BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029265
Article Type:	Research
Date Submitted by the Author:	28-Jan-2019
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Keywords:	skin cancer, melanoma, prevention, sun protection, sun protection behaviors

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Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

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Word count (abstract): 205

Word count (body): 3593

Tables: 4 **Figures:** 5

K**ey words:** skin cancer, melanoma, prevention, sun protection, sun protection behaviors, health behavior

Authorship

LJJ, GW, AT, LL, JCC, MH designed the study; LJJ, VS, LL, MH conducted the data extraction and analyses; all authors contributed to the interpretation of the analyses. LJJ drafted the manuscript; all authors contributed to the writing and review of the manuscript.

Disclosure

The authors declare no conflicts of interest.

Funding

LJJ is supported by the National Health and Medical Research Council (NHMRC) Better Evidence and Translation in Chronic Kidney Disease (BEAT-CKD) Program Grant (APP1092957). MH is supported by the BEAT-CKD Program Grant (APP1092957). AT is supported by the NHMRC Fellowship (APP1106716). The funding organizations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript.

Abbreviations

AZA, azathioprine

BCC, basal cell carcinoma

CNI, calcineurin inhibitors

CI, confidence intervals

MAL, methyl aminolaevulinate cream

MD, mean difference

MMF, mycophenolate mofetil

mTORI, mammalian target of rapamaycin inhibitors

NMSC, non-melanoma skin cancer

RCT, randomized controlled trial

RR, relative risk

SCC, squamous cell carcinoma

SMD, standardized mean difference

ABSTRACT

Objectives

Solid organ transplant recipients are at increased risk of skin cancer, affecting more than 50% of recipients. We aimed to determine the effectiveness of interventions for behavioral change for sun protection or skin cancer prevention in solid organ transplant recipients.

Design

Systematic review

Methods

Electronic databases were searched from inception to January 2018. We included randomized controlled trials that evaluated the effect of behavioral or pharmaceutical interventions on behavioral change or skin cancer prevention in solid organ transplant recipients. Risks of bias and evidence certainty were assessed using Cochrane and the GRADE framework.

Results

Twenty trials (n=2,295 participants) were included. The overall risk of bias was low or unclear and the quality of evidence was very low for all outcomes. Compared with standard care, behavioral interventions appear to improve sun protection behavior (N=3, n= 414, SMD 0.89, 95% CI -0.84-2.62, I^2 =98%) and knowledge (N=4, n=489, SMD 0.50, 95% CI 0.12-0.87, $I^{2=}$ 76%). Compared with calcineurin inhibitors, conversion to mammalian target of rapamaycin inhibitors may reduce the incidence of non-melanocytic skin cancer (N=5, n=1080, RR 0.46 95% CI 0.28-0.75, $I^{2 =}$72%).

Conclusions

Behavioral and pharmaceutical preventive interventions may improve sun protective behavior and knowledge, and reduce the incidence of non-melanocytic skin cancer, but the overall quality of the evidence is very low and insufficient to guide decision-making and clinical practice.

PROSPERO Registration number

CRD420170639

ARTICLE SUMMARY

Strengths and limitations

- A comprehensive review summarising evidence for interventions aimed at the behavioural change and skin cancer prevention in solid organ transplant recipients
- Few trials included important outcomes of skin cancer and none included melanoma or mortality
- The overall quality of evidence was very low for all outcomes and therefore insufficient to guide decision-making and clinical practice

1. INTRODUCTION

Skin cancer, including melanoma and nonmelanoma skin cancer (NMSC), is the most frequently diagnosed malignancy among solid organ transplant recipients, affecting more than 50% of post-transplantation recipients.[1,2] The cumulative incidence of NMSC increases with time after transplantation, from 5-10% at 2 years to 40-80% at 20 years.[2-4] Squamous cell carcinomas (SCC) account for 95% of skin cancers diagnosed, with an incidence of 65 to 250 times greater than the age and gender-matched general population.[5-7] Once cancer develops, the excess risks of death from invasive and metastatic skin cancer, such as SCC and melanoma, are three times to nine times higher than the general population, with five-year overall survival of less than 30%.[6,8-11]

Sun exposure behaviors remain the most significant and modifiable risk factor in the prevention of skin cancers in the general population.[12] However, with the dramatic increase in skin cancers in solid organ transplant recipients, pharmaceuticals have also been used to reduce and delay the development of skin cancer.[12,13] Current recommendations for preventive strategies have often been extrapolated from guidelines in the general population, which may not be applicable to solid organ transplant recipients.[14] For example, frequent skin self-examination and annual to biannual total body skin examination are generally recommended for the general population.[14-16] Sun protective behaviors including use of sunscreen, protective clothing and limiting sun exposure during peak hours are potential measures for skin cancer prevention.[3,4,10] Further, alteration of maintenance immunosuppression such as conversion to mammalian target of rapamaycin inhibitors (mTORi) and secondary prevention using retinoid acitretin are recommended for management of skin cancers in high risk transplant recipients.[15]

The aim of this study is determine the effectiveness of interventions that promote behavioral change and skin cancer prevention in solid organ transplant recipients.

2. METHODS

This systematic review followed a pre-specified protocol registered in PROSPERO (CRD4201706392) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[17] The study was exempt from approval from an ethics' board. There was no patient or public involvement.

2.1 Inclusion criteria

All randomized controlled trials (RCTs) or quasi RCTs (allocated to trial arms by investigators) of interventions for skin cancer prevention (both melanoma and non-melanoma skin cancer) in solid organ transplant recipients were included. Behavioral interventions defined as any strategy used to promote sun protective behavior including passive (e.g. pamphlets), active (e.g. group workshops, counselling, dermatology clinic) and provision of sun protective equipment; and pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers, nicotinamide and oral retinoids) and studies that reported skin cancer related outcomes as their primary outcomes were included. Studies that did not report these outcomes as primary end-points were excluded. Studies of interventions for the treatment of skin cancer were excluded.

2.2 Search strategies

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from inception to January 2018 without language restriction, using search strategies

designed by a specialist information manager (Figure S1). Reference lists of included studies were also searched.

2.3 Data extraction

Titles and abstracts were reviewed by two independent authors (LJJ & LL) and those that did not meet the inclusion criteria were excluded. Full text articles were reviewed by 3 independent reviewers (LJJ, VS, LL) and any disagreements were resolved by discussion. Data on study design, geographic location, sample size, type of transplant, measurement of interventions, interventions and comparators were extracted. We sought unclear or missing information from authors where possible.

2.4 Outcome measures

The pre-specified outcome measures were incidence of precancerous and cancerous lesions, sun protection behavior (including use of sunscreen, use of protective clothing including hats and sunglasses, shade and sun avoidance), knowledge and attitude, skin self-examination, sun exposure (including skin irritation, sunburn) and biologic measures (including measurement of melanin index and sun damage assessment).

