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The effects of complex interventions in 'skin cancer prevention and treatment'

A protocol for a mixed-method systematic review with qualitative comparative analysis

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Abbreviations

ADP – Association for Dermatological Prevention

BCC – Basal cell carcinoma

MM – Malignant Melanoma

NNT – Number Needed to Treat

OR – Odds Ratio

QCA – Qualitative Comparative Analysis

RCT – Randomized Clinical Trials

RR – Relative Risk

SCC – Squamous Cell Carcinoma

WHO – World Health Organization

Abstract

Introduction Occurring from UV-radiation combined with impairing ozone levels, uncritical sun exposure, and use of tanning beds an increasing number of people are affected by different types of skin cancer. But preventive interventions like skin cancer screening are still missing the evidence for effectiveness and therefore are criticised. Fundamental for an appropriate course of action is to approach the defined parameters as measures for effectiveness critically. A prerequisite should be the critical application of used parameter that are defined as measures for effectiveness. This research seeks to establish, through the available literature, the effects and conditions that prove the effectiveness of prevention strategies in skin cancer.

Method and analysis A mixed-method approach is employed to combine quantitative to qualitative methods and answer *what effects can display effectiveness considering time horizon, perspective and organizational level?* and *what are essential and sufficient conditions to prove effectiveness and cost-effectiveness in skin cancer prevention strategies?* A systematic review will be performed to spot studies from any design and assess the data quantitatively and qualitatively. Included studies from each key question will be summarized by characteristics like population, intervention, comparison, outcomes, study design, endpoints, effect estimator, etc. Beside statistical relevancies for a systematic review the qualitative method of qualitative comparative analysis (QCA) will be performed. The estimated outcomes from this review and QCA are the accomplishment and absence of effects that are appropriate for application in effectiveness assessments and further cost-effectiveness assessment.

Ethics and dissemination Formal ethical approval is not required as primary data will not be collected.

Trial registration number International Prospective Register for Systematic Reviews (PROSPERO) number CRD42017053859.

Strengths and limitations of this study

- This approach accomplishes the opportunity to complement a qualitative method to evidence-based medicine efforts and combine outcomes from different study designs.
- This study will contribute to frame appropriate effect parameters to utilize for assessments of effectiveness and cost-effectiveness and therefore prove these.
- This protocol is written following the published PRISMA-P guidelines.
- The qualitative comparative analysis is dependent to the quantity of appropriate and included studies.

Background

Skin cancer is an increasing health risk factor all over the world. Occurring from UV-radiation combined with impairing ozone levels, uncritical sun exposure, and use of tanning beds an increasing number of people are affected by different types of skin cancer. The incidences of non-melanoma skin cancer account for 2-3 million and for malignant melanoma 132,000 annually worldwide. (1) The burdens of illness in melanoma and non-melanoma skin cancer are multifaceted and affect sick persons, family members, as well as the society and furthermore governmental institutions as responsible instance for all individuals in a country.

By causing slight symptoms in the early stages persons suffering from skin cancer often run into high stages of illness. Delayed medical attention in higher stages demand a more invasive and cost-intensive therapy. Also patients undergo losses in their quality of life from symptoms and invasive therapy. Accompanied losses of income from absenteeism in patients as well as in their caregiving family members appear. Despite continually increasing incidences in skin cancer entities like malignant melanoma (MM), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) most people are still misunderstanding the hazard from UV-radiation from sun or tanning beds. The use of sunbeds has been identified as the most significant risk increasing factor of melanoma and non-melanoma skin cancer. (2) Over 65% of whites aged 18-29 years reported at least one sunburn in the past 12 months in the USA. (3)

Prevention strategies in each stage, primary, secondary, and tertiary are in high demand. But interventions like skin cancer screening are still missing the evidence for effectiveness and therefore are criticised. A prerequisite should be, however, the critical application of the defined parameters as measures for effectiveness.

In the current literature there is no distinct evidence for the effectiveness of skin cancer screening for example. Endpoints like mortality and morbidity increases are employed to prove the effectiveness of screening. But endpoints like these need an adjusted view on the stage of prevention, a corresponding time horizon, the perspective of account, etc.

Still studies rated in high quality by Evidence-based Medicine like randomized clinical trials (RCT), observational studies, ecological studies were taken into consideration. The recent issue is the report from the US Preventive Services Task Force by Wernli et al. (4)

Certainly prevention interventions have to be characterized as complex interventions. The Medical Research Council defines some key features for complex interventions as:

- number of interacting components,
- number and difficulty of behaviours required by those delivering or receiving the intervention,
- number of groups or organisational levels targeted by the intervention,
- number and variability of outcomes,
- non-pharmacological,
- behavioural,
- lack of linear, well-evidence causal pathways linking between interventions and the health outcomes as well as
- feedback loops, synergies, and phase changes. (5)

All interventions of prevention primary, secondary, and tertiary can be classified as complex interventions by fulfilling all the mentioned key features. Therefore they should be handled with approaches that include more study designs besides RCTs and similar controlled designs. To understand and evaluate complex interventions there is a need for quasi-experimental study designs, using control/comparison groups/areas, and also uncontrolled studies e.g. time series analysis, before-and-after studies, etc.

