Leitlinienprogramm Onkologie

Evidenztabellen zur S3-Leitlinie Prävention von Hautkrebs

Version 3.0 – Oktober 2026
AWMF-Registernummer: 032/052OL

Leitlinienreport

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1. Informationen zu den Evidenztabellen

In diesem Dokument sind die Evidenztabellen der im Rahmen der Version 3.0 durchgeführten Leitlinienaktualisierung aufgeführt. Die Evidenztabellen der vorherigen Versionen der Leitlinie sind auf der Website des Leitlinienprogramms Onkologie abrufbar (https://www.leitlinienprogramm-onkologie.de/leitlinien/hautkrebs-praevention).

1.1. Kontakt

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1.2. Zitierweise der Evidenztabellen

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Prävention von Hautkrebs, Evidenztabellen 3.0, 2026, AWMF-Registernummer: 032/052OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/hautkrebs-praevention, (Zugriff am TT.MM.JJJJ)

2. Evidenztabellen

2.1. Evidenztabellen Recherche Risikofaktoren von Hautkrebs

2.1.1. Occupational exposure

<table>
<tr><th colspan="5">Occupational exposure</th></tr>
<tr><th>Reference</th><th>AMSTAR-II</th><th>Characteristics I</th><th>Characteristics II</th><th>Comment</th></tr>
<tr><td rowspan="2">The effect of occupational exposure to solar ultraviolet radiation on malignant skin melanoma and nonmelanoma skin cancer: a systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
<u>https://www.who.int/publications/i/item/9789240040830</u></td><td>Low quality</td><td>Aim
- association between occupational exposure to solar ultraviolet radiation (UVR) and both malignant skin melanoma (melanoma) and non-melanoma skin cancer (NMSC),
- estimation of the numbers of deaths and disability-adjusted life years from melanoma and NMSC attributable to occupational exposure to solar UVR
Databases (search period):
- WHO Internat. Clinical Trials Registry Platform (5/10/2020)
- Ovid MEDLINE (1 January 1946–8/8/2018)
- PubMed (1/1/1946–8/8/2018, to 5/10/2020)
- EMBASE (1/1/1947–8/8/2018)
- Web of Science (1/1/1945–8/8/2018)
- 2 grey literature databases, internet search engines, hand searches, organizational websites
Population
- Working age (≥ 15y)
- any industrial setting or occupational group</td><td>Intervention/ Exposure
- any occupational exposure to solar UVR
Control
- no (or low) occupational exposure to solar UVR
Relevant exclusion criteria
- airplane crew
- studies defining the outcome as in situ melanoma only
- studies where conversions from absolute to relative measures were not possible
Type of study
- RCTs, cohort, case-control and other non-randomized studies
Outcomes
- melanoma (excluding melanoma of the lip or eye) or NMSC prevalence, incidence or mortality
Funding
CDC (America), BMG (Germany), AECID (Spain), VZF (European Union)</td><td>See publication for sensitivity analyses (table 21; page 85/204)</td></tr>
<tr><td colspan="4">Results

Characteristics of included studies
- 48 case-control-, 3 case-case-, 2 cohort studies identified
- > 457 000 participants, 26 countries
- most frequently based in: Italy (N=9), Germany (N= 8), USA (N= 8).
- most commonly studied industrial sectors: agriculture, forestry and fishing, construction
- exposure assessment: standardized questionnaires in (face to face or telephone) interviews by trained personnel (N= 37), self-completed questionnaires (N= 8), job title as a proxy (N=2), by expert in industrial hygiene or occupational health (N= 3)
- outcomes: melanoma incidence (N= 33) and mortality (N= 2), NMSC incidence (N= 25) and mortality (N= 1). No studies on prevalence of melanoma or NMSC
→ see table 7, 9, 10 (original publication) for study specific study characteristics

<u>Melanoma incidence</u></td></tr>
</table>

Occupational exposure	
	Main meta-analysis (19 Case-control-studies, see figure 7, page 74/204 in publication) - Lentigo maligna melanoma (LMM) included: RR: 1.45; 95% CI: 1.08–1.94; 14 studies; > 26 907 participants; I^2= 81% (higher risk in exposed) - LMM excluded: RR: 0.69; 95% CI: 0.55–0.86; 5 studies; I^2= 4% (higher risk in unexposed) - Total: RR: 1.16; 95% CI: 0.91–1.49; 19 studies; > 28 314 participants; I^2= 81% → rated as sufficiently clinically homogeneous → still somewhat heterogeneous regarding: population, geographical locations, industrial sectors and occupations; exposure and comparator definition etc. **supporting evidence** - **10 case-control studies** o excluded from meta-analysis o reasons: exposure, comparator and/or outcome defined too differently from included studies; or reported only unadjusted effect estimates o their point estimates: generally close to 1; 7 studies indicated a reduction in odds or risk; 3 indicated increased odds or risk o judged to provide little support to the evidence presented in the main meta-analysis - **3 case-case studies:** o too heterogeneous to be combined in a quantitative meta-analysis o all had an increased point estimate, but 2/3 included the null value in their 95% CI (see table 15, page 76/204 in original publication) - **1 cohort study:** o RR: 1.1; 95% CI: 0.8–1.6 o high-level occupational exposure to solar UVR increased the risk of melanoma incidence by an estimated 10%, compared with no (or low) occupational exposure to solar UVR, but the 95% CI included the null value → strength of evidence: "limited evidence for harmfulness", i.e. a positive relationship was observed between exposure and outcome where chance, bias and confounding cannot be ruled out with reasonable confidence **<u>Melanoma mortality</u>** **2 case-control studies (n= 20 231)** o OR: 1.3 (95% CI: 0.6–2.5) o OR: 0.99 (95% CI: 0.87–1.12) → strength of evidence: "Inadequate evidence of harmfulness", i.e. the effect of occupational exposure to solar UVR on melanoma mortality is very uncertain **<u>NMSC incidence</u>** **Main meta analysis (20 case-control studies, see figure 8, page 81/204)** - RR: 1.60; 95% CI: 1.21–2.11; 20 studies; > 88 448 participants; I2 = 91%; i.e. compared with no (or low) occupational exposure to solar UVR, any (or high) occupational exposure to solar UVR increased the risk of NMSC incidence by an estimated 60% when followed up over an unclear period >> subgroup analyses - BCC: RR 1.50 (1.10–2.04), I^2= 81%, 15 studies - SCC: RR 2.43 (1.64–3.62), I^2= 47%, 6 studies **Supportive evidence** - **2 case-control studies** - not included in the meta-analysis, as they did not report adjusted effect estimates - **1 case-case-study** o Compared with no occupational exposure to solar UVR, any occupational exposure to solar UVR led to a large increase in the risk of NMSC incidence, with the 95% CIs indicating a moderate to large increase for each estimate o BCC: RR for females: 2.7 (95% CI: 1.8–4.1); RR for males: 2.9 (95% CI: 2.2–3.9) o SCC: RR for females: 3.6 (95% CI: 1.6–8.10); RR for males: 2.5 (95% CI: 1.4–4.7) - **2 cohort studies**

Occupational exposure	
	○ RR: 1.16; 95% CI: 0.88–1.52; 2 studies; 196 481 participants; I^2 = 6% (see figure 9, page 82/204) → strength of evidence: "Sufficient evidence of harmfulness", i.e. a positive relationship is observed between exposure and outcome where chance, bias and confounding can be ruled out with reasonable confidence **NMSC mortality** - 1 case-control study - outdoor workers excluding farmers (OR: 1.30; 95% CI: 1.14–1.47) - farmers (OR: 1.15; 95% CI: 1.00–1.32) → strength of evidence: "Inadequate evidence of harmfulness", i.e. The effect of occupational exposure to solar UVR on NMSC mortality is very uncertain

2.1.2. Patients with previous melanoma

Patients with previous melanoma				
Reference	**AMSTAR-II**	**Characteristics I**	**Characteristics II**	**Comment**
Smith J. Risk factors for subsequent primary melanoma in patients with previous melanoma: a systematic review and meta-analysis. Br J Dermatol. Jan 23 2024;190(2):174-183. **https://pubmed.ncbi.nlm.nih.gov/37562043/**	Low quality	**Aim** - identify and determine the strength of the risk factors for subsequent primary melanoma **Databases/ search period:** - CINAHL, Central Register of Controlled Trials (CENTRAL), Embase and MEDLINE (1982 – 08/2022) **Population** - should have had at least one previous cutaneous melanoma. **Exposure of interest** - demographic, environmental, genetic, histopathological, phenotypic, and behavioural factors **Further inclusion criteria** - Studies that provided raw frequencies or the following effect sizes were included: hazard ratio (HR), odds ratio (OR), relative risk (RR) or standardized incidence ratio (SIR).	**Relevant exclusion criteria** - studies focusing only on first primary melanoma or non-cutaneous melanoma (e.g. uveal, occult), or on melanoma spread (recurrence/metastases) - qualitative studies - melanoma that was not a primary lesion **Type of studies** - cohort and case-control study **Outcomes** - risk of cutaneous Melanoma (multiple primaries) **Funding** - A.E.C. receives a National Health and Medical Research Council Investigator Grant (2008454). S.N.L. is supported by Melanoma Institute Australia.	Please note: Only content related to the risk factor of UV exposure was extracted.
	Ergebnisse			
	Characteristics of included studies - 27 studies included - Patients with single primary melanoma: n= 388 424 - patients with multiple melanoma: n= 24 757 **Quality of the evidence** - Newcastle-Ottawa scale: ○ scored 9: n= 4 ○ score 8: n= 17 ○ score 6: n= 3 - Based on the GRADE criteria for assessing quality (certainty) of evidence: high to very low confidence in the pooled effect estimates. **Results**			

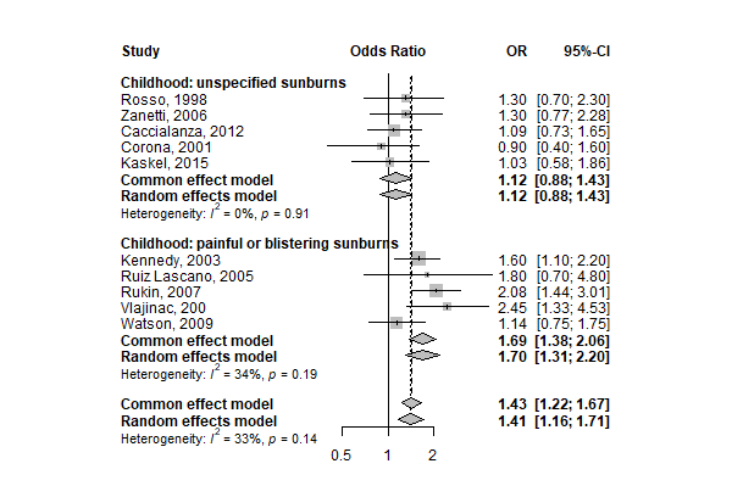
Patients with previous melanoma	
	- Risk of subsequent melanoma was not significantly related to sun-exposure factors in two studies (n = 6437): o high exposure to ultraviolet (UV) radiation at 10 years of age [pooled OR 1.59 (95% CI 0.90–2.82); I^2 = 0% (low certainty of evidence)], o sunny vacations high/any vs. none/low [pooled OR 1.58 (95% CI 0.58–4.32); I^2 = 0% (low certainty of evidence)] o waterside activities [pooled OR for high/ any vs. none 1.40 (95% CI 0.45–4.35); I^2 = 0% (certainty of evidence not specified)], - univariable analysis of two studies (n = 1916) o those who never, rarely or sometimes used sun protection had an increased risk vs. those reporting often or always using sun protection [pooled HR 1.85 (95% CI 0.98–3.50); I^2 = 1% (low certainty of evidence)

2.1.3. Sunburn and basal cell carcinoma risk

Sunburn and basal cell carcinoma risk				
Reference	**AMSTAR-II**	**Characteristics I**	**Characteristics II**	**Comment**
Lashway SG. A meta-analysis of sunburn and basal cell carcinoma risk. Cancer epidemiol. 08 2023;85:102379 https://pubmed.ncbi.nlm.nih.gov/37201363/ .	Critically low	**Aim** - to quantify the impact of sunburn at different life stages on BCC risk in general populations. **Databases/ search period** - PubMed, Embase, Web of Science, CINAHL - 12/2020 **Population** - general population - no restriction regarding previous skin cancer status **Exposure of interest** - sunburn	**Relevant exclusion criteria** - animal studies - case reports, or review articles) - explicitly conducted only in high-risk populations (e.g., organ transplant patients or those with Gorlin-Goltz syndrome) **Type of studies** - cohort-, case-control-studies, **Outcomes** - BCC **Funding** - none	prioritized exposures extracted only for further results see publication (limitation: RoB of included studies not evaluated)
	Characteristics of included studies - 38 studies included, reporting: o childhood sunburns as never/ever: N= 10 case-control studies with histologically verified diagnoses of BCC o ever/never lifetime sunburns: 3 cohort studies and 10 case-control studies o numerical categories of sunburns: N= 18 o count ranges for sunburns experienced during adulthood: N= 3 o count ranges for sunburns experienced during childhood: N= 7 o numerical categories of lifetime sunburns: N= 10 **Quality of the evidence** - not reported in publication - for appraisal by dEBM: see table NOS and ROBINS-E **Results** cave: prioritized exposures extracted only - Childhood - unspecified sunburn [5 studies]: o OR 1.15 (95% CI 0.91; 1.47), I^2= 0% [both random and common effects model, respectively] o Cave: extracted effect estimate for Corona et al. were not identical with reported effect estimate in original publication		

- Therefore, re-analysis with original effect estimate conducted: OR 1,12 (95% KI 0,88; 1,43), I^2= 0%.

- Childhood – painful or blistering sunburn [5 studies]:
  - Random effects model: OR 1.70 (95% CI 1.31; 2.20), I^2= 34%
  - Common effects model: OR 1.69 (95% CI 1.38; 2.06), I^2= 34%
- Childhood sunburn (never/ever):
  - Random effects model: OR 1.43 (95% CI 1.19; 1.72), I^2= 27%
  - Common effects model: OR 1.44 (95% CI 1.24; 1.68), I^2= 27%
- Re-calculated Meta-Analysis of childhood sunburn (never/ever):



- Please note: the meta-analyses were re-calculated using the effect estimates and confidence intervals reported in the primary studies

- Lifetime sunburn (never/ever):
  - Meta-analysis with 3 cohort studies: 1 publication with 2 cohorts (Wu et al.: NHS cohort and HPFS cohort) and 1 publication (Lee et al.) with a very specific population (radiologic technologists) included
    →Lee et al. excluded by guideline group, narrative synthesis of Wu et al.:
  - NHS cohort:
    - Never sunburned: 1.311 cases / 239.738 person-years
    - Ever sunburned: 14.781 cases / 1.631.398 person-years
    - Multivariate adjusted HR: 1.42 (95% CI 1.34; 1.51)
  - HPFS cohort:
    - Never sunburned: 377 cases / 35.557 person-years
    - Ever sunburned: 5.077 cases / 350.893 person-years
    - Multivariate adjusted HR 1.18 (95% CI 1.06; 1.32)

Zur Priorisierung gestellte systematische Reviews

Die in der folgenden Tabelle aufgezeigten systematischen Reviews haben einige methodische Mängel. Diese Mängel können durch eine Nachbearbeitung behoben werden. Aus Ressourcengründen war es nicht möglich, die Mängel aller Publikationen zu berichtigen. Die Leitliniengruppe hat daher eine Priorisierung der Fragestellungen vorgenommen, für die die eingeschlossenen Primärstudien nachbewertet werden sollen.

Zitat	Thema	Nachbearbeitungsbedarf
Rahman SM, Ahmed F, Amanullah A, Haque A. Impact of UV Modifying Factors on the Incidence of Keratinocyte Carcinomas in Solid Organ Transplant Recipients: A Systematic Review. Review. *Dermatol.* Jul 01 2023;13(3):01. https://dx.doi.org/10.5826/dpc.1303a65	**Population/Exposition:** Organtransplantierte Personen **Endpunkt:** BCC, SCC, NMSC	Das Verzerrungsrisiko für 4 Primärstudien muss nachbewertet werden
Lashway SG, Worthen ADM, Abuasbeh JN, et al. A meta-analysis of sunburn and basal cell carcinoma risk. Meta-Analysis Review. Cancer epidemiol. 08 2023;85:102379. https://dx.doi.org/10.1016/j.canep.2023.102379	**Population/Exposition:** Personen mit Sonnenbrand **Endpunkt:** BCC	In der Publikation befinden sich folgende Subgruppenanalysen mit der aufgezeigten Studienanzahl (N). Es wird nicht möglich sein, alle Primärstudien (n= 38) nachzubewerten. Eine Priorisierung der Subgruppen wäre hilfreich. - Kinder mit unspezifiziertem Sonnenbrand: N= 5 - Kinder mit blasenbildendem oder schmerzhaftem Sonnenbrand: N= 5 - Lebenszeit: blasenbildender Sonnenbrand: N= 3 - Lebenszeit: schmerzhafter Sonnenbrand: N= 3 - Lebenszeit: anderer Sonnenbrand: N= 5 - Lebenszeit: blasenbildender, schmerzhafter Sonnenbrand: N= 8 - Lebenszeit: unspezifizierter Sonnenbrand: N= 2 - Lebenszeit: Sonnenbrand (jemals/niemals): N= 3
Li Y, Wang J, Xiao W, Liu J, Zha X. Risk Factors for Actinic Keratoses: A Systematic Review and Meta-Analysis. Indian J Dermatol. Jan-Feb 2022;67(1):92. https://dx.doi.org/10.4103/ijd.ijd_859_21	**Population/Exposition:** Personen mit Sonnenexposition bzw. Sonnenbrand **Endpunkt:** Aktinische Keratose	Das Verzerrungsrisiko der eingeschlossenen Primärstudien muss nachbewertet werden. Folgende Subgruppenanalysen sind vorhanden: - Sonnenbrand in der Kindheit: N= 6 - chronische UV-Exposition im Arbeitskontext und /oder in der Freizeit: N= 6 - Anwendung von Sonnenschutzmitteln: N= 5
Jiang AJ, Rambhatla PV, Eide MJ. Socioeconomic and lifestyle factors and melanoma: a systematic review. Br J Dermatol. Apr 2015;172(4):885-915. https://dx.doi.org/10.1111/bjd.13500	**Population/Exposition:** Personen mit UV-Exposition im Arbeits- oder Freizeitkontext **Endpunkt:** Melanom	Das Verzerrungsrisiko der eingeschlossenen Primärstudien muss nachbewertet werden. Folgende Subgruppenanalysen sind vorhanden: - Berufsgruppen: N= 16

Zitat	Thema	Nachbearbeitungsbedarf
		- UV-Exposition im Arbeitskontext: N= 10 (Hinweis: durch WHO/ILO bearbeitet) - UV-Exposition in der Freizeit: N= 28 - Bräunung: N= 13
Lopes F, Sleiman MG, Sebastian K, Bogucka R, Jacobs EA, Adamson AS. UV Exposure and the Risk of Cutaneous Melanoma in Skin of Color: A Systematic Review. JAMA Dermatology. 2021;157(2):213-219. https://dx.doi.org/10.1001/jamadermatol.2020.4616	**Population/Exposition:** People with skin of Color **Endpunkt:** Melanom	Nachbewertung des Verzerrungsrisikos notwendig: Natürliche UV-Exposition: N= 8 Nicht natürliche UV-Exposition: N= 5
Kolitz E, Lopes F, Arffa M, Pineider J, Bogucka R, Adamson AS. UV Exposure and the Risk of Keratinocyte Carcinoma in Skin of Color: A Systematic Review. JAMA Dermatology. 05 01 2022;158(5):542-546. https://dx.doi.org/10.1001/jamadermatol.2022.0263	**Population/Exposition:** People with skin of Color **Endpunkt:** BCC, SCC, Bowen disease	Nachbewertung des Verzerrungsrisikos notwendig: Natürliche UV-Exposition: N= 4 Nicht natürliche UV-Exposition: N= 8
Nayman T, Bostan C, Logan P, Burnier MN, Jr. Uveal Melanoma Risk Factors: A Systematic Review of Meta-Analyses. Curr Eye Res. 08 2017;42(8):1085-1093. https://dx.doi.org/10.1080/02713683.2017.1297997	**Population/Exposition:** Personen mit UV-Exposition im Arbeits- oder Freizeitkontext **Endpunkt:** Uveamelanom	Umbrella Review - ein eingeschlossener systematischer Review untersucht UV-Exposition im Arbeitskontext als Risikofaktor (Shah CP, Weis E, Lajous M, Shields JA, Shields CL. Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. Ophthalmology. 2005;112(9):1599–1607. https://pubmed.ncbi.nlm.nih.gov/16051363/) - das Verzerrungsrisiko der 4 darin eingeschlossenen Primärstudien müsste nachbewertet werden
Watson TPG, Tong M, Bailie J, Ekanayake K, Bailie RS. Relationship between climate change and skin cancer and implications for prevention and management: a scoping review. Public Health. Feb 2024;227:243-249. https://dx.doi.org/10.1016/j.puhe.2023.12.003	**Aim:** explore the published research on the relationship between climate change and skin cancer and the implications for prevention, management and further research.	In den Scoping review wurden 9 Primärstudien sowie 36 Meinungsäußerungen (reviews, perspectives, commentaries, editorials, or essays) eingeschlossen - 9 Primärstudien müssten nachbewertet werden
Porcherie M, Linn N, Gall ARL, et al. Relationship between urban green spaces and cancer: A scoping review. International Journal of Environmental Research and Public Health. 02 Feb 2021;18(4):1-19. 33670207. https://dx.doi.org/10.3390/ijerph18041751	**Aim:** to explore the relationships between urban green spaces (UGSs) and the onset, remission and recovery of cancer.	Für die Entität Hautkrebs wurden 2 Studien eingeschlossen. Wenn die Fragestellung eine Relevanz hat, wird geprüft, ob die Primärstudien einen Bezug zur UV-Exposition vornehmen. Die Studien können nachbewertet werden.

