorter or longer latency period was tested and showed that the strategy of a ban on sunbed use remained cost-saving in case of a 10y or 30y period. A one-way sensitivity analysis of both primary prevention strategies showed the most influencing parameters to be the utility (~ health-related quality of life) of MSC and SCC patients, the direct cost of diagnosis and treatment of MSC stage III-IV, the cost of the prevention campaign, the relative risk on sunburn in case of a prevention campaign, the relative risk on MSC and SCC if sunbed use (Figure A2). The higher the utility of MSC and SCC, the direct cost of MSC stage III-IV and the relative risk on MSC or SCC if sunbed use, the better the cost-effectiveness. The higher the cost of the prevention campaign, the relative risk on sunburn in case of a prevention campaign, the worse the ICER. 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 result.

Also several screening scenarios were tested and results are depicted in Table 10. Screening from the age of 40 would not change the results to a great extent. Supposing a time horizon of 50 years instead of 20 years, the cost-effectiveness changed in a positive way. Screening every 5 or 2 years during 20 years (assuming a time horizon of 50 years) was cost-effective, but less than the one-time screening. The one-way sensitivity analysis showed the most influencing parameters to be the natural progression of melanoma, the utility (~ health-related quality of life) of MSC patients (only for males), the direct cost of follow-up of BCC, the indirect as well as direct cost of melanoma III and IV (diagnosis and treatment) and the sensitivity of dermoscopy for melanoma (Figure A4). A higher value on these parameters led to a more cost-effective result, except for the cost of BCC (long-term follow-up) in which the effect was the opposite. In all cases however, the result remained cost-effective. The PSA created credible intervals around the deterministic ICER. Over a 20-year time horizon, the PSA resulted in an ICER for TBE of €18,322 (95%CI €13,089– €24,283) in males and €8,716 (95%CI €5,201 – €12,457) in females and for LDS in €19,794 (95%CI €14,392 – €26,016) in males and €8,858 (95%CI €4,907 – €12,996). The cost-effectiveness planes represent all simulations (Figure A5). These planes show that all simulations are located in the north-east quadrant and are below the willingness-to-pay threshold of €35,000/QALY, which means that all simulations show a cost-effective result. Furthermore, the probability of screening being cost-effective reaches 100% in females from a threshold of

€20,000/QALY while in males this probability is reached from a threshold of €30,000/QALY. In other words, a one-time screening in females is estimated to be always cost-effective concerning a threshold ≥€20,000/QALY and in males ≥€30,000/QALY.

Table 10: Results of the scenario analysis

	TBE (cost/QALY)		**LDS (cost/QALY)**	
	males	*females*	*males*	*females*
Base case	€ 19,575	€ 7,763	€ 21,865	€ 8,031
Screening from 40 years	€ 21,173	€ 10,732	€ 25,203	€ 11,852
Time horizon 50 years	€ 5,888	€ 2,491	€ 6,984	€ 2,411
Screening every 5 years*	€ 7,110	€ 2,497	€ 8,281	€ 2,493
Screening every 2 years*	€ 7,281	€ 2,443	€ 8,037	€ 2,302
ICER PSA	€ 18,322	€ 8,716	€ 19,794	€ 8,858
(95% CI)	(€ 13,089 - € 24,283)	(€ 5,201 - € 12,457)	(€ 14,392 - € 26,016)	(€ 4,907 - € 12,996)

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*

Discussion

In order to perform the bottom-up cost analysis, we used individual skin cancer patient data which were aggregated to the national level based on skin cancer epidemiologic data. Although a bottom-up approach is more time-consuming, it has the advantage of providing more detailed information on the incurred costs (20). Moreover, it has been shown that the self-reported healthcare use of responders to surveys does not differ significantly from the observed healthcare use in the total population and that a self-reporting questionnaire is a valid instrument to estimate healthcare use, especially for general practitioner consultations and inpatient care (43;44). Specialist consultations tend to be underestimated when self-reported, which makes our cost-analysis rather conservative. This analysis on the burden of skin cancer showed that if the rising trend in incidence continues, skin cancer burden in Belgium will triple in 20 years. In comparison, a recent study in the US estimated melanoma incidence rates to double from 2011 to 2030 (45). We estimated the current annual total cost for society due to skin cancer in Belgium to be €103 million (for 8.8 million adult inhabitants), of which almost €64 million to be paid by the healthcare payer (government), resulting in about 0.15% of the total healthcare budget in Belgium. Since only the first NMSC is registered in the IKNL epidemiologic data, it is expected that this estimated total cost is an underestimation of the real cost of skin cancer. 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 healthcare budget (46). In Sweden (9 million inhabitants in 2005) the total societal cost for melanoma was €79.7 million and €36.2 million for NMSC in 2005 (47). A bottom-up cost-of-illness study in England calculated an annual direct cost of 106.4 million pound in 2008 (€124.7 million in 2015) for MSC and NMSC (48). A top-down method generated a similar result. This is relatively low compared to the Belgian situation (direct cost healthcare payer and patient estimated to be about €77 million) since there are almost 5 times more inhabitants in the UK. According to our data melanoma was responsible for 62% of the costs, in contrast to a study examining the hospitalization costs of skin cancer in Germany (14). The latter study concluded that NMSC-related costs for hospitalizations are about twice the rates of melanoma. Part of this discrepancy can probably be explained by the recent development of novel expensive (combination) therapies for metastatic melanoma. Nonetheless, in Sweden and Denmark, the proportion of cost due to melanoma was similar to the Belgian situation (resp. 68.7% and 59%, although the latter only included direct costs) (46;47). In comparison, the annual societal cost of established arteriosclerotic cardiovascular disease in Belgium was €2,1 billion (49), and all brain disorders combined accounted for €10.6 billion in 2004 (50), showing the burden of melanoma to be relatively modest. Projections of the economic burden of skin cancer to 2034 showed an estimated

annual discounted cost of €153 million, and a total cumulative cost of €3.2 billion. This estimated future annual cost of 2034 is in line with other studies that made projections into the future. 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) (48).

Both primary and secondary prevention programs resulted in a modest skin cancer mortality reduction. However, no prospective studies currently support a reduction in skin cancer mortality due to screening. 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 according to Boniol et al.(51;52). In addition, no decrease in melanoma mortality has been documented since the nation-wide skin cancer screening has been introduced in Germany in 2013 (52).

The cost-effectiveness analysis of primary prevention showed that both primary prevention strategies are cost-saving over a period of 50 years. On average, an estimated €227 million of the healthcare budget could be redirected to other diseases by implementing a primary prevention strategy. Although a ban on sunbed use would gain more health benefits, both interventions are cost-saving and thus dominant on the long term. However, 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). Nonetheless, if we would assume an extra costs of €5 per adult, then the primary prevention campaign would not be cost-effective anymore. Besides, 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 obtain a specific behavior. The sensitivity analysis revealed that the higher the medical costs of treating metastatic melanoma, the more cost-effective primary prevention would be, since the financial benefit of prevention would be higher. Recently, new expensive treatments for metastatic melanoma were introduced and it is expected that in the future treatment costs will continue to rise, which further favors preventive strategies for melanoma.

A one-time TBE would result in gain of 2,825 healthy life-years in the total population (8.8 million) and LDS would gain 459 healthy life-years, over 20 years. Due to the screening cost, and the extra costs for treatment and follow-up, screening is more expensive than no screening. Nevertheless, the balance between costs and health effects is shown to be beneficial, both for TBE and LDS (ICER below the accepted threshold of 35,000euro). The ICER for TBE was better than for LDS, which can be explained by the low participation rate in this screening arm (17). 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. 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. When the time horizon of the model was extended to 50 years, then the ICER was better than with a 20-year time horizon, because the effect of the screening is assumed 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. Sensitivity analysis showed that the natural progression of skin cancer had the highest influence on the cost-effectiveness outcome, arguing for better approaches to estimate the natural progression of skin cancer. Other important nfluencing parameters were the cost of melanoma III and IV (for diagnosis and treatment) and the sensitivity of the dermoscopy for melanoma. It is possible that the cost for treating melanoma 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 melanoma did not affect the ICER to a great extent (see tornado diagram), which shows that even in case of good primary prevention programs for skin cancer, screening would still be cost-effective.