Further multiple players in the complex interventions of prevention are affecting the process and influencing the outcomes. Thus time horizon, professional skills, and compliance in patients or population are factors with influence on the outcomes.

The research field of Health Services Research provides approaches from the population´s as well as the individual treatment perspective. Outcomes are evaluated in organisational, process and structural levels including actors in health care and the context, which is shaped and influenced then again by professionals, patients, systems, and organisations (6) societal and politically.

Interventions are highly context-sensitive and on the other side the context is complex and often poorly anticipated and accommodating to interventions. The "double complexity" of intervention and context and their interaction is a central and important issue, which is essential and necessarily to be evaluated or at least mentioned. (6)

Against this background an analytical framework has been conceptualized which is examining the diversity of the structures in complex interventions of prevention and also interactions in the context. Research questions are conceived for different levels. The divers expected and factual effects as well as outcomes are implemented in this framework.

Relevance of review

This review seeks to outline effects of medical, social, communicative, and economical aspects relevant for complex interventions in prevention in different skin cancer stages with the understanding of health services research.

Based on two scientifically established theories, the natural history of disease and the steps of prevention, this framework (figure 1) provides a working basis to point out key questions for the review. The effects and outcomes in the different levels with concomitant interactions can be displayed graphically.

Figure 1: Analytical framework

Source: own compilation

In this framework three main issues are in focus:

1. *Prevention stage*: each stage of prevention implicates specific interventions.

In secondary prevention e.g. screening can be provided. In primary prevention entirely different approaches have to be utilized.

2. *Time horizon*: time progression figures into several aspects, which are reciprocally combined. So the time horizon has to be considered in natural history of disease and also in proceeding prevention stages from primary to tertiary. Points in time do also impact if potential harms from screenings are expected, such as over-diagnosis.

3. *Participants and structure in the process of prevention*: patients, professionals, and in the end the whole society have to be included in the evaluation process of complex interventions. These players have influence with their behaviours, decisions, skills, etc., and consequently influence the given context for complex interventions where they have to operate within. Participants and their perspectives are displayed in the different levels (macro, meso, and micro) based on the World Health Organization (WHO) working definition on integrated health services. (7)

Method

Objective and key questions

This review seeks to establish, through the available literature, the effects and conditions that prove the effectiveness of prevention strategies in skin cancer. The review protocol is authored according to PRIMA-P reporting guideline (8) and registered in PROSPERO with the registration number CRD42017053859.

The specific research questions to be addressed are:

Key question 1 - Aspects of effects and effectiveness

What effects can display effectiveness considering time horizon, perspective and organizational level?

a. *What interventions against skin cancer have been realized?*
b. *What effects have been reported from skin cancer prevention strategies?*
c. *What effects and outcomes have been assigned in each organizational level (structure, process, outcome)?*
d. *What time horizon has been declared for the effects?*

e. *Is the interaction between intervention and context considered?*
f. *What are essential and sufficient conditions to reach the effect that was reported?*
g. *What reasons hampered the achievement of the requested effect?*

Key question 2 - Aspects of costs and effectiveness

What are essential and sufficient conditions to prove effectiveness and cost-effectiveness in skin cancer prevention strategies?

a. *What health economic analyses have been performed for primary, secondary, and tertiary prevention up to now?*
b. *What health economic aspects have been evaluated?*
c. *What are reported endpoints for effectiveness from skin cancer prevention and what time horizon do they require?*

Each key question considers the tumor entities malignant melanoma, BCC, and SCC. The key questions will be approached in particular systematic reviews.

Searching strategy

For all key questions the search will be conducted in following databases:

- PubMed (including Medline)
- PMC via PubMed
- PubMed Health
- EMBASE
- NHSEED
- CIN AHL
- CRD
- DARE
- PsycInfo
- Scopus.

Following searching terms (figure 2) will be employed for complex 1:

Figure 2: Searching terms for key question 1

In complex 2 applied search terms (figure 3):

Figure 3: Searching terms for key question 2:

The key questions are processed within the PICO-schema (figure 4). Using aspects for the evaluation in health economics according to German Institute for Quality and Efficiency in Health Care the PICO-schema is extended. (9)

Figure 4: Examples for issues in an extended PICO-schema

Source: own compilation

Inclusion and exclusion criteria

Titles and abstracts will be screened for eligibility according to the following inclusion criteria:

- international studies,
- language English and German,
- human relation,
- studies with any design dealing with primary, secondary, and tertiary prevention of skin cancer,
- studies up to 40 years retrospective
- studies with any design containing information on effects (quantitative and qualitative) from prevention interventions,
- quality of life in patients suffering from MM, BCC, or SCC,
- quality of life affected by therapy options against MM, BCC, SCC,
- costs.