2.5 Risk of bias and quality of evidence

The risk of bias was assessed independently by LJJ and VS using the Cochrane risk of bias tool.[18] The domains included in the assessment were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, trial registration and industry involvement. Each criterion was assigned a judgment of high, low or unclear risk of bias. Intention to treat and lost to follow up were also assessed for each study. The quality of the evidence informing summary estimates for

each outcome was then assessed by LJJ using the Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines.[19]

2.6 Data synthesis and statistical analyses

Continuous outcomes were summarized as mean difference (MD) or standardized mean difference (SMD) and dichotomous outcomes as relative risk (RR). A MD/SMD greater than zero and/or a RR greater than 1 could be interpreted as favoring the intervention group relative to the control, unless specified elsewhere. Risk estimates were reported with 95% confidence intervals (CI), using random-effects meta-analysis. We considered P values <0.05 to be statistically significant. We quantified the heterogeneity using the I^2 statistic. An I^2 value of <25% was considered to represent low heterogeneity and >75% as high heterogeneity. When sufficient data were available, possible sources of heterogeneity were investigated using subgroup analysis based on pre-specified study characteristics including sample size, trial duration, setting and overall risk of bias. Funnel plots were planned to evaluate small study effects when at least ten studies were included in meta-analysis. All analyses were conducted using Review Manager version 5.3 software.

3. RESULTS

3.1 Study selection

The literature search identified 1099 articles, of which, 854 were excluded after abstract and title review. Full text assessment of 78 studies found 21 eligible articles for inclusion (Figure 1).

3.2 Studies characteristics

We included 21 reports of 20 RCTs, including 2,295 participants (Figure 1). The study characteristics are summarized in Table 1 and Table 2. The median number of participants was 44 (range 17 to 824) and the median follow-up duration was 10 months (range 1 day to 36 months).

All studies included kidney transplant recipients, with some also including heart transplant recipients (n=1), liver, heart, pancreas, lung, heart/lung and other transplants (n=1), and lung and liver transplant recipients (n=2). In total, 15 of 21 (76%) studies provided sufficient data for the meta-analyses. Six studies did not meet final criteria for meta-analysis as they had the same sample of participants (n=1),[20] or did not provide data that was able to be meta-analyzed (n=5).[21-25]

3.3 Risk of bias and quality of the evidence

Overall studies were at low or unclear risk of bias for many domains (Figure 2; Figure S2). Allocation concealment was adequate in 7 (35%) of 20 studies, and unclear in 12 (60%) studies. Participants were blinded in 4 (20%), and outcome assessors were blinded in 10 (50%). Intention to treat analyses were used in 6 (30%) studies and 256 (11%) patients were lost to follow-up. A total of 3 (15%) studies had incomplete outcome data, and all studies were at low risk for selective reporting. Seven studies (35%) reported industry involvement in authorship, design, or data analysis, and of the 16 trials requiring trial registration, only 9 (56%) reported accordingly.

The overall quality of the evidence was very low for all outcomes (Table S1) due to limitations in study design, heterogeneity in the intervention and outcomes measures, the very small sample size of individual studies and the small number of studies for each specific outcome. Obtaining an overall summary estimate was difficult for many outcomes due to the variability in the analytical methods and reporting in individual studies. In particular, assessment of reporting of sun protection behavior and sun protection knowledge was not possible as outcomes were inconsistent and there was large diversity of interventions used (e.g. written education material versus a mobile app program). Furthermore, formal testing of publication bias was not performed due to insufficient data.

3.4 Interventions

The interventions in the included studies were grouped in three broad categories, behavioral (n=6), switch to mTOR inhibitors (n=6), and other pharmaceutical interventions (photodynamic therapy, immune response modifiers, oral retinoids and nicotinamide) (n=9). Studies of behavioral interventions used passive methods of delivery including written educational material (n=2), both written educational material and text messages (n=1), mobile app programs (n=2) and a video (n=1).

All six studies of immunosuppression compared mTORis (sirolimus) to calcineurin inhibitors (CNI) based therapies.

Four of the eight studies of other pharmaceutical interventions assessed the effect of photodynamic therapy using methyl aminolevinate creams compared to placebo (n=1), no treatment to contralateral area (n=2) or a topical immune response modifier cream (n=1). Three studies assessed oral retinoid using acitretin compared to placebo (n=1), lower dose (n=1) or a drug free period (n=1), one study assessed nicotinamide compared to placebo and a single study assessed the benefits of topical immune response modifier compared to placebo in kidney transplant recipients.

3.5 Effect of behavioural interventions on sun protection outcomes

Sun protection behavior

Sun protection behavior, defined as hours spent outdoors per week, use of sunscreen, wearing protective clothing and seeking shade, was assessed in three trials[26-28]. Educational workbooks,[26] educational workbooks and text messages[27] and a mobile app program[28] were compared with standard care. Patients who received behavioral interventions reported improved sun protection

behavior scores[26-28] (3 studies, 414 participants, SMD 0.89, 95% CI -0.84-2.62, I^2 98%) (Table 3; Figure 3). A single trial assessed a standardised and validated educational workbook and found an improvement in the proportion of participants engaging in skin self-examination after one month (75 participants, RR 4.14, 95% CI 2.22-7.72).[29] One trial assessed a mobile app program and reported a reduction in daily hours spent outdoors among the intervention group (170 participants, SMD -6.12, 95% CI -711 to -5.13).[28]

Sun protection knowledge

The effectiveness of educational workbooks, text messages, mobile app programs and videos on sun protection knowledge was assessed in 6 studies[20,24,26-29], four of which provided data for a meta-analysis. There was an improvement in knowledge scores (4 studies, 489 participants, SMD 0.50, 95% CI 0.12-0.87, I^2 76%) in the intervention group compared to standard care (Figure 4).[26-29] One study compared an interactive visual representation of the educational program with standard information pamphlets and found that knowledge of sun protection improved among those who received the educational video.[24]

Sun protection attitude

Three studies assessed sun protective attitude after receiving an educational workbook, text messages or a mobile app program over a period of 0.5 months to 1.5 months.[27-29] Compared to standard care, there was an overall improvement in scores of concern about developing cancer (3 studies, 348 participants, SMD 1.85, 95% CI 1.59-2.11, I^2 96%).[27-29] Two studies involving 273 participants reported an improvement in scores of understanding the personal risk of skin cancer (SMD 0.61, 95% CI -0.60-1.82, I^2 96%), adherence to sun protection (SMD 0.77 95% CI -0.14-1.68, I^2 92%) and willingness or intention to change behavior (SMD 1.70, 95% CI -1.68-5.07, I^2 99%).[27,28] A single study involving 75 participants also reported an improvement in scores of ability to

recognize a potential skin cancer (MD 1.80, 95% CI 1.35-2.25), importance of skin self-examination (MD 1.05, 95% CI 0.61-1.49) and having a partner help for skin self-examination (MD 1.59, 95% CI 1.10-2.08).[29] Another single study reported an improvement in the importance of engaging in sun protection (measured using 5-point Likert scale) (101 participants, MD 7.00, 95% CI 2.94-11.06).[27]