To our knowledge, no similar cost-effectiveness analysis in combination with an economic burden-of-illness analysis as well as budget impact analysis of primary and secondary prevention of skin cancer has been performed up to now. Gordon & Rowell included 11 studies in their review of the cost-effectiveness of primary and secondary prevention (5). Although all studies had different designs and context, they concluded that skin cancer 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. (24) 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 €5.7. Other studies on the cost-effectiveness of skin cancer screening have been conducted especially in the U.S. and Australia and only included melanoma. Most of these studies expressed the cost-effectiveness of melanoma 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 ICER of $12.137/life-year saved (AUD) (9). One-time screening by dermatologists in a self-selected population resulted in $51,481/life-year saved (USD) (40) and in a high-risk population $39.600/life-year saved (USD) (11). One study

calculated the cost per QALY of visual one-time screening from the age of 50 to be $10,100/QALY (USD) (~ €9,256/QALY) (10). When implemented biennially the ICER rose to $80,700/QALY (~ €73,882/QALY) and if annually to $586,800/QALY (~ €537,220/QALY). Our results support the latter, although 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 melanoma higher in U.S. 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. It 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. In our model, the screening examination itself did not affect the quality-of-life. To our knowledge no study has shown the effect of a skin cancer screening on the quality-of-life of the screenees. The study of Hoorens et al. (17) 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 though. First, since for some skin cancer stages the sample of returned patient questionnaires was too small, we had to rely on expert opinion and literature data for these groups. Second, the simulation of the primary prevention programs is hypothetically, which means that we could not rely on the results of a trial. 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 Germany 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 (53). 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 het Dutch cancer registry, since they have a more systematic registration of NMSC. Fourth, 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. Lastly, It should 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.

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Appendix

Natural progression 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 BCC and SCC 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 was set to 0.75% per six months, the output of the model showed 11,000 deaths, which is in line with the estimated number of deaths in reality. Natural progression of BCC was derived from the study of Wolberink et al. (54), 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) (55).

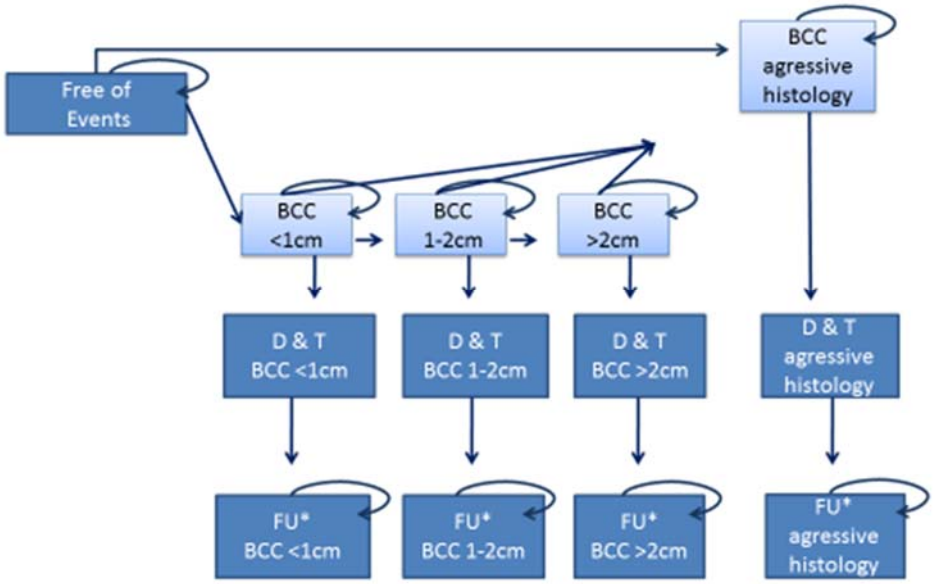
Health-related quality of life: utilities

Undiagnosed BCC, SCC stage 0-II and melanoma stage 0-I were assigned the same utility as the population norm, which is 0.81 (56) (Table A3). The utility for undiagnosed SCC stage III-IV and melanoma stage III-IV was calculated as the average of the population norm and the utility for diagnose and treatment. There were too few returned patient questionnaires for SCC and melanoma stage II-III and IV to have sufficient sample power, so these stages (diagnosed) were calculated as the ratio to the utility of stage I, taken from the study of Tromme et al. (57). The utility for patients with BCC, who are in treatment or intense follow-up is derived from the study of Gaulin et al. (58). The utility for patients in long-term follow-up for BCC, SCC 0-II and melanoma 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. A disutility was applied in the model, to take into account the psychological stress due to a false-positive screening result. Since, to our knowledge, no study has ever evaluated the impact of a false-positive screening result on the skin cancer patients' quality of life in detail, we assumed a disutility of 10% of the health state during one month.

Figure A1: visualization of the Markov model

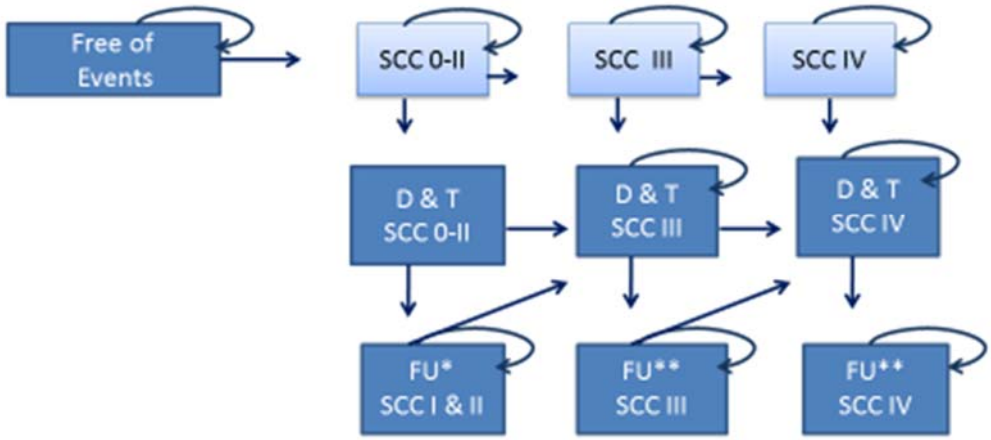
BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; FU: Follow-up; D & T: Diagnosis and treatment. Light-colored states correspond to undiagnosed cancer

a) *Markov model for BCC lesions*



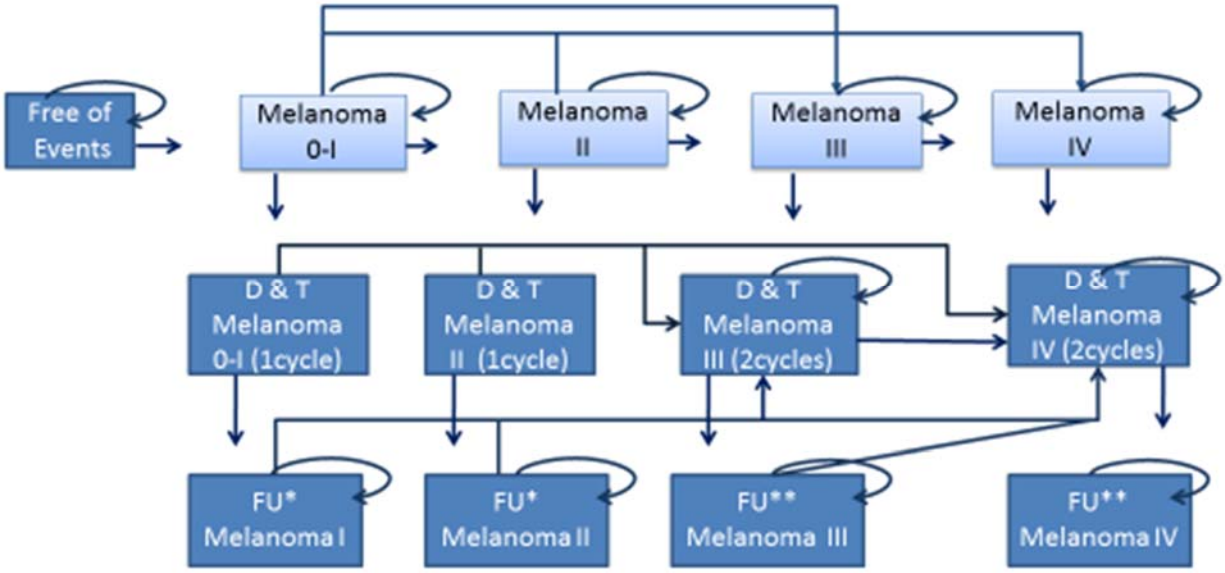
**FU is divided in intense FU (3 cycles) and long-term FU*
From BCC one can also develop a melanoma lesion

b) *Markov model for SCC lesions*



**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 melanoma lesion*

c) *Markov model for melanoma lesions*



**FU is divided in intense FU (3 cycles) and long-term FU*

*** FU is divided in intense FU (8 cycles) and long-term FU*

Figure A2a: Tornado-diagram showing the results of the one-way sensitivity analysis for the prevention campaign in males