Exclusion criteria are denoted by:

- studies in other languages than German or English,

- other cancer entities than skin cancer,
- studies dealing with treatment and behaviour in other primary disease than skin cancer,
- studies only dealing with effects from pharmaceutical agent tests,
- duplicates,
- systematic reviews,
- meta analysis.

Data management and selection process

Articles identified through reference lists in included studies, grey literature, and bibliographic searches will also be considered for data collection based on their title, abstract, and full text. Two reviewers will independently select articles regarding the inclusion criteria. Disagreements in reviewer selections will be resolved at a meeting between reviewers prior to selected articles being retrieved. Established tools for quality assessment of included studies are not completely suitable in the applied approach because of diversity of study designs. Therefore studies will be assessed by the reviewer with tool for quality of reporting corresponding to study design. In this expectation checklists CHEERS (10), CONSORT (11), ENTREQ (12), STaRI (13), and STROBE (14) will be applied. The inter-rater reliability between the two will be assessed.(15) Included studies from each key question will be summarized by characteristics like population, intervention, comparison, outcomes, study design, context characteristics, endpoints, effect estimator, etc. Studies will be categorized into affiliation to prevention level. The process of literature research will be displayed following the PRISMA flowchart. (16) Study collection and assorting will be performed in BibTex (Vers 0.99d).

Data synthesis

Statistical analysis

Included studies will be summarized by study design to achieve statistical outcomes from systematic review. If possible all effect estimators like Odds Ratios (OR), Relative Risks (RR), Number Needed to Treat (NNT), risk reduction, costs etc. will be extracted pooled. Depending on heterogeneity a fixed or random effect model will be used. The determination of heterogeneity will be tested with I2 statistics.

For statistical analysis STATA (Vers. 12, StataCorp, Texas) will be employed.
Anyway all outcomes will be reported in a narrative way.

Qualitative analysis

Furthermore a qualitative analysis will be conducted within a qualitative comparative analysis (QCA).

QCA is used for the purpose of methodological advantages:

- complex causalities are an underlying assumption,
- a cross-case comparison: studies from review of each design and quality can be compared by contents and outcomes,
- each study is treated as an "case" in QCA and brings along a combination of factors (characteristics of study as describes ahead); the combination of factors is called "conditions",
- conditions produce outcomes or they do not (both results are provable),
- the synergy of the conditions is a pivotal component of the QCA = "conjunctural causation",
- QCA captures the assumption that multiple paths may coexist to a desired outcome = "equifinality",
- occurrence of outcomes has another reason than their absence = "asymmetric causation".(17, 18)

Following working steps will be applied for the QCA in this review:

1. prepare data characteristics tables;
2. creating a truth table for a crips set QCA;
3. evaluation of essential and sufficient conditions by using Boolean and Quine-McClusky algorithms = analysis to check on consistency (degree to which combinations in the studies induce outcomes) and coverage (proportion of cases with an desired outcome);
4. crisp truth table aids a fuzzy set analysis;
5. fuzzy set analysis will be utilized to evaluate the degree to which each study answers the question on essential and sufficient conditions for the evidence of effectiveness from reported outcomes.

QCA will be performed with the software fsQCA 3.0.

Dealing with protocol amendments

Divergences from the protocol in the ongoing review process will be registered and documented for appearance, estimated reason, and resolving strategy. This documentation will be reported in the respective review publication for the key questions.

Discussion

The applied quantitative and qualitative methods and expected outcomes offer an appropriate method to reveal experienced interventions, their context, and effects.

By extending the purpose of evidence-based medicine by qualitative efforts with regard to the underlying conditions for the attainability of effects and their absence this presents an indispensable groundwork in order to frame all suitable endpoints for effectiveness measures and furthermore cost-effectiveness.

Acknowledgements

This work has been funded by the Association of Dermatological Prevention (ADP) kindly supported by professionally qualified help of Prof. Eckhard Breitbart and Susanne Fengler from the ADP in Buxtehude.

Contributor ship statement

Karolina Beifus conceived the idea, the literature review, evaluation design, and preparation of this study protocol. Juliane Köberlein-Neu contributed to refinement of the study protocol and approved the final manuscript. The accomplishment of literature review, selection and quality assessment resides by Karolina Beifus and Juliane Köberlein-Neu. Statistical expertise and qualitative comparative analysis are planned and performed by Karolina Beifus.

Funding

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare to have no competing interests.

Data sharing statement

This study protocol is the source for the ongoing systematic review with QCA. No additional unpublished data is available. No primary data will be collected. Data is not associated with individuals.