Skin complications and biologic measures

Two trials of behavioral interventions in 271 kidney transplant recipients compared a mobile app or an educational workbook and text messages to standard care on reported skin complications and biologic measures of sun exposure.[27,28] The intervention group experienced a reduced incidence of skin irritation (a culturally relevant term for sun exposure[30]) (RR 1.00, 95% CI 0.89-1.13, I^2 95%) or sunburn (RR 3.19, 95% CI 2.47-4.10, I^2 99%). They also had a decreased melanin index (right forearm, SMD -0.42, 95% CI -0.66 to -0.18; cheek SMD -0.25, 95% CI -0.64 to -0.15) and reduced severity of sun damage (SMD -0.13, 95% CI -0.40 to 0.13) on sun exposed areas (measured using clinical images of chronic sun damage and scored 1-10).

3.6 Effect of pharmaceutical interventions on skin cancer prevention

The incidence and responses of pre-cancerous lesions were measured only in trials of pharmaceutical interventions (Table 4). These included the switch to mTOR inhibitors (n=1),[31] photodynamic therapy (n=2)[32,33] and immune response modifiers (n=1)[34] to current treatment, lower dose or no treatment. The incidence of non-melanocytic skin cancers (NMSC) was assessed in nine pharmaceutical studies.[1,31,34-40] None included melanoma as an outcome.

Topical/local interventions

One trial of 14 participants compared an immune response modifier, 5% imiquimod cream with placebo and found a reduction in the incidence of skin dysplasia (RR 2.14, 95% CI 0.31-14.65), skin atypia (RR 3.00, 95% CI 0.47-19.35), and viral warts (RR 7.00, 95% CI 0.46-106.10).[34]

One Danish study of 26 kidney transplant recipients compared photodynamic therapy with no treatment and reported a relative reduction by approximately 40% in the incidence of NMSC on the treated area (RR 0.59, 95% CI 0.34-21.03, p 0.06).[40] A lower incidence of SCC was also reported in one trial comparing two areas of skin using an immune response modifier and placebo (14 participants, RR 0.09, 95% CI 0.0.01-1.70).[34] Two trials comparing photodynamic therapy to an immune response modifier or photodynamic therapy to placebo in recipients with diagnosed keratoses reported a complete response rate of 60% compared to 24% in the control group (50 participants, RR 5.03, 95% CI 0.14-176.17, I^2 85%).[32,33] Further, one trial which was not included in the meta-analysis, reported a higher cumulative incidence of actinic keratosis lesions in untreated skin (63%) compared with skin treated by photodynamic therapy (28%).[23]

Systemic interventions

mTORis therapy reduced the incidence of NMSC compared to CNIs maintenance therapy (5 trials, 1082 participants, RR 0.46, 95% CI 0.28-0.75, I^2 72%) (Figure 5).[1,31,35,37,39] However evidence was limited due to short follow-up periods, variability in dosing of mTORis and significant rates of loss to follow up. A single trial involving 21 patients reported a reduction in the overall incidence of SCC by 49% in the conversion arm, but reported a drop out rate of 77% and follow-up time of less than 2 years.[21] Further, a single trial which compared mTORi conversion from CNI based therapy reported a significant improvement in skin dysplasia (32 participants, RR 24.35, 95% CI 1.55-381.99).[31]

Two trials comparing an oral retinoid, acitretin, with placebo or a drug free period reported an increased lower risk of both SCCs and BCCs (46 participants, RR 0.40, 95% CI 0.19-0.85, p 0.02; RR 0.50, 95% CI 0.14-1.76[38]) or development of a new skin cancer (19 participants, RR 0.22, 95% CI 0.06-0.90). However, there were no differences in the incidence of new SCCs.[36] One trial, which was not included in the meta-analysis, showed approximately a 50% reduction in the incidence of actinic keratosis which compared a high dose to a low dose of acitretin.[22]

One Australian trial of 22 kidney transplant recipients compared nicotinamide with placebo and reported an estimated relative rate difference of 0.35 (95% CI -0.62 to 0.74), 0.67 (95% CI -0.40 to 0.90) and 0.07 (95% CI -1.51 to 0.65) for NMSC, BCCs and SCCs respectively.[25]

3.6 Subgroup analysis

Study size, trial duration, setting and risk of bias did not modify the effects of CNIs and mTORIs on skin cancer incidences (Figure S3). Sources of heterogeneity for other treatment effects could not be explored due to insufficient data.

4. DISCUSSION

Skin cancers (both non-melanoma and melanoma) are major causes of morbidity and mortality in solid organ transplant recipients. Despite this, trials of interventions aimed at preventing skin cancer in solid organ transplant recipients are few in number (20 trials), small with half comprising of 50 patients or less, of short duration (48% have <12 months follow up) and 52% do not include incidence of skin cancer as an outcome. Our review included 21 reports of 20 trials involving 2,295 transplant recipients, who were predominately kidney transplant recipients. The studies covered a broad range of interventions, including behavioral to improve sun protection behavior and

pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence. None of the behavioral intervention studies included precancerous lesions or skin cancer incidence as outcomes. Although interventions showed plausible improvements to sun protection behaviors, precancerous lesion responses and cancer incidence, there was considerable variability across interventions types, variability in outcomes assessed and outcome estimates. Overall, the current evidence for interventions for skin cancer prevention in solid organ transplant recipients is of very low quality and is insufficient to guide decision-making and clinical practice.

Although behavioral interventions appeared to improve sun protection attitude, knowledge and behavior, there were inconsistencies detected and none of these studies included skin cancer as an outcome. Due to limited number of studies, we were unable to compare specific behavioral interventions (e.g. mobile app vs. written education) to ascertain the most effective method of delivering sun protection education. While there may be some modest benefits in the reduction in cancer incidence (for NMSC) among solid organ transplant recipients who were converted to mTORIs compared to those on CNI maintenance, there was substantial heterogeneity across the studies that was unable to be explained by subgroup analyses. Heterogeneity may be attributed to the absence of long term follow up, large discontinuation rates owing to adverse events and variability in the doses of mTORIs. Pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers) showed a reduction in precancerous lesions compared to standard care or a comparator group. However uncertainty exists in the treatment effects and there were too few studies, interventions were incomparable, follow-up times were variable and considerable loss to follow up for some studies to conclude that the benefits are sustainable.