[range of variation in relative terms]
D&T: diagnosis & treatment; RR: relative risk
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

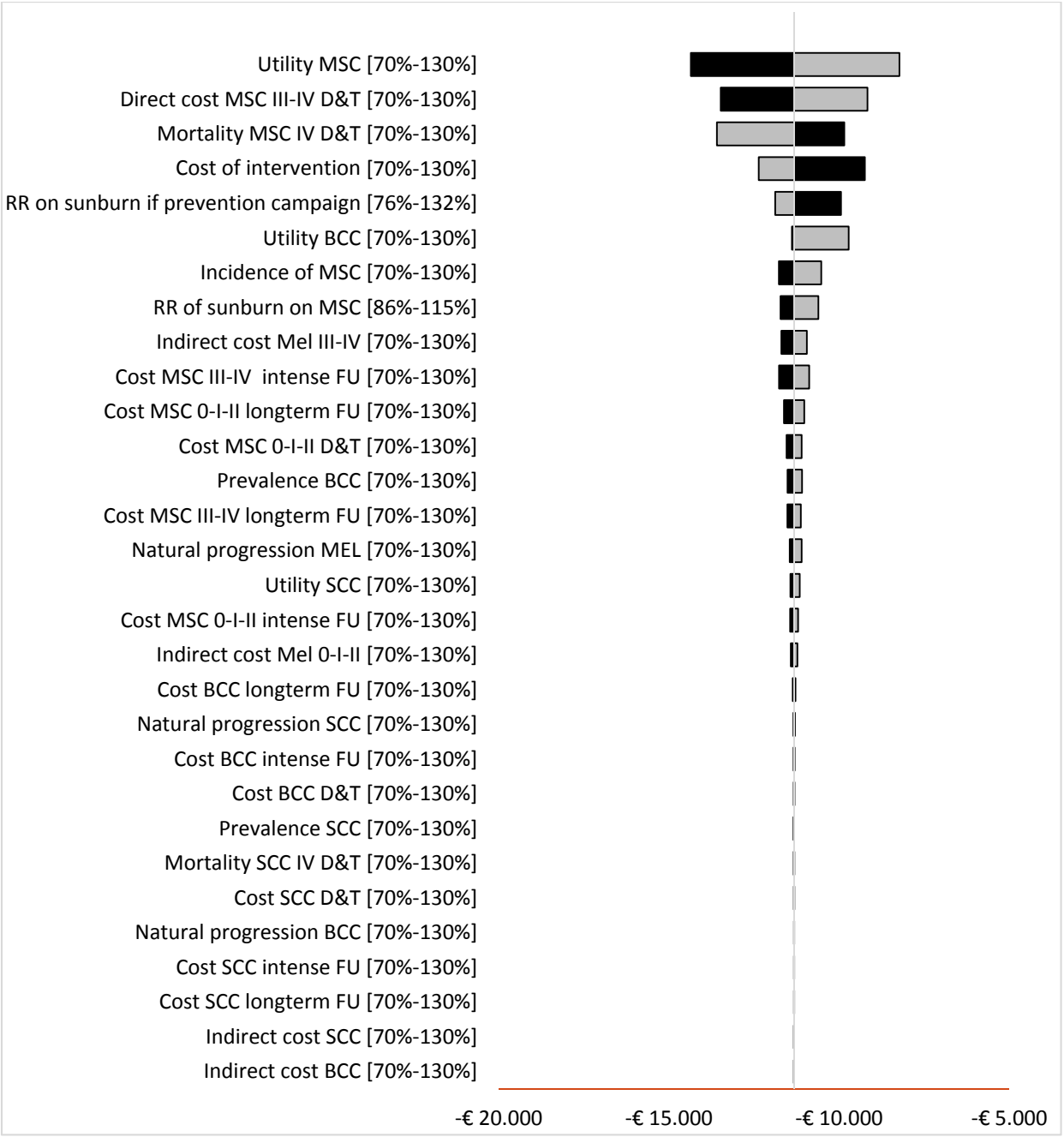


Figure A2b: Tornado-diagram showing the results of the one-way sensitivity analysis for the prevention campaign in females

[range of variation in relative terms]
D&T: diagnosis & treatment; RR: relative risk
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

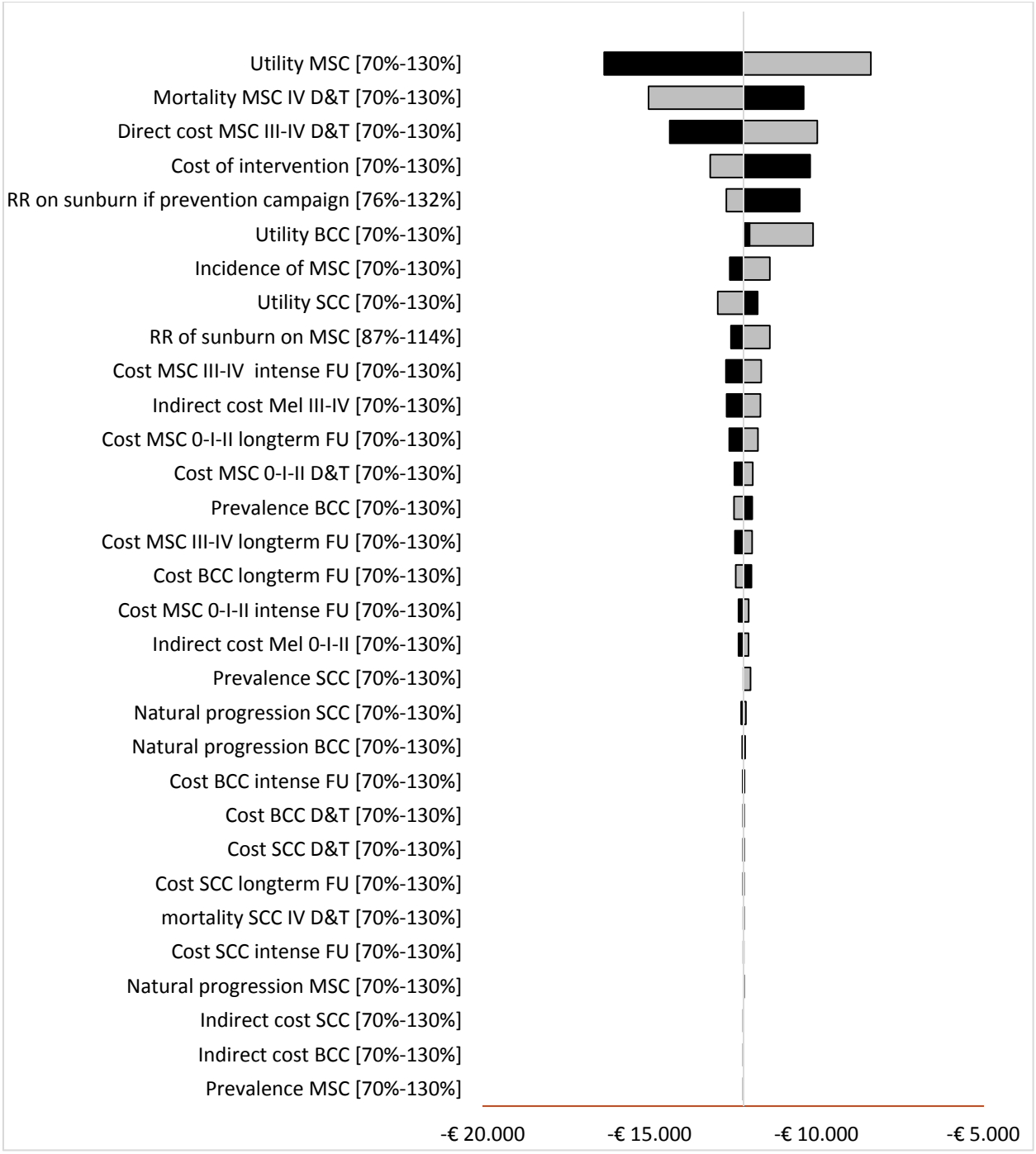


Figure A2c: Tornado-diagram showing the results of the one-way sensitivity analysis for the ban on sunbeds in males