Literature

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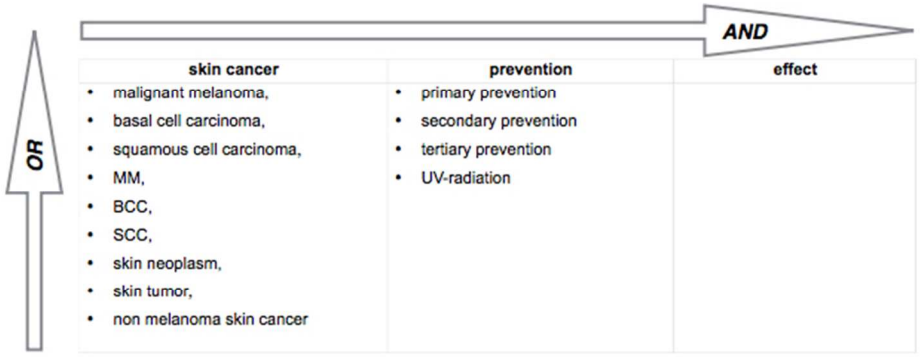

Figure 2: Searching terms for key question 1

237x94mm (72 x 72 DPI)

Figure 3: Searching terms for key question 2:

232x89mm (72 x 72 DPI)

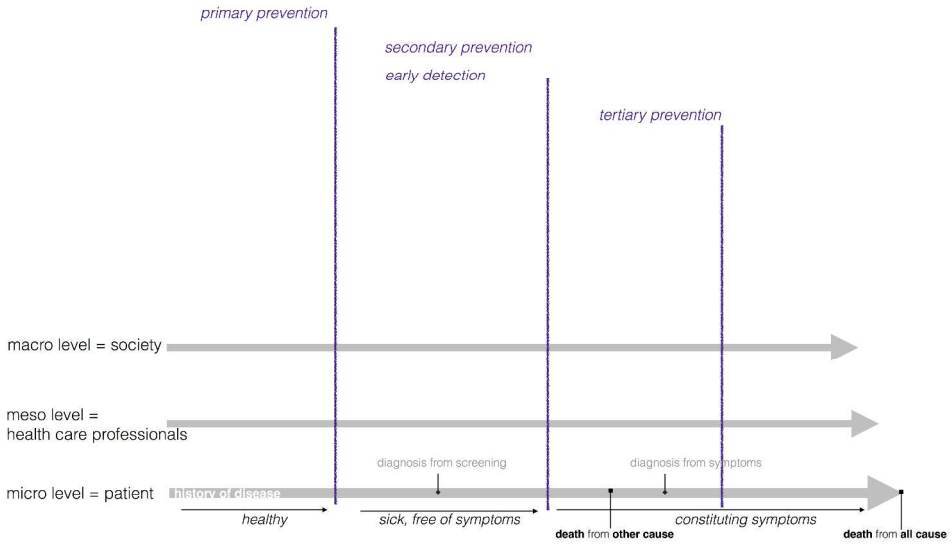

Figure 1: Analytical framework

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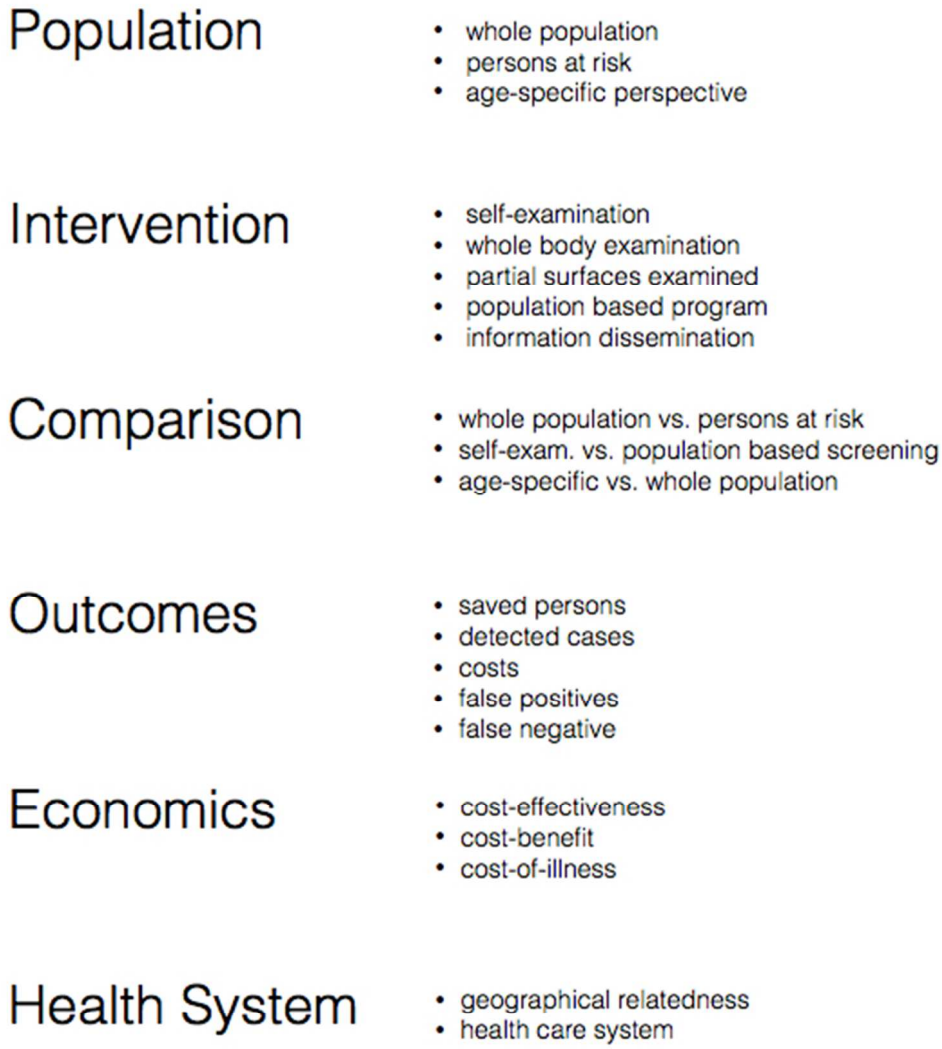