Previous systematic reviews have evaluated the impact of behavioral interventions on skin cancer prevention in the general population,[41] and concluded that computer programs may increase sun protective behaviors, and 'appearance-focused' interventions may decrease sun tanning and UV exposure in adolescents and young women, respectively. Reviews conducted in other populations at high-risk including outdoor workers,[42] family history, personal history and phenotypic factors[43] have found similar improvement in sun protective behaviors, including use of sunscreen, as well as a decreased incidence of keratoses. A systematic review of the benefits and harms of oral retinoids for the prevention of skin cancer among high risk transplant recipients led to inconclusive results on the effect of acitretin due to the small number of included trials.[44]

Despite the inclusion of all interventions aimed at the prevention of skin cancer in solid organ transplant recipients and the comprehensive systematic search for eligible studies, there are some potential limitations. Due to the heterogeneity of the studies, the high risk of bias, the potential for reporting bias and imprecision in the point estimates of individual studies, there is a high degree of uncertainty in the estimate of the effect of skin cancer prevention interventions. Further, given the small number of studies included in the meta-analysis, we were unable to perform any detailed subgroup analyses or assess for publication bias. Finally, few trials included the important outcomes of skin cancer and none included melanoma or mortality.

Although behavioral change is a simple strategy, long-term adherence remains challenging. While behavioral counseling has been shown to increase sun protective behaviors in non-transplant populations,[41] there is no direct evidence to show that the behavioral change led to a reduction in morbidity and mortality. Previous studies have suggested that transplant recipients do not practice sun protective behaviors regularly,[45-47] were less likely to use sunscreen[48] and that patients have to perceive skin cancer as being an important risk to be motivated to change

behavior.[49,50] However, studies on risk perception of transplant recipients remain conflicting. Given this complexity and the observed inconsistencies in the existing trials, process evaluations including facilitators and barriers to behavioral change should be included in future trials. Such evaluations could include the use of qualitative methodology to support the trial design, ascertain the perspectives of participants on the intervention and evaluate the implementation.[51,52]

We suggest that further strategies for skin cancer prevention in transplant recipients require a multifaceted and individualized approach. Transplant recipients are likely to benefit from early implementation of education, particularly before transplantation occurs and recipients may be preoccupied with other health needs related to transplantation. Although recipients understand the importance of ongoing education for the ability to self-manage their disease, they may experience difficulty in concentrating and learning new knowledge, and are often unable to look beyond their graft and the anxiety/fear of graft loss.[53-55] Interventions should be integrated into routine appointments and tailored to meet the individual needs of patients. This would be best achieved through a shared decision-making approach to identify the patient's preferences and priorities and thereby enhance the likelihood of success of self-management and prevention.[56]

Additional large-scale and high-quality RCTs are needed to demonstrate the effectiveness of interventions used to prevent skin cancer in transplant recipients in terms of patient important outcomes, in particular morbidity and mortality associated with skin cancer. Determining patient's preferences for prevention and management of skin cancer are also warranted to ensure interventions and outcomes for trials are relevant to patient needs and priorities and better support patient-centered treatment decisions.[57] Evidence of the efficacy of sun protective behavior interventions need to be strengthened, with use of measures that are homogenous, reliable and validated.

Preventative measures including behavioral, switch to mTOR inhibitors and other pharmaceuticals may improve skin cancer outcomes for solid organ transplant recipients. However, the overall quality of evidence is of very low and insufficient to guide decision-making and clinical practice. Future robust studies that are well powered, have long-term follow up, and use clinical and patient important outcome measures in a consistent manner are required to therefore optimize outcomes for solid organ transplant recipients.

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Table 1. Characteristics of included studies (n=21)

Characteristics	N (%)
Type of transplant	
Kidney	17 (81.0)
Multiple*	4 (19.0)
Sex	
≥ 50% Male	19 (90.5)
< 50% Male	1 (4.8)
Not specified	1 (4.8)
Age (mean)	
< 60	11 (52.4)
≥ 60	5 (23.8)
Not specified	5 (23.8)
Sample size	
10 – 50	11 (52.4)
50 – 100	3 (14.3)
100 – 200	5 (23.8)
>200	2 (9.5)
Setting	
Single center	8 (38.1)
Multi center	12 (57.1)
Not specified	1 (4.8)
Country of origin	
Australia	3 (14.3)
Denmark	4 (19.0)
France	1 (4.8)
Germany	1 (4.8)
Netherlands	2 (9.5)
New Zealand	2 (9.5)
Switzerland	1 (4.8)
Sweden	1 (4.8)
United Kingdom	3 (14.3)
United States	7 (33.3)
Other†	1 (4.8)
Intervention Type	
Behavioral	6 (28.6)
Switch to mTOR inhibitors	6 (28.6)
Photodynamic therapy	4 (19.0)
Oral retinoid	3 (14.3)
Nictotinamide	1 (4.8)
Topical immune response modifier	1 (4.8)
Duration of follow up	
<12 months	10 (47.6)
12 months	4 (19.0)
24 months	5 (23.8)
>24 months	1 (4.8)
Not specified	1 (4.8)
Year of publication	
1995 – 1999	1 (4.8)
2000 – 2004	3 (14.3)
2005 – 2009	4 (19.0)
2010 – 2014	8 (38.1)
2015 – 2017	5 (23.8)

* Kidney, liver and lung (n=2); kidney and heart (n=1); Kidney and multiple other types (n=1) – see text

† 111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Table 2. Characteristics of individual studies

Study	N	Type of transplant	Setting	Type of intervention	Measures	Intervention	Comparator	Primary outcomes	Time (mths)
Behavioral interventions (n=6)									
Clowers-Webb 2006[26]	202	Kidney, liver, heart, pancreas, lung, heart/lung, other§	Single centre, United States	Behavioral	Self-reported questionnaire	Repetitive written material	Standard care	Knowledge & behavior	10
Robinson 2011[29]	75	Kidney	United States	Behavioral	Self-reported questionnaire	Workbook	Standard care	Knowledge & behavior	1
Robinson 2014[27]	101	Kidney	Single centre, United States	Behavioral	Self-reported questionnaire Physical examination	Workbook Text messages	Standard care	Knowledge & behavior	1.5
Robinson 2015[20]‡	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire	Mobile app program	Standard care	Knowledge & behavior	0.5
Robinson 2016[28]	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire Physical examination	Mobile app program	Standard care	Knowledge & behavior	1.5
Trinh 2014[24]*	100	Kidney, liver, lung	Single centre, United States	Behavioral	Self-reported questionnaire	Video	Pamphlet	Knowledge	1 day
Switch to mTOR inhibitors (n=6)									
Alberu 2011[35]	830	Kidney	Multi centre§	**Switch to mTOR inhibitors**	Investigator reported adverse events	Conversion to sirolimus	CNI	Cancer Incidence	24
Campbell 2009[37]	86	Kidney	Multi centre, Australia, New Zealand, United States	**Switch to mTOR inhibitors**	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer Incidence	12
Carroll 2013[21]*	32	Kidney	Multi centre, UK	**Switch to mTOR inhibitors**	Physical examination +/- biopsy	Conversion to prednisolone & sirolimus	CNI/AZA	Cancer incidence	24
Euvrard 2012[1]	120	Kidney	Multi centre, France	**Switch to mTOR inhibitors**	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	24
Hoogendijk-van den Akker	155	Kidney	Multi centre, Netherlands, UK	**Switch to mTOR inhibitors**	Physical examination +/- biopsy	Conversion to sirolimus	AZA/MMF/ CNI	Cancer incidence	24