[range of variation in relative terms]
D&T: diagnosis & treatment; RR: relative risk
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

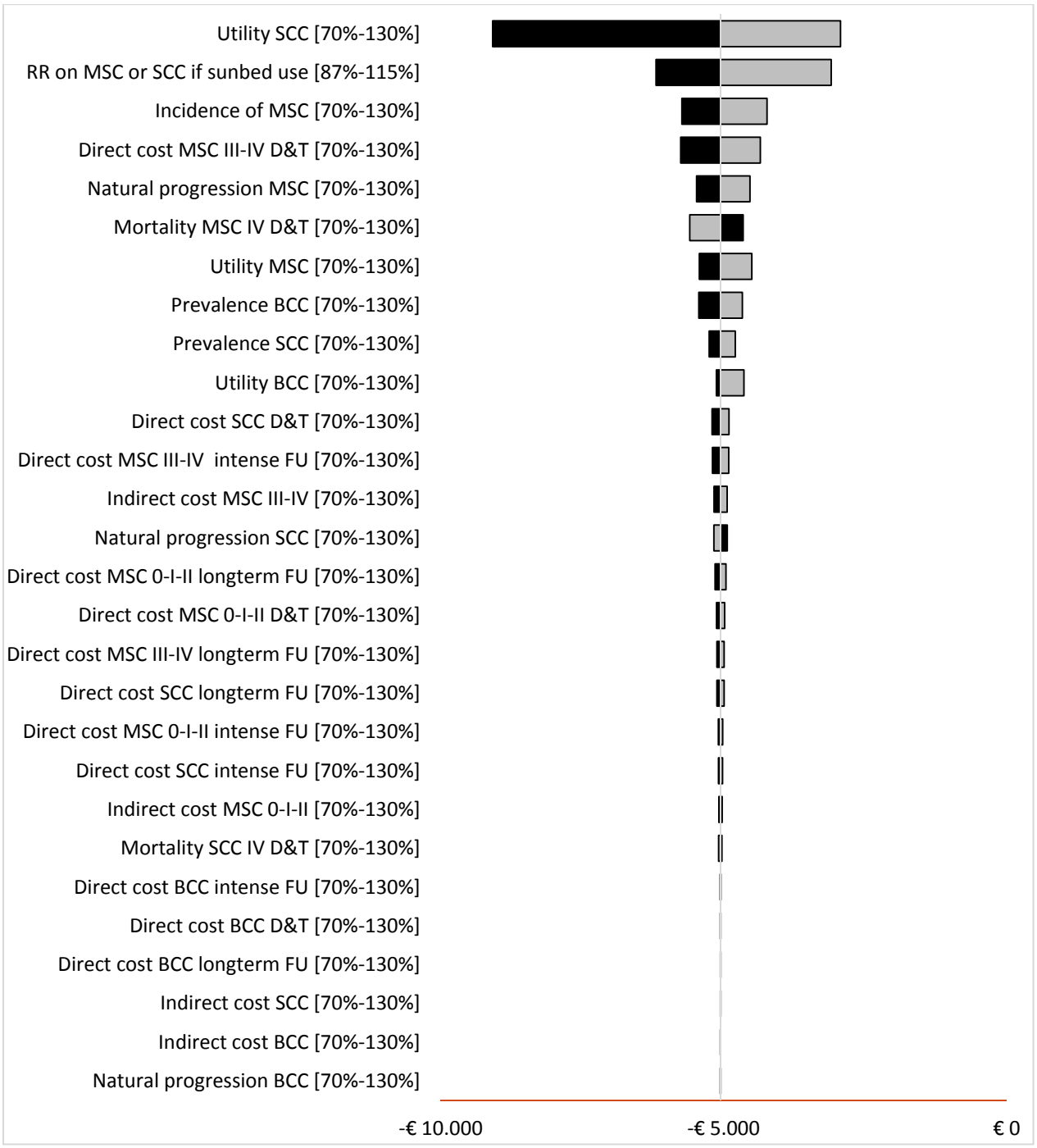


Figure A2d: Tornado-diagram showing the results of the one-way sensitivity analysis for the ban on sunbeds in females

[range of variation in relative terms]
D&T: diagnosis & treatment; RR: relative risk
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

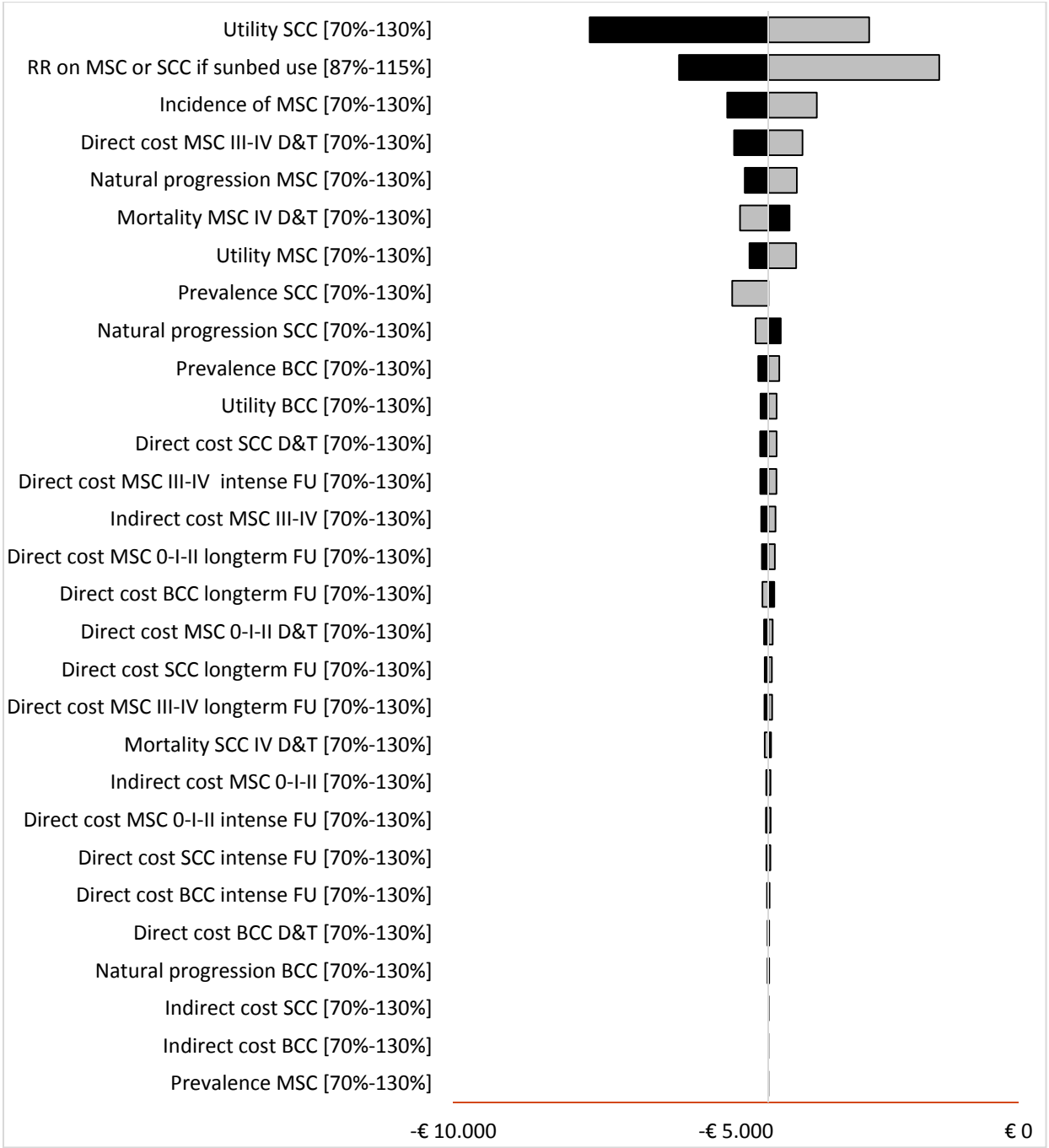


Figure A3: Cost-effectiveness planes displaying the 5,000 simulations for primary prevention