Figure 4: Examples for issues in an extended PICO-schema

194x222mm (72 x 72 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review first page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such no
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number page 1 Abstarct; page 5
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author covering page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review page 11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments no amendment
Support:		
Sources	5a	Indicate sources of financial or other support for the review page 11
Sponsor	5b	Provide name for the review funder and/or sponsor covering page; page 11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol page 11
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known pages 2-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) page 7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review pages 7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage pages 6-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated pages 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review pages 7-8

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) page 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators pages 8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications effect, effectiveness, cost-effectiveness, essential and sufficient conditions for achievement or fail to reach abovementioned endpoints; pages 5-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale outcomes are not pre-defined because of special combination of systematic review and qualitative comparative analysis; outcomes are expected to define effects (and so on) of prevention
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis assessing quality of reporting by use of several checklists; page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised pages 8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) pages 8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) QCA; pages 8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned QCA; see above pages 8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) because of different study designs of included studies divers checklist will be employed; page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Prevention strategies in each stage, primary, secondary, and tertiary are in high demand. But interventions like skin cancer screening are still missing the evidence for effectiveness and therefore are criticised. A prerequisite should be, however, the critical application of the defined parameters as measures for effectiveness.

In the current literature there is no distinct evidence for the effectiveness of skin cancer screening for example. Endpoints like mortality and morbidity increases are employed to prove the effectiveness of screening. But endpoints like these need an adjusted view on the stage of prevention, a corresponding time horizon, the perspective of account, etc.

Still studies rated in high quality by Evidence-based Medicine like randomized clinical trials (RCT), observational studies, ecological studies were taken into consideration. The recent issue is the report from the US Preventive Services Task Force by Wernli et al. (4)

Certainly prevention interventions have to be characterized as complex interventions. The Medical Research Council defines some key features for complex interventions as:

- number of interacting components,
- number and difficulty of behaviours required by those delivering or receiving the intervention,
- number of groups or organisational levels targeted by the intervention,
- number and variability of outcomes,
- non-pharmacological,
- behavioural,
- lack of linear, well-evidence causal pathways linking between interventions and the health outcomes as well as
- feedback loops, synergies, and phase changes. (5)

All interventions of prevention primary, secondary, and tertiary can be classified as complex interventions by fulfilling all the mentioned key features. Therefore they should be handled with approaches that include more study designs besides RCTs and similar controlled designs. To understand and evaluate complex interventions there is a need for quasi-experimental study designs, using control/comparison groups/areas, and also uncontrolled studies e.g. time series analysis, before-and-after studies, etc.

Further multiple players in the complex interventions of prevention are affecting the process and influencing the outcomes. The WHO defined the different participants and structures that are involved in the process of implementation, execution, maintenance, and continuous modification of preventive and curative interventions within the technical brief “Integrated health services”. (6) This approach is adopted to clarify the delivery of services or interventions and the acceptance or claim of interventions. The defined different levels such as the micro level for the “user” or “patient”, the meso level for the “provider” or “professionals” and the macro level for “policy-makers” by deciding, financing, and regulating health services are employed. (6) These different levels show the circumstances that can be understood as the “context” for an intervention and will be henceforth be referred to as “organizational levels”. Interventions are highly context-sensitive and on the other side the context is complex and often poorly anticipated and accommodating to interventions. The “double complexity” of intervention and context and their interaction is a central and important issue, which is essential and necessarily to be evaluated or at least mentioned. (7) To exceed a broad outline of the organizational levels each is examined in several dimensions. Therefore Donabedian´s framework for quality improvement (8) is adduced. Structure, process, and outcome can be evaluated on that base. Structure is defined by permanent capabilities of provider and requirement of user. The process covers all activities of each participant in the intervention and the outcome concerns all results from produced and demanded performances.