2013[39]									
Salgo 2010[31]	44	Kidney	Single centre, Germany	**Switch to mTOR inhibitors**	Physical examination +/- biopsy Clinical photographs	Conversion to sirolimus and prednisone	AZA/MMF/ CNI	Precancerous skin dysplasia incidence	12
Pharmaceutical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); nicotinamide (n=1); 5% imiquimod cream (n=1)									
Bavinck 1995[36]	44	Kidney	Multi centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	Acitretin	Placebo	Cancer incidence precancerous lesion reduction	6
Brown 2005[34]	21	Kidney	Multi centre, UK	Topical immune response modifier cream	Physical examination +/- biopsy Clinical mapping and photographs	5% Imiquimod cream	Placebo	Reduction of precancerous lesions	4
Chen 2016[25]*	22	Kidney	Single centre, Australia	Nicotinamide	Physical examination	Nicotinamide	Placebo	Cancer incidence	6
de Sevaux 2003[22]*	26	Kidney	Single centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	High dose acitretin	Low dose acitretin	Cancer and precancerous incidence	12
Dragieva 2004[32]	17	Kidney, heart	Single centre, Switzerland	Photodynamic therapy	Physical examination +/- biopsy Clinical photographs	Methyl aminolevulinate cream	Placebo	Precancerous lesion response	4
George 2002[38]	23	Kidney	Multi centre, Australia	Oral retinoid	Physical examination Annual radiological evaluation	Acitretin	Drug free period	Cancer incidence	24
Togsverd-Bo 2015[23]*†	25	Kidney	Single centre, Denmark	Photodynamic therapy	Physical examination Clinical photographs	Methyl aminolevulinate cream	No treatment contralateral area	Actinic keratosis incidence	36
Togsverd-Bo 2017[33]†	35	Kidney, lung, liver	Multi-centre, Denmark and Sweden	Photodynamic therapy	Physical examination Questionnaire/Diary	Methyl aminolevulinate cream	5% imiquimoid cream	Actinic keratosis lesion response	6

Wulf 2006[40†]	27	Kidney	Multi centre, Denmark and Netherlands	Photodynamic therapy	Clinical mapping and photographs	Methyl aminolevulinate cream	No treatment contralateral area	Cancer incidence	12

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

‡Excluded from analyses – same participants as Robinson 2016

§111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Abbreviations: CNI, Calcineurin inhibitor; AZA. Azathioprine; MMF, Mycophenolate mofetil

Table 3. Effect of behavioral interventions on sun protection outcomes

Outcome	Studies	Participants	Weighted MD[a]/SMD[b] [95% CI]	Relative risk	P	I^2	Intervention	Comparator
BEHAVIORALINTERVENTION (n=5)								
SUN PROTECTION BEHAVIOR								
General sun protection behavior	3	414	0.89 [-0.84, 2.62]		0.31	98%	Workbook, text messages, mobile app program	Standard care
Skin self-examination								
1 month after visit	1	75		4.14 [2.22, 7.72]	<0.001	—	Workbook	Standard care
If checked, concerned	1	42		6.43 [0.42, 98.58]	0.18	—		
If concerned, saw dermatologist	1	12		Not estimable[c]		—		
Decrease daily hours outdoors	1	170	-1.84 [-2.20, -1.48][d]		<0.001	—	Mobile app program	Standard care
SUN PROTECTION KNOWLEDGE	4	489	0.50 [0.12, 0.87]		0.01	76%	Workbook, text messages, mobile app program	Standard care
SUN PROTECTION ATTITUDE								
Concern about developing skin cancer	3	348	1.88 [0.96, 2.80]		<0.001	92%	Workbook, text messages, mobile app program	Standard care
Recognise personal risk	2	273	0.61 [-0.60, 1.82]		0.32	96%	Workbook and text messages, mobile app program	Standard care
Confidence in ability to perform sun protection	2	273	0.77 [-0.14, 1.68]		0.10	92%		
Willingness/intention to change behavior	2	273	1.70 [-1.68, 5.07]		0.32	99%		
Knowledge of significance of skin cancer, relevance of sun protection, risk of having a tan	1	101	0.67 [0.27, 1.07]		0.001	—	Workbook and text messages	Standard care
Confidence in ability to recognise a skin cancer	1	75	1.76 [1.23, 2.30]		<0.001	—	Workbook	Standard care
Importance of skin self-examination	1	75	1.08 [0.60, 1.57]		<0.001	—		
Importance of partner help for skin self-examination	1	75	1.44 [0.93, 1.95]		<0.001	—		
COMPLICATIONS								
Skin irritation								

None	2	271		1.00 [0.89, 1.13]	0.95	95%	Workbook and text messages, mobile app program	Standard care
> 1	2	271		0.77 [0.43, 1.36]	0.36	89%		
Sunburn (past week)								
None	2	271		3.19 [2.47, 4.10]	<0.001	99%		
> 1	2	271		2.68 [1.81, 3.96]	<0.001	95%		
BIOLOGIC MEASURES								
Melanin index - RU arm (sun protected	2	271	0.12 [-0.12, 0.35]		0.34	0%	Workbook and text messages, mobile app program	Standard care
Melanin index - R forearm (sun exposed)	2	271	-0.42 [-0.66, -0.18][d]		0.001	0%		
Cheek (sun exposed)	2	271	-0.25 [-0.64, 0.15][d]		0.22	61%		
Sun damage assessment - R forearm	2	271	-0.13 [-0.40, 0.13][d]		0.33	16%		

[a]Mean difference
[b]Standardised mean difference
[c]Unable to estimate due to absence of comparator group
[d]Reduction of outcome of interest represents an improvement