Abkürzungen: N Anzahl der Primärstudien

2.2. Evidenztabellen Recherche Sonnenschutzmittel und Hautkrebs

2.2.1. Melanom

Übersicht der eingeschlossenen Primärstudien (Endpunkt Melanom)

Referenz	AMSTAR-II	Suchzeitraum	Autier 1995	Bakos 2002	Beitner 1990	Cho 2005	Cress 1995	Espinosa Arranz 1999	Fargnoli 2004	Ghiasvand 2016	Gandini 2014*	Graham 1985	Green 2011	Herzfeld 1993	Holly 1995	Holman 1986	Klepp 1979	Klug 2010	Kojo 2006	Lazovich 2011	Luiz 2012	Naldi 2000	Nikolaou 2008	Olsen 2015	Osterlind 1988	Ródenas 1996	Savoye 2018	Stenehjem 2017	Vranova 2012	Westerdahl 1995	Westerdahl 2000	Whiteman 1997	Wolf 1998	Youl 2002
Rueegg CS. 2019	low	02/2018	x	x	x	x	.	x	.	x	.	x	x	x	x	x	x	x	x	x	x	x	x	.	x	x	x	x	x	x	x	x	x	x
Silva ESD. 2018	low	05/2017	x	x	x	.	x	x	x	x	.	x	x	x	x	x	x	x	.	x	x	x	.	x	x	x	x	.	.	.	x	x	x	x	x
Xie F. 2015	critically low	10/2014	x	x	x	.	.	x	.	.	x	x	x	x	x	x	x	x	.	x	.	x	.	.	x	x	.	.	.	x	x	x	x	x	x

*Referenz, die in keinem der beiden eingeschlossenen systematischen Reviews zitiert ist

Referenz	Inhalt	Kommentar
Gandini S, Stanganelli I, Magi S, Mazzoni L, Medri M, Agnoletti V, Lombi L, Falcini F. Melanoma attributable to sunbed use and tan seeking behaviours: an Italian survey. Eur J Dermatol 2014; 24: 35-40. https://pubmed.ncbi.nlm.nih.gov/24334101/	**Fragestellung:** […] in this analysis we assess sun exposure attitudes, sunscreen and sunglass use during sun exposure and sunbed use, in particular among the young. We also estimated the number of melanoma cases in Italy attributable to sunbed use in youth and to excessive sun exposure **Ergebnis:** The probability of using sunscreen was inversely associated with long time sunbathing: subjects who stayed more than 5 hours in the sun had a significantly lower probability of using sunscreen than subjects who sunbathed for a lesser number of hours (OR = 0.82; 95% KI: 0.71; 0.96), adjusting for phenotypic and socio-demographic factors.	Das Ergebnis, das in die Metaanalyse von Xie et al. inkludiert wurde, bildet nicht die Assoziation zwischen Sonnenschutzmittel und Melanomrisiko ab. **Schlussfolgerung:** - Ausschluss der Primärstudie in den beiden MA (Rueegg 2019 und Silva 2018) nachvollziehbar

Legende

x	.			
Primärstudie eingeschlossen	**Primärstudie nicht eingeschlossen**	**extrahieren**	**Auf Relevanz prüfen**	**Nicht extrahieren**

Evidenztabelle Endpunkt Melanom

Referenz	AMSTAR-II	Charakteristika I	Charakteristika II	Kommentar
Rueegg C. S., et al. Challenges in assessing the sunscreen-melanoma association. International Journal of Cancer. 2019.144(11): 2651-2668. **https://pubmed.ncbi.nlm.nih.gov/30447006/**	low	**Ziele** 1) die Literatur zur Anwendung von Sonnenschutzmitteln und Melanom zusammenfassen 2) den Effekt von "Jemals-" und "Niemals-Nutzern" auf das Melanomrisiko untersuchen 3) den Effekt von verschiedenen Anwendungsgraden und -Mustern untersuchen 4) die Ursachen für Verzerrungsrisiko und Heterogenität zwischen den identifizierten Studien untersuchen 5) den Zusammenhang zwischen der Lokalisation des Sonnenschutzmittels und der Lokalisation des Melanoms beschreiben **Suchzeitraum** ▪ Bis 02/2018 **Datenbanken** ▪ Pubmed, Embase, Cochrane Library, PROSPERO, Referenzlisten	**Population** ▪ Menschen **Intervention/ Exposition** ▪ Anwendung von Sonnenschutzmitteln **Kontrolle** . **Weitere relevante Einschlusskriterien** . **Relevante Ausschlusskriterien** ▪ Für die quantitative Synthese (Metaanalyse) wurden Studien an Kindern ausgeschlossen **Studientypen** ▪ Kohortenstudien, Fall-Kontroll-Studien, weitere Beobachtungsstudien (ökologische Studien), Interventionsstudien, klinische Studien **Endpunkte** ▪ Melanom ▪ Länge des Follow-up nicht definiert	
	Ergebnisse			
	Baseline-Charakteristika ▪ 11 krankenhausbasierte, 12 populationsbasierte Fall-Kontroll-Studien (F-K-S), 1 Ökologische Studie, 3 prospektive Kohortenstudien, 1 randomisiert kontrollierte Studie → methodische Qualität heterogen (Details siehe Tabelle 3 im Supplement der Publikation) ▪ Publikationszeitraum: 1979-2018 ▪ Australien (n = 4), Europa (n = 16), Brasilien (n = 2); USA (n = 6) ▪ Erhebung der Nutzung der Sonnenschutzmittel: heterogen in Methodik und Detail ▪ Detaillierte Darstellung der Baseline-Charakteristika (u.a. zum SPF und der Anwendung der Sonnenschutzmittel): siehe Tabelle 1 in Publikation und Tabelle 4 im Supplement zur Publikation ▪ Studien- sowie Evidenzqualität in Tabellen 3 bzw. 5 im Anhang berichtet **Assoziation zwischen Jemals-Anwendung („ever use") vs. Niemalsanwendung („never-use") von Sonnenschutzmitteln und dem Endpunkt „Melanom"** ▪ stratifiziert nach Studientyp ▪ Hinweis: maximal adjustierte Ergebnisse extrahiert (siehe Abbildung 3 und Tabelle 2 in Publikation)		

Referenz	AMSTAR-II	Charakteristika I	Charakteristika II	Kommentar
	▪ <u>Begründung:</u> Im Bewertungsinstrument AMSTAR-2 wird empfohlen, Metaanalysen mit möglichst vollständig adjustierten Effektschätzern zu rechnen, selbst wenn die verschiedenen Adjustierungen der eingeschlossenen Primärstudien zu weiterer Heterogenität führen können. Daher werden an dieser Stelle jeweils die Studienergebnisse berichtet, die maximal für Störgrößen (Confounder) adjustiert waren. Die Autor:innen der systematischen Übersichtsarbeit weisen darauf hin, dass die maximal adjustierten Ergebnisse in allen stratifizierten Auswertungen Tendenzen zu einem weniger ausgeprägten Melanomrisiko bei Anwendung von Sonnenschutzmitteln aufwiesen als die minimal adjustierten Effektschätzer. <u>krankenhausbasierte Fall-Kontroll-Studien</u> ▪ OR 0,57, 95% KI 0,37; 0,87, I^2= 85,5%, 9 Studien, n= 5.499 (Qualität der Evidenz sehr gering) → inverse Sonnenschutz-Melanom-Assoziation <u>Ökologische Studie</u> ▪ RR 0,48, 95% KI 0,35; 0,66, 1 Studie, n= 11.535 (Qualität der Evidenz sehr gering) → inverse Sonnenschutz-Melanom-Assoziation <u>RCT</u> ▪ HR 0,49, 95% KI 0,24; 1,01, 1 Studie, n= 1.621 (Qualität der Evidenz moderat) <u>populationsbezogene Fall-Kontroll-Studien</u> ▪ OR 1,17, 95% KI 0,90; 1,51, I^2= 81,4%, 8 Studien, n= 10.256 (Qualität der Evidenz sehr gering) <u>prospektive Kohortenstudien</u> ▪ HR 1,27, 95% KI 1,07; 1,51, I^2= 30,8%, 3 Studien, n= 323.754 (Qualität der Evidenz sehr gering) → positive Sonnenschutz-Melanom-Assoziation **Effekt von verschiedenen Anwendungsgraden und -mustern** <u>Vergleich von “Manchmal-“ mit “Niemals-Anwendern”</u> ▪ OR 1,07 (95% KI 0,80; 1,42) in krankenhausbasierten F-K-S ▪ OR 1,13 (95% KI 0,98; 1,30) in populationsbasierten F-K-S ▪ HR 1,38 (95% KI 1,17; 1,62) in Kohortenstudien (positive Sonnenschutz-Melanom-Assoziation) <u>Vergleich von “Häufig/Immer-“ mit “Niemalsanwendern”</u> ▪ OR 1,01 (95% KI 0,38; 2,67) in krankenhausbasierten F-K-S ▪ OR 1,01 (95% KI 0,67; 1,52) in populationsbasierten F-K-S ▪ HR 1,32 (95% KI 1,10; 1,59) in Kohortenstudien (positive Sonnenschutz-Melanom-Assoziation) <u>Vergleich von jeweils niedrigem oder hohem Lichtschutzfaktor vs. Keine Sonnenschutzmittel</u> ▪ Gepoolte Effektschätzer nicht berichtet, sondern nur grafisch in Abbildung 1B des Anhangs dargestellt <u>Vergleich von jeweils Kurzzeit- oder Langzeitanwendung vs. Keine Sonnenschutzmittel</u> ▪ Gepoolte Effektschätzer nicht berichtet, sondern nur grafisch in Abbildung 1C des Anhangs der Publikation dargestellt **Ursachen für Heterogenität** ▪ Siehe Tabelle 3 in Publikation und Abbildung 2 im Anhang **Zusammenhang zwischen der Lokalisation des Sonnenschutzmittels und des Melanoms** ▪ In identifizierten Studien nicht untersucht		
Silva E. S. D., et al. Use of sunscreen and risk of	low	**Ziel** Den Zusammenhang zwischen Hautkrebs (Melanom sowie Nichtmelanom) und der Anwendung von Sonnenschutzmitteln bei Kindern und Erwachsenen untersuchen.	**Weitere relevante Einschlusskriterien** . **relevante Ausschlusskriterien** .	

Referenz	AMSTAR-II	Charakteristika I	Charakteristika II	Kommentar
melanoma and non-melanoma skin cancer: a systematic review and meta-analysis. European Journal of Dermatology. 2018.28(2):186-201. **https://pubmed.ncbi.nlm.nih.gov/29620003/**		**Suchzeitraum** Bis 05/2017 **Datenbanken** ▪ PubMed, Google Scholar, Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information (BIREME), die Medline, LILACS und > 20 andere Datenbanken beinhaltet, Referenzlisten **Population** ▪ Erwachsene, Kinder oder gemischt **Intervention/ Exposition** ▪ Anwendung von Sonnenschutzmitteln, klassifiziert in ≥ 2 Kategorien bezüglich Häufigkeit der Anwendung **Kontrolle** .	**Studientypen** ▪ Beobachtungsstudien (Fall-Kontroll-, Querschnitt- oder Kohortenstudien) oder kontrollierte Studien **Endpunkte** ▪ Jegliche Form von Hautkrebs (Melanom, Basalzellkarzinom, Plattenepithelkarzinom)	
	Ergebnisse			
	Baseline-Charakteristika ▪ 25 F-K-S, 2 Kohortenstudien, 1 Querschnittstudie, 1 RCT ▪ Amerika (n= 11), Europa (n= 12), Asia-Pacific (n= 6) ▪ Methodische Qualität der Studien: gut (n= 4), moderat (n= 22), gering (n= 3), Information nicht verfügbar (n= 1) ▪ Detaillierte Darstellung der Baseline-Charakteristika (u.a. zum SPF und der Anwendung der Sonnenschutzmittel): siehe Tabelle 1 in Publikation **melanomspezifische Auswertung** ▪ Gepoolter Effektschätzer OR 1,10 (95% KI 0,92; 1,33) I^2 = 89,4%, N= 25, 203.948 Teilnehmer, 9.813 Fälle ▪ In 10 Studien zeigte sich ein erhöhtes Risiko für das Auftreten eines Melanoms bei Anwendern von Sonnenschutzmitteln ▪ In 5 Studien wurde ein protektiver Effekt des Sonnenschutzmittels berichtet **jegliche Tumorform** ▪ Beobachtungsstudien: Gepoolter Effektschätzer: OR 1,11 (95% KI 0,93; 1,33) I^2 = 90,2%, N= 28 ▪ RCT: Basalzellkarzinom OR 1,03 (95% KI 0,73; 1,46) N= 1; Plattenepithelkarzinom OR 0,88 (95% KI 0,50; 1,55), N= 1 (Hinweis: dieser RCT untersucht eigentlich die Inzidenzratenverhältinisse und wird ausführlich in der systematischen Übersichtsarbeit von Roensch et al. zitiert) → Subgruppenanalysen (z.B. für Alter, Frequenz der Anwendung etc.) nur für Metaanalyse berichtet, die jegliche Tumorformen gemeinsam betrachtet: siehe Tabelle 2 in Publikation		

2.2.2. Basalzellkarzinom (BCC) und Plattenepithelkarzinom (SCC)

Übersicht der eingeschlossenen Primärstudien (Endpunkt BCC)

Referenz	AMSTAR-II	Suchzeitraum	Ulrich 2009	Green 1999	Pandeya 2005	van der Pols 2006	Gon 2011	Kricker 1995
Rönsch H. 2021	Kritisch niedrig	01/2020	x	x	x	x	.	.
Silva ESD. 2018	niedrig	05/2017	.	x	.	.	x	x
Sanchez G. 2016	hoch	05/2016	.	x	.	.	.	.
Kommentar				Nambour Trial	Nambour Trial: Datengrundlage wie in Green 1999, neue Analyse: time to multiple occurrences, fehlende Power: Verzicht auf Extraktion	Nambour Trial: Verlängerung der Nachbeobachtungszeit 1996-2004		

Übersicht der eingeschlossenen Primärstudien (Endpunkt SCC)

Referenz	AMSTAR-II	Suchzeitraum	Ulrich 2009	Green 1999	van der Pols 2006	Grodstein 1995	Sànchez 2013
Rönsch H. 2021	Kritisch niedrig	01/2020	x	x	x	.	.
Silva ESD. 2018	niedrig	05/2017	.	x	.	x	x
Sanchez G. 2016	hoch	05/2016	.	x	.	.	.
Green AC. 2014	Kritisch niedrig	08/2013	.	x	x	.	.
Kommentar				Nambour Trial	Nambour Trial: Verlängerung der Nachbeobachtungszeit 1996-2004		

Legende

x	.				
Primärstudie eingeschlossen	**Primärstudie nicht eingeschlossen**	**extrahieren**	**Methodik nacharbeiten und extrahieren**	**zurückstellen**	**Nicht extrahieren**

Evidenztabelle BCC und SCC

<table>
<tr><th>Referenz</th><th>Methodische Qualität</th><th colspan="2">Charakteristika</th><th>Kommentar</th></tr>
<tr><td rowspan="2">Rönsch, H. and A. Bauer, The preventive Value of Sun Protection. Current Problems in Dermatology, 2021. 55: p. 316-328.
<u>https://pubmed.ncbi.nlm.nih.gov/34698024/</u></td><td>AMSTAR-2: kritisch niedrig</td><td>Ziel
▪ die Evidenz zur Effektivität der Anwendung von Sonnenschutzmitteln hinsichtlich der Inzidenz von präkanzerösen Läsionen und epithelialem Hautkrebs anhand von kontrollierten und randomisiert kontrollierten Studien zusammenfassen
Suchzeitraum
▪ bis 01/2020
Datenbanken
▪ Embase und Medline, jeweils via Ovid
Population
▪ Menschen, unabhängig von Alter, Hauttyp, Beruf etc.
Intervention/ Exposition
▪ Sonnenschutzmittel oder Sonnenschutzmittel mit zusätzlicher Komponente
Kontrolle
Keine Intervention, Placebo, Träger (Vehikel) oder anderer Lichtschutzfaktor</td><td>Studientypen
▪ Randomisiert kontrollierte Studien oder nicht-randomisiert kontrollierte Studien
Endpunkte
▪ Epithelialer Hautkrebs (Basalzellkarzinom (BCC), Plattenepithelkarzinom (SCC)),
▪ Aktinische Keratose (AK) (Synonym: solare Keratose, aktinische Präkanzerose, Photokeratose),
▪ Hautalterung durch Licht (Photoaging),
▪ unerwünschte Effekte
Weitere relevante Einschlusskriterien
▪ Publikationssprache: Englisch oder deutsch
relevante Ausschlusskriterien
▪ Studientypen: Beobachtungsstudien, Laborexperimente
▪ Endpunkte: Melanom, Sonnenschutzverhalten
▪ Keine Volltextpublikation</td><td>zur AMSTAR-2-Bewertung:
- zunächst 4 kritische Items nicht erfüllt
- Liste der im VT-Screening ausgeschlossenen Studien von Autorengruppe nachgereicht
- Bewertung des Verzerrungs-risikos der eingeschlossenen Primärstudien durch dEBM erfolgt
→ daher Einschluss der Publikation</td></tr>
<tr><td colspan="4">Ergebnisse
Baseline-Charakteristika
▪ Insgesamt: 5 Primärstudien in Form von 13 Publikationen
▪ BCC-spezifisch: 2 Primärstudien, 4 Publikationen
▪ SCC-spezifisch: 2 Primärstudien, 3 Publikationen
Ergebnisse
<u>Green, 1999</u>
▪ Australien, 1992-1996
▪ RCT (Nambour Studie), n= 1.621, davon 1.383 analysiert (auch Personen mit Beta-Carotin abgebildet), Sonnenschutzmittelspezifische Auswertung: n= 696
▪ Risiko für Verzerrung für beide Endpunkte: einige Bedenken (u.a. bedingt durch Domäne ‚Auswahl der berichteten Endpunkte‘)
▪ Allgemeinbevölkerung, 56% weiblich
▪ Alter (Mittelwert, SD): 48,8 ± 13,2 Jahre
▪ Hauttyp (tägliche Anwendung vs. Anwendung nach eigenem Ermessen):
o immer Verbrennung: 171/812 (21,1%) vs. 169/809 (20,9%)
o Verbrennung/Bräunung: 552/812 (68%) vs. 547/809 (67,6%)
o Nur Bräunung: 89/812 (11%) vs. 93/809 (11,5%)</td></tr>
</table>

Referenz	Methodische Qualität	Charakteristika	Kommentar

- Hautkrebs in der Anamnese (tägliche Anwendung vs. Anwendung nach eigenem Ermessen): 215/812 (26,5%) vs. 221/809 (27,3%)
- Intervention: Tägliche Anwendung (Kopf, Hals, Arme, Hände); SPF 16; Auscreen Ultrablock Lotion SPF 15-plus (Ross Cosmetics, Melbourne, Australia); 8% 2-ethylexyl-p-methoxycinnamate, 2% 4-tertbutyl-4´-methoxy-4-dibenzoylmethane; nach Australischem Standard 2604 als wasserfest eingeschätzt SPF 16 mit/ohne 30 mg Beta-Carotin
- Kontrolle: Anwendung von Sonnenschutz nach eigenem Ermessen mit/ohne 30 mg Beta-Carotin
- Follow-up: 4,5 Jahre
- Verhältnis der Inzidenzrate bei täglichem Sonnenschutz vs. Sonnenschutz nach eigenem Ermessen:
  - vom Basalzellkarzinom betroffenen Personen: 1,03 (95% KI 0,73; 1,46)
  - der Basalzellkarzinome: 1,05 (95% KI 0,82; 1,34)
- Verhältnis der Inzidenzraten bei täglicher Sonnenschutz vs. Sonnenschutz nach eigenem Ermessen:
  - der vom Plattenepithelkarzinom betroffenen Personen: 0,88 (95% KI 0,50; 1,56)
  - der Plattenepithelkarzinome: 0,61 (95% KI 0,46; 0,81), zugunsten täglicher Anwendung

Van der Pols, 2006

- Australien, 1992-2004
- Verlängerungsstudie zu Green et al. 1995 (Nambour Studie), n= 1.621; davon 1.484 analysiert
- Risiko für Verzerrung für beide Endpunkte: kritisch (u.a. bedingt durch fehlende Kontrolle für Störfaktoren (Confounder), Messung der Endpunkte)
- Allgemeinbevölkerung
- Alter, Hauttyp, Anteil weiblicher Personen: nicht berichtet
- Follow-up: 8 Jahre nach Interventionsende
- Verhältnis der Inzidenzraten (Zeitraum: 1993-2004)
  - der vom Basalzellkarzinom betroffenen Personen: 1,02 (95% KI 0,78; 1,35)
  - der Basalzellkarzinome: 0,87 (95% KI 0,64; 1,20)
- Verhältnis der Inzidenzraten (Zeitraum: 1993-2004)
  - der vom Plattenepithelkarzinom betroffenen Personen: 0,65 (95% KI 0,45; 0,94)
  - der Plattenepithelkarzinome: 0,59 (95% KI 0,38; 0,90)

Pandeya, 2005

Extraktion nach RS mit Arbeitsgruppe nicht erfolgt

→ gleiche Datengrundlage wie in Green et al. verwendet, gleichen Endpunkt (Basalzellkarzinom) betrachtet, und eine Ereignis-Zeitanalyse durchführt (Hazard ratio models for first BCC)

Ulrich, 2009

- Deutschland, Studienzeitraum nicht identifiziert
- Nicht randomisierte kontrollierte Studie, n= 120
- Organtransplantierte Patienten ≥ 40 Jahre, 50% weiblich
- Alter, Median (Spanne): 60,7 (40–77) Jahre
- Hauttyp: II oder III
- Anzahl der aktinischen Keratosen bei Einschluss (Intervention vs. Kontrolle), Mittelwert ± SD: 3,18 (3,42) vs. 3,23 (3,66)

Referenz	Methodische Qualität	Charakteristika		Kommentar
	▪ Intervention: vor dem ersten Verlassen des Hauses; SPF 60+; Daylong actinica (Spirig Pharma Ltd., Egerkingen, Switzerland); bis-ethylhexyloxyphenol methoxyphenyl triazine, ethylhexyl triazone, isoamyl p-methoxycinnamate, ethylhexyl methoxycinnamate and methylene bis-benzotriazolyl tetramethylbutylphenol, butyl methoxydibenzoylmethane; eingestuft als "very high protective" nach Empfehlung der EU-Kommission (26/9/2006), entspricht gemessenem SPF >60 für UV-B; guter UV-A Schutz nach Australischem Standard (AS/NZS 2604– 1997); wasserfeste Cremelotion + allgemeine Informationen zum Sonnenschutzverhalten (Schatten, Kleidung, Meiden der Mittagssonne) ▪ Kontrolle: Sonnenschutz nach eigenem Ermessen + allgemeine Informationen zum Sonnenschutzverhalten (Schatten, Kleidung, Meiden der Mittagssonne) ▪ Follow-up: 2 Jahre ▪ schwerwiegendes (serious) Risiko für Verzerrung für beide Endpunkte (BCC, SCC) (u.a. bedingt durch Domänen: ‚Störfaktoren', ‚Messung des Endpunktes') ▪ <u>Inzidenz Basalzellkarzinome:</u> ○ Sonnenschutzmittel: n= 2 ○ Kontrollgruppe: n= 9 ○ Matching durchgeführt für Alter, Geschlecht, Zeit nach Transplantation, erhaltenes Organ, Malignome in der Eigenanamnese nach Organtransplantation (inkl. ähnlicher Anzahl der AK) ▪ <u>Inzidenz Plattenepithelkarzinome:</u> ○ Sonnenschutzmittel: n= 0 ○ Kontrollgruppe: n= 8 → $p < 0,01$ ○ Matching durchgeführt für Alter, Geschlecht, Zeit nach Transplantation, erhaltenes Organ, Malignome in der Eigenanamnese nach Organtransplantation (inkl. ähnlicher Anzahl der AK)		
Silva E. S. D., et al. Use of sunscreen and risk of melanoma and non-melanoma skin cancer: a systematic review and meta-analysis. European Journal of Dermatology. 2018.28(2):186-201. **https://pubmed.ncbi.nlm.n**	AMSTAR-2: niedrig	**Ziel** ▪ Den Zusammenhang zwischen Hautkrebs (Melanom sowie Nichtmelanom) und der Anwendung von Sonnenschutzmitteln bei Kindern und Erwachsenen untersuchen. **Suchzeitraum** ▪ Bis 05/2017 **Datenbanken** ▪ PubMed, Google Scholar, Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information (BIREME), die Medline, LILACS und > 20 andere Datenbanken beinhaltet, Referenzlisten **Population** ▪ Erwachsene, Kinder oder gemischt	**Intervention/ Exposition** ▪ Anwendung von Sonnenschutzmitteln, klassifiziert in ≥ 2 Kategorien bezüglich Häufigkeit der Anwendung **Kontrolle** . **Weitere relevante Einschlusskriterien** . **Relevante Ausschlusskriterien** . **Studientypen** ▪ Beobachtungsstudien (Fall-Kontroll-, Querschnitt- oder Kohortenstudien) oder kontrollierte Studien **Endpunkte** ▪ Jegliche Form von Hautkrebs (Melanom, Basalzellkarzinom, Plattenepithelkarzinom)	
	Baseline-Charakteristika ▪ 25 F-K-S, 2 Kohortenstudien, 1 Querschnittstudie, 1 RCT			

Referenz	Methodische Qualität	Charakteristika	Kommentar
ih.gov/29620003/		▪ Amerika (n= 11), Europa (n= 12), Asia-Pacific (n= 6) ▪ Methodische Qualität der Publikationen: gut (n= 4), moderat (n= 22), gering (n= 3), Information nicht verfügbar (n= 1) ▪ Detaillierte Darstellung der Baseline-Charakteristika (u.a. zum SPF und der Anwendung der Sonnenschutzmittel): siehe Tabelle 1 in Publikation **Ergebnisse übergreifend für jegliche Tumorformen** ▪ Siehe Evidenztabelle Melanom **Nicht-melanomspezifische Auswertung** ▪ keine signifikante Assoziation zwischen dem Risiko für nicht-melanozytären Hautkrebs und der Anwendung von Sonnenschutzmitteln (OR 0,99 (95% KI 0,62; 1.57); I^2= 87.3%; 110 914 Teilnehmer:innen, 857 Fälle). ▪ Limitation: es wurden RCT und Beobachtungsstudien gepoolt **Basalzellkarzinom-spezifische Ergebnisse** **Kricker et al., 1995:** ▪ Australien, populationsbasierte Fall-Kontroll-Studie, Studienqualität moderat ▪ Alter: 40-64 Jahre ▪ N= 892 Assoziation zwischen Anwendung von Sonnenschutzmitteln, SPF10+ (≥ Hälfte der Zeit: 1-9 Jahre, 10+ Jahre kombiniert) und Basalzellkarzinom (Re-Analyse von Silva et al.) ▪ OR 1,51 (95% KI 0,99; 2,31) Assoziation zwischen Häufigkeit der Anwendung von Sonnenschutzmitteln und Basalzellkarzinom, SPF10+ ▪ niemals, < Hälfte der Zeit: 1,0 ▪ ≥ Hälfte der Zeit: 1-9 Jahre: OR 1,92, (95% KI 1,17; 3,13) ▪ 10+ Jahre: OR 1,25, (95% KI 0,82; 1,90) ▪ adjustiert für Alter, Geschlecht, Fähigkeit zu bräunen und Lokalisation **Gon et al., 2011** ▪ Brasilien, krankenhausbasierte F-K-S, moderate Studienqualität ▪ Alter: 18-80 Jahre ▪ n= 407 Assoziation zwischen Anwendung von Sonnenschutzmitteln und Basalzellkarzinom (Re-Analyse von Silva et al.) ▪ OR 1,69 (95% KI 0,82; 3,49) Assoziation zwischen Häufigkeit der Anwendung von Sonnenschutzmitteln und Basalzellkarzinom ▪ Häufige Anwendung von Sonnenschutzmitteln: OR 1,0 ▪ Niemals oder selten: OR 0,59 (95% KI 0,29; 1,21) ▪ adjustiert für Alter, Geschlecht, Augen-, Haarfarbe, Hauttyp, Hautkrebs in der Anamnese, Vorhandensein aktinischer Keratosen **Green et al., 1999** ▪ Nicht extrahiert, da bereits in Rönsch et al. abgebildet **Plattenepithelkarzinom-spezifische Ergebnisse** **Grodstein et al., 1995** ▪ USA, populationsbezogene Kohortenstudie, gute Studienqualität	