Against this background an analytical framework has been conceptualized which is examining the diversity of the structures in complex interventions of prevention and also interactions in the context. Research questions are conceived for different levels. The divers expected and factual effects as well as outcomes are implemented in this framework.

Relevance of review

This review seeks to outline effects of medical, social, communicative, and economical aspects relevant for complex interventions in prevention in different skin cancer stages with the understanding of health services research.

Based on two scientifically established theories, the natural history of disease and the steps of prevention, this framework (figure 1) provides a working basis to point

out key questions for the review. The effects and outcomes in the different levels with concomitant interactions can be displayed graphically.

In this framework three main issues are in focus:

1. *Prevention stage*: each stage of prevention implicates specific interventions. In secondary prevention e.g. screening can be provided. In primary prevention entirely different approaches have to be utilized.

2. *Time horizon*: time progression figures into several aspects, which are reciprocally combined. So the time horizon has to be considered in natural history of disease and also in proceeding prevention stages from primary to tertiary. The choice of time frame or point in time has high impact on the effects of prevention such as over-diagnosis in screenings for example.

3. *Participants and structure in the process of prevention*: patients, professionals, and in the end the whole society have to be included in the evaluation process of complex interventions. These players have influence with their behaviours, decisions, skills, etc., and consequently influence the given context for complex interventions where they have to operate within. These participants and their specific perspective implicate divergent aspects of effects (benefits and costs) which all have to be considered individually. The participants and their perspectives are displayed in the different “organizational levels” (macro, meso, and micro) based on the World Health Organization (WHO) working definition on integrated health services. (6) Within each level the structure, process, and outcome that result from interactions are considered.

Method

Objective and key questions

This review seeks to establish, through the available literature, the effects and conditions that prove the effectiveness of prevention strategies in skin cancer. The

review protocol is authored according to PRIMA-P reporting guideline (9) and registered in PROSPERO with the registration number CRD42017053859.

The specific research questions to be addressed are:

Key question 1 - Aspects of effects and effectiveness

What effects can display effectiveness considering time horizon, perspective and organizational level?

a. *What interventions against skin cancer have been realized?*
b. *What effects have been reported from skin cancer prevention strategies?*
c. *What effects and outcomes have been assigned in each organizational level in structure, process, and outcome?*
d. *What time horizon has been declared for the effects?*
e. *Is the interaction between intervention and context considered?*
f. *What are essential and sufficient conditions to reach the effect that was reported?*
g. *What reasons hampered the achievement of the requested effect?*

Key question 2 - Aspects of costs and effectiveness

What are essential and sufficient conditions to prove effectiveness and cost-effectiveness in skin cancer prevention strategies?

a. *What health economic analyses have been performed for primary, secondary, and tertiary prevention up to now?*
b. *What health economic aspects have been evaluated?*
c. *What are reported endpoints for effectiveness from skin cancer prevention and what time horizon do they require to prove cost-effectiveness?*

Each key question considers the tumor entities malignant melanoma, BCC, and SCC. The key questions will be approached in particular systematic reviews.

Searching strategy

For all key questions the search will be conducted in following databases:

- PubMed (including Medline)

- PMC via PubMed
- PubMed Health
- EMBASE
- NHSEED
- CIN AHL
- CRD
- DARE
- PsycInfo
- Scopus.

Following searching terms (figure 2) will be employed for complex 1:

In complex 2 applied search terms (figure 3):

Listing all relevant terms in hierarchical form performed the selection of keywords for the electronic search. All synonyms, alternative terminology, related terms, word-stems, truncation, abbreviations, and acronyms were checked and included.
For databases a keyword search and phrases search in title and abstract fields is performed using the particular thesaurus option (e.g. MeSH, EMTREE,etc.).
To access grey literature international databases will be examined. PhD theses and dissertations, current trials, and conference proceedings are searched for the databases Health Management Information Center (Ovid) and Global Health (Ovid), Scopus, Web of Science. Further the search repositories www.greylit.org, Open Grey, and GreyNet International are browsed. An additional hand-search is performed in Google Scholar as well as reference lists in the included literature.
The key questions are processed within the PICO-schema (figure 4). Using aspects for the evaluation in health economics according to German Institute for Quality and Efficiency in Health Care the PICO-schema is extended. (10)

Figure 1: Examples for issues in an extended PICO-schema

Source: own compilation

Inclusion and exclusion criteria

Titles and abstracts will be screened for eligibility according to the following inclusion criteria:

- international studies,
- language English and German,
- human relation,
- studies with any design dealing with primary, secondary, and tertiary prevention of skin cancer,
- grey literature,
- studies up to 40 years retrospective,
- studies with any design containing information on effects (quantitative and qualitative) from prevention interventions,
- quality of life in patients suffering from MM, BCC, or SCC,
- quality of life affected by therapy options against MM, BCC, SCC,
- costs.