Table 4. Effect of pharmaceutical interventions on skin cancer prevention

Outcome	Studies	Participants	Relative risk	P	I^2	Intervention	Comparator
SWITH TO mTOR INHIBITORS (n=5)							
PRE-CANCEROUS LESIONS							
Skin dysplasia							
Any improvement	1	32	24.35 [1.55, 381.99]	0.02	—	Sirolimus	CNI[b]
Unchanged	1	32	0.85 [0.28, 2.61]	0.78	—		
Any worsening	1	32	0.04 [0.00, 0.66]	0.02	—		
CANCEROUS LESIONS							
SCC[d]/BCC[e] incidence	5	1082	0.46 [0.28, 0.75]	0.002	72%	Sirolimus	CNI
PHOTODYNAMIC THERAPY (n=3)							
PRE-CANCEROUS LESIONS							
Actinic keratosis reduction (1-2 sessions)							
Complete response	2	50[a]	5.03 [0.14, 176.17]	0.37	85%	MAL[c]	Placebo, Imiquimod 5% cream
Partial response	1	17[a]	7.00 [0.39, 125.99]	0.19	—	MAL	Placebo
No reduction	1	17[a]	0.09 [0.02, 0.40]	0.002	—		
CANCEROUS LESIONS	1	26[a]	0.59 [0.34, 1.03]	0.06	—	MAL	No treatment
IMMUNE RESPONSE MODIFIERS (n=1)							
PRE-CANCEROUS LESIONS							
Reduced skin atypia	1	14[a]	3.00 [0.47, 19.35]	0.25	—	Imiquimod 5% cream	Placebo
Reduced dysplasia	1	14[a]	2.14 [0.31, 14.65]	0.44	—		
Reduced keratoses	1	14[a]	2.14 [0.31, 14.65]	0.44	—		
Reduced no. viral warts	1	14[a]	7.00 [0.46, 106.10]	0.16	—		
CANCEROUS LESIONS							
SCC incidence							
Treated (cream vs. placebo)	1	14[a]	0.09 [0.01, 1.70]	0.11	—	Imiquimod 5% cream	Placebo
Untreated (control site)	1	14[a]	0.43 [0.08, 2.37]	0.33	—		
ORAL RETINOIDS (n=2)							
CANCEROUS LESIONS							
Decreased incidence:							
> 1 SCC	1	46[a]	0.40 [0.19, 0.85]	0.02	—	Acitetrin	Drug free period
> 1 BCC	1	46[a]	0.50 [0.14, 1.76]	0.28	—		

New skin cancer	1	19[a]	0.22 [0.06, 0.90]	0.03	—	Acitretin	Placebo

[a]Control is the contralateral or similar area of skin on the same participant
[b]Calcineurin inhibitor
[c]Methyl aminolaevulinate cream
[d]Squamous cell carcinoma
[e]Basal cell carcinoma

Figure legends

Figure 1. Study selection

Figure 2. Risk of bias of included studies

Figure 3. Behavioral interventions – Sun protection behavior (general)

Figure 4. Behavioral interventions – Sun protection knowledge

Figure 5. Switch to mTOR inhibitors – Non melanoma skin cancer incidence

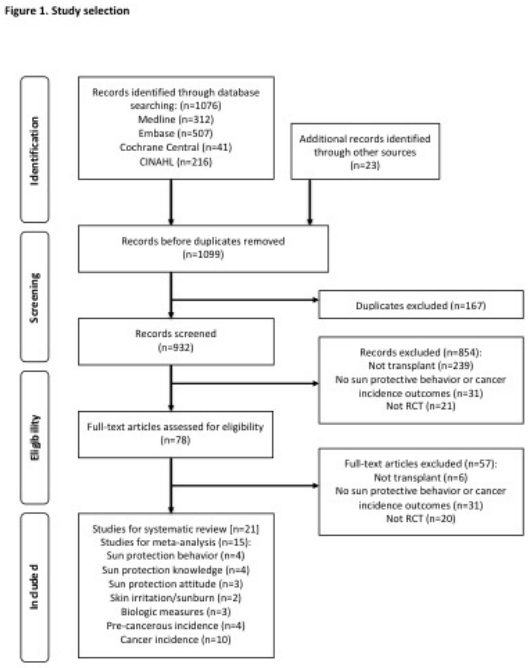

Figure 1. Study selection

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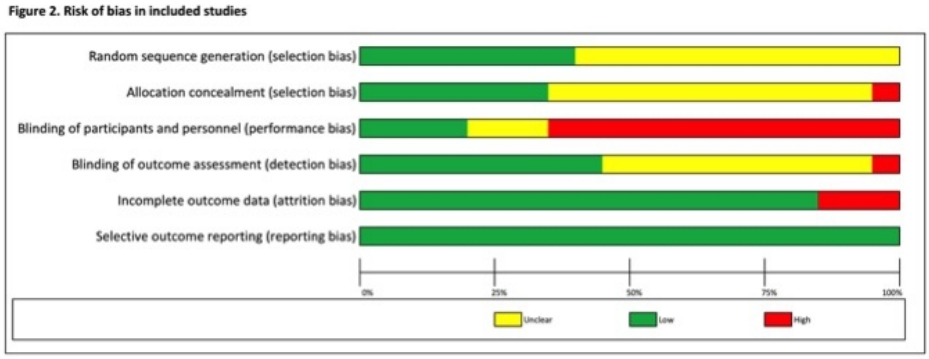

Figure 2. Risk of bias of included studies

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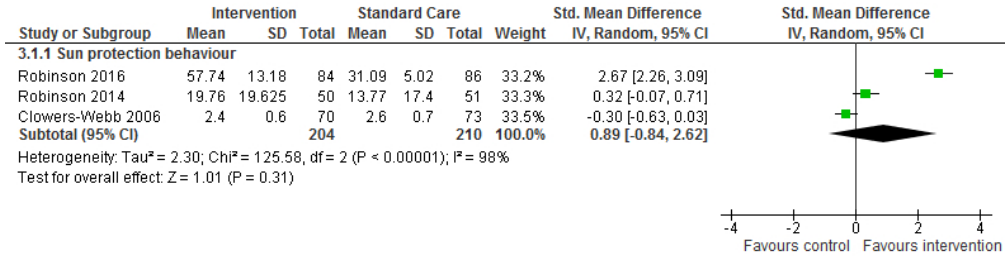

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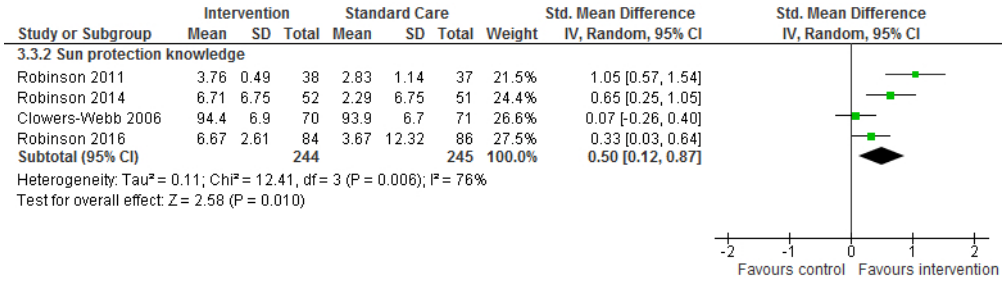