Referenz	Methodische Qualität	Charakteristika	Kommentar
		▪ n= 107.900 ▪ Alter: 30-55 Jahre <u>Assoziation zwischen Anwendung von Sonnenschutzmitteln und Plattenepithelkarzinom (Re-Analyse von Silva et al.)</u> ▪ OR 1,11 (95% KI 0,83; 1,66) <u>Assoziation zwischen Häufigkeit der Anwendung von Sonnenschutzmitteln und Plattenepithelkarzinom</u> ▪ Use sunscreen: RR 1,0 ▪ No sunscreen: RR 0,90 (95% KI 0,60; 1,20) ▪ Adjustiert für Alter, Rauchen, Region, Haarfarbe, Reaktion auf Sonne, Anzahl der Sonnenbrände, Tendenz zur Bräunung, Anzahl der Leberflecke („mole“), in der Sonne verbrachte Zeit **<u>Sànchez and Nova, 2013</u>** ▪ Kolumbien, krankenhausbasierte F-K-S, geringe Studienqualität ▪ n= 332 ▪ Alter: 32-94 Jahre ▪ Keine Adjustierung für Störgrößen <u>Assoziation zwischen Anwendung von Sonnenschutzmitteln und Plattenepithelkarzinom (Re-Analyse von Silva et al.)</u> ▪ OR 0,43 (95% KI 0,33; 0,56) (Nichtanwendung von Sonnenschutzmittel im Alter von < 15 Jahren (J), zwischen 15-30J, > 30J; kombiniert als „keine Anwendung“ <u>Assoziation zwischen Häufigkeit der Anwendung von Sonnenschutzmitteln und Plattenepithelkarzinom</u> ▪ Anwendung von Sonnenschutzmitteln: 1,0 ▪ Nichtanwendung von Sonnenschutzmittel im Alter von < 15 J: OR 2,96 (95% KI 0,15; 176,9) ▪ Nichtanwendung von Sonnenschutzmittel im Alter von 15-30J: OR 0 (95% KI 0; 3,25) ▪ Nichtanwendung von Sonnenschutzmittel im Alter von >30J: OR 1,74 (95% KI 0,22; 13,6) ▪ Keine Adjustierung erfolgt <u>Green et al., 1999</u> nicht extrahiert, da bereits in Rönsch et al. abgebildet	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
Sanchez G., et al. Sun protection for preventing basal cell and squamous cell skin cancers. Cochrane	AMSTAR-2: hoch	**Ziel** ▪ Die Effekte von Sonnenschutzmaßnahmen (z.B. Sonnenschutzmitteln) zur Prävention von Basalzellkarzinomen, und Plattenepithelkarzinomen. **Suchzeitraum** ▪ Bis 05/2016 **Datenbanken**	**Baseline-Charakteristika** ▪ 1 RCT (Nambour trial) mit mehreren Publikationen **Ergebnisse** ▪ Bereits aus Rönsch et al. extrahiert.	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
Database of Systematic Reviews. 2016.7:CD011161. **https://pubmed.ncbi.nlm.nih.gov/27455163/**		▪ Medline via Ovid, Embase via Ovid, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), diverse Studienregister, Referenzlisten **Population** ▪ Allgemeinbevölkerung (Kinder und Erwachsene) **Intervention/ Exposition** ▪ Sonnenschutzmittel mit jeglichem Lichtschutzfaktor ▪ Tragen von Hüten, Sonnenbrillen oder spezieller Kleidung ▪ Vermeidung von Sonne **Kontrolle** . **Weitere relevante Einschlusskriterien** . **relevante Ausschlusskriterien** ▪ spezielle Populationen (z.B. Menschen mit aktinischer Keratose, Empfänger von Organtransplantaten) **Studientypen** ▪ RCTs **Primäre Endpunkte** ▪ Basalzellkarzinom, klinisch und histopathologisch bestätigt ▪ Kutanes Plattenepithelkarzinom, klinisch und histopathologisch bestätigt ▪ Unerwünschte Effekte **Sekundäre Endpunkte** ▪ Anzahl der selbstberichteten Sonnenbrände ▪ Aktinische oder solare Elastose ▪ Anzahl der Stunden UV-Exposition zu Tageszeiten mit hoher UV-Exposition ▪ Anzahl der Stunden im Freien ▪ Minimale Erythemdosis (MED) ▪ Adhärenz zur Präventionsstrategie		

2.2.3. Aktinische Keratose (AK)

Übersicht der eingeschlossenen Primärstudien (Endpunkt AK)

Referenz	AMSTAR-II	Suchzeitraum	Thompson 1993	Darlington 2003	Naylor 1995	Ulrich 2009
Eisen DB. 2021	critically low	Verschiedene Angaben: 01/2019 und 06/2021	x	x	.	.
Rönsch H. 2021	critically low	01/2020	x	x	x	x
Sanchez G. 2016	high	05/2016	.	x (zitiert als Green 1999)	.	.
Green AC. 2014	critically low	08/2013	x	x	.	.
Werner RN. 2013	low	07/2012	x	x	.	x
Kommentar				Nambour trial AK prädefinierter Endpunkt: Extraktion sinnvoll		

Legende

x	.				
Primärstudie eingeschlossen	**Primärstudie nicht eingeschlossen**	**extrahieren**	**Methodik nacharbeiten und extrahieren**	**zurückstellen**	**Nicht extrahieren**

Evidenztabelle Endpunkt AK

Referenz	Methodische Qualität	Charakteristika		Kommentar
Rönsch, H. and A. Bauer, The preventive Value of Sun Protection. Current Problems in Dermatology, 2021. 55: p. 316-328.	AMSTAR-2: kritisch niedrig	**Ziel** ▪ die Evidenz zur Effektivität der Anwendung von Sonnenschutzmitteln hinsichtlich der Inzidenz von präkanzerösen Läsionen und epithelialem Hautkrebs anhand von kontrollierten und randomisiert kontrollierten Studien zusammenfassen **Suchzeitraum** ▪ bis 01/2020 **Datenbanken** ▪ Embase und Medline, jeweils via Ovid **Population**	**Studientypen** ▪ Randomisiert kontrollierte Studien oder nicht-randomisiert kontrollierte Studien **Endpunkte** ▪ Epithelialer Hautkrebs (Basalzellkarzinom, Plattenepithelkarzinom), ▪ Aktinische Keratose (AK) (Synonym: solare Keratose, aktinische Präkanzerose, Photokeratose), ▪ Hautalterung durch Licht (Photoaging), ▪ unerwünschte Effekte **Weitere relevante Einschlusskriterien** ▪ Publikationssprache: Englisch oder deutsch	zur AMSTAR-2-Bewertung: - ursprünglich 4 kritische Items nicht erfüllt - Liste der im VT-Screening ausgeschlossenen Studien von Autorengruppe nachgereicht

Referenz	Methodische Qualität	Charakteristika		Kommentar
https://pubmed.ncbi.nlm.nih.gov/34698024/		▪ Menschen, unabhängig von Alter, Hauttyp, Beruf etc. **Intervention/ Exposition** ▪ Sonnenschutzmittel oder Sonnenschutzmittel mit zusätzlicher Komponente **Kontrolle** ▪ Keine Intervention, Placebo, Träger (Vehikel) oder anderer Lichtschutzfaktor	**relevante Ausschlusskriterien** ▪ Studientypen: Beobachtungsstudien, Laborexperimente ▪ Endpunkte: Melanom, Sonnenschutzverhalten ▪ Keine Volltextpublikation	- Bewertung des Verzerrungs-risikos der eingeschlossenen Primärstudien durch dEBM erfolgt → daher Einschluss der Publikation
	Ergebnisse			
	Baseline-Charakteristika ▪ Insgesamt: 5 Primärstudien in Form von 13 Publikationen ▪ AK-spezifisch: 4 Primärstudien **Ergebnisse** **<u>Naylor 1995</u>** ▪ USA, 1987-1990 ▪ RCT, n= 50, davon 37 mit 2-Jahres-Nachbeobachtungszeit ▪ Hohes Risiko für Verzerrung (u.a. bedingt durch „some concerns“ in Domänen: ‚Randomisierungsprozess‘, ‚Abweichung von der geplanten Intervention‘, ‚Auswahl der berichteten Ergebnisse‘) ▪ Veteranen mit nicht-melanozytärem Hautkrebs und aktinischer Keratose und anhaltender Sonnenexposition ▪ Charakteristika zu Studienbeginn (n= 50): ○ Männliches Geschlecht (Kontrolle vs. Intervention): 80% vs. 92% ○ Alter (Kontrolle vs. Intervention) (Mittelwert, Standardabweichung (SD), Spanne): 64,2 Jahre ± 8,5 (44–77) vs. 63,3 Jahre ± 8,0 (39-78) ○ Initiale AK (Kontrolle vs. Intervention) (Mittelwert, SD): 11,4 ± 15,4 vs. 8,12 ± 17,7 ○ Hautkrebs in der Anamnese (Form des „previous skin cancer“ nicht näher definiert): (Kontrolle vs. Intervention) (Mittelwert, SD): 1,4 ± 2,05 vs. 1,36 ± 2,50 ○ Hauttyp (Kontrolle vs. Intervention): I: 20% vs. 20%, II: 52% vs. 32%, III: 20% vs. 44%, IV: 8 vs. 4% ▪ Intervention: Sonnenschutzmittel (SPF 29; 7% octyl methoxycinnamate, 6% oxybenzone, 5% octyl-salicylate) ▪ Kontrolle: Vehikel ▪ Beide Gruppen erhielten Hinweise zum Sonnenschutzverhalten (Vermeidung von Überexposition + mechanischer Schutz) ▪ Follow-up: 2 Jahre ▪ Häufigkeit der Anwendung der Sonnenschutzmittel widersprüchlich in 2 Publikationen zur Primärstudie berichtet: ≥ 1x oder ≥ 2x pro Tag ▪ <u>Jährliche AK Rate, SD:</u> ○ Sonnenschutzmittel: 13,6 ± 18,5 AKs/Jahr; Kontrolle: 27,9 ± 31,8 AKs/Jahr (Mann-Whitney U test, p = 0,023; 51% Reduktion) ▪ <u>Jährliche AK Rate, unter Einbezug von Risikofaktoren:</u> ○ Sonnenschutzmittel: 13,6 AKs/Jahr; Kontrolle: 21,1 AKs/Jahr (Poisson Regression, p= 0,001; 36% Reduktion) ○ Anzahl der AK zu Studienbeginn (chi^2= 475,4, df= 1, P< 0,001), Geschlecht (chi^2= 25,1, df= 1, P < 0,001), Hauttyp (chi^2= 52,0, df= 2, P< 0,001), Interaktion von Hauttyp mit initialen AK (chi^2= 25,1, df= 2, P< 0,001) waren signifikante Risikofaktoren für die Anzahl AK, die im Studienverlauf gemessen wurden ○ 2 Interkationen mit der Behandlung waren signifikant: initiale AK (chi^2= 4,2, df= 1, P= 0,041); Hauttypen (chi^2= 41,2, df= 2, P< 0,001). ○ Ein aggregierter Test für den Effekt der Behandlung und aller Interaktionen war signifikant (chi^2= 82,3, d/=4, P= 0,001)		

Referenz	Methodische Qualität	Charakteristika	Kommentar

Darlington, 2003

- Australien, 1992-1996
- RCT (Nambour Studie), n= 1.621, davon 1.116 analysiert
- Hohes Risiko für Verzerrung (u.a. bedingt durch Domänen: ‚Fehlende Endpunktdaten', ‚Auswahl der berichteten Ergebnisse')
- Allgemeinbevölkerung
- Alter (Spanne): 25-74 Jahre
- Hauttyp und Hautveränderungen: in Darlington et al. nicht berichtet, Extraktion erfolgte aus Green et al.
- Hauttyp (tägliche Anwendung vs. Anwendung nach eigenem Ermessen):
  - immer Verbrennung: 171/812 (21,1%) vs. 169/809 (20,9%)
  - Verbrennung/Bräunung: 552/812 (68%) vs. 547/809 (67,6%)
  - Nur Bräunung: 89/812 (11%) vs. 93/809 (11,5%)
- Hautkrebs in der Anamnese (tägliche Anwendung vs. Anwendung nach eigenem Ermessen): 215/812 (26,5%) vs. 221/809 (27,3%)
- Intervention: Tägliche Anwendung (Kopf, Hals, Arme, Hände); SPF 16; Auscreen Ultrablock Lotion SPF 15-plus (Ross Cosmetics, Melbourne, Australia); 8% 2-ethylexyl-p-methoxycinnamate, 2% 4-tertbutyl-4´-methoxy-4-dibenzoylmethane; nach Australischem Standard 2604 als wasserfest eingeschätzt SPF 16 mit/ohne 30 mg Beta-Carotin
- Kontrolle: Anwendung von Sonnenschutz nach eigenem Ermessen mit/ohne 30 mg Beta-Carotin
- Follow-up: 4,5 Jahre
- Relatives Verhältnis solarer Keratosen am gesamten Körper bei täglichem Sonnenschutz vs. Sonnenschutz nach eigenem Ermessen:
  - Zeitraum 1992-1994: 0,76 (95% KI 0,62; 0,94); zugunsten täglicher Anwendung (Hinweis: Zeitraum des Ergebnisberichtes war nicht prädefiniert)
  - Zeitraum 1994-1996: 0,95 (95% KI 0,75; 1,19)
- Relatives Verhältnis solarer Keratosen an eingecremten Körperstellen bei täglichem Sonnenschutz vs. Sonnenschutz nach eigenem Ermessen:
  - Zeitraum 1992-1994: 0,78 (95% KI 0,64; 0,96); zugunsten täglicher Anwendung (Hinweis: Zeitraum des Ergebnisberichtes war nicht prädefiniert)
  - Zeitraum 1994-1996: 0,94 (95% KI 0,75; 1,19)

→ Jeweils adjustiert für Alter, Geschlecht, Beta-Carotin-Anwendung, Augen- sowie Haarfarbe, Hautreaktion auf akute Sonnenexposition, berufliche Sonnenexposition (bezogen auf Lebenszeit), Rauchverhalten, Hautkrebs in der Eigenanamnese

Thompson, 1993

- Australien, 09/1991-03/1992 (australischer Sommer)
- RCT, n= 588; davon 431 analysiert
- Hohes Risiko für Verzerrung (u.a. bedingt durch ‚Abweichung von der geplanten Intervention')
- Allgemeinbevölkerung, älter als 40 Jahre mit 1-30 AK, 58% weiblich (bezogen auf die analysierten Pat.)
- Alter (Mittelwert, Standardabweichung (SD), Spanne): 63 ± 11 (40–93) Jahre (bezogen auf die analysierten Pat.)
- Hauttyp: nicht berichtet
- Intervention: ≥ 1×/d; SPF 17; 8% (wt/wt) 2-ethylhexyl p-methoxycinnamate, 2% (wt/wt) 4-tert-butyl-4-methoxy-4-dibenzoylmethane; nach Australischem Standard 2604 eingestuft als SPF 17 für UVB (94% Reduktion 290–320 nm) und als Breitspektrumfilter für UVA (90% Reduktion 320–360 nm)
- Kontrolle: Placebo (Basiscreme ohne aktive Inhaltsstoffe, dafür mit 10% Mineralöl, um die gleiche Konsistenz sicherzustellen)
- Follow-up: 7 Monate
- Anzahl der aktinischen Keratosen:
  - Unterschied seit Anwendungsbeginn: Sonnenschutz: -0,6 ± 0,3; Kontrolle: +1 ± 0,3; nicht signifikant

Referenz	Methodische Qualität	Charakteristika	Kommentar
		○ Verhältnis des Unterschiedes seit Behandlungsbeginn: 1,53 (95% KI 0,81; 2,25) ○ Relativer Unterschied mit der Kontrollgruppe als Referenz: 0,83 (95% KI 0,78; 0,89) (durch Alter und Hauttyp nicht modifiziert) ▪ Neue aktinische Keratosen ○ Durchschnittliche Anzahl pro Person: Sonnenschutzmittel: 1,6; Kontrollgruppe: 2,3; p = 0,014 ○ Verhältnis der Inzidenzrate: Sonnenschutzmittel vs. Kontrollgruppe: 0,62 (95% KI 0,54; 0,71) ▪ AK Remissionen ○ Sonnenschutzmittel: 25%; Kontrollgruppe: 18%; p: nicht berichtet ○ Wahrscheinlichkeit Sonnenschutzmittel vs. Kontrollgruppe: 1,53 (95% KI 1,29; 1,80) (adjustiert für Geschlecht und Hauttyp) ▪ Dosis-Wirkungs-Beziehung in Sonnenschutzgruppe ○ Neue AK: p = 0,04 ○ Remission: p = 0,001 **Ulrich, 2009** ▪ Deutschland, Studienzeitraum nicht identifiziert ▪ Nicht randomisierte kontrollierte Studie, n= 120 ▪ schwerwiegend (serious) Risiko für Verzerrung (u.a. bedingt durch Domänen: ‚Störfaktoren', ‚Messung des Endpunktes') ▪ Organtransplantierte Patienten ≥ 40 Jahre, 50% weiblich ▪ Alter, Median (Spanne): 60,7 (40–77) Jahre ▪ Hauttyp: II oder III ▪ Anzahl der aktinischen Keratosen bei Einschluss (Intervention vs. Kontrolle), Mittelwert ± SD: 3,18 (3,42) vs. 3,23 (3,66) ▪ Intervention: vor dem ersten Verlassen des Hauses; SPF 60+; Daylong actinica (Spirig Pharma Ltd., Egerkingen, Switzerland); bis-ethylhexyloxyphenol methoxyphenyl triazine, ethylhexyl triazone, isoamyl p-methoxycinnamate, ethylhexyl methoxycinnamate and methylene bis-benzotriazolyl tetramethylbutylphenol, butyl methoxydibenzoylmethane; eingestuft als "very high protective" nach Empfehlung der EU-Kommission (26/9/2006), entspricht gemessenem SPF >60 für UV-B; guter UV-A Schutz nach Australischem Standard (AS/NZS 2604– 1997); wasserfeste Cremelotion + allgemeine Informationen zum Sonnenschutzverhalten (Schatten, Kleidung, Meiden der Mittagssonne) ▪ Kontrolle: Sonnenschutz nach eigenem Ermessen + allgemeine Informationen zum Sonnenschutzverhalten (Schatten, Kleidung, Meiden der Mittagssonne) ▪ Follow-up: 2 Jahre ▪ Aktinische Keratosen: ○ Veränderung der Anzahl der aktinischen Keratosen im Studienverlauf: Sonnenschutzmittel: 53% Reduktion (n= -102); Kontrollgruppe: 43% Anstieg (n= +82) ○ Anzahl der aktinischen Keratosen nach 24 Monaten: Sonnenschutzmittel (n= 89) vs. Kontrollgruppe (n= 273); MD 3,07 (95% KI 1,76; 4,36) ○ Matching durchgeführt für Alter, Geschlecht, Zeit seit Transplantation, erhaltenes Organ, Malignome in der Eigenanamnese nach Organtransplantation (inkl. ähnlicher Anzahl der AK)	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
Sanchez G., et al. Sun	AMSTAR-2: hoch	**Ziel**	**Baseline-Charakteristika** ▪ 1 RCT (Darlington 2003, Nambour trial)	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
protection for preventing basal cell and squamous cell skin cancers. Cochrane Database of Systematic Reviews. 2016.7:CD011161. **https://pubmed.ncbi.nlm.nih.gov/27455163/**		▪ Die Effekte von Sonnenschutzmaßnahmen (z.B. Sonnenschutzmitteln) zur Prävention von Basalzellkarzinomen, und Plattenepithelkarzinomen. **Suchzeitraum** ▪ Bis 05/2016 **Datenbanken** ▪ Medline via Ovid, Embase via Ovid, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), diverse Studienregister, Referenzlisten **Population** ▪ Allgemeinbevölkerung (Kinder und Erwachsene) **Intervention/ Exposition** ▪ Sonnenschutzmittel mit jeglichem Lichtschutzfaktor ▪ Tragen von Hüten, Sonnenbrillen oder spezieller Kleidung ▪ Vermeidung von Sonne **Kontrolle** . **Weitere relevante Einschlusskriterien** . **relevante Ausschlusskriterien** ▪ spezielle Populationen (z.B. Menschen mit aktinischer Keratose, Empfänger von Organtransplantaten) **Studientypen** ▪ RCTs **Primäre Endpunkte** ▪ Basalzellkarzinom, klinisch und histopathologisch bestätigt ▪ Kutanes Plattenepithelkarzinom, klinisch und histopathologisch bestätigt ▪ Unerwünschte Effekte **Sekundäre Endpunkte** ▪ Anzahl der selbstberichteten Sonnenbrände ▪ Aktinische oder solare Elastose ▪ Anzahl der Stunden UV-Exposition zu Tageszeiten mit hoher UV-Exposition ▪ Anzahl der Stunden im Freien ▪ Minimale Erythemdosis (MED) ▪ Adhärenz zur Präventionsstrategie	▪ Ergebnisse bereits aus Rönsch et al. extrahiert	

2.2.4. Aktinische Cheilitis

Evidenztabelle (Endpunkt Aktinische Cheilitis)

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
Moon S. H., et al. Use of lip protecting agents in the prevention of actinic cheilitis, herpes labialis and cancer of lip: A systematic review. Open Dentistry Journal. 2021.15(1):428-438. https://opendentistryjournal.com/VOLUME/15/PAGE/428/FULLTEXT/	AMSTAR-2: niedrig	**Ziel** ▪ die Wirksamkeit von lippenschützenden Substanzen mit Lichtschutzfaktor hinsichtlich der Prävention von aktinischer Cheilitis (AC), rezidivierendem Herpes labialis (RHL), Lippenkarzinom (LC) zu evaluieren **Suchzeitraum** ▪ bis 04.04.2020 **Datenbanken** ▪ SCOPUS, Google Scholar, Medline (Ovid), Pubmed, CINAHL, Cochrane Library, Handsuche **Population** ▪ Menschen **Intervention/ Exposition** ▪ lippenschützenden Substanzen (LPA) mit Lichtschutzfaktor **Kontrolle** . **Weitere relevante Einschlusskriterien** ▪ Volltext verfügbar **Relevante Ausschlusskriterien** ▪ lippenschützenden Substanzen, die antivirale Wirkstoffe beinhalten **Studientypen** ▪ randomisiert kontrollierte Studien (RCTs), Beobachtungsstudien, jeweils peer-reviewed **Endpunkte** ▪ Prävalenz: aktinische Cheilitis (AC), wiederkehrender Herpes labialis (RHL), Lippenkarzinom (LC)	5 RCTs, 4 Beobachtungsstudien **Aktinische Cheilitis (AC)** <u>Kontrollarm eines 1 RCTs (de Oliveira BH, Gonzaga A, et al. 2019)</u> ▪ unklares RoB für Randomisierung und verdeckte Zuteilung; hohes RoB für fehlende Werte in der Endpunkterhebung ▪ Lokalisation: unbekannt ▪ n= 23, keine Information zur Geschlechtsverteilung ▪ AC bereits prävalent ▪ Interventionsgruppe: Fludroxycortide 0.125mg/g + LPA mit SPF 60 (n= 15) ○ Hinweis: Ergebnisse nicht extrahiert, da Intervention nicht Gegenstand der Fragestellung der Leitlinie ▪ Kontrollgruppe: LPA mit SPF 60 (n= 8) ▪ Ergebnisse der Kontrollgruppe: Remission 1/8 (12,5%), partielle Verbesserung 4/8 (50%), keine klinischen Veränderungen der Lippe 3/8 (37,5%), → keine Verschlechterungen der Läsionen berichtet <u>1 Querschnittstudie (de Oliveira RA, da Silva L, et al. 2014.)</u> ▪ moderates Verzerrungsrisiko ▪ Hinweis aus Diskussionsteil: unklar, ob Anwendung spezifisch auf den Lippen erfolgte ▪ Brasilien, Berufsgruppe Fischerei ▪ n= 210 (männlich und weiblich) ▪ Prävalenz der AC bei Anwendern von lippenschützenden Substanzen mit Lichtschutzfaktor: 0% ▪ Prävalenz bei Nicht-Anwendern: 21,7% ▪ lippenschützenden Substanzen mit Lichtschutzfaktor nicht näher definiert <u>1 Querschnittsstudie (dos Santos R, de Oliveira R, et al. 2018.)</u> ▪ niedriges Verzerrungsrisiko ▪ Brasilien, Berufsgruppe Bergbau ▪ n= 201 (alle männlich)	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
			▪ Häufigkeit von AC bei Anwendung lippenschützender Substanz: 11/19 (57,9%) ▪ Häufigkeit von AC ohne Anwendung lippenschützender Substanz: 62/117 (36,2%) ▪ Lippenschützende Substanz nicht näher definiert **Lippenkarzinom (LC)** 1 Fall-Kontroll-Studie (fragebogenbasiert) (Pogoda and Preston-Martin S. 1996.) ▪ Niedriges Verzerrungsrisiko ▪ USA ▪ Patientinnen mit Lippenkarzinom: n= 74 ▪ Patientinnen ohne Lippenkarzinom: n= 105 ▪ „Lippenbedeckende Applikation“ nicht näher definiert ▪ Gruppiert nach durchschnittlicher UV-Strahlung und Anwendung lippenbedeckender Applikation ▪ Patientinnen mit einer durchschnittlich höheren UV-Exposition (≥ 430 UV Flux) und mit weniger als einer lippenbedeckenden Applikation pro Tag hatten das höchste Risiko für Lippenkarzinome **Herpes labialis (RHL)** ▪ 5 Studien identifiziert ▪ Ergebnisse nicht extrahiert, da kein priorisierter Endpunkt	

2.2.5. Zeichen lichtgealterter Haut (Surrogatendpunt)

Evidenztabelle (Endpunkt 'Lichtgealterte Haut')