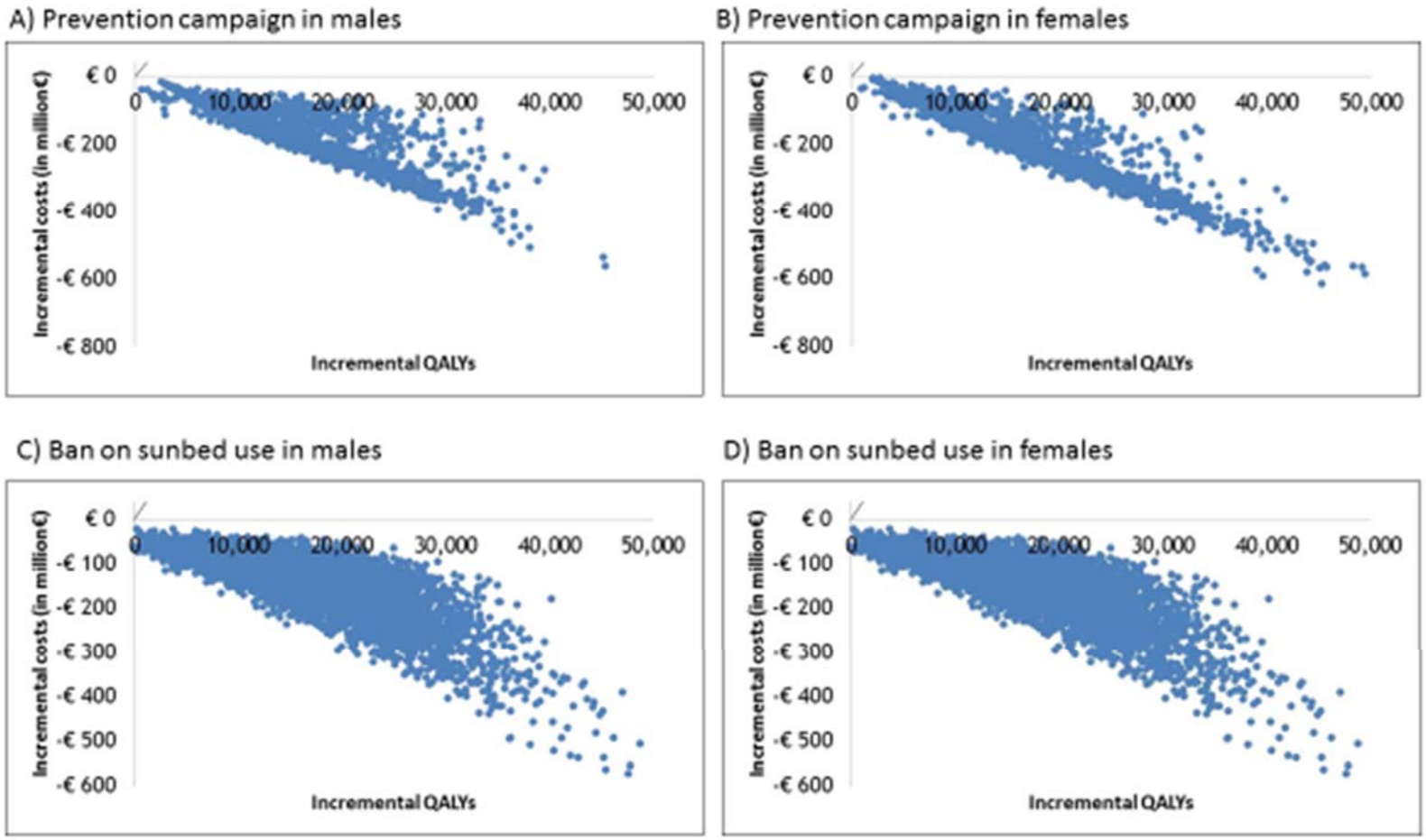


Figure A4a: Tornado-diagram showing the results of the one-way sensitivity analysis for TBE in males

MSC: melanoma skin cancer; BCC: basal cell carcinoma: SCC: squamous cell carcinoma
D&T: Diagnosis and treatment; FU: follow-up
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

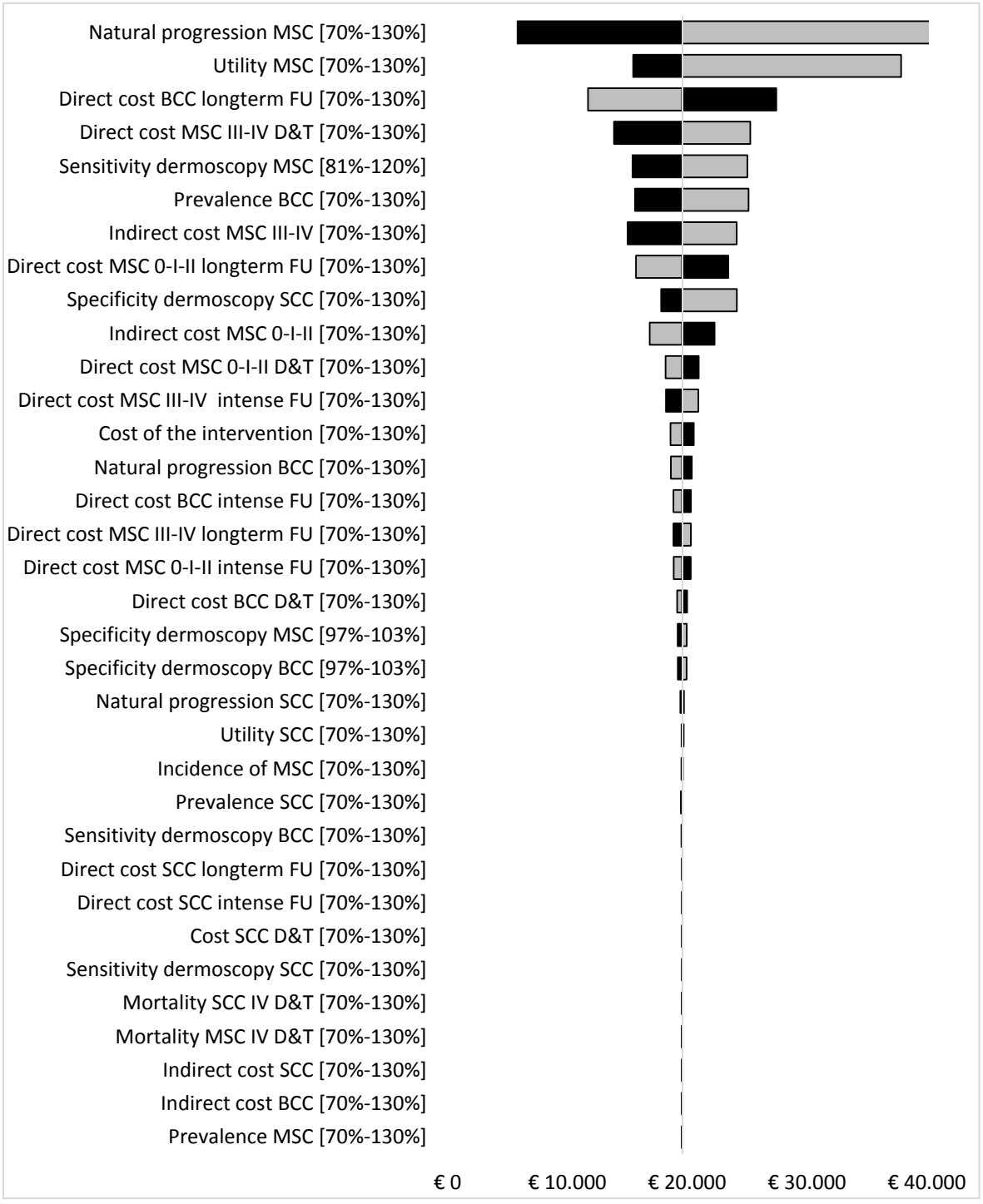


Figure A4b: Tornado-diagram showing the results of the one-way sensitivity analysis for TBE in females