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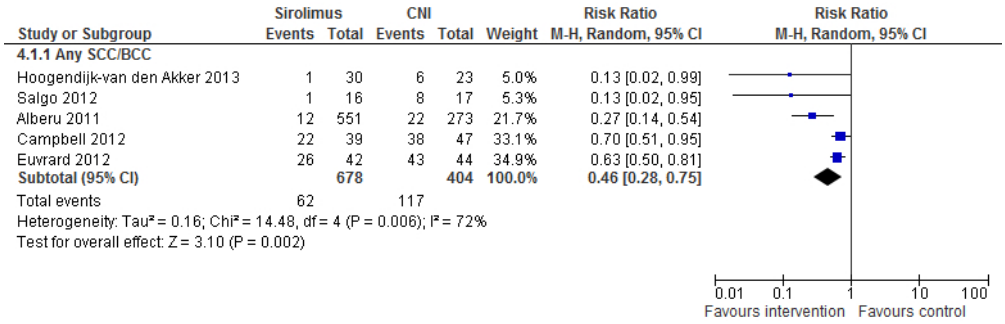

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Figure S1. Search Strategy

1. exp Neoplasms, Basal Cell/
2. basal cell carcinoma.ti,ab.
3. exp Neoplasms, Squamous Cell/
4. squamous cell carcinoma.ti,ab.
5. nonmelanom*.ti,ab.
6. non melanom*.ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Melanoma/
9. melanoma*.ti,ab.
10. Skin Neoplasms/
11. skin cancer*.ti,ab.
12. 8 or 9 or 10 or 11
13. 7 or 12
14. sun exposure.ti,ab.
15. sun exposed.ti,ab.
16. Sunburn/
17. sunburn.ti,ab.
18. sunbath*.ti,ab.
19. Sunlight/
20. Ultraviolet Rays/
21. solar radiation.ti,ab.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. sunlamp*.ti,ab.
24. sunbed*.ti,ab.
25. tanning bed*.ti,ab.
26. tanning booth*.ti,ab.
27. tanning salon*.ti,ab.
28. tanning device.ti,ab.
29. artificial light*.ti,ab.
30. artificial uv.ti,ab.

31. indoor tan*.ti,ab.

32. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

33. Sunscreening Agents/

34. sunscreen.ti,ab.

35. 33 or 34

36. 22 or 32 or 35

37. 13 and 36

38. exp Organ Transplantation/

39. solid organ transplant*.mp.

40. transplant recipient*.tw.

41. exp Immunosuppression/

42. Immunocompromised Host/

43. 38 or 39 or 40 or 41 or 42

44. 37 and 43

45. 38 or 39 or 40

46. 13 and 45

47. randomized controlled trial.pt.

48. controlled clinical trial.pt.

49. randomized.ab.

50. placebo.ab.

51. Clinical Trials as Topic/

52. randomly.ab.

53. (crossover or cross-over).tw.

54. trial.ti.