Referenz	Methodische Qualität	Charakteristika		Kommentar
Rönsch, H. and A. Bauer, The preventive Value of Sun Protection. Current Problems in	AMSTAR-2: kritisch niedrig	**Ziel** ▪ die Evidenz zur Effektivität der Anwendung von Sonnenschutzmitteln hinsichtlich der Inzidenz von präkanzerösen Läsionen und epithelialem Hautkrebs anhand von kontrollierten und randomisiert kontrollierten Studien zusammenfassen **Suchzeitraum** ▪ bis 01/2020	**Studientypen** ▪ Randomisiert kontrollierte Studien oder nicht-randomisiert kontrollierte Studien **Endpunkte** ▪ Epithelialer Hautkrebs (Basalzellkarzinom, Plattenepithelkarzinom), ▪ Aktinische Keratose (AK) (Synonym: solare Keratose, aktinische Präkanzerose, Photokeratose),	zur AMSTAR-2-Bewertung: - zunächst 4 kritische Items nicht erfüllt - Liste der im VT-Screening ausgeschlossenen Studien von

<table>
<tr><th>Referenz</th><th>Methodische Qualität</th><th colspan="2">Charakteristika</th><th>Kommentar</th></tr>
<tr><td rowspan="2">Dermatology, 2021. 55: p. 316-328.
<u>https://pubmed.ncbi.nlm.nih.gov/34698024/</u></td><td></td><td>Datenbanken
▪ Embase und Medline, jeweils via Ovid
Population
▪ Menschen, unabhängig von Alter, Hauttyp, Beruf etc.
Intervention/ Exposition
▪ Sonnenschutzmittel oder Sonnenschutzmittel mit zusätzlicher Komponente
Kontrolle
▪ Keine Intervention, Placebo, Träger (Vehikel) oder anderer Lichtschutzfaktor</td><td>▪ Hautalterung durch Licht (Photoaging),
▪ unerwünschte Effekte
Weitere relevante Einschlusskriterien
▪ Publikationssprache: Englisch oder deutsch
relevante Ausschlusskriterien
▪ Studientypen: Beobachtungsstudien, Laborexperimente
▪ Endpunkte: Melanom, Sonnenschutzverhalten
Keine Volltextpublikation</td><td>Autorengruppe nachgereicht
- Bewertung des Verzerrungs-risikos der eingeschlossenen Primärstudien durch dEBM erfolgt
→ daher Einschluss der Publikation</td></tr>
<tr><td colspan="4">Ergebnisse</td></tr>
<tr><td colspan="5">Baseline-Charakteristika
▪ Insgesamt: 5 Primärstudien in Form von 13 Publikationen
▪ Spezifisch für Endpunkt „Hautalterung durch Licht“: 2 Primärstudien
Ergebnisse
<u>Boyd, 1995</u>
▪ USA, 1987-1990
▪ RCT, n= 53, Anzahl der Patienten, die den 2-Jahreszeitraum erfüllt haben: n= 35
▪ Hohes Risiko für Verzerrung (u.a. bedingt durch die Domänen: Messung des Endpunktes)
▪ Veteranen mit nicht-melanozytärem Hautkrebs oder aktinischer Keratose und anhaltender Sonnenexposition, 13 % weiblich
▪ Alter, Mittelwert (Spanne): 63 (39–77) Jahre
▪ Intervention: Sonnenschutzmittel (SPF 29; 7% octyl methoxycinnamate, 6% oxybenzone, 5% octyl-salicylate)
▪ Kontrolle: Placebo (Vehikel)
▪ Beide Gruppen erhielten Hinweise zum Sonnenschutzverhalten (Vermeidung von Überexposition + mechanischer Schutz)
▪ Häufigkeit der Anwendung der Sonnenschutzmittel widersprüchlich in 2 Publikationen zur Primärstudie berichtet: ≥ 1x oder ≥ 2x pro Tag
▪ Follow-up: 2 Jahre
▪ <u>Computergestützte Analyse der solaren Elastose in Haubiopsien nach 24 Monaten (periauriculär)</u>
○ Sonnenschutzmittel: 30,1%
○ Placebo: 39,4%
→ t-test: p = 0,0001
○ RMANOVA (unter Berücksichtigung der Baseline-Werte), 16 Personen analysiert: nicht signifikant
▪ <u>Routine Histologie (keine Zahlenwerte berichtet)</u>
○ Epitheliale Dicke: nicht signifikant
○ Epitheliale Struktur: nicht signifikant
○ Dermale Infiltration: nicht signifikant
<u>Hughes, 2013</u></td></tr>
</table>

Referenz	Methodische Qualität	Charakteristika	Kommentar
		▪ Australien, 1992-1996 ▪ RCT (Nambour Studie), n= 903; 604 analysiert ▪ Allgemeinbevölkerung, jünger als 55 Jahre, 58% weiblich ▪ Risiko für Verzerrung: einige Bedenken (some concerns) (bedingt durch Selektion der berichteten Ergebnisse, Abweichung von der intendierten Intervention) ▪ Alter, Mittelwert (SD, Spanne): 39 ± 7 (25–55) Jahre ▪ Hauttyp: hauptsächlich hell (fair), 90% Sonnenbrand nach akuter Exposition ▪ Intervention: Tägliche Anwendung (Kopf, Hals, Arme, Hände); SPF 16; Auscreen Ultrablock Lotion SPF 15-plus (Ross Cosmetics, Melbourne, Australia); 8% 2-ethylexyl-p-methoxycinnamate, 2% 4-tertbutyl-4´-methoxy-4-dibenzoylmethane; nach Australischem Standard 2604 als wasserfest eingeschätzt SPF 16 mit/ohne 30 mg Beta-Carotin ▪ Kontrolle: Anwendung von Sonnenschutz nach eigenem Ermessen mit/ohne 30 mg Beta-Carotin ▪ Follow-up: 4,5 Jahre ▪ Chance für ausgeprägtere Mikrotopographiegrade nach Beagley und Gibson an Silikonabdrücken des linken Handrückens (Zeitraum 1996 vs. 1992) o Täglicher Sonnenschutz vs. Anwendung nach eigenem Ermessen: OR 0,76 (95% KI 0,59; 0,98), zugunsten täglicher Anwendung o Adjustiert für Anzahl der Sonnenbrände, Lichtalterung des Halses und „within-person“-Korrelation	

2.2.6. Unerwünschte Ereignisse

Übersicht der eingeschlossenen Primärstudien (unerwünschte Ereignisse)

Referenz	AMSTAR-II	Suchzeitraum	Boyd 1995	Naylor 1995	Ulrich 2009	Green 1999	Lindstrom 2019	Foley 1993	Marks 1995	Farrerons 2001	Thompson 1993
Rönsch H. 2021	Kritisch niedrig	01/2020	x	x	x	x	x	x	x	x	.
Sanchez G. 2016	hoch	05/2016	.	.	.	x	.	.	.	.	.
Green AC. 2014	Kritisch niedrig	08/2013	.	.	.	x	.	.	.	.	x
Kommentar						Nambour Studie	Nambour Studie	Publikation zu Studie von Thompson et al.	Publikation zu Studie von Thompson et al.	Nicht extrahiert, Zufallstreffer durch endpunktspezifische Suchstrategie in Rönsch et al.	Keine zusätzliche Information im Vgl. Foley

Übersicht der eingeschlossenen Primärstudien (Frontal fibrosierende Alopezie)

Referenz	AMSTAR-II	Suchzeit-raum	Aldoori 2016	Cranwell 2019	Moreno-Arrones 2018	Panchaprateep 2020	Westphal 2021	Kidambi 2017	Leecharoen 2021	Porrino-Bustamente 2019	Ramos 2020
Kam O. 2023	Kritisch niedrig	07 oder 08/2022	x	x	x	x	x	x	x	x	(x)
Maghfour J. 2022	Kritisch niedrig	08/2021	x	x	x	x	x	x	x	x	x
Kommentar	Maghfour nur als Letter veröffentlicht, Links zu Supplements z.T. nicht funktionsfähig, entsprechend geringe Berichtsqualität										Ramos in Kam et al. eingeschlossen, aber nicht in MA analysiert (Grund: Niemalsanwender und gelegentliche Anwender gemeinsam analysiert)

Legende

x	.				
Primärstudie eingeschlossen	**Primärstudie nicht eingeschlossen**	**extrahieren**	**Methodik nacharbeiten und extrahieren**	**zurückstellen**	**Nicht extrahieren**

Evidenztabelle (unerwünschte Ereignisse und Frontal fibrosierende Alopezie)

Referenz	Methodische Qualität	Charakteristika I	Charakteristika II	Kommentar
Rönsch, H. and A. Bauer, The preventive Value of Sun Protection. Current Problems in	AMSTAR-2: kritisch niedrig	**Ziel** ▪ die Evidenz zur Effektivität der Anwendung von Sonnenschutzmitteln hinsichtlich der Inzidenz von präkanzerösen Läsionen und epithelialem Hautkrebs anhand von kontrollierten und randomisiert kontrollierten Studien zusammenfassen **Suchzeitraum** ▪ bis 01/2020 **Datenbanken**	**Studientypen** ▪ Randomisiert kontrollierte Studien oder nicht-randomisiert kontrollierte Studien **Endpunkte** ▪ Epithelialer Hautkrebs (Basalzellkarzinom, Plattenepithelkarzinom), ▪ Aktinische Keratose (AK) (Synonym: solare Keratose, aktinische Präkanzerose, Photokeratose), ▪ Lichtalterung (Hautalterung),	zur AMSTAR-2-Bewertung: - zunächst 4 kritische Items nicht erfüllt - Liste der im VT-Screening ausgeschlossenen Studien von Autorengruppe nachgereicht

Referenz	Methodische Qualität	Charakteristika I	Charakteristika II	Kommentar
Dermatology, 2021. 55: p. 316-328. **https://pubmed.ncbi.nlm.nih.gov/34698024/**		▪ Embase und Medline, jeweils via Ovid **Population** ▪ Menschen, unabhängig von Alter, Hauttyp, Beruf etc. **Intervention/ Exposition** ▪ Sonnenschutzmittel oder Sonnenschutzmittel mit zusätzlicher Komponente **Kontrolle** ▪ Keine Intervention, Placebo, Träger (Vehikel) oder anderer Lichtschutzfaktor	▪ unerwünschte Effekte **Weitere relevante Einschlusskriterien** ▪ Publikationssprache: Englisch oder deutsch **relevante Ausschlusskriterien** ▪ Studientypen: Beobachtungsstudien, Laborexperimente ▪ Endpunkte: Melanom, Sonnenschutzverhalten Keine Volltextpublikation	- Bewertung des Verzerrungs-risikos der eingeschlossenen Primärstudien durch dEBM erfolgt → daher Einschluss der Publikation
	Ergebnisse			
	Baseline-Charakteristika ▪ Insgesamt: 5 Primärstudien in Form von 13 Publikationen ▪ Spezifisch für Endpunkt „unerwünschte Effekte“: 5 Primärstudien, 8 Publikationen **Wichtiger Hinweis** ▪ Die Recherchestrategie wurde in Rönsch et al. endpunktspezifisch für AK, BCC, SCC, Lichtalterung gestaltet. ▪ Wenn Publikationen neben diesen Endpunkten auch unerwünschte Effekte berichteten, wurden diese hier extrahiert. ▪ Eine Publikation (Farrerons et al.) untersucht nur den Endpunkt Knochendichte. Da die Recherche von Rönsch et al. endpunktspezifisch für AK, BCC, SCC, Lichtalterung erfolgte, wird diese Publikation als Zufallstreffer eingeschätzt und an dieser Stelle nicht extrahiert. **Ergebnisse** ▪ Die Baseline-Charakteristika der zitierten Studien sind in den Evidenztabellen der Wirksamkeitsendpunkte abgebildet (Siehe Erstautor) **Naylor, 1995** ▪ Hohes Risiko für Verzerrung, u.a. bedingt durch fehlende Endpunktdaten ▪ jeweils Intervention vs. Kontrolle o Brennen nach Augenkontakt: 14/25 (56%) vs. 14/25 (56%) o Sonnenempfindlichkeit: 0/25 vs. 2/25 (8%) o Akneiforme Läsionen: 3/25 (12%) vs. 1/25 (4%) o Hautfarbende Papeln: 1/25 (4%) vs. 1/25 (4%) o Brennen oder Jucken außerhalb des Auges: 1/25 (4%) vs. 3/25 (12%) **Boyd, 1995** ▪ Nicht extrahiert, da gleiche Population wie Naylor, 1995 **Ulrich, 2009** ▪ schwerwiegend Risiko für Verzerrung (serious), u.a. bedingt durch fehlende Kontrolle für Störfaktoren und Messung des Endpunktes ▪ jeweils Intervention vs. Kontrolle o Akne und Seborrhoe: 12/60 (20%) vs. 7/60 (11,7%) o Keine Unterschiede im Auftreten von Herpes simplex, Herpes zoster, HPV-Warzen oder Dermatomykosen im Gruppenvergleich (keine absoluten Zahlen berichtet) **Green, 1999 (Nambour Studie)**			

Referenz	Methodische Qualität	Charakteristika I	Charakteristika II	Kommentar

- Hohes Risiko für Verzerrung, u.a. bedingt durch fehlende Informationen hinsichtlich möglicher Abweichungen von der Intervention, fehlende Endpunktdaten
- Unerwünschte Effekte bei täglichen Anwendung von Sonnenschutzmitteln
  - Kontaktallergie oder Hautirritationen: n= 25/692 (3,6%)
  - Fettigkeit der Haut: n= 10/692 (1,5%)
  - Brennende Augen: n= 6/692 (0,9%)
  - ➔ Zusatzinformationen:
    - Abbruch der Studienteilnahme aufgrund von Hautirritationen: n= 1
    - Linderung der Symptome nach Wechsel auf ein Ersatzprodukt mit ähnlichem Lichtschutzfaktor vom selben Herstellen: n= 28

Lindstrom, 2019 (Nambour Studie)

- RCT, Australien, (1993-2014)
- kritisches Risiko für Verzerrung, u.a. bedingt durch fehlende Kontrolle für Störfaktoren in der Nachbeobachtungszeit
- Intervention: Tägliche Anwendung (Kopf, Hals, Arme, Hände); SPF 16; Auscreen Ultrablock Lotion SPF 15-plus (Ross Cosmetics, Melbourne, Australia); 8% 2-ethylexyl-p-methoxycinnamate, 2% 4-tertbutyl-4´-methoxy-4-dibenzoylmethane; nach Australischem Standard 2604 als wasserfest eingeschätzt SPF 16 mit/ohne 30 mg Beta-Carotin
- Kontrolle: Anwendung von Sonnenschutz nach eigenem Ermessen mit/ohne 30 mg Beta-Carotin
- Dauer der Intervention: 4,5 Jahre (1992-1996)
- Nachbeobachtungszeit: 18 Jahre nach Interventionsende
- n= 1.621, 56% weiblich
- jegliche Todesfälle: HR 0,94 (95% KI 0,76; 1,17)
- kardiovaskuläre Todesfälle: HR 0,77 (95% KI 0,55; 1,08)
- Todesfälle durch maligne Erkrankungen (nicht hautspezifisch): HR 1,09 (95% KI 0,76; 1,57)
- Andere Todesursachen: HR 1,02 (95% KI 0,67; 1,54)

Foley, 1993

- Australien, 09/1991-03/1992 (australischer Sommer)
- RCT, n= 603
- Hohes Risiko für Verzerrung (u.a. bedingt durch Abweichung von der intendierten Intervention und fehlende Endpunktdaten)
- Allgemeinbevölkerung, älter als 40 Jahre mit 1-30 AK, 58% weiblich
- Alter: nicht berichtet
- Hauttyp: nicht berichtet
- Intervention: ≥ 1×/d; SPF 17; 8% (wt/wt) 2-ethylhexyl p-methoxycinnamate, 2% (wt/wt) 4-tert-butyl-4-methoxy-4-dibenzoylmethane; nach Australischem Standard 2604 eingestuft als SPF 17 für UVB (94% Reduktion 290–320 nm) und als Breitspektrumfilter für UVA (90% Reduktion 320–360 nm)
- Kontrolle: Placebo (Basiscreme ohne aktive Inhaltsstoffe, dafür mit 10% Mineralöl, um die gleiche Konsistenz sicherzustellen)
- Follow-up: 7 Monate

Unerwünschte Effekte:

- 114 Personen gaben an, unerwünschte Effekte zu haben, davon haben 105 einen Fragebogen für eine genauere Evaluation beantwortet
- keine Gruppenzugehörigkeit berichtet
- Entzündliche Hautreaktion: n= 90 (z.B. Juckreiz, trockene Haut, Blasenbildung, periorbitale Schwellungen, Ausschlag, variierende Hautveränderungen: urtikarial, makulopapulös, akneiform, versikulär, erythematös)

Referenz	Methodische Qualität	Charakteristika I	Charakteristika II	Kommentar
		▪ Nicht entzündliche Reaktionen: Brennen in den Augen: n= 5, irritierte aktinische Keratosen: n= 3, Exanthem (Körperstelle, an der kein Sonnenschutzmittel verwendet wurde): n= 1, weiße Flecken auf den Händen: n= 1, fettige Haut: n= 1, Bräunung: n= 1, weißer Belag auf der Zunge: n= 1 ▪ Aus Primärpublikation zu der Studie (Thompson et al.) geht hervor, dass Studienabbrüche aufgrund von Hautreaktionen in beiden Gruppen auftraten: Intervention: 32/210 (15,24 %) vs. Kontrolle: 28/221 (12,67 %); unklar, ob diese in den 114 von Foley et al. genannten enthalten sind **Marks, 1995 (Subgruppe der Population aus Foley bzw. Thompson, 1993)** ▪ Australien, 09/1991-03/1992 (australischer Sommer) ▪ RCT, n= 153, davon 113 analysiert ▪ Hohes Risiko für Verzerrung, u.a. bedingt durch Abweichungen von der intendierten Intervention ▪ Allgemeinbevölkerung, älter als 40 Jahre mit 1-30 AK, 59% weiblich ▪ Alter: <70 J: n = 59; ≥70 J: n = 54 ▪ Hauttyp: Verbrennung: n= 31/113; Bräunung/Verbrennung: n= 56/113; Bräunung: n= 26/113 ▪ Interventions-/ Beobachtungszeitraum: australischer Sommer: September 1991 - März 1992 25-hydroxyvitamin D3 ▪ Unterschied zum Studienbeginn: Sonnenschutzmittel: 11,8 nmol/L (95% KI 7,6; 15,9); Kontrollgruppe: 12,8 nmol/L (95% KI 8,4; 17,1); p = 0,75 ▪ Unterschied des Anstiegs zwischen Kontrolle und Sonnenschutzmittel: 0,99 nmol/L (95% KI -7,0; 5,0) 1,25-dihydroxyvitamin D3 ▪ Unterschied zum Studienbeginn: Sonnenschutzmittel 1,3 pmol/L (95% KI -2,3; 4,9); Kontrollgruppe: 10,8 pmol/L (95% KI 6,7; 14,9); p = 0,0009	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
Sanchez G., et al. Sun protection for preventing basal cell and squamous cell skin cancers. Cochrane Database of Systematic Reviews. 2016.7:CD011161. **https://pubmed.ncbi.nlm.nih.gov/27455163/**	AMSTAR-2: hoch	**Ziel** ▪ Die Effekte von sonnenschutzmaßnahmen (z.B. Sonnenschutzmitteln) zur Prävention von Basalzellkarzinomen, und Plattenepithelkarzinomen. **Suchzeitraum** ▪ Bis 05/2016 **Datenbanken** ▪ Medline via Ovid, Embase via Ovid, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), diverse Studienregister, Referenzlisten **Population** ▪ Allgemeinbevölkerung (Kinder und Erwachsene) **Intervention/ Exposition** ▪ Sonnenschutzmittel mit jeglichem Lichtschutzfaktor ▪ Tragen von Hüten, Sonnenbrillen oder spezieller Kleidung	**Baseline-Charakteristika** ▪ 1 RCT (Nambour trial) mit mehreren Publikationen **Ergebnisse** ▪ Bereits aus Rönsch et al. extrahiert.	

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
		▪ Vermeidung von Sonne **Kontrolle** . **Weitere relevante Einschlusskriterien** . **relevante Ausschlusskriterien** ▪ spezielle Populationen (z.B. Menschen mit aktinischer Keratose, Empfänger von Organtransplantaten) **Studientypen** ▪ RCTs **Primäre Endpunkte** ▪ Basalzellkarzinom, klinisch und histopathologisch bestätigt ▪ Kutanes Plattenepithelkarzinom, klinisch und histopathologisch bestätigt ▪ Unerwünschte Effekte **Sekundäre Endpunkte** ▪ Anzahl der selbstberichteten Sonnenbrände ▪ Aktinische oder solare Elastose ▪ Anzahl der Stunden UV-Exposition zu Tageszeiten mit hoher UV-Exposition ▪ Anzahl der Stunden im Freien ▪ Minimale Erythemdosis (MED) ▪ Adhärenz zur Präventionsstrategie		
Kam, O., et al., Frontal fibrosing alopecia and personal care product use: a systematic review and meta-analysis. Archives of Dermatological Research, 2023. 04: p. 04.	AMSTAR-2: kritisch niedrig	**Ziel** ▪ Den Zusammenhang zwischen der Verwendung von Kosmetikprodukten (u.a. Sonnenschutzmittel) und dem Auftreten von Frontal fibrosierender Alopezie (FFA) untersuchen **Suchzeitraum** ▪ Laut Abstract: Bis 08/2022; Laut Volltext: Bis 07/2022 **Datenbanken** ▪ The Cochrane Library, Medline via PubMed, Medline via Ovid, EMBASE **Population** ▪ Menschen **Exposition**	**Baseline Charakteristika** <u>Alle Kosmetika/Nicht spezifisch für Sonnenschutzmittel:</u> ▪ 1 retrospektive Kohortenstudie, 7 Fall-Kontroll-Studien, 1 Querschnittstudie eingeschlossen ▪ Insgesamt 1.248 Personen mit FFA und 1.459 Personen ohne FFA ▪ Studienqualität mit Newcastle-Ottawa-Scale bewertet, Spanne 6-8, Ergebnisse studienspezifisch in Abbildung 2 und 3 der Publikation ▪ Exposition in allen Studien mittels Fragebogen erfasst <u>Spezifisch für Sonnenschutzmittel:</u> ▪ 9 Studien berichten zu Sonnenschutzmitteln im Gesicht	Einschluss, obwohl 5 kritische Domänen nicht erfüllt wurden → Primärstudien geprüft, keine adjustierten Ergebnisse berichtet, Metanalyse daher nur von nicht-adjustierten Daten möglich → Funnel Plot bei 8 analysierten Studien nicht notwendig

Referenz	Methodische Qualität	Charakteristika	Ergebnisse	Kommentar
https://pubmed.ncbi.nlm.nih.gov/37014396/		▪ Anwendung von Kosmetikprodukten (inkl. Gesichts- und Körpersonnenschutz, Shampoo, Gesichts- und Körperfeuchtigkeitscreme, Anti-Aging-/Faltencremes, Gesichtsreiniger, Gesichtspeeling, Aftershave, Haarschaum, Haargel, Haarfärbemittel, Haarglättung, Dauerwelle, Make-up und alle anderen Produkte, die zur Reinigung, Pflege, Veränderung oder Verschönerung des Erscheinungsbilds einer Person verwendet werden) **Kontrolle** . **Weitere relevante Einschlusskriterien** . **Relevante Ausschlusskriterien** ▪ Standpunktartikel/ Meinungsäußerung, Übersichtsarbeiten, Letter ohne Forschungsbezug und Fallberichte **Studientypen** ▪ Fall–Kontroll-Studien, Querschnittsstudien und Kohortenstudien ▪ Volltext auf Englisch verfügbar **Endpunkte** ▪ Auftreten von FFA	▪ 8 in quantitative Analyse eingeschlossen: 1 berichtet Niemalsanwendung und gelegentliche Anwendung gemeinsam ▪ 2 Studien zu Sonnenschutzmitteln am Körper ▪ Frequenz der Verwendung von Sonnenschutz uneinheitlich. „täglich“ in 1 Studie, „regelmäßig“ in 1 Studie, „2 Mal oder mehr pro Woche“ in 5 Studien. ▪ Sonnenschutzmittel/ SPF: nicht näher beschrieben ▪ Darstellung der Baseline-Charakteristika (u.a. zur Diagnostik der FFA und Häufigkeit der Anwendung der Sonnenschutzmittel): siehe Tabelle 1 und 2 in Publikation **Ergebnisse** <u>Chancenverhältnis spezifisch für FFA und Nutzung von Sonnenschutzmittel im Gesicht (FFA vs. Kontrolle):</u> ▪ <u>Beide Geschlechter:</u> 507/797 vs. 403/1.008; OR 3,02 (95% KI 1,67; 5,47); I^2= 82%; 8 Studien ▪ <u>Männer:</u> 39/72 vs. 47/219; OR 4,61 (95% KI 1,54; 13,78); I^2= 58%; 3 Studien ▪ <u>Frauen:</u> 473/730 vs. 355/789; OR 2,74 (95% KI 1,32; 5,70); I^2= 88%; 6 Studien → keine Kontrolle für Störfaktoren erfolgt	→ RoB in Interpretation nicht ausreichend betrachtet, Interpretation wird nicht herangezogen, sondern von LL-Gruppe vorgenommen → kein Protokoll und die im VT-Screening ausgeschlossenen Primärstudien nicht berichtet: Maghfour et al. haben identische Primärstudien eingeschlossen, Hinweis, dass Publikationsgeschehen abgebildet wurde