MSC: melanoma skin cancer; BCC: basal cell carcinoma: SCC: squamous cell carcinoma
D&T: Diagnosis and treatment; FU: follow-up
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

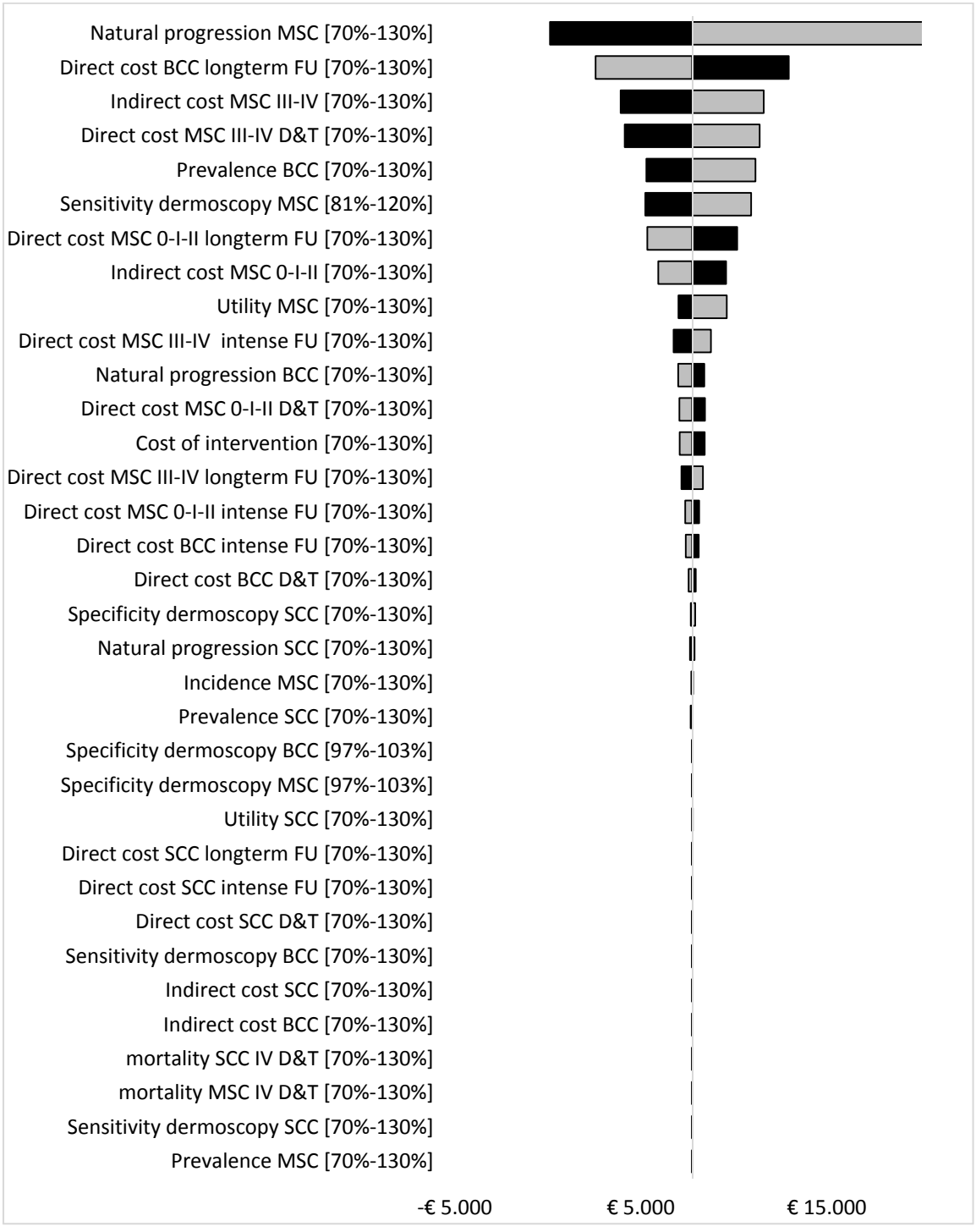


Figure A4c: Tornado-diagram showing the results of the one-way sensitivity analysis for LDS in males

MSC: melanoma skin cancer; BCC: basal cell carcinoma: SCC: squamous cell carcinoma
D&T: Diagnosis and treatment; FU: follow-up
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

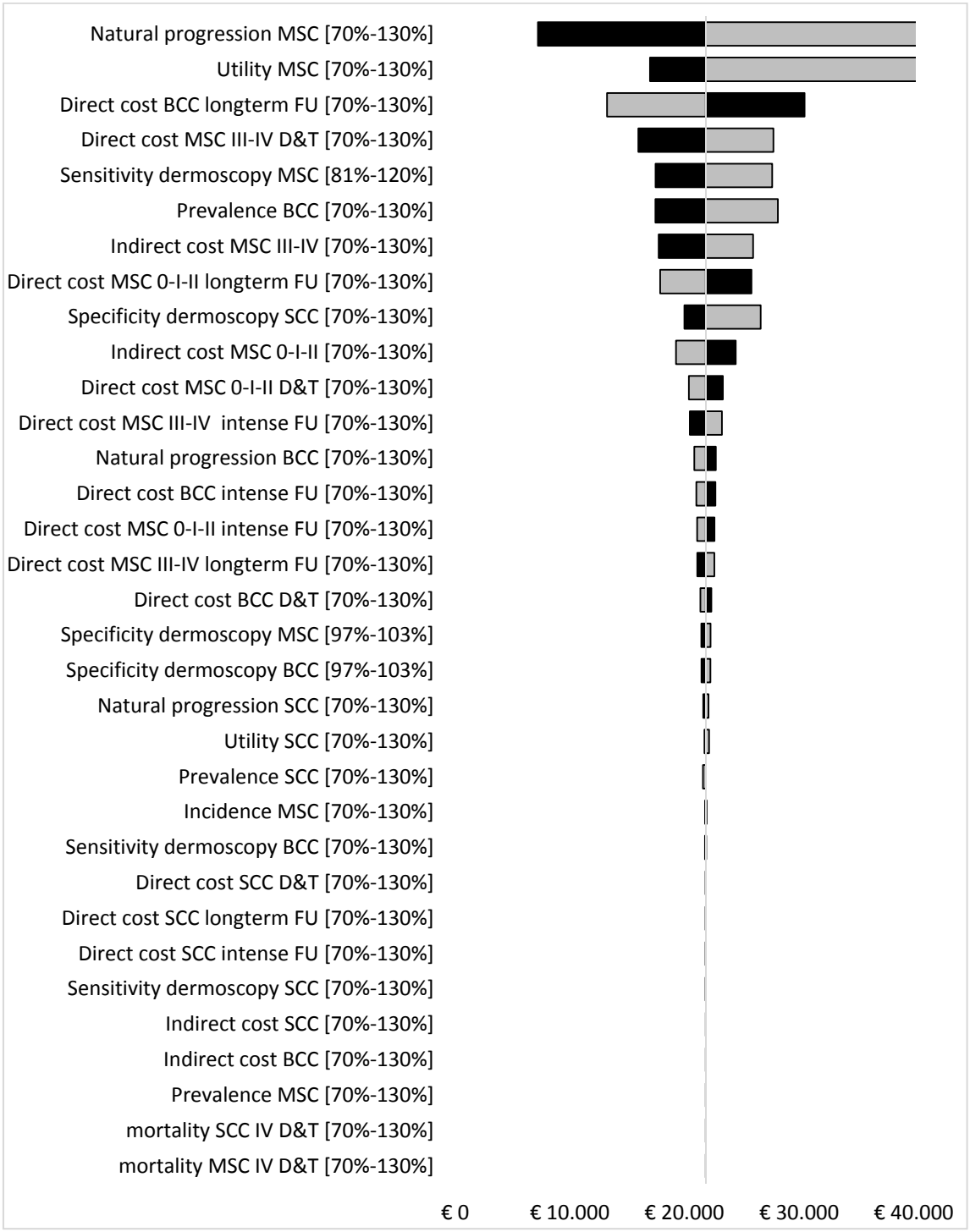


Figure A4d: Tornado-diagram showing the results of the one-way sensitivity analysis for LDS in females