Exclusion criteria are denoted by:

- studies in other languages than German or English,
- other cancer entities than skin cancer,
- studies dealing with treatment and behaviour in other primary disease than skin cancer,
- studies only dealing with effects from pharmaceutical agent tests,
- duplicates,
- systematic reviews,
- meta analysis.

Data management and selection process

Articles identified through reference lists in included studies, grey literature, and bibliographic searches will also be considered for data collection based on their title, abstract, and full text. Two reviewers will independently select articles regarding the inclusion criteria. Disagreements in reviewer selections will be resolved at a meeting between reviewers prior to selected articles being retrieved. Established tools for quality assessment of included studies are not completely suitable in the applied approach because of diversity of study designs. Therefore studies will be assessed

by the reviewer with tool for quality of reporting corresponding to study design. In this expectation checklists CHEERS (11), CONSORT (12), ENTREQ (13), STaRI (14), and STROBE (15) will be applied. The inter-rater reliability between the two will be assessed.(16) Included studies from each key question will be summarized by characteristics like population, intervention, comparison, outcomes, study design, context characteristics, endpoints, effect estimator, etc. Studies will be categorized into affiliation to prevention level. The process of literature research will be displayed following the PRISMA flowchart. (17) Study collection and assorting will be performed in BibTex (Vers 0.99d).

Data synthesis

Statistical analysis

Included studies will be summarized by study design to achieve statistical outcomes from systematic review. If possible all effect estimators like Odds Ratios (OR), Relative Risks (RR), Number Needed to Treat (NNT), risk reduction, costs etc. will be extracted pooled. Depending on heterogeneity a fixed or random effect model will be used. The determination of heterogeneity will be tested with I2 statistics.

For statistical analysis STATA (Vers. 12, StataCorp, Texas) will be employed.

Anyway all outcomes will be reported in a narrative way.

Qualitative analysis

Furthermore a qualitative analysis will be conducted within a qualitative comparative analysis (QCA).

QCA is used for the purpose of methodological advantages:

- complex causalities are an underlying assumption,
- a cross-case comparison: studies from review of each design and quality can be compared by contents and outcomes,
- each study is treated as an “case” in QCA and brings along a combination of factors (characteristics of study as describes ahead); the combination of factors is called “conditions”,
- conditions produce outcomes or they do not (both results are provable),
- the synergy of the conditions is a pivotal component of the QCA = “conjunctural causation”,

- QCA captures the assumption that multiple paths may coexist to a desired outcome = “equifinality”,
- occurrence of outcomes has another reason than their absence = “asymmetric causation”.(18, 19)

Following working steps will be applied for the QCA in this review:

1. prepare data characteristics tables;
2. creating a truth table for a crips set QCA;
3. evaluation of essential and sufficient conditions by using Boolean and Quine-McClusky algorithms = analysis to check on consistency (degree to which combinations in the studies induce outcomes) and coverage (proportion of cases with an desired outcome);
4. crisp truth table aids a fuzzy set analysis;
5. fuzzy set analysis will be utilized to evaluate the degree to which each study answers the question on essential and sufficient conditions for the evidence of effectiveness from reported outcomes.

QCA will be performed with the software fsQCA 3.0.

Dealing with protocol amendments

Divergences from the protocol in the ongoing review process will be registered and documented for appearance, estimated reason, and resolving strategy. This documentation will be reported in the respective review publication for the key questions.

Discussion

The applied quantitative and qualitative methods and expected outcomes offer an appropriate method to reveal experienced interventions, their context, and effects.

By extending the purpose of evidence-based medicine by qualitative efforts with regard to the underlying conditions for the attainability of effects and their absence this presents an indispensable groundwork in order to frame all suitable endpoints for effectiveness measures and furthermore cost-effectiveness.

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Contributor ship statement

Karolina Beifus conceived the idea, the literature review, evaluation design, and preparation of this study protocol. Juliane Köberlein-Neu contributed to refinement of the study protocol and approved the final manuscript. The accomplishment of literature review, selection and quality assessment resides by Karolina Beifus and Juliane Köberlein-Neu. Statistical expertise and qualitative comparative analysis are planned and performed by Karolina Beifus.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare to have no competing interests.

Data sharing statement

This study protocol is the source for the ongoing systematic review with QCA. No additional unpublished data is available. No primary data will be collected. Data is not associated with individuals.