2.3. Evidenztabelle Recherche Sonnenschutzmittel und Sonnenbrand

Referenz	Studiencharakteristika	Ergebnisse

Granger C., et al. Evaluation of a Sunscreen Product Compared with Reference Standards P3, P5 and P8 in Outdoor Conditions: a Randomized, Double-Blinded, Intra-individual Study in Healthy Subjects. Dermatology And Therapy. 2022.12(11):2531-2546.
 	
https://pubmed.ncbi.nlm.nih.gov/36173595
	Aim: […] to test a new broad-spectrum SPF 50 sunscreen [investigational product (IP)], to provide evidence of how it actually performs in outdoor conditions of extreme solar exposure compared with established reference products from the ISO norm 24444:2019.
	Study design:
	- Single-centre, double-blind, randomized, intra-individual clinical study
	- Conducted:
	  ○ Tamarin, Mauritius (20.3378° S, 57.3751° E)
	  ○ between November 2021 and December 2021 (summer)
	Inclusion criteria:
	- 18–55 years
	- individual typology angle (ITA) ≥ 28°, with uniform skin colour throughout the investigational area (ITA ± 4° difference between any 2 zones)
	- absence of dermatological disorders affecting the investigational areas (multiple nevi, freckles, excess hair or uneven skin tones, tattoos, vitiligo or other pigmentary disorders).
	Exclusion criteria:
	- history of skin cancer,
	- abnormal response to sun,
	- cosmetic allergies or hypersensitivities,
	- medications likely to interfere with the study outcomes.
	Intervention:
	- 6 test areas per subjects' backs (3x3 cm)
	- Each area randomly treated with a different sunscreen or no sunscreen (positive control) or cover up (negative control)
	- Products applied at 2 mg/cm²
	- 15–30min after application: exposure time: 2 or 3h, depending on subject's baseline ITA (ITA ≤41°=3h exposure, ITA >41°=2h exposure).
	- If ITA ≤41° (intermediate colour): treatment area was subdivided into 2, a left and a right. one sub-area covered after 2 h exposure and one remained uncovered for 1 h.
	- Positive control area: exposure time 1h (due to severe sunburn risk).
	- If immediate erythema score of ≥2, it was covered.
	- Subjects lay prone outdoors for the duration of the study.
	- Protection of non-investigational areas with: clothing, hats and sunglasses. After interventional exposure further exposure was avoided until end of study.
	- Interventional product (IP):
	  ○ sunscreen containing lipophilic organic and a hydrophilic organic sun filters in a water-rich oil-in-water emulsion. Broad-spectrum, SPF 50 and UVAPF of 22.8
		Baseline characteristics:
		- n= 74 randomized, n= 65 completed and analysed
		- 40 females, 25 males,
		- Mean age: 28 y (Min 18 y, Max 53 y)
		- ITA distribution: ≤41°: n=23, >41° to 55°: n=40, >55°: n=2
		- Ethnicity: white European ethnicity (59/65), mixed Mauritian white ethnicity (6/65) (one parent of Mauritian origin and one parent of European origin); none reported Chinese ethnicity.
		- Mean cumulative UVA dose: 18.69 J/cm² - 40.75 J/cm² after 2h and 54.11 J/cm² after 3h. The mean cumulative erythemally weighted UVB dose ranged from 83.41 mJ/cm2 (in four subjects due to a change in weather conditions) to 201.09 mJ/cm2 after 2 h and 260.76 mJ/cm2 after 3 h.
		- 6 subjects did not receive the minimum cumulative erythemal weighted UVB dose of 100 mJ/cm²
		Results:
		Erythema grade at 24 h
		- grouped into grade 0-1 (defined as protection success) and grade 2-4 (defined as protection failure), no grade of 4 or 5 was recorded:
		  ○ P3/SPF 15 (grade 0-1: n=19 (29.23%); grade 2-4: n= 46 (70.77%))
		  ○ P5/SPF 30 (grade 0-1: n=35 (53.85%); grade 2-4: n= 30 (46.15%))
		  ○ P8/SPF 50+ (grade 0-1: n=62 (95.38%); grade 2-4: n= 3 (4.62%))
		  ○ IP/50 (grade 0-1: n=64 (98.46%); grade 2-4: n= 1 (1.54%))
		  ○ Positive control (grade 0-1: n=1 (1.54%); grade 2-4: n= 64 (98.46%))
		  ○ Negative control (grade 0-1: n=65 (100%); grade 2-4: n= 0 (0%))
		Mean clinical erythema score at 24h
		- Significant differences (p<0.001) with higher erythema score for lower SPF-products between:
		  ○ P3/SPF 15 vs. P5/SPF 30
		  ○ P5/SP F30 vs. P8/SPF 50+
		  ○ SPF 50 IP vs. reference standards SPF 15 and SPF 30 (p< 0.001 for each)
		- Difference between and P8/SPF 50+ and IP/SPF 50 not significant (p=0.136).
		- Significant differences between IP and positive control (higher score) and negative control (lower score).
		- Subgroup analyses of ITA >41° and ITA ≤41° similar patterns but comparisons between adjacent protection levels did not always reach statistical significance (see figure 4A in publication).

Referenz	Studiencharakteristika	Ergebnisse
	○ Octocrylene (8%), butyl methoxydibenzoylmethane (4.8%), ethylhexyl salicylate (4.8%), polysilicone-15 (3%), bis-ethylhexyloxyphenol methoxyphenyl triazine (1.5%), phenylbenzimidazole sulfonic acid (3%) - Reference products from ISO 24444: ○ P3 (SPF 15 & UVAPF of 2.5): ethyl hexyl methoxycinnamate (3%), butyl methoxydibenzoylmethane (0.5%), phenylbenzimidazole sulfonic acid (2.78%) ○ P5 (SPF 30 & UVAPF 13.4): butyl methoxydibenzoylmethane (3%), octocrylene (10%), ethylhexyl salicylate (5%), benzophenone-3 (5%) ○ P8 (SPF 50+ & UVAPF 27.5): ethyl hexyl methoxycinnamate (5%), bis-ethylhexyloxyphenol methoxyphenyl triazine (3%), ethylhexyl salicylate (3%), methylene bisbenzotriazolyl tetramethyl-butylphenol (10%) <u>Outcomes:</u> Primary: 6-point clinical erythema score - (0=no erythema, 1= Equivocal reaction, slight, barely perceptible erythema (not clearly defined or does not cover the entire exposed area), 2= Clearly visible erythema with well-defined borders, 3= Moderate erythema, 4=Severe erythema, 5= Very severe erythema with blistering) at 24h after exposure; - assessed by a board-certified dermatologist or by a physician under their supervision at 24h after exposure. - Secondary: Delayed pigmentation (grades 0–4) 1 week after exposure (not an outcome relevant to the systematic review question) - Photoprotection failure: clinical erythema score ≥ 2 (reported as frequencies) Colorimetry parameter - Chromameter CR-400 (Konica Minolta, Inc.,Tokyo, Japan): ○ a* (redness) at 24h (20 ± 4h) ○ L* (lightness) performed and at day 8 ○ ITA (overall colour) performed and at day 8 <u>Statistical methods:</u> - Clinical scoring and chromameter parameters: analysed using univariate analysis of variance (ANOVA) with ''product'' as the fixed factor and ''subject'' as the random factor followed by Tukey's procedure for pairwise comparisons. - Analysis was conducted on rank transformed data (equivalent to a non-parametric alternative) for the clinical scores and on the change from baseline for the chromameter measurements. - If ITA ≤ 41° (1 sub-area exposed for 2h and 1 for 3h), the primary analysis used values from the 3-h exposure. A secondary analysis of all 2-h data was also performed (Supplementary Material) <u>Funding:</u> Isdin	colorimetry parameter a* (redness): - Statistically significant difference between reference product levels (with lower a* for higher SPF-products): ○ P3/SPF 15 versus P5/SPF 30 (p = 0.038) ○ P5/SPF 30 versus P8/SPF50+ (p<0.001). - The SPF 50 IP was significantly different from the P3/SPF 15 and the P5/SPF 30 (p<0.001 for both), but not from the reference standard P8/SPF 50+ (p = 0.991). - Subgroup analyses of ITA >41° similar patterns but comparisons between adjacent protection levels did mostly not reach significance for ITA ≤41° (see figure 4B in publication) Reduction of Risk of Severe Burns: - In multiple subjects: areas had to be covered (27 subjects; 35 areas) before the 2 h period had elapsed owing to immediate grade C 2 erythema. - Most of these (23/35) were in the SPF 15 area, and most were in subjects with an ITA > 1° (15/27).
Granger C., et al. Outdoor	<u>Aim:</u> determine whether this outdoor method would be able to differentiate more subtle differences between photoprotection levels by introducing an intermediate level of SPF,	<u>Baseline characteristics:</u> - n=79 enrolled, n=63 analysed

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sunscreen testing with high-intensity solar exposure in a Chinese and Caucasian population. Photodermatology, Photoimmunology & Photomedicine. 2022.38(1):19-28 https://pubmed.ncbi.nlm.nih.gov/34157168	comparing products labelled as SPF 15 (P3), 30 (P5), and 50 (P8), as measured by erythema and delayed pigmentation. Study design: - single-center, double-blind, randomized, intra-individual clinical study - outdoor facility in Singapore in June/July 2019 Inclusion criteria: - healthy volunteers Exclusion criteria: - sunbed use, or depigmenting treatment within 3 months prior - dermatological conditions (eg, multiple nevi, freckles, excess hair or uneven skin tones, vitiligo, and photodermatoses) - topical or oral medications (eg, vitamin A derivatives, psoralen, aminolevulinic acid derivatives, antiinflammatories, and corticosteroids) that would affect assessment of efficacy or safety. Intervention: - five 12 cm^2 squares on the back - sunscreens, applied at 2 mg/cm^2 or no sunscreen (two squares) - 15-30 minutes after application: subjects spent 2-3 hours outdoors (earliest start time, 12.05; latest end time, 17.10), in a prone position, with the rest of the body covered. - Duration of exposure depended on skin color: o intermediate or tan skin color: 3 hours, o light skin color: 2 hours, or until they had received approximately 1200 J/m2 eff. - For safety reasons: if any area became erythematous, it was to be covered with the same protective tape used to mark out the test areas. - Protection of unexposed areas. After exposure, subjects were instructed not to expose their back again until the final evaluation (day 8). Products: - P8 (SPF 50+; UVAPF 20.2) - P5 (SPF 30; UVAPF 9.2) - P3 (SPF 15; UVAPF 2.5) of ISO norm 24444:2019 Control: - Two squares without sunscreen: o exposed to sunlight for 1 hour (unprotected skin, positive control), o not exposed at all (unexposed skin, negative control). Outcomes *Primary: 6-point clinical erythema score at 24h after exposure* - by a trained physician under supervision of a board-certified dermatologist	- 31 females, 32 males, - Age: mean 30 (Min-Max: 21-45) years, - ethnic: 53 Chinese, 10 Caucasian - ITA distribution: o ITA 20-28 ”tan”: n= 11 (17%) o ITA 29-41 “intermediate”: n= 26 (41%) o ITA 42-55 “light”: n= 26 (41%) - UVB dose: min 716.9 J/m^2 eff; max 1905.3 J/m^2 eff - UVA dose: min 11.41 J/cm^2; max 42.22 J/cm^2. - Exposure to high UV index (≥6): all volunteers - Exposure to very high UV index (8-10): 35 subjects (53.8%) 6-point clinical erythema score - Mean erythema score at 24 hours: o highest in the positive control area (no sunscreen, exposed). o statistically significant difference among test areas; with higher erythema score for areas treated with lower SPF products (see figure 1A in publication) o no statistically significant difference between the SPF 50+ and the unexposed area. Failure of photoprotection (erythema score ≥2): - N= 1 failure with SPF 50+ (grade 2 erythema in one individual with light skin color), - N= 3 failures with SPF 30 (grade 2 erythema in two individuals with intermediate, and one with tan skin color), - N= 13 failures with SPF 15 (12 grade 2 and one grade 3 erythema; three light, six intermediate, four tan; the grade 3 erythema was in an individual with tan skin color). - N= 52 grade 2 erythema in exposed participants without sunscreen One subject had a zone where the SPF 15 product was applied, which required premature covering at 1:36h from the start of exposure; otherwise, the areas were exposed as per the protocol colorimetry assessment for a* (erythema): - At 24 hours a* values (erythema) reported as percentage difference vs. unexposed skin decrease (less erythema) as SPF increased.

Outcome		Not treated, exposed area	SPF15	SPF30	SPF50+
Delta a* (24h)	Mean	6.12	2.32	1.61	1.08
	SD	3.07	1.85	1.70	1.11
Delta a* (one week)	Mean	2.11	0.94	0.74	0.36
	SD	1.86	1.17	1.14	0.98

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	- 0=no erythema, 1= Equivocal reaction, slight, barely perceptible erythema (not clearly defined), 2= Clearly visible erythema with well-defined borders, 3= Moderate erythema, 4=Severe erythema, 5= Very severe erythema with blistering, - Failure of photoprotection: erythema grade ≥2, that is, unequivocal erythema. *Secondary: delayed pigmentation was assessed 1 week after exposure* - not prioritized for this SR *colorimetry assessment for a* (erythema)* - at 24 hours and 1 week after sun exposure - CR400 Chroma Meter (Konica Minolta Inc.) - additionally, for L* = pigmentation, and ITA°= skin color typing: not prioritized for this SR Statistical methods: - clinical assessment: Wilcoxon signed-rank test for pairwise comparisons between concerned zones. - colorimetry assessment: paired samples t-test - followed by Bonferroni's adjustment Funding: Isdin	**At 24 h**: no product but exposed vs. P3/SPF15 (p<0.001); P3/SPF 15 vs. P5/SPF 30 (p=0.001); P5/SPF 30 vs. P8/SPF 50+ (p=0.007) **At 1 week**: no product but exposed vs. P3/SPF15 (p<0.001); P3/SPF 15 vs. P5/SPF 30 (p=0.289); P5/SPF 30 vs. P8/SPF 50+ (p=0.008)
Granger C., et al. Outdoor clinical testing with reference sunscreens to determine differences in skin response between populations of different ethnicity: A combined data analysis from 128 subjects. Photodermatology, Photoimmunology & Photomedicine. 2023.39(5):419-427.	**Abstract** Background: Two previously published clinical studies by our group assessed erythema and pigmentation responses in outdoor conditions with three reference sunscreens, comparing their effectiveness under the full spectrum of natural sunlight. These studies followed an almost identical protocol but were conducted in two different locations and in two ethnic groups: broadly, Chinese (Singapore) and White European (Mauritius). We analysed the data from these two study populations to compare differences in skin response according to ethnicity. Methods: The analysis included 128 subjects (53 were Chinese from Singapore and 75 were White European from Mauritius and Singapore). Products used were the reference sunscreens P3 (sun protection factor [SPF] 15), P5 (SPF 30) and P8 (SPF 50+) from ISO norm 24444:2019. Participants were exposed to outdoor sunlight for 2-3 h, depending on baseline ITA. Endpoints were erythema at 24 h: clinical score and colorimetry (Δa*) and pigmentation at 1 week based on colorimetry (ΔL* and ΔITA). Results: Among those with baseline ITA > 41, there were differences in erythemal response between the Chinese and White European groups, the White European group being more erythematous and also having a higher rate of photoprotection failure particularly at SPFs 15 and 30. Conclusion: Differences in skin response to sun influenced by ethnicity should be taken into account when making recommendations on sun safety.	**Methodological comment:** - Not extracted yet - Pooled analysis, not predefined - Research Question/ subgroup analysis relevant for our guideline?

Referenz	Studiencharakteristika	Ergebnisse
https://pubmed.ncbi.nlm.nih.gov/36867064		

Kohli I., et al. Greater efficacy of SPF 100+ sunscreen compared with SPF 50+ in sunburn prevention during 5 consecutive days of sunlight exposure: A randomized, double-blind clinical trial. Journal of the American Academy of Dermatology. 2020.82(4):869-877. https://pubmed.ncbi.nlm.nih.gov/31542406	Aim:
	To compare the sunburn protective efficacy of SPF 501 and SPF 1001 sunscreens under actual use at the beach.
	Study design:
	- prospective, randomized, double-blind, single-center, split-body/face study
	- May 27 - June 1, 2016 (5 consecutive days)
	- Upham Beach, St Petersburg, Florida (27° 44’ 10.1148’’ N, 82° 45’ 4.95’’ W)
	Inclusion criteria:
	- Healthy individuals
	- 18 - 60 years
	- Fitzpatrick skin phototypes (SPT) I through III
	Exclusion criteria:
	- pre-existing sunburn
	- visual differences in pigmentation between right and left sides
	- tattoos/nevi that would obscure sites
	Interventions:
	- Banana Boat Sport Performance, broad-spectrum SPF 50+ (Edgewell Personal Care Brands, Shelton, CT; containing avobenzone 3%, homosalate 10%, octocrylene 6%)
	- Neutrogena Ultra Sheer Dry-Touch Sunscreen, broad spectrum SPF 100+ (Neutrogena, Los Angeles, CA; containing avobenzone 3%, homosalate 15%, octisalate 5%, octocrylene 10%, oxybenzone 6%)
	- Both: spectrum (critical wavelength, ≥370 nm), water resistant to 80 minutes,
	- group 1 (left SPF 50+/right SPF 100+)
	- group 2 (left SPF 100+/right SPF 50+)
	- exposed areas: face and neck, arms and shoulders, lower legs and feet
	- exposure time: minimum of 3.5 hours daily for 5 days (10 AM- 3PM, ≤30 minutes of discretionary shade from 12 PM-1 PM)
	- preweighed sunscreens
	- Initial application supervised: 15 min before first exposure each day
	- subsequent applications not supervised or mandated, diary
	- if erythema score ≥ 2: exclusion from remaining sun exposure
	Outcomes:
	- erythema clinically assessed the morning after each exposure day (total of 5)
	Comparison of sunburn between left and right side of each exposure area:
	- scoring 2-sided difference scale,
	- L (-1): more sunburned on the left
		Baseline characteristic:
		- n=55 randomized and analysed
		- 37 females and 18 males
		- Fitzpatrick skin phototypes (SPT) I (1.8%, n = 1), II (40.0%, n = 22), and III (58.2%, n = 32)
		- 89% (49 of 55) self-identifying as white not of Hispanic or Latino origin.
		- Solar conditions: 3.64 ± 0.25 hours of direct sun exposure per day
		Comparison of sunburn between left and right side of each exposure area
		[table_1]
		mean change in clinical erythema score (± standard error of the mean)
		- cumulative evaluation*: SPF 100+ side (0.274 ± 0.029) vs. SPF 50+ side (0.353 ± 0.039)
		  ○ treatment effect: -0,080 (p< 0,001)
		- after 1st day of exposure: SPF 100+ side (0.093 ± 0.020) vs. SPF 50+ side (0.148 ± 0.029)
		  ○ treatment effect: -0,057 (p= 0,004)
		Overall change in mean Δa*(Colorimetric assessment) (± standard error of the mean)
		- cumulative evaluation*: SPF 50+ protected areas (0.61 ± 0.087) vs. SPF 100+ protected areas (0.31 ± 0.096)
		  ○ treatment effect: -0.295 (p< 0,001)
		- after first day of exposure: SPF 50+ protected areas (0.36 ± 0.096) vs. SPF 100+ protected areas (0.12 ± 0.108)
		  ○ treatment effect: -0.235 (p = 0.012)
		Overall mean Skin oxyhemoglobin (HbO_2) (± standard error of the mean)
		- cumulative evaluation*: SPF 50+ protected areas (0.060 ± 0.012) vs. SPF 100+ protected areas (0.032 ± 0.011)
		  ○ treatment effect: -0.028 (p = 0.003)
		- after first day of exposure: SPF 50+ protected areas (0.051 ± 0.013) vs. SPF 100+ protected areas (0.021 ± 0.013)
		  ○ treatment effect: -0.030 (p = 0.003)
		*methodological comment:
		- not all participants exposed over 5 days
		- exclusion of further sun exposure during study due to erythema score ≥ 2: n= 27
		- 8/27 (29.6%) observed after the fifth and final day of sun exposure.

[table_1]

	More sunburned on SPF 50+ side	No difference	More sunburned on SPF 100+ side
After 1 day of exposure	16,7% (9/54)	83,3% (45/54)	0% (0/54)
Cumulative 5d of exposure	56,4% (31/55)	36,4% (20/55)	7,3% (4/55)

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	- 0: no difference - R (+1): more sunburned on the right side 5-point clinically assessed Erythema score - 0= no burn; 1= possible burn; 2= defined redness; 3= severe sunburn; 4= edema and blisters Colorimetric assessment of post-sun exposure skin redness a* - with chromameter (model CR-400; Konica Minolta Sensing Americas, Ramsey, NJ) Skin oxyhemoglobin (HbO_2) - via diffuse reflectance spectroscopy (DRS) (model DRS1, Princeton Scientific Instruments, Monmouth Junction, NJ) Statistical Methods: - Analysis after the very 1st day of exposure and cumulative (=average of all post-sun exposure clinical comparison from 5 days). - Treatment effect significance determined by comparing the 2 treatment groups with a 2-sample t test adjusted for side *Methological comment: Despite not using a paired t-test, the results are reported. As reported in the publication of Hirsch et al. [16] it is assumed that this procedure underestimates the effect and a paired test would also have delivered significant results.* Funding: Johnson & Johnson Consumer Inc	
Trullas C., et al. Linear and exponential sunscreen behaviours as an explanation for observed discrepancies in sun protection factor testing. Photodermatology Photoimmunology and Photomedicine. 2020.36(5):351-356. https://pubmed.ncbi.nlm.nih.gov/31376288	Aim: 1. In this study, […] we selected 8 commercially available products claiming SPF50/SPF50+ and the two reference standard sunscreens SPF15 (P2 and P3) and the reference standard sunscreen SPF43 (P6) of the ISO 24444:2010 and ISO/DIS 24444:2019, respectively. We used several CROs to evaluate their SPF values according to the in vivo SPF laboratory method ISO 24444:2010. (not prioritized for the evidence synthesis) 2. For 5 of the products, we evaluated their capacity to prevent erythema at 24 hours after exposure in outdoor conditions under very high or even extreme exposure to natural sunlight. Study design: - Intraindividual, single-centre, double-blind, randomized clinical study conducted in Tamarin City (Mauritius) - during summertime - latitude −20°19' 32.02"S/ longitude 57°22' 14.02"E, altitude 460 m above sea level Inclusion/exclusion criteria: no information available Intervention: - applied at 2 mg/cm² on selected areas of the volunteers' backs. - subjects lay on their front; - exposed to sun for 2 hours - non-sunscreen-protected area was covered with fabric after 1 hour of exposure in all subjects.	Baseline characteristics: - N=35 included (number of analysed unclear) - healthy volunteers - skin phototype II to IV Results Mean erythema scores at 24h: - S1 SPF 50+ (exponential): 0,6 - S2 SPF 50+ (linear): 0,3 - S3 SPF 50+ (linear): 0,5 - S7 SPF 50 (exponential): 0,2 - P3 SPF 15 (linear): 1,2 → a mean erythema scores below grade 1 = equivocal reaction - exponential products S1 and S7 vs. linear SPF50+ products S2 and S3: no statistically significant differences - linear (S2 and S3) and exponential products (S1 and S7) vs. SPF15 reference standard (P3): statistically significant difference ($p < 0.001$) - linear and exponential products (S2, S3, S1, S7) vs. unprotected area: statistically significant difference ($p < 0.001$)

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	Products tested: Interventional products (categorized as exponential= the SPF varied clearly depending on the level of irradiation used by the contract research organization): - products S1: labelled SPF 50+, UV-filter: Butyl methoxydibenzoylmethane, Ethylhexyl methoxycinnamate, Ethylhexyl triazone, Titanium dioxide - product S7: labelled SPF 50, UV-filter: Butyl methoxydibenzoylmethane, Ethylhexyl methoxycinnamate, Ethylhexyl triazone, Titanium dioxide, Homosalate Comparator (categorized as linear= the SPF varied only slightly depending on the level of irradiation used by the contract research organization) - ISO 24444 standard SPF product (P3), SPF 15: Butyl methoxydibenzoylmethane, Ethylhexyl methoxycinnamate, Phenylbenzimidazole sulfonic acid, - Product S2: labelled SPF 50+, UV-filters: Butyl methoxydibenzoylmethane, Ethylhexyl triazone, Bis-ethylhexyloxyphenol methoxyphenyl triazine, Octocrylene, Ethylhexyl salicylate, Terephthalylidene dicamphor sulfonic acid - product S3, labelled SPF 50+, Uv-filters: Butyl methoxydibenzoylmethane, Bis-ethylhexyloxyphenol methoxyphenyl triazine, Titanium dioxide, Octocrylene Outcome 6-point clinical erythema score at 24 hours after the end of sunlight exposure from 0 (no erythema) to 5 (very severe erythema with blistering), tested as differences in erythema prevention by the test products Statistitical methods - one-way ANOVA was done with products as the fixed factor and subject as random components, - followed by Tukey's post hoc procedure for pairwise comparison between means. - performed on rank-transformed data since the abnormality assumption of the standardized residuals was violated at 1% level of Shapiro-Wilk test. Funding: Isdin	
Granger C., et al. Outdoor testing of the photoprotection provided by a new water-based broad-spectrum SPF50+ sunscreen product: two double-blind, split-face, randomized controlled	Aim: to test this product in conditions more representative of real-life solar exposure, to confirm its reported laboratory efficacy. Study design: - 2 double-blind, split-face, randomized controlled studies - conducted in different months: July (study 1) to September 2018 (study 2) - Barcelona Inclusion criteria: - healthy male and female adults - aged 18–60 years old (18–55 in study 2) - all skin types, with Fitzpatrick phototype I–IV (I–III in study 2) - ITA (individual typology angle) over 28 on the back, - at least occasional users of cosmetic products or sun care products Exclusion criteria:	Baseline characteristics: Study 1: n=38 Study 2: n=29 (analysed=27) Study 1 / Study 2 Mean age (min/max): 43 (21-59) / 39 (18-55) male: 8 (21%) / 10 (37%) female: 30 (79%) / 17 (63%) Phototype I: 0 (0%) / 2 (7%) Phototype II: 12 (32%) / 11 (41%) Phototype III: 25 (66%) / 14 (52%) Phototype IV: 1 (3%) / NA