MSC: melanoma skin cancer; BCC: basal cell carcinoma: SCC: squamous cell carcinoma
D&T: Diagnosis and treatment; FU: follow-up
dark-colored bars: maximum value paramter – light-colored bars: minimum value parameter

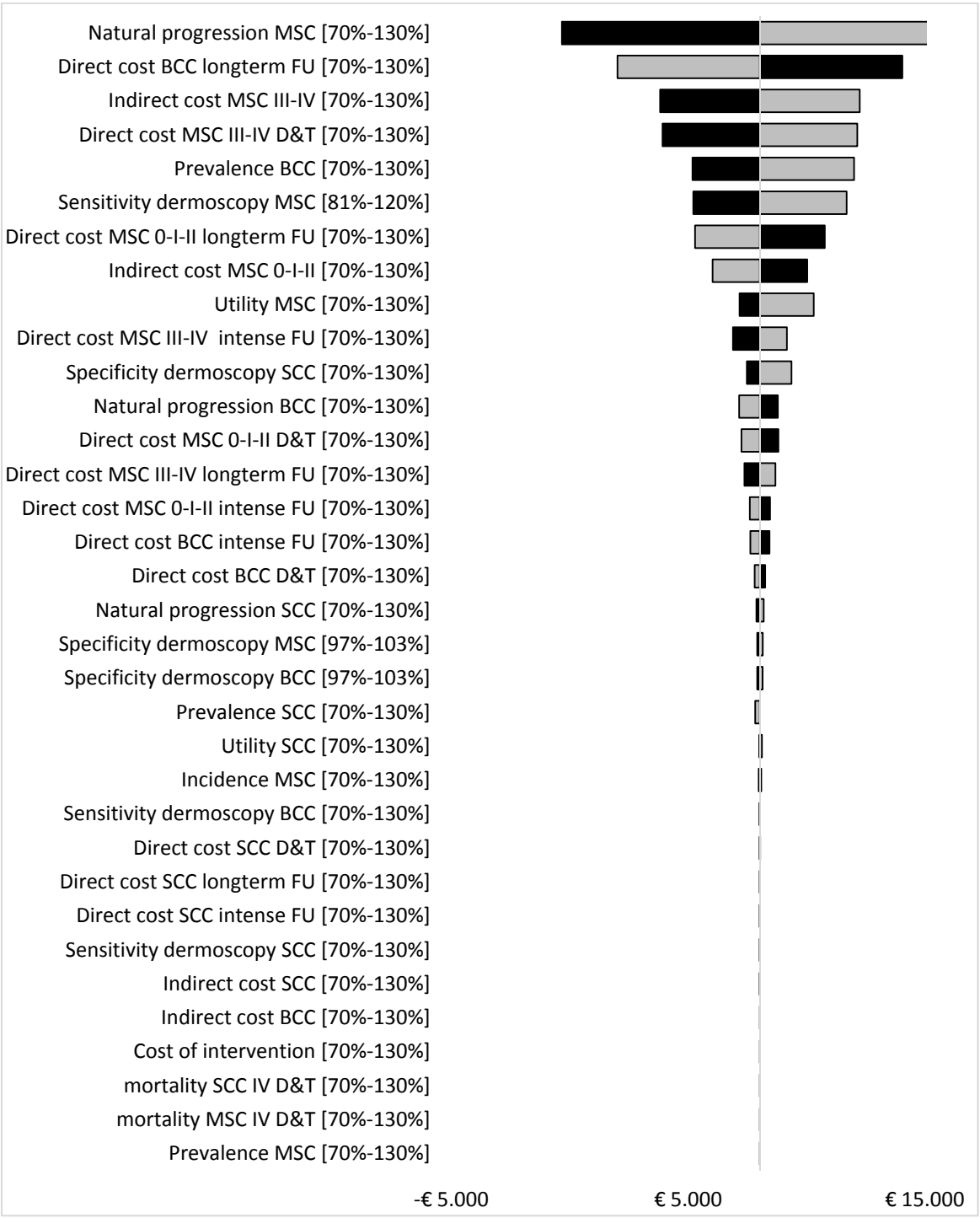


Figure A5: Cost-effectiveness planes displaying the 5,000 simulations for secondary prevention (screening)