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Figure 2: Analytical framework

Source: own compilation

Figure 3: Searching terms for key question 1

Figure 4: Searching terms for key question 2:

Figure 5: Examples for issues in an extended PICO-schema

Source: own compilation

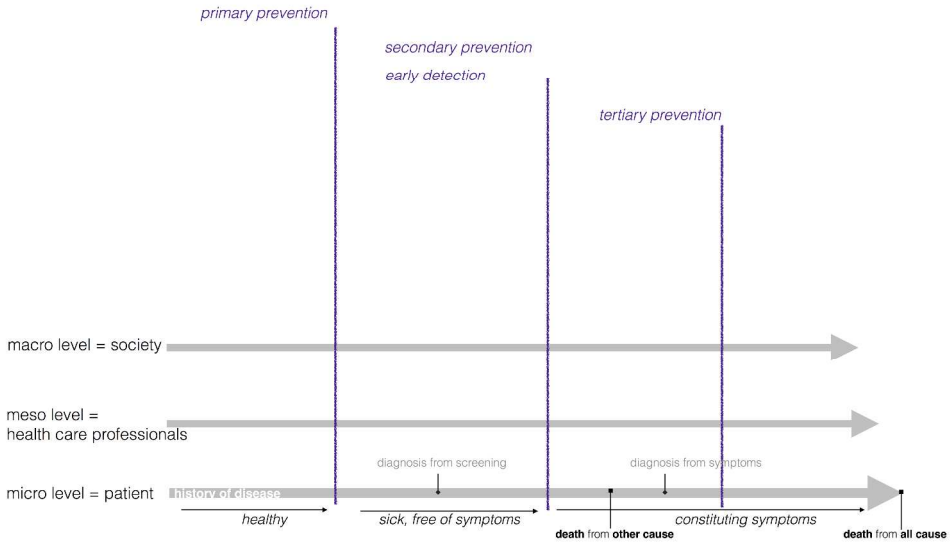

Figure 1: Analytical framework

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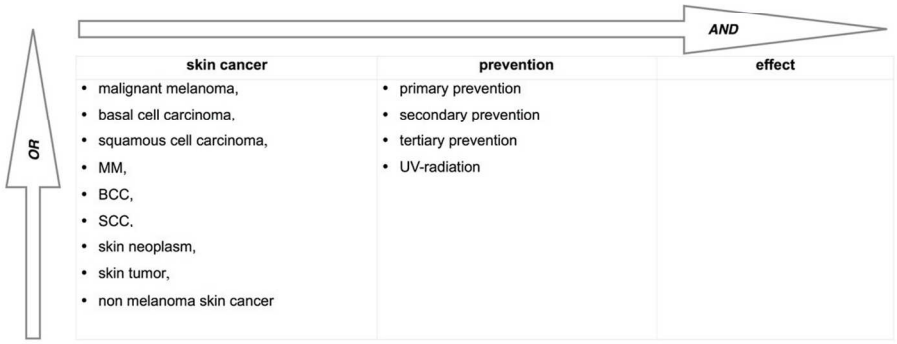

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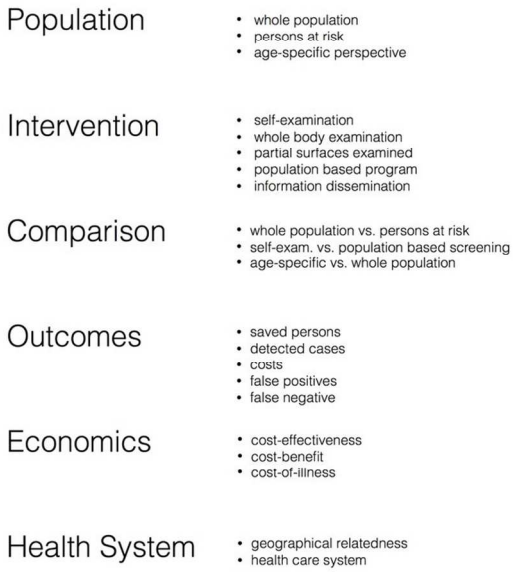

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review first page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such no
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number page 1 Abstarct; page 5
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author covering page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review page 11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments no amendment
Support:		
Sources	5a	Indicate sources of financial or other support for the review page 11
Sponsor	5b	Provide name for the review funder and/or sponsor covering page; page 11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol page 11
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known pages 2-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) page 7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review pages 7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage pages 6-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated pages 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review pages 7-8

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) page 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators pages 8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications effect, effectiveness, cost-effectiveness, essential and sufficient conditions for achievement or fail to reach abovementioned endpoints; pages 5-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale outcomes are not pre-defined because of special combination of systematic review and qualitative comparative analysis; outcomes are expected to define effects (and so on) of prevention
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis assessing quality of reporting by use of several checklists; page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised pages 8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) pages 8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) QCA; pages 8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned QCA; see above pages 8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) because of different study designs of included studies divers checklist will be employed; page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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