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studies in healthy adults. Clinical, Cosmetic and Investigational Dermatology CCID. 2019.12:461-467. https://pubmed.ncbi.nlm.nih.gov/31303776	- those with skin marks that could interfere with assessment (pigmentation disorders, scarring, large number of nevi, etc.) - history of allergic reactions to similar products - history of skin cancer or dysplastic nevi - active facial skin disease - endocrine disease, immunosuppressive conditions or medications, and any treatments (topical or oral, including food supplements) that may affect skin pigmentation or reactions. - Pregnant or breastfeeding women. Intervention: Interventional product (IP) - lipophilic organic sun filters: ethylhexyl methoxycinnamate, butyl methoxydibenzoylmethane, ethyl hexyl triazone, and a physical filter: titanium dioxide - a water-based galenic formulation (SPF50+) Comparator - Study 1: SPF15 sunscreen (reference standard P3 of ISO 24444: 2010) ethylhexyl methoxycinnamate, butyl methoxydibenzoylmethane and phenylbenzimidazole sulfonic acid - Study 2: SPF50+ sunscreen: octocrylene, butyl methoxydibenzoylmethane, bis-ethylhexyloxyphenol methoxyphenyl triazine and titanium dioxide Both studies - sunny days with clear skies/ low cloud cover (studies postponed at cloudy weather) - application of 2 mg/cm^2, 30 mins before exposure by study technician Study 1 (IP vs SPF15) - sun terrace of a fitness center - 6 hrs (10.30 am–12.30 pm and 1.30 pm–5.30 pm, 30-min break) - free quiet activities (no water-related or excessive sweat-inducing activities). - reapplication of sunscreen products as felt necessary, technician applied them on their request, after first 2 hrs. Study 2 (IP vs SPF50+) - public square over 4 hrs. - subgroup of 4 subjects began the study with prescribed activities at 30-min intervals: walking, sitting, and lying face upward. - after 2 hrs outdoors (10 am–12 noon) sunscreen was reapplied during a 30-min indoor break, before a further 2 hrs' exposure (12.30–2 pm). → period of exposure was too long during critical hours - remaining 25 subjects started and finished earlier in the day (9 am–1 pm) - 5-min shade breaks upon request - reapplication of sunscreen products upon subjects' request any time after the first 2 hrs.	<table><tr><td>maximum UV index</td><td>5.9</td><td>8.5</td></tr><tr><td>total cumulative dose of erythemal UVB radiation</td><td>6 hrs: 200.3±14.8 mJ/cm^2</td><td>4 hrs: 164.9±15.8 mJ/cm^2</td></tr><tr><td>Mean sunscreen application</td><td>6 hrs: 3.2 times (min 2–max 5)</td><td>4 hrs: 1.7 times (min 1–max 2)</td></tr></table> Facial erythema score: Study 1 - IP product (mean, SD) ○ baseline score= 3.05 ±1.43 ○ 24h score= 3.08±1.30 ○ mean erythema score increase of 6% ± 24%, (P= 0,65) - SPF15 product (mean, SD) ○ baseline score= 2.89±1.37 ○ 24h score= 3.16±1.26 ○ mean erythema score increase of 16% ± 32%, (P<0.01) → Mean %-change IP vs. SPF15: p= 0.02 - increase in erythema score (of 1 point) for the IP area (n= 3), vs SPF15 area (n=9; 8 with an increase of 1 point and 1 with an increase of 2 points) Study 2 - IP product (mean, SD) ○ baseline score= 0.3±0.5 ○ 24h score= 0.5±0.6 ○ mean erythema score increase of 5%±10% (P= 0.06) - SPF50+ product (mean, SD) ○ baseline score= 0.4±0.5 ○ 24h score= 0.7±0.6 ○ mean erythema score increase of 7%±14% (no significance test performed) → Mean %-change IP vs. SPF50+: p= 0.14 - increase in erythema score (of 1 point) for the IP area (n= 5), vs SPF50+ area (n=7; 6 with an increase of 1 point and 1 with an increase of 2 points) - A post-hoc analysis (Wilcoxon test) by Fitzpatrick skin type subgroups (type II vs type III in study 1 and type I+II vs type III in study 2) revealed no statistically significant differences between groups for changes at 24 hrs

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	Outcomes Primary: facial erythema at baseline and at 20±4 hrs postexposure Study 1: - 10-point clinical erythema score (0= No erythema, 1,2,3= Very slight erythema, 4,5= Slight erythema, 6,7= Moderate erythema, 8,9= Marked erythema). Study 2: - 5-point clinical erythema score (0= No erythema, 1= Very slight erythema (barely perceptible), 2= Slight erythema (well defined), 3= Moderate erythema, 4= Strong erythema). Secondary (not relevant for this SR) - Is study design suitable to discriminate between the photoprotective ability of water-based IP and control sunscreens Statistical methods: - Means and SD were calculated for clinical scoring - Wilcoxon signed rank test Funding: Isdin	
Narbutt J., et al. Sunscreen applied at ≥ 2 mg/cm² during a sunny holiday prevents erythema, a biomarker of ultraviolet radiation-induced DNA damage and suppression of acquired immunity. British Journal of Dermatology. 2019.180(3):604-614. https://pubmed.ncbi.nlm.nih.gov/30307614	Aims: to determine - whether typical sunscreen use resulted in erythema, epidermal DNA damage and photoimmunosuppression during a sunny holiday - whether optimal sunscreen use inhibited erythema - whether erythema is a biomarker for photoimmunosuppression in a laboratory study. Study design: - 2 parts of the study: ○ "Laboratory" (not extracted as not relevant for this SR) ○ "holiday" (only information regarding randomized interventions extracted) - Pair-wise (room-sharing) randomized double-blind study - conducted in Playa de Fanabe, Tenerife (28° 080 N16° 730 W) - 20–27 March 2011 in two hotels - Control location: Łodz (51° 790 N19° 560 E) in central Poland (not relevant for this SR, as not randomized) Inclusion criteria: - Healthy volunteers, recruited in Lódz, Poland Exclusion criteria: - history of skin disease (including skin cancer), - taking photosensitizing medication, vitamin D supplements; - sunbed or holiday sun exposure within the previous 4 months. Intervention/Comparison: - shown only for group A and B (as they are the only randomized) - two sunscreens with SPF 15 according to ISO 24444:	Baseline characteristics: N= 79 total reported here: results Group A and B (others not randomized): n= 40 | | Group A | Group B | |---|---|---| | N | 20 | 20 | | Male | 8 | 11 | | Female | 12 | 11 | | Age (mean ± SD) | 33±7y | 38±7y | | Phototype II | 13 | 12 | | Phototype III | 7 | 8 | | Phototype IV | 0 | 0 | | Total means SED during intervention | 41.0 ± 13.6 | 38.6 ± 15.4 | | total hours outside | 39.5 ± 6.5 | 38.0 ± 6.4 | Quantitative measurements of redness - Post hoc tests: no erythemal differences between sunscreens A and B for any body site (P = 0.36–1.00) - progression of redness over the intervention period by different body parts is shown in the following figure (consider red and blue line only) Average sunscreen application thickness (mg/cm²):

Referenz	Studiencharakteristika	Ergebnisse
	○ Sunscreen A: mean ±SD in vivo SPF of 18.9 ± 2.8 with **high UVA protection, 5*** ▪ Butyl methoxydibenzoylmethane, octocrylene, ethylhexyl salicylate, bis-ethylhexyloxyphenol methoxyphenyl triazine, diethylhexyl butamido triazone and titanium dioxide ○ Sunscreen B: mean ±SD in vivo SPF of 17.7 ± 2.7 with **poor UVA protection**, **2*** ▪ Octocrylene, ethylhexyl salicylate, bis-ethylhexyloxyphenol methoxyphenyl triazine, diethylhexyl butamido triazone and titanium dioxide - 3 tubes daily (morning/middle of the day/afternoon) - Reapplication after swimming or physical activity - For 7 days <u>Outcome (only those reported):</u> Quantitative measurements of redness - on six body sites (buttock, forehead, shoulder, chest, outer upper arm and outer lower arm) - with a reflectance meter (UV Optimize Scientific 558; Chromo-Light, Espergaerde, Denmark) - day before the holiday and at the end of each day during the holiday. - Cave: no measurement after the last day due to timing of the return flight - measurements used to generate person- and body-site-specific time courses for erythema. Average sunscreen application thickness <u>Statistical methods:</u> - Comparisons before and after the holiday within the same individuals: paired t-tests - comparisons between sunscreens: unpaired t-tests - area under the curve (AUC) per body site: overall measure of individual cumulative erythema during the week. <u>Funding:</u> - The European Commission (EC): Impact of Climate and Environmental Factors on Personal Ultraviolet Radiation Exposure and Human Health (ICEPURE). - Medical University of Łodz, Poland - U.K. National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, U.K.	<table><tr><td></td><td>Group A (mean ± SD)</td><td>Group B (mean ± SD)</td></tr><tr><td>All</td><td>2.43 ± 0.55</td><td>2.44 ± 0.48</td></tr><tr><td>Male</td><td>2.26 ± 0.21</td><td>2.28 ± 0.49</td></tr><tr><td>Female</td><td>2.55 ± 0.68</td><td>2.67 ± 0.40</td></tr></table>
Granger C., et al. New Methodology to Evaluate Sunscreens Under Outdoor Conditions: A Double-Blind,	<u>Aim:</u> to assess its [water-based sun screen] efficacy in a setting with more extreme solar radiation, incorporating the full solar spectrum, and in which external temperatures and humidity could potentially exert an effect, to assess if the WBS maintained its protective capacity. <u>Study design:</u> - Double-Blind, Randomized Intra-Individual Study - in December (summer) 2018 in Mauritius	<u>Baseline characteristics</u>: - N=35, 16 men, 19 women - all Caucasian, - Mean age: 25±7 years (Min: 18y; Max: 44y), - distribution by phototype (type I: ITA > 55; type II: 42–55; type III: 29–41; type IV: 11–28).: ○ type I (an inclusion error): n= 1 ○ Type II: n= 12

Referenz	Studiencharakteristika	Ergebnisse
Randomized Intra-Individual Clinical Study of a Water-Based Broad-Spectrum SPF50+ Versus SPF15 (P3) and SPF50+. Dermatology and Therapy. 2019.9(3):589-599. https://pubmed.ncbi.nlm.nih.gov/31352672/	Inclusion criteria: - aged 18–45 years - healthy - skin phototype II - IV (based on individual typology angle (ITA) Measurements) Exclusion criteria: - pigmentation or photoaging disorders, excess hair or nevi, history of skin cancer, or intensive sun exposure within 3 months prior - concomitant medications judged by the investigator as having the potential to interfere with the study, namely anti-inflammatories and photosensitizing drugs (thiazides, quinolones, tetracyclines, fluoroquinolones, topical and oral vitamin A derivatives, psoralens, and amino levulinic acid derivatives) Intervention: - Five 12 cm^2 rectangular areas on volunteers' backs - 30 minutes before exposure: application of sunscreens at a dose of 2 mg/cm^2 - Non-investigtional areas were protected with hats, sunglasses, and UV protective t-shirts. - subjects lay face down outdoors, back exposed to the sun (a poolside location). - Sun exposure time: o Phototype II skin: 1 h o Phototype III or IV: 2 h - afterwards: no further sunlight exposure to the back was permitted until completion of study assessment (24 h) - Clinical erythema: scored at 1 and 2 h for safety purposes, and any areas with a score > 2 were to be covered. - Interventional product: o SPF50+ sunscreen (water-based sunscreen, WBS), UV-filter: Butyl methoxydibenzoylmethane, Ethylhexyl methoxycinnamate, Ethylhexyl triazone, Titanium dioxide - Comparator: o ISO2444:2010 reference standard sunscreen P3 (SPF 15), UV-filter: Butyl methoxydibenzoylmethane, Ethylhexyl methoxycinnamate, Phenylbenzimidazole sulfonic acid o Commercially available SPF50+ sunscreen (1), UV-filter: Butyl methoxydibenzoylmethane, Ethylhexyl triazone, Bisethylhexyloxyphenol methoxyphenyl triazine, Octocrylene, Ethylhexyl salicylate, Terephthalylidene dicamphor sulfonic acid o Commercially available SPF50+ sunscreen (2), UV-filter: Butyl methoxydibenzoylmethane, Bis-ethylhexyloxyphenol methoxyphenyl triazine, Titanium dioxide, Octocrylene. o untreated control Outcomes	o type III: n= 13 o type IV: n= 9 - mean hourly UV radiation was 103.47 mJ/cm^2. The minimum total UV radiation was 89.20 mJ/cm2 (1 h of exposure for type II subjects) and the maximum was 256.35 mJ/cm2 (2 h of exposure). - All participants were exposed to a very high UV index (≥8), and 30/35 participants were exposed to an extreme UV index (≥11). 6-point clinical erythema score at 24 h after UV exposure **Absolute clinical erythema score at 24h** unprotected: Mean ± SD: 3.0±1.0; Median (Min; Max): 3.0 (0; 4) WBS: Mean ± SD: 0.6±1.0; Median (Min; Max): 0.0 (0; 4) SPF15 (P3): Mean ± SD: 1.2±1.1; Median (Min; Max): 1.0 (0; 4) SPF50+ (1): Mean ± SD: 0.3±0.8; Median (Min; Max): 0.0 (0; 4) SPF50+(2): Mean ± SD: 0.5±0.8; Median (Min; Max): 0.0 (0; 3) **Percentage difference in erythema vs. unprotected area at 24h** WBS: Mean ± SD: -81.0±29.6; Median (Min; Max): -100 (-100; 0) SPF15 (P3): Mean ± SD: -61.0±33.1; Median (Min; Max): -66.7 (-100; 0) SPF50+ (1): Mean ± SD: -88.6±26.7; Median (Min; Max): -100 (-100; 0) SPF50+(2): Mean ± SD: -80.5±40.1; Median (Min; Max): -100 (-100; 100) **Number of patients with erythema score ≥ 2** unprotected: n/N (%): 31/35 (88,57%) WBS: n/N (%): 7/35 (20%) SPF15 (P3): n/N (%): 13/35 (37,14%) SPF50+ (1): n/N (%): 3/35 (8,57%) SPF50+(2): n/N (%): 4/35 (11,43%) - Mean difference after 24h absolute clinical erythema score: o WBS vs. unprotected: -2.371 (p<0.001) o WBS vs. SPF 15: -0,600 (p<0.001) o WBS vs. SPF50+ (1): +0.286 (p=0.302) o WBS vs. SPF 50+ (2): -0.143 (p=0.977) - Mean percentage difference versus unprotected skin in clinical erythema score: o WBS and SPF15 control: - 20.000 (P<0.001) o WBS and SPF50+ (1): +7.619 (P = 0.381) o WBS and SPF50+ (2): - 0.476 (P = 0.999) Colorimetry parameters: - Difference in mean absolute a* values (redness) at 24 h (higher values indicating redder skin) o WBS (11.38 ± 3.25) vs. unprotected area: (17.59 ± 3.37) (P <0.001) o WBS (11.38 ± 3.25) vs. SPF15 (12.42 ± 3.60); difference was not statistically significant. o Mean and SD of colorometrie for SPF 50+ (1) and SPF50+ (2) not reported - Mean percentage differences from unprotected skin: o WBS (-34.51% ± 17.46%) vs. SPF15 (- 29.10% ± 16.89%) (P =0.011),

Referenz	Studiencharakteristika	Ergebnisse
	6-point clinical erythema score at 24 h after UV exposure - 0 = no erythema; 1 = equivocal reaction, slight, barely perceptible erythema (not clearly defined); 2 = clearly visible erythema with well-defined borders; 3 = moderate erythema; 4 = severe erythema; 5 = very severe, erythema with blistering - at baseline and at 24 h was made - by a trained technician under the supervision of a certified dermatologist Colorimetry parameters: - a* (indicative of redness, higher values indicating redder skin) - L* (indicative of pigmentation, lower values indicating greater pigmentation) (not reported in SR) - ITA (individual typology angle, calculated according to the following formula: {arctan [(L* - 50)/b*]} 9 180/p) - Chroma Meter CR400 (Konica Minolta, Inc., Tokyo, Japan) - mean of 3 readings Tolerance and safety: - after a single application of the products, assessed by a technician under the supervision of a certified dermatologist with experience in skin tolerance testing at 1, 2, and 24 h. Statistical methods - performed as univariate ANOVA with ''product'' as the fixed factor and ''subject'' as the random factor followed by Tukey's procedure for pairwise comparisons. - conducted on rank transformed data whenever the Shapiro–Wilk test (at 1%) indicated that the assumption of normality was not met. Funding: Isdin	○ not significantly different to either of the SPF50+ controls (-36.95% ± 18.76% and -36.50% ±20.58%, respectively) ○ Mean-%-difference of colorometrie for unprotected area not reported
Williams J. D., et al. SPF 100+ sunscreen is more protective against sunburn than SPF 50+ in actual use: Results of a randomized, double-blind, split-face, natural sunlight exposure clinical trial. Journal of the American Academy of Dermatology.	Aim: To compare the sunburn protection provided by SPF 100+ and SPF 50+ sunscreen in conditions of actual use. Study design: - randomized, double-blind, split-face clinical trial - March 21, 2016 - during normal recreational skiing/ snowboarding - in Vail, Colorado Inclusion criteria: - Healthy men and women - Fitzpatrick skin types I to III, - ≥18 years of age Exclusion criteria: - skin disease, - use of sun-sensitizing medications (eg, tetracyclines, antifungals, certain diuretics), - allergies to topical skin care products (including sunscreens),	Baseline characteristics: n=199 randomised and analysed | | Left SPF 50+/right SPF 100+ | Left SPF 100+/right SPF 50+ | |---|---|---| | N | 99 | 100 | | Male | 61 (61.6%) | 54 (54%) | | Female | 38 (38.4%) | 46 (46%) | | Age (mean ± SD) | 36.9±16.40 | 38±16.22 | | Skin type I | 14 (14.1%) | 18 (18.0 %) | | Skin type II | 71 (71.7%) | 75 (75.0 %) | | Skin type III | 14 (14.1%) | 7 (7.9 %) | | White | 95 (96.0%) | 98 (98.0%) | | Asian | 2 (2.0 %) | 0 | | Other | 1 (1.0%) | 0 |

Referenz	Studiencharakteristika	Ergebnisse
2018.78(5):902-910.e2 https://pubmed.ncbi.nlm.nih.gov/29291958	- pre-existing sunburn (baseline erythema score >0.5). Interventions: - Neutrogena Ultra Sheer Dry-Touch Sunscreen, broad-spectrum SPF 100+ (Johnson & Johnson Consumer Inc) (containing avobenzone 3%, homosalate 15%, octisalate 5%, octocrylene 10%, and oxybenzone 6%) - Banana Boat Sport Performance broad-spectrum SPF 50+ (Edgewell Personal Care Brands LLC) (containing avobenzone 3%, homosalate 10%, and octocrylene 6%) - application (face and neck) as normally for outdoor activities - hand cleaning to avoid cross-contamination - unrestricted reapplication - Sun exposure diary Outcomes: - board-certified dermatologist during morning following exposure period Primary: Bilateral comparison of sunburn between areas (left/right sides) - condensed two-side difference scale o L1: left side was noticeably more sunburned than their right side, o 0: no difference in sunburn between sides o R1: right side was noticeably more sunburned than their left side Secondary: 5-point (including half-point grades) erythema score determined for each treatment area - 0= no burn, 1= possible burn, 2= defined redness, 3= severe sunburn, 4= edema and blisters product dosage (dispensed in mg/cm2) derived by simplified body surface area calculation Statistical methods: Primary outcome: - Fisher's exact test on the side-by-side score between treatment randomization groups. - The 0 outcomes (no difference) were excluded from the analysis. Secondary outcome: - exact Wilcoxon rank sum test Funding: Johnson and Johnson	<table><tr><td>Missing</td><td>1 (1.0%)</td><td>2 (2.0 %)</td></tr></table> - average exposure duration: 6.1 ± 1.3 hours. - Average cumulative unweighted exposure doses over the study period: o UVA (320-400 nm): 54.9 ± 11.8 o UVB (290-320 nm): 1.0 ± 0.22 J/cm^2 Bilateral comparison of sunburn between treatment areas (left and right sides) - Overall distribution of comparison scores: o More sunburned on SPF50+ side: 55.3% o no difference: 39.7% o more sunburned on SPF100+ side: 5.0% *(methodological comment: Due to the use Fisher's exact test on the side-by-side score between treatment randomization groups rather than a Binomal test, no reporting of significance test results)* - distribution with which the SPF 50+ or SPF 100+ protected side of the face was evaluated to be more sunburned was not observed to relate to: o more frequent product reapplication nor o Fitzpatrick skin type groups 5-point (including half-point grades) erythema score determined for each treatment area, - postexposure erythema score ≥ 1 on the: o SPF 50+ protected side: 40.7% (81/199) o SPF 100+ protected side: 13.6% (27/199). - Mean increase in postexposure erythema score was significantly lower on the SPF 100+ protected side than on the SPF 50+ protected side of the face (0.14 ± 0.31 vs 0.330 ± 0.44 ($p < 0.001$) Amount of sunscreen applied: - Average: o SPF 50+: 1.15 ± 1.76 g o SPF 100+: 1.09 ± 1.62 g - application densities: o SPF 50+: 1.1 ± 1.3 mg/cm2 o SPF 100+: 1.0 ± 0.98 mg/cm2 - average number of reapplications o both test products: 1.1
Ou-Yang H. Sun protection by beach umbrella vs sunscreen with a high sun protection factorl	Aim: to compare the sunburn protection effects of a beach umbrella vs. a high-SPF sunscreen side by side in a beach setting under actual use conditions. Study design: - single-center, evaluator-blinded, randomized clinical - from August 13 to 15, 2014,	Baseline characteristics: - N= 92, N=81 completed and analysed - Age: mean [SD] 41 [16] y - 25 male, 56 female - Fitzpatrick skin types I (n = 1), II (n = 42), III (n = 38)

Referenz	Studiencharakteristika	Ergebnisse
a randomized clinical trial. JAMA Dermatology. 01 Mar 2017;153(3):304-308. 28114650. https://pubmed.ncbi.nlm.nih.gov/28114650	- in Lake Lewisville, Texas (altitude, 159 m above sea level) Inclusion criteria: - Males/females, at least 18 years old, generally in good health - Fitzpatrick Skin Types I-III Exclusion criteria (see study protocol for full list): - history of skin conditions (e.g phototoxic and photoallergic reactions, that could interfere with the study were excluded) - sunburn, suntan, scars, tattoos, active dermal lesions, dysplastic nevi etc. at baseline - systemic or topical medication known to alter responses to UV radiation Intervention: - Sunscreen lotion with an SPF of 100+ (Neutrogena Ultra Sheer SPF 100+, Neutrogena Corp), UV-filter: 3% Avobenzone, 15% Homosalate, 5% Octisalate, 10% Octocrylene, 6% Oxybenzone) - preweighed tubes; application to exposed areas 15 min before exposure - reapplication of sunscreen at least every 2 hours or as needed - permission for shaded resting time for ≤ 30 minutes Comparison: - commercially available beach umbrella (JGR Copa LLC; roundshaped, 203 cm diameter, and 190 cm high) - instructed to stay under the umbrella without wearing clothes that could block the evaluated areas during the duration of the study. - permission to leave for ≤ 30 minutes after covering up. - Positioning under umbrella: monitored and adjusted as the solar angle changed to minimize any direct exposure of UV rays to evaluated areas. Both groups: - no water activities - exposure time: 3½ hours between 10 AM and 2 PM - placed at least 33 m away from the water. - Sun exposure was avoided after the conclusion of the study until evaluation. Outcomes: 5-point clinically assessed erythema score - accumulated to global sunburn score for each participant by averaging 7 exposed sites (0= no sunburn; 1= possible sunburn, not clearly defined; 2=defined redness clearly caused by UV rays; 3= severe sunburn with pronounced redness; 4=edema and/or blisters), - clinical evaluation for sunburn by a clinician at 7 body parts (face, upper chest, back of neck, right arm, left arm, right leg, left leg) at 22 to 24 hours following sun exposure sunscreen use and time absent - analyzed based on tube weight and diaries Statistical methods:	- Total accumulated dose of UV radiation: > 15 minimal erythema doses. Sunscreen application: - initial application: mean (SD) of 15.8 (8.6) g of sunscreen (range, 4.5-41.5 g) to exposed skin sites, corresponding to a density of approximately 1 mg/cm^2 - Reapplication: mean (SD) of 2.3 (1.1) times (range, 0-4) with a mean (SD) total of 29.6 (16.6) g of sunscreen (range, 9.1-72.9 g), or approximately 2 mg/cm2. postexposure global erythema score (22-24h) - Comparison of means of global postexposure erythema scores: o Mean: sunscreen (0.05) vs. umbrella (0.75), p<0.001 o Median (IQR): sunscreen 0 (0.05) vs. umbrella 0,57 (0.96) - no of participants with increased global erythema score: o sunscreen group: n= 10 (25%) o umbrella group: n= 32 (78%) - increase mean in global erythema scores from baseline o umbrella group, 0.75 vs 0; p< .001 o sunscreen group, 0.05 vs 0; p= .002 - postexposure erythema score of every single area: see table 2 in full text o Participants in the umbrella group had a significant increase in sunburn scores from baseline for all of the body sites examined. (p < 0,001) o Participants in the sunscreen group had significant increase in sunburn scores vs baseline only for the face (0.18 vs 0; P = .02). - total number of sunburned areas: o umbrella group: n= 142 o sunscreen group: n= 17 - sunburn score of ≥ 2: o umbrella group: n= 17 (in ≥1 sites) o sunscreen group: n= 2 (in facial area)

Referenz	Studiencharakteristika	Ergebnisse
	- Wilcoxon signed rank test (preexposure and postexposure scores) - Wilcoxon rank sum test (Intergroup data were compared). Funding: Johnson & Johnson	
Russak JE. A comparison of sunburn protection of high-sun protection factor (SPF) sunscreens: SPF 85 sunscreen is significantly more protective than SPF 50. J Am Acad Dermatol. Feb 2010;62(2):348-9.	Aim: to evaluate whether a statistically significant difference exists between the sunburn protective effects of a SPF 50 sunscreen versus a SPF 85 formulation. Study design: - double-blind, randomized, split-face clinical study - January 2008 (bright and sunny day) - Vail, CO, at an altitude of 2500 to 3000 meters above sea level. Inclusion criteria: - Not reported Intervention: - SPF 85 sunscreens (avobenzone, homosalate, oxybenzone, octocrylene, and octisalate) Comparison: - SPF 50 sunscreens (avobenzone, homosalate, oxybenzone, octocrylene, and octisalate) Valid for both sides: - Application under investigator observation - Reapplication during the day not permitted Outcomes: - Dichotomous variable (sunburned / not sunburned): criteria for decision not described - Skin evaluation the morning after sun exposure - dermatologist blinded for application sides - posttest photography - self assessment Statistical methods: - Fisher exact test Funding: Johnson and Johnson	Baseline-Characteristics: - 58 included - 56 analysed - Age: not reported - average outdoor exposure time: 5 h Dermatologist grading of erythema (morning after a 5h sun exposure): - SPF 85: 1/56 sides sunburned - SPF 50: 8/56 sides sunburned p-value not reported as Binomial test would have been correct to analyse a paired sample

2.4. Evidenztabellle Recherche Effektivität deutsches Hautkrebsscreening

Anmerkung: Die Recherche wurde ohne Begrenzung auf bestimmte Studientypen durchgeführt. Eine Vielzahl der eingeschlossenen Studien basiert daher auf Querschnittsdaten bzw. ökologischen Auswertungen, bei denen per se ein kritisch hohes Verzerrungsrisiko angenommen werden muss. In Ermangelung höherwertiger Studien zur Effektivität des deutschen Hautkrebs-Screenings, hat die Leitliniengruppe beschlossen, dennoch Studien mit kritisch hohem Verzerrungsrisiko zu berücksichtigen, was bei der weiteren Bearbeitung und Interpretation berücksichtigt werden muss.