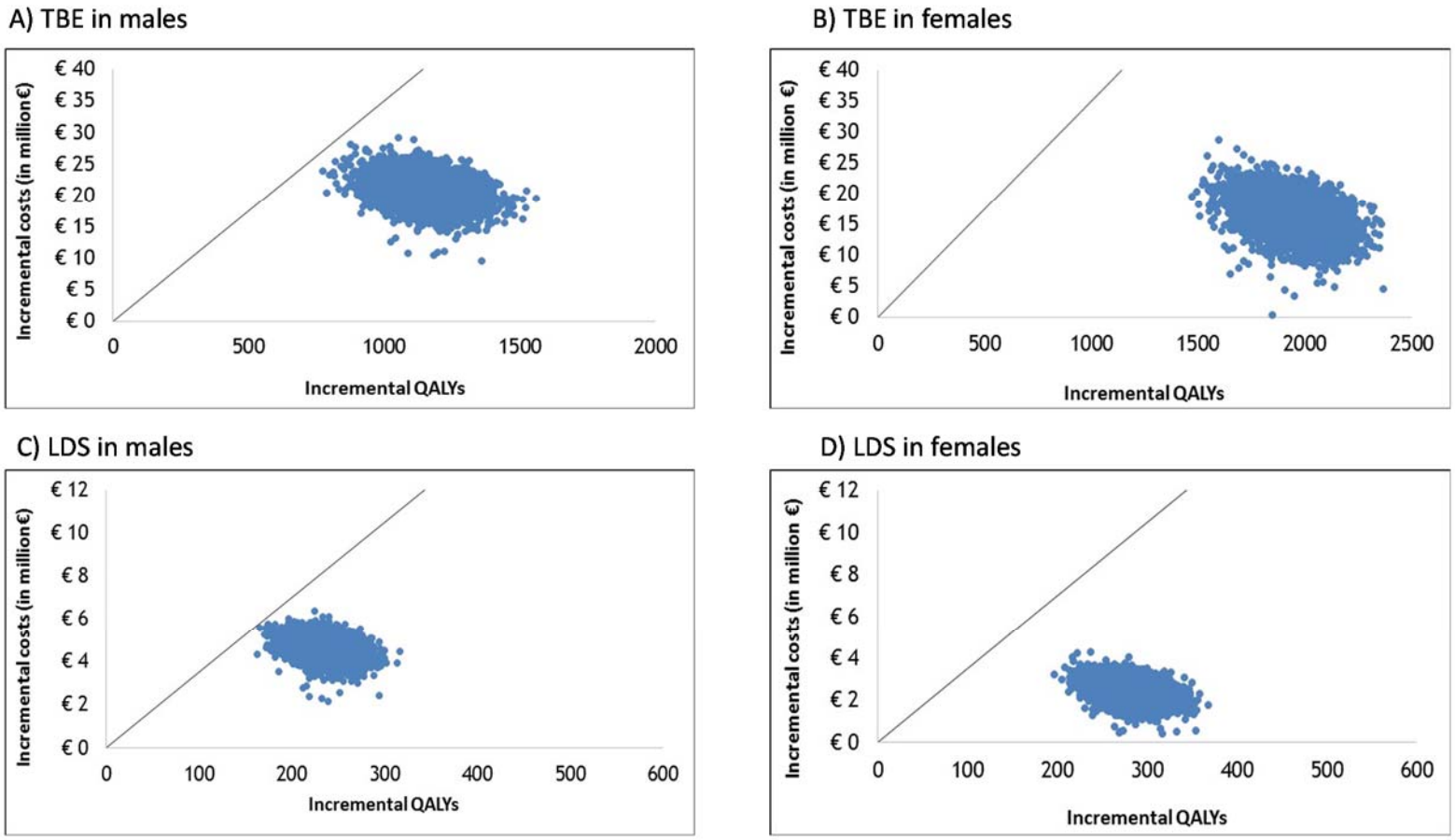


Table A1: Epidemiologic input parameters

M: Males F: Females

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%	*(17)*
BCC <1cm F	0.035%	0.150%	0.633%	0.799%	1.419%	2.033%	2.275%	*(17)*
BCC 1-2cm M	0.008%	0.075%	0.209%	0.387%	0.846%	1.674%	2.109%	*(17)*
BCC 1-2cm F	0.019%	0.083%	0.350%	0.443%	0.786%	1.126%	1.260%	*(17)*
BCC >2cm M	0.002%	0.021%	0.059%	0.109%	0.238%	0.470%	0.592%	*(17)*
BCC >2cm F	0.005%	0.023%	0.098%	0.124%	0.221%	0.316%	0.354%	*(17)*
BCC agr. hist. M	0.011%	0.101%	0.282%	0.522%	1.141%	2.257%	2.844%	*(17)*
BCC agr. hist. F	0.026%	0.112%	0.472%	0.597%	1.059%	1.518%	1.699%	*(17)*
SCC stage 0-II M	0.000%	0.001%	0.002%	0.013%	0.048%	0.268%	0.967%	*(17)*
SCC stage 0-II F	0.001%	0.002%	0.010%	0.033%	0.095%	0.222%	0.419%	*(17)*
SCC stage III M	0.000%	0.000%	0.000%	0.001%	0.006%	0.031%	0.112%	*(17)*
SCC stage III F	0.000%	0.000%	0.001%	0.004%	0.011%	0.026%	0.049%	*(17)*
SCC stage IV M	0.000%	0.000%	0.000%	0.000%	0.001%	0.007%	0.026%	*(17)*
SCC stage IV F	0.000%	0.000%	0.000%	0.001%	0.003%	0.006%	0.011%	*(17)*
MSC stage 0-I M	0.039%	0.103%	0.195%	0.314%	0.479%	0.688%	0.674%	*(17)*
MSC stage 0-I F	0.090%	0.218%	0.342%	0.382%	0.494%	0.538%	0.352%	*(17)*
MSC stage II M	0.036%	0.095%	0.179%	0.288%	0.440%	0.632%	0.619%	*(17)*
MSC stage II F	0.052%	0.125%	0.196%	0.219%	0.283%	0.308%	0.202%	*(17)*
MSC stage III M	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	*(17)*
MSC stage III F	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	*(17)*
MSC stage IV M	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	*(17)*
MSC stage IV F	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	*(17)*
Correction factor IKNL prevalence BCC/SCC	0.51							*Based on mortality (IARC) and incidence (2010) BE versus NDL*

Table A1: Epidemiologic input parameters (contd)

M: Males F: Females

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%	(31)
BCC F	0.002%	0.006%	0.024%	0.029%	0.055%	0.075%	0.078%	(31)
SCC M	0.000%	0.000%	0.001%	0.005%	0.018%	0.053%	0.123%	(31)
SCC F	0.000%	0.000%	0.002%	0.006%	0.017%	0.038%	0.076%	(31)
MSC M	0.002%	0.004%	0.007%	0.010%	0.013%	0.019%	0.017%	(59)
MSC F	0.005%	0.011%	0.017%	0.016%	0.015%	0.017%	0.009%	(59)
NATURAL PROGRESSION								
BCC				12.5%				(54)
SCC stage 0-II => III				1.0%				(55)
SCC stage III => IV				7.0%				calibration
MSC				0.8%				calibration
SPONTANEOUS CLINICAL DETECTION								
BCC				4.0%				calculation average 1y prevalence (IKNL) / average total prevalence (diagn. and undiagn.)
SCC				31.4%				
MSC stage 0-I				2.4%				
MSC stage II				0.8%				
MSC stage III-IV				100.0%				

Table A1: Epidemiologic input parameters (contd)

M: Males F: Females

Parameter	Input value							Source
	18-29y	*30-39y*	*40-49y*	*50-59y*	*60-69y*	*70-79y*	*79+y*	
PROGRESSION TO METASTASES, AFTER TREATMENT								
SCC				0.5%				*(33)*
Decrease in risk after the first year				25.0%				*(60)*
MSC stage I => MSC stage IV				0.3%				*(36)*
MSC stage II => MSC stage III				0.3%				*(36)*
MSC stage II => MSC stage IV				0.5%				*(36)*
MSC stage III => MSC stage IV				0.7%				*(37)*
RR OF DEVELOPING MSC AFTER DIAGNOSES OF NMSC								
MSC after BCC				3.28				*(38)*
MSC after SCC				3.62				*(38)*
MORTALITY RATES								
Mortality due to skin cancer (first year)								
MSC stage IV				26.66%				*(40),, corrected for new therapies*
SCC stage IV				6.69%				*(61)*
Mortality due to skin cancer (follow-up)								
MSC stage IV				12.45%				*(40), corrected for new therapies*
SCC stage IV				6.69%				*(18)*
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 A2: 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
MSC 0-I	€ 1,891	€ 161	€ 2,663	€ 385	€ 71	€ 1,872	€ 231	€ 41	€ 26
MSC II	€ 2,119	€ 244	€ 1,213	€ 318	€ 60	€ 1,872	€ 258	€ 43	€ 26
MSC III	€ 4,737	€ 200	€ 6,591	€ 1,082	€ 72	€ 11,864	€ 822	€ 72	€ 3,401
MSC IV	€ 51,034	€ 344	€ 6,591	€ 6,758	€ 147	€ 16,688	€ 1,401	€ 141	€ 3,401
Death	-	-	-	-	-	-	-	-	€ 16,200

Hist.: histology; prod.: productivity

Table A3: utilities assigned to the model states

Parameter	Value	Source
General population	0.812	*(56)*
BCC undetected	0.812	
D&T BCC	0.790	*(58)*
intensive FU BCC	0.790	*(58)*
longterm FU BCC	0.812	*General population*
SCC 0-II undetected	0.812	
SCC III undetected	0.631	
SCC IV undetected	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) (ref = 1)*
SCC III intense FU	0.620	
SCC IV intense FU	0.702	
SCC 0-II longterm FU	0.812	*General population*
SCC III longterm FU	0.617	
SCC IV longterm FU	0.699	
Melanoma 0-I undetected	0.812	
Melanoma IIundetected	0.812	
Melanoma III undetected	0.672	
Melanoma IV undetected	0.695	
Melanoma 0-I D&T	0.682	*patient questionnaires (n=15) (ref = 1)*
Melanoma II D&T	0.575	
Melanoma III D&T	0.531	
Melanoma IV D&T	0.579	
Melanoma 0-I intense FU	0.701	*patient questionnaires (n=43) (ref = 1)*
Melanoma II intense FU	0.695	
Melanoma III intense FU	0.609	
Melanoma IV intense FU	0.690	
Melanoma 0-I longterm FU	0.812	*General population*
Melanoma II longterm FU	0.812	
Melanoma III longterm FU	0.665	
Melanoma IV longterm FU	0.753	
False positive result on screening	0.805	*Assumption*

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