Aus diesem Grund ist die folgende Evidenztabelle der inkludierten Publikationen nach Qualität und Höhe des Verzerrungsrisikos gegliedert:

1. Publikationen mit hohem/sehr hohem Verzerrungsrisiko bzw. geringer Qualität

Reference	Quality	Characteristics I	Characteristics II	Comment
Henrikson, N. B., et al. (2023). "Skin Cancer Screening: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force." Jama 329(15): 1296-1307. https://pubmed.ncbi.nlm.nih.gov/37071090/	**AMSTAR-II** Low quality Systematic review	**Aim** - To systematically review the benefits and harms of screening for skin cancer to inform the US Preventive Services Task Force **Databases/ search period:** - MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from June 1, 2015, through January 7, 2022; surveillance through December 16, 2022 **Population** - asymptomatic populations 15 years - or older **Further inclusion criteria** - Primary care–relevant settings In-person or virtual settings Countries categorized as “Very High” on the 2019 Human Development Index	**Relevant exclusion criteria** - Restricted to publication in English **Type of studies** - Fair- and good-quality studies (rated with USPTF quality criteria) - KQ1, KQ2: Randomized, controlled trials; controlled clinical trials; nonrandomized studies with a contemporaneous control **Outcomes** - Morbidity; mortality; skin cancer stage, precursor lesions, or lesion thickness at detection; harms of screening	
	Ergebnisse			

	Characteristics of included studies
	- In total: 29 articles included comprising 3 studies from the previous review and 17 new studies;
	- Studies of interest: German SCS and not yet include in guideline due to prior review
	  ○ KQ1: Two studies
	  ○ KQ2: One studies
	- **Quality of the evidence:** USPSTF design-specific quality criteria scored 9 rated as good to fair
	Results
	KQ1: What is the effectiveness of routine skin cancer screening with visual skin examination by clinicians in reducing skin cancer morbidity and mortality or all-cause mortality? (extracted only results from German analyses that are not already included through previous guideline review):			

- **SCREEN: Eisemann (2018):** Comparing SCREEN participants (Schleswig-Holstein, n=360.196, with person years analyzed 1.981.078) with routine skin cancer screening offered through SCREEN study 2003–2004 with Saarland (n=approx. 1 mio, with person years analyzed 5.763.767) with no routine skin cancer screening until 2008 in follow up time July 2003 to December 2008. Incident melanoma cases: 1.472 vs 1.026, observed deaths: 31 vs. 11, observed mortality rate 1.56 vs. 1.93, expected deaths adjusted for age, sew and population size: 52,7 vs. 52,7; standardized mortality rate age and sex adjusted: 0.59 (0.40, 0.83) vs. 0.59 (0.40, 0.83). (USPTF quality criteria: fair)
- **Statutory SCS: Datzmann (2022)**: Analyses of individual-level data, included enrollees in a health insurance plan that administers German national statutory health insurance. The sample, who were enrollees 35 years or older between 2010-2016 (n = 1 431 327), had a mean age of 63.9 years and 55.7% were female; race, ethnicity, and skin type were not reported. Data analyzed from persons with incident melanoma diagnosed during 2013-2016 with no history of melanoma in the previous 3 years (n = 2475). People with documented skin cancer screening as identified through billing codes in the 2 years before diagnosis were considered to have received screening. The observation period was 4 years. Of 325 melanoma deaths, a higher proportion was observed in the unscreened group compared with the screened group (154 deaths, 22.8% of the unscreened group; 171 deaths, 9.5% of the screened group; unadjusted hazard ratio [HR], 0.37 [95% CI, 0.30-0.46]; P < .05) (see Table 2 in review). On adjustment for age, sex, comorbidity, health-seeking behavior (estimated by receipt of flu vaccine), personal history of melanoma, and stage categories (estimated by documented melanoma metastasis or receipt of systemic anticancer therapy): adjusted HR, 0.62 [95% CI, 0.48-0.80]; P < .05). Sensitivity analyses to assess lead time bias: unadjusted HR, 0.50 [95% CI not reported]; P < .05) and adjusted HR, 0.75 [95% CI not reported]; not significant). (USPTF quality criteria: good)

KQ2: Does routine skin cancer screening lead to higher rates of detection of precancerous lesions or earlier stage skin cancer compared to usual care (for example, lesion-directed skin examination)?

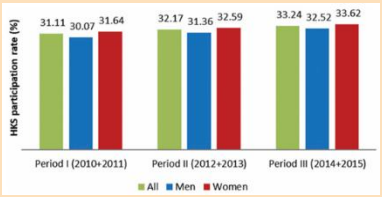
- **Statutory SCS 2013–2016: Krensel (2021):**
  Non randomized study with enrollees in health insurance company BARMER; age 35 years and older with incident diagnosis of cutaneous melanoma, KC, and preliminary stages of skin cancer who had undergone routine skin cancer screening within the quarter of the year in which the excision took place or the previous quarter
  Outcomes:
  - Skin Cancer or Precursor Lesion Detection Rates, Screened vs. Unscreened: Melanoma 815 vs. 721; NMSC: 5,378 vs. 5,466 (between group differences not reported)
  - Stage or Thickness at Melanoma or KC Detection, Screened vs. No Routine Skin Cancer Screening:

Study, year Quality Country	Population description	Type of skin cancer	Cases detected, N	Stage or thickness at detection*	Routine skin cancer screening n (% of cases); 95% CI	No routine skin cancer screening n (% of cases); 95% CI	Between group difference
Krensel, 2020[133]† Fair Germany	German national skin cancer screening program 2013-2016	Melanoma	1,536	In situ	10 (1.23); NR	In situ: 10 (1.43); NR	Screening – no screening (%): 0 (-0.20)
				Stage I/II:	799 (98.04); NR	707 (98.09); NR	Screening – no screening (%): 92 (-0.05)
				Stage III/IV:	6 (0.74); NR	3 (0.48); NR	Screening – no screening (%): 3 (0.26)
		KC	10,844	In situ	4 (0.07); NR	10 (0.18); NR	Screening – no screening (%): -6 (-0.10)
				Stage I/II	5373 (99.91); NR	5454 (99.77); NR	Screening – no screening (%): -81 (0.13)
				Stage III/IV	1 (0.02); NR	3 (0.05); NR	Screening – no screening (%): -2 (-0.03)

* Author-reported stage/thickness data categories.
† Uses TNM / AJCC staging system to report on melanoma and KC stage at detection. This information was calculated using an algorithm used in other publications for estimating stage from claims data.
‡ Estimated from the graphic representation of confidence intervals (point estimates of confidence intervals not reported).
§ Cases excluded due to missing information.
‖ Adjusted for age, sex, race/ethnicity, and insurance status.

(USPTF quality criteria: fair)

Reference	Quality	Characteristics I	Results	Comment
Garbe C, Augustin M, Augustin J, et al. (2023).	**ROBINS-I** Serious risk of bias	**Aim:** - developing and testing different evaluation approaches of the SCS using secondary data **Study design and data sources:**	**SCS participation rate:**	

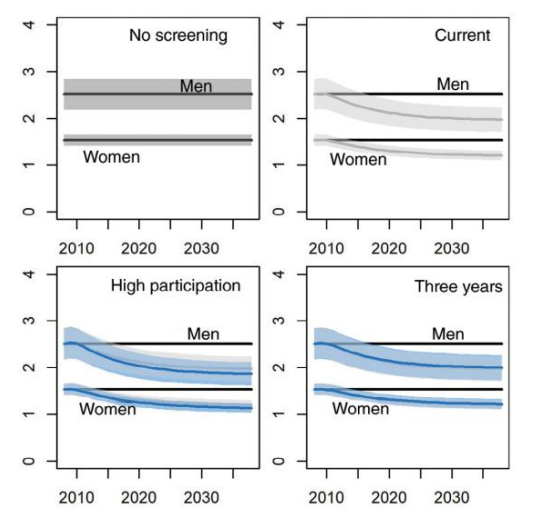
"Evaluation of skin cancer screening in Germany–participation, tumor detection and interval tumors based on SHI data." JDDG:Journal der Deutschen Dermatologischen Gesellschaft. 21(5):3–11. https://pubmed.ncbi.nlm.nih.gov/38063281/	Non-randomised study	- retrospective, healthcare-related secondary data analysis - calculation of SCS participation rates related to two-year periods (Period I (2010 and 2011), Period II (2012 and 2013), and Period III (2014 and 2015)) - SCS identification by GOPs 01745 and 01746 - Coded: D03, D04, C43, C44 **Population:** - DAK-G insured persons at least 35 years old in 2010 and continuously insured from 31 December 2010 until 31 December 2015 - randomly anonymized 40% sample (n = 2,319,584; 61% women, average age 47.4 years) **Tumordetection rates I and II:** - tumor diagnosis during SCS or subsequent quarter between 2012 and 2015 - diagnosis-free for eight quarters prior to the SC diagnosis quarter - validation of SC diagnoses via excision (in the SC diagnosis quarter or one quarter before) - persons with a tumor detected in the SCS related to 1. all SCS participants with the last SCS between 2012 and 2015 (tumor detection rate I) and 2. all insured persons with the last incisional SCS diagnosis between 2012 and2015 (tumor detection rate II) **Interval tumors:** - cancer diagnosis occurred after SCS without findings and before next SCS (but after a maximum of eight quarters) - last SCS without findings performed between 2012 and 2013 - comparison of interval tumor rate with the rate of incident skin tumor diagnoses between 2012 and 2015 of a comparison cohort without SCS participation in the entire observation period **Statistics:** - estimates of incidences and SCS participation rates as percentages (with 95% confidence intervals) - Relative frequencies (in percent) for categorical variables and means and standard deviations for continuous variables - T-tests or chi-square tests to calculate statistical group differences analyses calculated with SAS Version 9.4 German (SASInstituteInc. Cary,NC27513-2414,USA).	- 2/3 women [852,511] and 1/3 men [438,214]  **Tumor detection rate I:** - last SCS between 2012 and 2015 (673,546 persons (33.2% men and 66.8% women) - excision with an incisional SCS diagnosis in 4.1% of participants (women 4.9%, men (3.7%) - excision in connection with incidental HC diagnosis in 8.1% screened by dermatologist **Tumor detection rate II:** - incisional SCS diagnosis with previous excision between 2012 and 2015 (55,375 insured persons (39.3% [21,774] men and 60.7% [33,601] women) - previous SCS in 50.1% **Type of diagnosis** / **Total** / **Dermatologist** / **Family doctor** *Insured with SC and SCS* / *Percent** / *Insured with SC and SCS* / *Percent (%*)* / *95% CI* / *Insured with SC and SCS* / *Percent (%*)* / *95% CI* Melanoma in situ: 430 / 1.55 / 368 / 85.58 (1.56) / 82.26 / 88.90 / 29 / 6.74 (1.05) / 4.37 / 9.11 Carcinoma in situ: 7,463 / 26.91 / 6,373 / 85.39 (27.03) / 84.59 / 86.20 / 744 / 9.97 (27.04) / 9.29 / 10.65 Melanoma in situ and carcinoma in situ: 50 / 0.18 / 47 / 94.00 (0.20) / 83.40 / 98.70 / 3 / 6.00 (0.11) / 1.26 / 16.55 MM: 2,142 / 7.72 / 1,818 / 84.87 (7.71) / 83.36 / 86.39 / 193 / 7.80 (7.02) / 7.80 / 10.22 NMSC: 17,244 / 62.18 / 14,639 / 84.89 (62.08) / 84.36 / 85.43 / 1,745 / 9.67 (63.43) / 9.67 / 10.57 MM and NMSC: 404 / 1.46 / 336 / 83.17 (1.42) / 79.52 / 86.82 / 37 / 6.35 (1.34) / 6.35 / 11.97 Total: 27,733 / 100.00 / 23,581 / 85.03 (100.00) / 84.61 / 85.45 / 2,751 / 9.57 (100.00) / 9.57 / 10.27 *Abbr.:* SCS, Skin cancer screening; SC, incidental skin cancer diagnosis with previous excision; CI, confidence interval Other specialist groups are not included in this presentation due to the low case numbers. *Share related to specialist group **Type of diagnosis** / **Interval carcinomas** (*Insured*, *Percent*) / **Comparison cohort (expected incidence)** (*Insured*, *Percent*) / **Observed/expected incidences** (*Ratio*, *95% CI*) Melanoma in situ: 93 / 1.42 / 71 / 0.92 / 1.31 / 1.06 / 1.60 Carcinoma in situ: 2,038 / 31.05 / 2,004 / 26.02 / 1.02 / 0.97 / 1.06 Melanoma in situ and carcinoma in situ: 4 / 0.06 / 6 / 0.08 / 0.67 / 0.18 / 1.71 MM: 394 / 6.00 / 369 / 4.79 / 1.07 / 0.96 / 1.18 NMSC: 3,978 / 60.61 / 5,168 / 67.11 / 0.77 / 0.75 / 0.79 MM and NMSC: 56 / 0.85 / 83 / 1.08 / 0.67 / 0.51 / 0.88 Total: 6,563 / 100.00 / 7,701 / 100.00 / 0.85 / 0.83 / 0.87 *Abbr.:* CI, confidence interval; MM, malignant melanoma; NMSC, non-melanocytic skin tumor **Interval tumors:** - SCS without findings and no further SCS in the following eight quarters in period II (449,172 insured persons) - of these, 1.5% (6,563) received a SC diagnosis (interval tumor) coded in the following eight follow-up quarters (1.8% [2,600] men and 1.3% [3,963] women) **Sensitivity of SCS:**	

			- comparison interval tumors (observed incidence) and incidence in persons without SCS (expected incidence) → fewer SC diagnoses occurred after an inconspicuous SCS than expected (ratio 0.9 (95%CI: 0.8–0.9) - positive effects in NMSC (0.8), MM and NMSC (0.7) - Negative effects in melanoma in situ (1.3), carcinoma in situ (1.0) and MM (1.0) - The program sensitivity for SCS was 67.1%. 67.1% of persons with SCS had a SCS diagnosis immediately (within the SCS quarter or one quarter after) (tumor detection) and 32.9% had a SCS diagnosis within eight quarters after the SCS (interval tumor).	

2. Publikationen mit kritisch hohem Verzerrungsrisiko

Reference	Quality	Characteristics I	Results	Comment
Augustin, J., et al. (2024). "Skin cancer in Germany: Characterising screening, prevalence and mortality from a spatial perspective." PLoS One 19(7): e0305915 https://pubmed.ncbi.nlm.nih.gov/38968293/	n.a. Critically low Ecological study	**Aim:** to characterise the association between screening, prevalence and mortality of skin cancer in Germany considering the spatial distribution **Study design and data sources:** cross-sectional ecological study conducted for the years 2011 to 2015 using a) nationwide outpatient billing data of the National Association of SHI Physicians (Kassenärztliche Bundesvereinigung, KBV), b) cause-of-death statistics of the statistical offices of the federal states (Statistische Landesa¨mter, StaLa) and c) data on socioeconomic and -demographic characteristics of counties from the Indicators and Maps of Spatial and Urban Development (Indikatoren und Karten zur Raum- und Stadtentwicklung, INKAR) **Outcome:** screening rates, skin cancer prevalence, skin cancer mortality in German regions (countries) considering six scenarios: **Statistical methods:** mean values with standard deviation, expected values, probability maps, logistic regression for scenarios with at least 5% overlapping rates considering different social determinants (e.g. unemployment rate, distance to dermatologist) rate of overlapping counties within the six scenarios: dividing the number of counties meeting both criteria for a scenario by the sum of counties meeting only one of the two criteria	Annual average of N = 1,290,213 skin cancer diagnoses and N = 7,534,581 skin cancer screenings were documented nationwide in the SHI system in the years 2011 to 2015 Scenario A.I: Overlap of 69 out of 321 significant counties (21.5%) with high screening and high prevalence. Scenario A.II: overlap of 113 of 408 counties (27.7%) with low screening and low prevalence. Scenario B.II: overlap of low screening rate and high mortality rate (19 out of 256 counties (7.4%)) Scenario C.I: Overlap of high mortality–high prevalence: 23 out of 201 (11.4%), all other scenario: Overlap <5%.	

Scenario	I	II
A	High screening–high prevalence	Low screening–low prevalence
B	High screening–low mortality	Low screening–high mortality
C	High mortality–high prevalence	Low mortality–low prevalence

Reference	Quality	Characteristics I	Results	Comment
Baltus, H., et al. (2025). "Evaluation of skin cancer screening in Germany - a Microsimulation." J Dtsch Dermatol Ges 23(1): 19-27. https://pubmed.ncbi.nlm.nih.gov/39520317/	n.a. Critically low Insilco study	**Aim:** - to simulate different screening scenarios: no screening, current screening, three years screening, high participation screening - to identify effect of the different scenarios on incidence and mortality **Study design and data sources:** - microsimulation model for MM, SCC, and BCC was programmed and validated separately by sex on skin cancer-specific mortality data. - Updated and expanded version of an established model for early detection of MM considering also SCC and BCC including in-situ forms - Life expectancy data from Federal Statistical Office of Germany - data on tumor growth and other parameters via literature research - data on costs and regularity of followup from medical billing codes and the relevant guidelines - Treatment costs from billing data supplied by DAK-Gesundheit - screening and excision costs from the German Physicians' Fee Schedule - Age and tumor stage (T stage) at diagnosis as well as survival times – depending on age, sex, and T stage –from data provided by the Center for Cancer Registry Data, or they were estimated. - Comparison with observational data on incidence and mortality of MM in Germany from the abovementioned selected cancer registries (2006–2016, incidence), and the "Causes of Death" statistics from GBE-Bund (2007–2017, mortality). **Analytical path:** - Four intervention scenarios: • No Screening: No skin cancer screening at all (Natural History model). • Current: Simulation of the currently practiced skin cancer screening program in Germany, with 30% participation in two years and an interval of at least two years between the examinations. • Three years: The parameters from the Current scenario remain the same, but the interval between examinations is at least three years. • High Participation: parameters from Current scenario with a participation rate of ten more percentage points in people who participate sometimes.	**Model validation:** - good validity of the MM partial model - moderate validity of the SCC partial model **Comparison of screening scenarios:**  **FIGURE 2** Simulated time courses of melanoma mortality for all four screening scenarios. *Abbr.*: ASR, age-standardized rate **Comparison of observed and simulated incidence and mortality rates for MM:** Incidence**:** increase in incidences after introduction of skin cancer screening predicted by the simulation model and in similar form in observed data. But predicted decrease in the following years can not be observed. Mortality: continuous decrease in mortality from 2y after initiation os screening and stabilizing after about 25 years at level of 1.53 per 100,000 in women and 2.51 in men predicted. Observed mortality shows a trend in the opposite direction which only reaches the original level again after about ten years.	

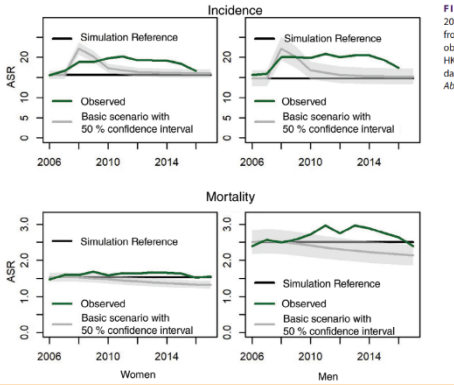
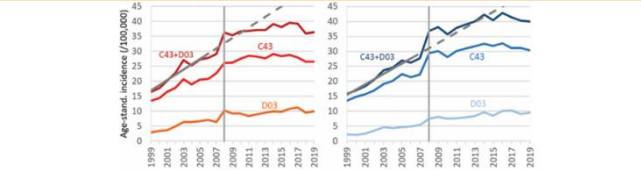
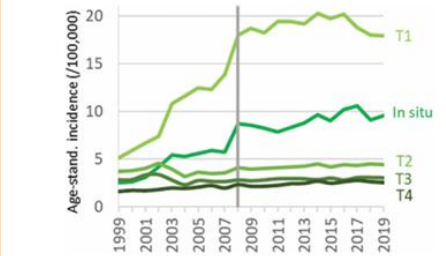
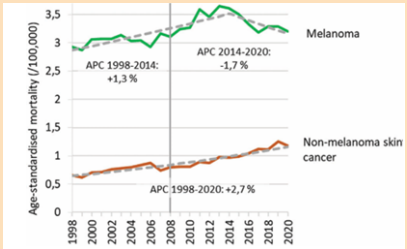


FIGURE 3 Melanoma incidence from 2006 to 2016 and melanoma mortality from 2007 to 2017 from the simulation scenario *Current* and from observations of the regions used for calibration; HKS 2008 was introduced both in the observed data and in the simulation.
Abbr.: ASR, age-standardized rate

Reference	Quality	Characteristics I	Results	Comment
Hübner J, Baltus H, Eisemann N, et al. (2023). „Evaluation of early skin cancer detection in Germany with cancer registry data challenges, solutions and current trends." JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 21(5):13–20. https://pubmed.ncbi.nlm.n	n.a. Critically low Ecological study	**Aim:** - to investigate what extent data from the German epidemiological cancer registries are suitable to contribute to the evaluation of skin cancer screening and report these evaluation results **Study design and data sources:** - anonymized individual case data on new skin cancer cases (ICD-10: C43, D03 and C44, D04 including TNM stage) by Centre for Cancer Registry Data (years 1999 - 2019) - skin cancer-related deaths (ICD-10: C43 and C44; years 1998–2020) according to the 5-year age group and sex from cause of death statistics of the Federal Statistical Office - population data to calculate sex-specific age-standardized rates from Federal Statistical Office **Completeness problems:** - Estimates of completeness of registration by RKI available until 2015 - missing data on tumor stage ➔ multiple imputation - five times imputation of melanoma dataset with R package "mice"13 in R 4.1.3 (R Core Team, Vienna, Austria) 14, results averaged **Data pools:** - Pool 1 (high validity): ➔ completeness over the years 2005–2015 is ≥95%. Each year must have a completeness of ≥ 90%(maximum one exception) - Pool 2 (limited validity): ➔ completeness over the years 2005–2015 is ≥80%. Each year must have a completeness of ≥ 70%(maximum one exception) - Pool 3 (severely limited validity):	- changes in distribution of T-stages by multiple imputation in pool 1 in the phase before SCS (2005/06) from 64% T1, 16% T2, 11% T3 and 8% T4 to 60%, 17%, 13% and 10% - no stage-specific evaluation performed for the N- and M-stages because of high proportion of missing values (46.7% and 44.5%) - proportion of missing data on localization around 9% **Total incidence** - increase of incidence rate for invasive and in situ melanoma for women and men from 2007 to 2008, screening-induced prevalence peak (Figure 3) - slight decrease in the incidence rate of invasive melanoma from 2016 onwards  FIGURE 3 Age-standardized incidence rate (per 100,000) for malignant melanoma (in situ, invasive and cumulative, pool 1 regions) for women (left) and men (right). The partly solid, partly dashed lines mark the trend between 1999 and 2006 with extrapolation (possible "zero effect line"). - percentage of overdiagnoses in invasive and in situ melanoma diagnoses in 2018/2019 (24% (women) and 34% (men)) - no stable incidence rates before introduction of SCS - between 1999 and 2006 respective rates approximately doubled → possible that this is a longer-term background trend, unaffected by the SCS, whose projection beyond 2006 represents a "zero effect line	

ih.gov/38063276		➔ completeness over the years 2005–2015 is ≥75%. Every year must have a completeness of ≥60% (no exception) (the incidence is higher the greater the completeness) **Calculation of incidence and mortality rates:** - age-standardized rates calculated for each year of the period studied (incidence:1999–2019, mortality:1998–2020) to capture developments in incidence and mortality independently of demographic change - age-specific incidence rates (20–34, 35–49, 50–64, ≥ 65 years) and age-standardized incidence rates by T stage (in situ, T1, T2, T3, T4) and location were calculated **Analysis:** - descriptive analyses of age-standardized melanoma incidence rates for trend changes that can be expected with the introduction of effective screening - before-after comparisons for Longer-term changes in incidence levels (difference between mean rates in 2005/2006 and 2018/19) join point analyses for age-standardized melanoma mortality rate (permutation test, maximum one join point) to calculate trends (annual percentage changes; APC) and points in time at which a trend changes	**Stage-specific incidence:** - increase in early stages in situ (D03) and T1 with introduction of SCS (Figure 5)  **FIGURE 5** Age-standardized incidence rate (per 100,000) for malignant melanoma by T stage (women and men, Pool 1 regions). - increase of incidence of 25% and 13% for T2 and T3 - increase of 20% for T4 **Mortality:** - decrease of melanoma mortality from 2014 onwards (2.7% per year) - increases of mortality from non-melanoma skin cancer 2.0% annually over the entire observation period  **FIGURE 7** Age-standardized mortality rate (per 100,000) for malignant melanoma (C43) and non-melanocytic skin cancer (C44) (women and men, all of Germany). The dashed lines mark the trends determined section by section using joinpoint regression analysis. APC: annual percentage change.	
Reference	**Quality**	**Characteristics I**	- **Results**	**Comment**
Stang, A. et al. (2022). **"The impossibility of mortality evaluation of skin cancer screening in**	**ROBINS-I** Critically low Case-Control-study	**Aim:** - to perform mortality evaluation of SCS in Germany using AOK data **Study design and data sources:** - case control study evaluating melanoma mortality - random sample of 450.000 AOK-insured individuals with cutaneous malignant melanoma (ICD 10:C43) in 2014/2015 - examination wether diagnosis C43 occurred first 2008-2015 **Cases:**	- 1037 melanoma death cases and 10370 numbers of controls included (matching of age, sex and place of residence) - no difference in Elixhauser comorbidity index between cases and controls - cumulative SCS prevalence in controls increased with increasing year of reference date (comparison cases and controls) - cumulative SCS prevalence among controls increased over calendar years (males and females, 2009: 13.5% and 12.5%; 2015: 52.1% and 55.1%)	

Germany based on health insurance data: a case control study" European Journal of Cancer, 173: 52-58. https://pubmed.ncbi.nlm.nih.gov/35863106/		- AOK-insured individuals 35 years and older - patients died in 2015-2016 - 1. interval between diagnosis and death at least one year - 2. interval between last melanoma diagnosis and death was 1 year or less - 3. no competing causes of death in 3 months before death **Controls**: - AOK- insured individuals who survived to the end of the year, the corresponding case died - ten controls for each case (matching criteria age, sex and date of cases death) - HKS history: o persons with billing code 01746 or 01732 considered as screened persons o comorbidity derived from Elixhauser comorbidity up to one year to reference date **Statistical methods:** - 1024 cases and 4095 controls calculated - comparison of age- and sex-specific SCS prevalences for 2009-2011 and 2012-2014 with published prevalence of the total of AOK-insured population - determination of expected number of melanoma deaths in 2014-2015 using sex- and age-specific nationwide melanoma mortality rates comparison of expected numbers of melanoma deaths with the numbers included in the study -	- comparison of SCS prevalence 3 and 24 months prior to reference date between cases and controls showed that SCS prevalence was markedly higher in cases than in controls at each age and sex stratum - overall, 36.4% (men) and 26.8% (women) billed for SCS in the 3 months before reference date at initial melanoma diagnosis - in contrast, cumulative SCS prevalence was already high in 2009 and did not show a monotonic increase over the years of diagnosis - first melanoma diagnosis already in 2009, about 1.5 years after the introduction of SCS in Germany, was already 57.4% and 38.0% in men and women Table 2 Skin cancer screening prevalence in relation to the year of diagnosis among 1037 skin melanoma deaths and in relation to the year of the pseudodiagnosis among 10,370 controls among General Local Health Insurance Fund ("Allgemeine Ortskrankenkasse, AOK") in Germany, 2014–2015 Year of (Pseudo) Diagnosis / Men / Cases / Controls / Women / Cases / Controls N n % N n % N n % N n % *Ever skin cancer screening (back to 2008)* 2009 68 39 57.4 680 92 13.5 71 27 38.0 710 89 12.5 2010 72 34 47.2 720 199 27.6 67 38 56.7 670 165 24.6 2011 56 33 58.9 560 192 34.3 63 28 44.4 630 197 31.3 2012 86 45 52.3 860 356 41.4 83 38 45.8 830 305 36.7 2013 104 62 59.6 1040 449 43.2 95 41 43.2 950 414 43.6 2014 116 66 56.9 1160 588 50.7 82 45 54.9 820 382 46.6 2015 39 21 53.8 390 203 52.1 35 20 57.1 350 193 55.1 *Skin cancer screening within the recent 24 months before date of diagnosis** 2009 68 39 57.4 680 92 13.5 71 27 38.0 710 89 12.5 2010 72 34 47.2 720 193 26.8 67 38 56.7 670 159 23.7 2011 56 32 57.1 560 158 28.2 63 25 39.7 630 153 24.3 2012 86 41 47.7 860 240 27.9 83 31 37.3 830 221 26.6 2013 104 52 50.0 1040 286 27.5 95 32 33.7 950 260 27.4 2014 116 59 50.9 1160 359 30.9 82 36 43.9 820 239 29.1 2015 39 16 41.0 390 112 28.7 35 10 28.6 350 112 32.0 *Skin cancer screening within the recent 3 months before date of diagnosis** 2009 68 31 45.6 680 33 4.9 71 21 29.6 710 23 3.2 2010 72 25 34.7 720 22 3.1 67 23 34.3 670 25 3.7 2011 56 25 44.6 560 21 3.8 63 17 27.0 630 25 4.0 2012 86 29 33.7 860 48 5.6 83 20 24.1 830 36 4.3 2013 104 36 34.6 1040 43 4.1 95 26 27.4 950 27 2.8 2014 116 37 31.9 1160 56 4.8 82 19 23.2 820 41 5.0 2015 39 14 35.9 390 12 3.1 35 7 20.0 350 15 4.3 *For controls, the pseudodiagnosis date were used; N: total number of cases or controls in the stratum; n: number of cases or controls in the stratum that had a positive screening history (back to 2008), the recent 24 months before diagnosis or the recent 3 months before diagnosis. - 224 of the 1037 melanoma deaths (21.6%) had at least one SCS billed in the 12 months after diagnosis, predominantly by dermatologists (171 of 224, 76.3%)	

Reference	Quality	Characteristics I	Results	Comment
Wolf S, Augustin M, Hagenström K, et al. (2023) "Evaluation of skin cancer screening in Germany–Spatiotemporal associations between skin cancer	n.a. Critically low Ecological study	**Aim:** - to investigate spatiotemporal associations between skin cancer screening and mortality **Study design and data sources:** - retrospective, longitudinal ecological study based on data from National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung, KBV) - 72.3 million statutory health insurance patients - EBM codes 01745 and 01746 - skin cancer mortality data from the cause-of-death statistics of the State Statistical Offices were used (ICD-10 codes C43 and C44) - variables from the Indicators and Maps of Spatial and Urban Development (Indikatoren und Karten zur Raum- und Stadtentwicklung, INKAR) used as independent variables to adjust confounders in the analysis	**Descriptive and spatial analyses:** - 7.246.904 early skin cancer diagnoses (EBM 01745: n = 3,797,548 and EBM 01746: n = 3,449,356) in 2011 - 4,421 deaths of skin cancer in 2011 - slight increase in screening and mortality to 7,790,533 (EBM 01745: n = 3,939,486 and EBM 01746: n = 3,851,047) and 4,712 deaths in 2015 - mean rate of skin cancer screening 10,201 (SD = 2,150) per 100,000 insured in 2011, and mortality was 5.62 (SD = 3.55) per 100,000 inhabitants at county level **Spaciotemporal cluster analyses:** - high clusters in Saxony, Hamburg and the south of North Rhine Westphalia - thin strip south-west to north-east of Germany - low clusters in north of Bavaria and Baden-Württemberg	

screening and skin cancer mortality based on ambulatory claims data." JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 21(5):22–31. https://pubmed.ncbi.nlm.nih.gov/38063275		- literature-based selection of variables - analysis level of n = 402 counties in Germany for the entire observation period 2011–2015 - analyses with SaTScan v9.6 (Boston, MA,USA) andR4.1.2 (R Core Team 2021,Vienna, Austria). **Spaciotemporal cluster analysis:** - Identification of spatiotemporal clusters of early skin cancer detection and mortality with scan statistic according to Kulldorf - Definition of maximum cluster size by using Gini coefficient - Modelling the number of individuals undergoing SCS or have died of skin cancer within framework of cluster analysis **Spaciotemporal regression analyses:** - after identification of regions with significantly more or less skin cancer screening or mortality cases → model the association between mortality and skin cancer screening - generalized mixed model adjusted with a spatiotemporal autoregressive process to account for the spatiotemporal dependence of the data - rate of billed early skin cancer diagnoses per 100,000 insured persons per year, first in general (models 1 and 3), then separately according to the billing codes EBM 01745 and EBM 01746 (models 2 and 4) as dependent variable	- calculation of 3 clusters for mortality: one high cluster (high mortality rates) in the north-east of German, one in the region of North Rhine-Westphalia and the other in Baden-Württemberg **TABLE 5** Results of the spatiotemporal cluster analyses shown in Figure 3. Cluster no. | Cluster type | Time slot | Average population in the time window | Observed cases | Expected cases | Observed/expected cases | Relative risk EBM 01745 1 High 01.01.2011–31.12.2015 7,310,885 2,828,963 2,023,840 1.40 1.47 2 High 01.01.2011–31.12.2015 4,809,163 1,824,209 1,331,299 1.37 1.41 3 Low 01.01.2011–31.12.2015 9,470,046 2,079,427 2,621,551 0.79 0.77 4 Low 01.01.2011–31.12.2015 9,723,623 2,297,742 2,691,747 0.85 0.83 5 High 01.01.2011–31.12.2015 2,135,984 685,426 591,295 1.16 1.17 EBM 01746 1 High 01.01.2011–31.12.2015 10,371,551 3,646,714 2,757,698 1.32 1.40 2 Low 01.01.2011–31.12.2015 10,351,755 1,949,355 2,752,435 0.71 0.67 3 Low 01.01.2011–31.12.2015 7,974,263 1,728,931 2,120,282 0.82 0.80 4 High 01.01.2011–31.12.2015 4,022,983 1,326,537 1,069,673 1.24 1.26 5 High 01.01.2011–31.12.2015 1,315,224 494,582 349,705 1.41 1.43 6 High 01.01.2011–31.12.2015 972,900 362,873 258,685 1.40 1.41 7 Low 01.01.2011–31.12.2015 1,318,176 259,068 350,490 0.74 0.74 Mortality 1 High 01.01.2011–31.12.2015 14,361,559 7,234 4,697 1.54 1.79 2 Low 01.01.2011–31.12.2015 16,828,566 4,126 5,501 0.75 0.69 3 Low 01.01.2011–31.12.2015 16,712,085 4,338 5,466 0.79 0.74	

			Spaciotemporal regression analyses: - no significant effect considering early skin cancer detection as predictor variable on skin cancer mortality - considering early skin cancer detection separately according to billing codes EBM 01745 and EBM 01746 → adjustment according to the average age in the county → increase in early skin cancer detection by dermatologists by 1,000 per 100,000 insured persons would mean a decrease in mortality by 2% - no significant effect of early skin cancer detection, if model is extended to include other socioeconomic factors **TABLE 6** Influence of early skin cancer detection on skin cancer mortality (spatiotemporal regression models). A posteriori median of the regression coefficient / 95% confidence interval Model 1: Both EBM billing codes combined, adjusted for age in the counties Early skin cancer detection (per 100,000 insured persons) 0.99 (0.98; 1.002) Model 2: EBM billing codes separately, adjusted for age in the counties EBM 01745 (per 100,000 insured persons) 0.98 (0.96; 0.99) EBM 01746 (per 100,000 insured persons) 1.01 (0.99; 1.02) Model 3: Both EBM billing codes combined, adjusted for age in the counties and other confounders Early skin cancer detection (per 100,000 insured persons) 0.99 (0.98; 1.01) Model 4: EBM billing codes separately, adjusted for age in the counties and other confounders EBM 01745 (per 100,000 insured persons) 0.99 (0.97; 1.00) EBM 01746 (per 100,000 insured persons) 1.01 (0.99; 1.03)	
Reference	**Quality**	**Characteristics I**	**Results**	**Comment**
Ziegler, P. (2022). "Der Einfluss der COVID-19-Pandemie auf das Hautkrebsscreening – Ergebnisse einer großen Hautarztpraxis im	n.a. Critically low Cross-sectional study	**Ziel:** Identifikation der Veränderung der Tumoreindringtiefe durch versäumte Hautkrebsscreeninguntersuchungen während der COVID-19-Pandemie **Studiendesign und Material:** - Auswertung und Analyse von Praxisdaten aus den Vergleichsquartalen II/19, II/20 und II/21 mit der einfaktoriellen Varianzanalyse (Anova) mit Welch's F-Test - Histologische Untersuchung von Basalzellkarzinom, Plattenepithelkarzinom und malignes Melanom bezüglich Eindringtiefe	- Rückgang der Patientenzahl in II/2020 bedingt durch die Pandemie - Stabilisierung der Patientenzahlen in 2021 - reduzierte Nachfrage zum Hautkrebsscreening **Tab. 1** Patientenzahlen in den betrachteten Quartalen in der Hautarztpraxis und durchführte Hautkrebsscreenings (HKS) Zeitraum Quartal / Gesamtzahl Patienten / Anzahl HKS / %-Anteil HKS II/2019 4221 861 20,4 II/2020 3425 508 14,8 II/2021 4281 777 18,2	

flächengrößten Landkreis Bayerns“. Hautarzt. 73:212-215.

https://pubmed.ncbi.nlm.nih.gov/35061055

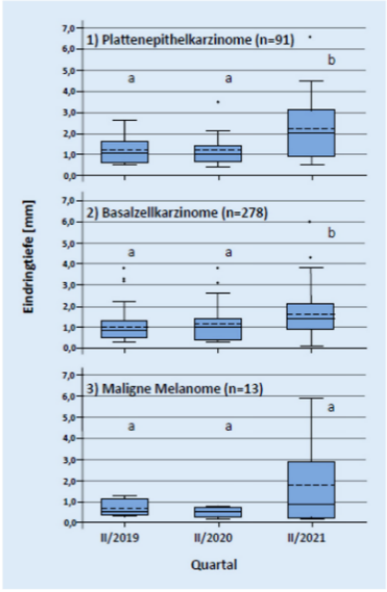


Abb. 3 ◂ Whisker-Boxplot-Darstellung der Verteilung der gefundenen Eindringtiefen der verschiedenen Hauttumorarten 1) Plattenepithelkarzinome, 2) Basalzellkarzinome, 3) maligne Melanome in den betrachteten Quartalen. Zwischen den Werten, die mit dem gleichen Buchstaben (*a* bzw. *b*) gekennzeichnet sind, besteht kein signifikanter Unterschied ($p > 0,05$, Scheffé-Test)

- signifikante Zunahme der Eindringtiefe bei Basalzell- und Plattenepithelkarzinom
- keine signifikante Änderung bei malignem Melanom trotz erkennbarer Zunahme der Tumoreindringtiefe aufgrund der geringen Anzahl der Befunde

Tab. 2 Eindringtiefe der Hauttumoren in mm in Abhängigkeit vom Betrachtungszeitraum (Quartale)

–	Plattenepithelkarzinome			Basalzellkarzinome			Maligne Melanome		
Quartal	*n*	MW	SD	*n*	MW	SD	*n*	MW	SD
II/2019	38	1,20	±0,60	128	1,02	±0,65	3	0,70	±0,53
II/2020	20	1,20	±0,76	23	1,17	±0,94	3	0,50	±0,30
II/2021	33	2,22	±1,50	127	1,58	±1,01	7	1,81	±2,11

MW Mittelwert, *SD* „standard deviation“ (Standardabweichung)

Tab. 3 Ergebnisse ANOVA (Welch's F-Test)

Plattenepithelkarzinome			Basalzellkarzinome		
F	df1/df2	*p*-Wert	F	df1/df2	*p*-Wert
6,71	2/44,32	0,003	13,8	2/58,61	< 0,001

Tab. 4 Ergebnisse Scheffé-Test

–	Plattenepithelkarzinome		Basalzellkarzinome	
Gruppenvergleich	F	*p*-Wert	F	*p*-Wert
II/2019–II/2020	0	0,993	0,56	0,454
II/2019–II/2021	16,53	< 0,001	27,48	< 0,001
II/2020–II/2021	11,72	0,001	4,61	0,033

2.5. Evidenztabellen Recherche Kosteneffektivität Hautkrebs-Screening

References	Country	MM or SCC/BCC	Population/Setting	Intervention and comparator(s)	Comparator	Model type; Analytic strategy	Perspective; Timing	Outcomes	Cost/effectiveness differences	Incremental cost-effectiveness ratio
Anderson et al. (2018)	USA	MM focus	Inflammatory bowel disease (IBD) patients	Annual melanoma screening in IBD patients. Starting age 40, screening by dermatologists.	Background rates of skin cancer screening by primary care practitioners.	State-transition model; Cohort simulation	Government; Lifetime model	Costs and effectiveness (QALYs)	Screening every second year: Average costs of $999 per person and 6.4 QALYs per 1000 persons. Comparator costs of $81 per person.	ICER of $143,959/QALY, which is over the WTP of $100,000/QALY.
Wilson et al. (2018)	UK	MM focus	UK general population	Risk-Stratified Surveillance Program using the Williams self-assessment questionnaire (eight questions on sex, age, hair color, density of freckles, history of severe sunburn, num- ber of raised moles on the arms, and history of nonmelanoma skin cancer yielding a summary score between 0 and 67)	Six policies (i.e., total-body skin examination (TBSE) for all risk patients, five policies with different Williams score and varying recall from 5-yearaly to annually) versus status quo.	State-transition cohort model combined with a decision tree model	Government; 30-year period	Costs, effectiveness (QALYs), net benefit.	The most cost-effective strategy: Williams score 15-21 one TBSE, with score >22 to be quinquennially monitored and if score >43 with annual recall. £164.89 additional costs per person, yielding an extra 0.016 QALYs per person.	ICER is £10,199/QALY gained for the risk-stratified policy.

Pil et al. (2016)	Belgium	All	Belgium general population	Screening general population, primarily >18years, onetime screen by dermatologists. General invitation or after observing suspicious lesion. Sensitivity analyses on different age inclusion, time horizon and screening frequencies.	(S1) Standard screening with total-body skin examination (TBSE); (S2) Lesion-directed screening (LDS); Versus no screening (S3).	State-transition model; Cohort simulation	Government; Latent period of 20 years and a time horizon of 50 years	Costs, effectiveness (QALYs), budget impact, epidemiological effect (incidence rate, mortality)	Incremental QALYs|Costs per 1000 persons: TBSE – Men 0.2|$6899, Women 0.34|$6831; LDS – Men 0.04|$1484, Women 0.05|$1045. One-time screening incur a net cost of $38.6 million for TBSE and $6.4 million for LDS.	Both screening strategies produced QALY gains. TBSE – Men $35,473/QALY. Women $20,044/QALY; LDS – Men $37,365/QALY, Women, $19,844/QALY.
Watts et al. (2016)	Australia	MM focus	High Risk Clinic participants - confirmed family history of relatives with melanoma and a confirmed personal history of invasive melanoma; or dysplastic nevus syndrome and a confirmed personal history of invasive melanoma; or a personal history of at least two confirmed invasive melanomas, one diagnosed in the past 10 years; or a confirmed high-	Screening high-risk participants by dermatologist, annual screen	Standard care	State-transition model; Cohort simulation	Government; 10-year period	Costs and effectiveness (QALYs)	Mean QALYs|Costs over 10 years: Specialized surveillance – 7.87| A$13,468; Standard care – 7.56| A$20,296	Specialized surveillance through the High Risk Clinic was both less expensive and more effective than standard care. The mean saving was A$6,828 per patient, and the mean QALY gain was 0.31

			penetrance mutation affecting melanoma risk.							
Okafor et al. (2013)	USA	SCC and BCC	Patients with Crohn's disease (CD). Additional risk stratification if >50 years, history of thiopurines treatment or history of non-malignant skin cancer.	Screening patients with CD, annual and biannual	(S1) Treat cases as they present and follow affected patients; (S2) Screen patients with CD annually once they turn 50 years old +(S1); (S3) Screen patients with CD annually once they start receiving thiopurines +(S1); (S4) Strategy S1+S2+S3; (S5) Screen all patients with CD	Discrete-event model; Microsimulation	Government; Lifetime model	Costs, effectiveness (QALYs), epidemiological effect (risk of metastatic skin cancer)	Screen all patients with CD annually (S5) is most cost-effective strategy. Average lifetime cost of $333,000 and quality adjusted life expectancy of about 26 QALYs. Second best strategy was again S5 but with biannual screening resulting with average lifetime costs of $328,000 and a quality-adjusted life expectancy of 24.5 QALYs	Annual S5 strategy- ICER of $3263/QALY compared with the next best strategy.

*Losina et al. (2007)	USA	MM focus	Three hypothetical cohorts representing: general population; One first degree relative having been diagnosed with melanoma; Third population if at least two first degree relatives have been diagnosed with melanoma.	Screening general population, biannual, family history	No screening	State-transition model; Cohort simulation	Government; Lifetime model	Costs and effectiveness (QALYs)	General population (QALYs|Costs): No screening 13.537|$236, Every two years beginning at age 50 13.542|$481. Second cohort: No screening 13.529|$316, Every two years beginning at age 50 13.539|$550. Third cohort: No screening 13.507|$537, Every two years beginning at age 50 13.530|$753.	General population: $80 700 per QALY gained. Second cohort:$35 500/QALY gained. Third cohort: $14 700/QALY gained. Additional info available on onetime screening and yearly screening in each of the three cohorts.

*Beddingfield (2002)	USA	MM focus	Self-selected highly risk group: >20 years, light-skinned people who burn easily and tan poorly or with family skin cancer history or extensive sun exposure or higher than average number of skin nevi (moles).	Screening by dermatologist white population average risk	No screening	Decision tree model	Government; Lifetime model	Costs and effectiveness (life-years saved)	Costs per person screening- $79; No screening - $37. Screening results with additional 87 LY per 100,000 patients screened.	$51,481 per life-year saved, one time, lower in over 50s
*Freedberg et al. (1999)	USA	MM focus	Highly risk group: >20 years, light-skinned people who burn easily and tan poorly or with family skin cancer history or extensive sun exposure or higher than average number of skin nevi (moles)	Screening high-risk, by dermatologist, onetime screen	No screening	Decision tree model	Government; Lifetime model	Costs and effectiveness (life-years saved and QALYs)	Costs for screening in a one million cohort- $861 M; No screening - $826 M. Screening results with an increase of 1200 years of life.	ICER is $29,170 per year of life saved or $30,360 per QALY saved.
*Girgis et al. (1996)	Australia	MM focus	Australian general population of men and women over 50 years old.	Screening individuals >50 years of age, by GP, 2-yearly screen	No screening	State-transition model; Cohort simulation	Government; Lifetime model	Costs and effectiveness (life-years saved)	**NOT CLEAR**	A$12,137 per life-year saved for men 50 years