55. 50 or 48 or 47 or 54 or 51 or 53 or 49 or 52

56. Animals/ not (animals/ and Humans/)

57. 55 not 56

58. 46 and 57

Figure S2. Risk of bias in individual studies

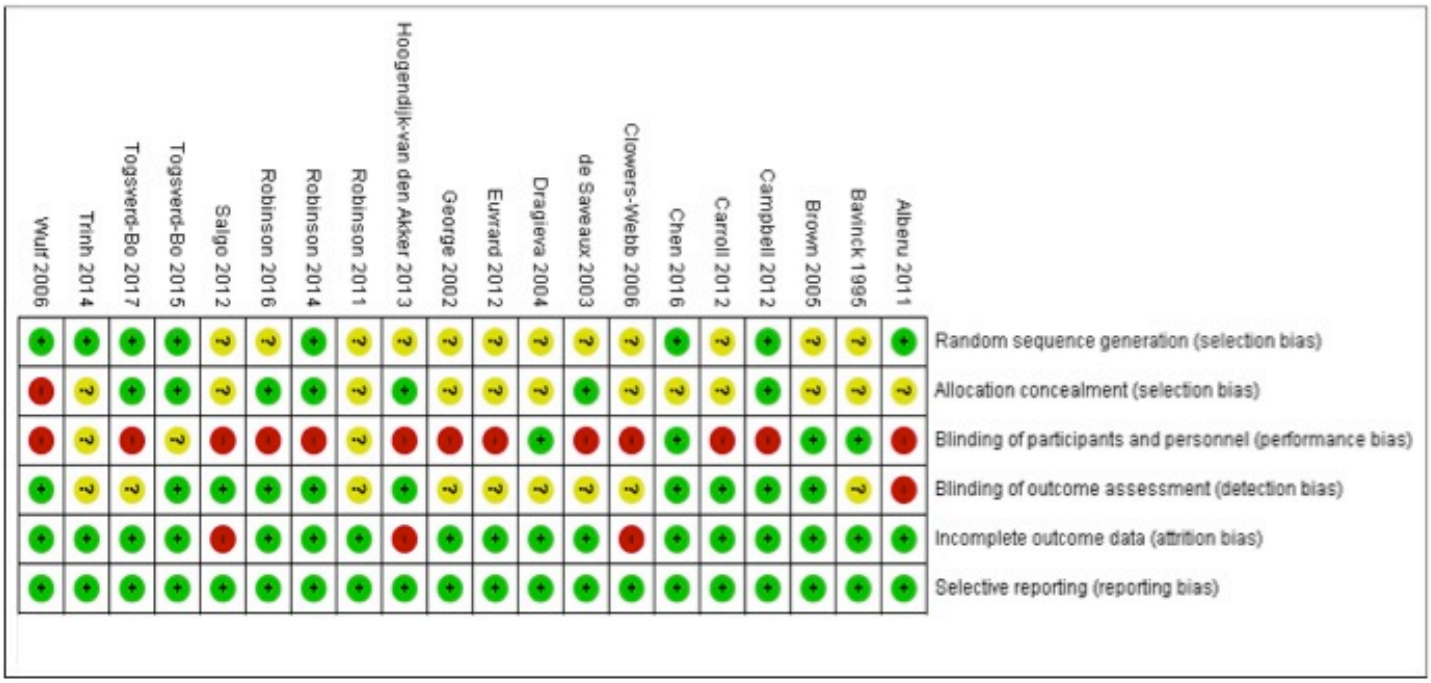
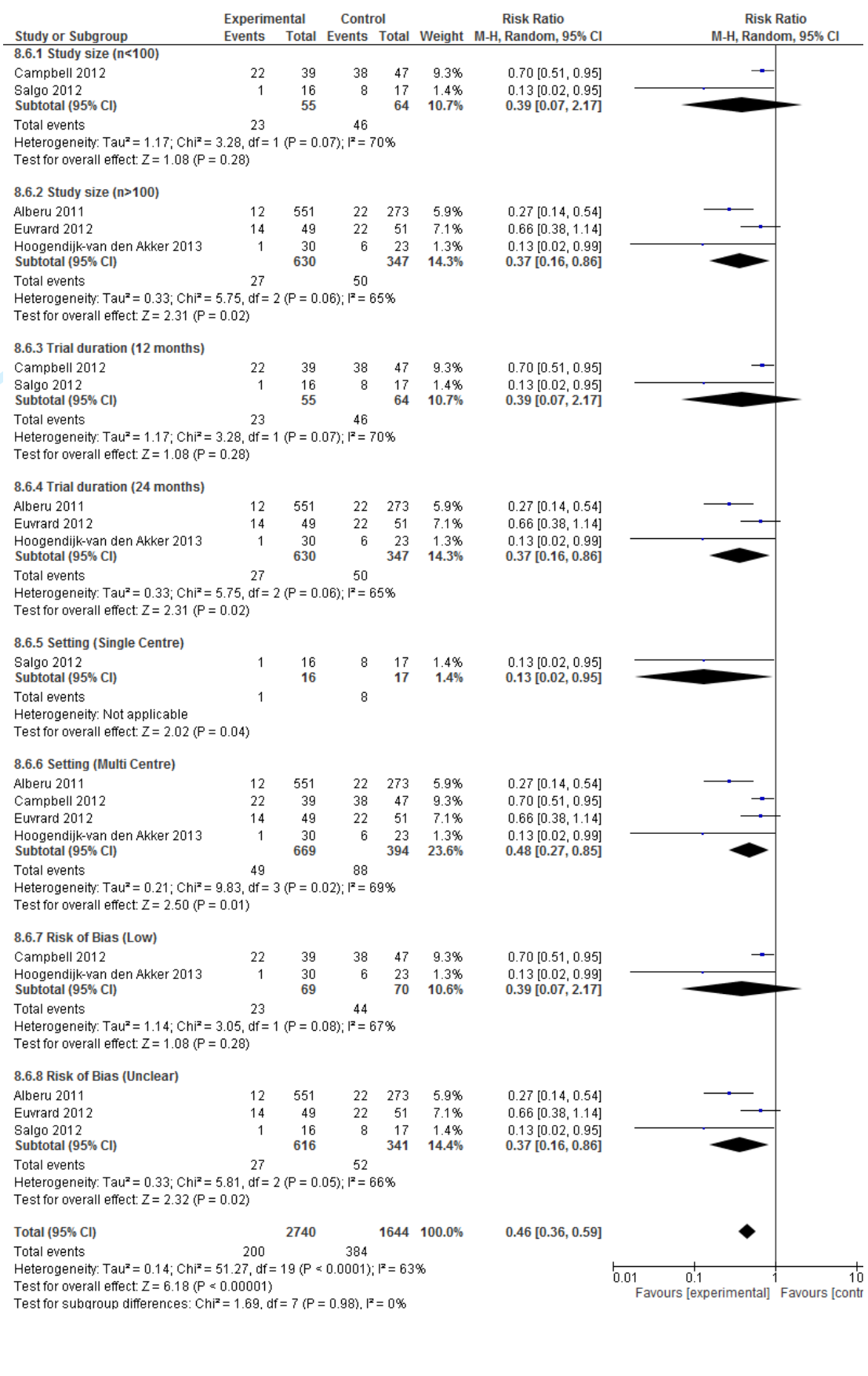


Table S1. Assessment of quality of studies using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

Number of studies	Quality of assessment (Decrease in quality score) Risk of bias/Quality of evidence	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
Sun protection behavior						
5 RCTs[20,26-29]	**Serious study limitations (-1)** Randomisation unclear[20,26,28,29] Participants not blinded or well described[20,26-29] Concealment of allocation not described.[26,29]	**Important inconsistency (-1)** Analysed in subgroups. heterogeneity (I^2=99%)[26-28]	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (2 weeks to 10 months) Same sample of participants[20,28]	**Serious imprecision (-1)** Small sample size, CIs crosses the null	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection knowledge						
6 RCTs[20,24,26-29]	**Serious limitations (-1)** Randomisation unclear[20,26,28,29] Participants not blinded or well described[20,24,26-29] Concealment of allocation not described[24,29]	**Important inconsistency (-1)** Heterogeneity (I^2 85%)	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (1 day to 10 months) Same sample[20,28]	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection attitude						
4 RCTs[20,27-29]	**Serious limitations (-1)** Randomisation unclear[20,28,29] Participants not blinded or well described[20,27-29] Concealment of allocation not described[28,29]	**Important inconsistency (-1)** Wide variation in the effect estimates, heterogeneity (I^2 97%).	**Indirectness (-1)** Diverse interventions (written vs. electronic), Similar duration. Same sample[20,28]	**Serious imprecision (-1)** Small sample size, small number of events	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**

Complications (skin irritation, sunburn)						
2 RCTs[27,28]	**Serious limitations (-1)** Participants not blinded[27,28]	**Important inconsistency (-1)** Heterogeneity (I^2=95-99%) Analysed in subgroups. Similar effect estimates.	**Indirectness (-1)** Diverse interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Biologic measures (melanin index, sun damage)						
2 RCTs[27,28]	**Serious limitations (-1)** Randomisation unclear[28] Participants not blinded[27,28]	**Important inconsistency (-1)** Analysed in subgroups. Heterogeneity (I^2 60%)	**Indirectness (-1)** Different interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Pre-cancerous incidence						
4 RCTs [23,31-34]	**Serious limitations (-1)** Randomisation or allocation unclear[31,32,34] Participants not blinded or well described[23,31-34]	**Important inconsistency (-1)** Analysed in subgroups.	**Indirectness (-1)** Diverse interventions, varying duration	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**
Cancer incidence						
10 RCTs [1,25,31,34-40]	**Serious limitations (-1)** Randomisation unclear[1,36,38,39] Allocation concealment not used or unclear[1,25,35,36,38,40] Participants not blinded.[1,31,35,37-40]	**Important inconsistency (-1)** Majority of participants came from 1 study[35] Small sample[1,25,31,34,36-40]	**Indirectness (-1)** Diverse interventions (immunosuppression, photodynamic therapy, immune response modifier, retinoid, nicotinamide), varying duration	**Serious imprecision (-1)** Majority of participants from one trial (n=551), small number of events	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**

Figure S3. Subgroup analyses of immunosuppression conversion interventions on skin can



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029265.R1
Article Type:	Original research
Date Submitted by the Author:	10-Dec-2019
Complete List of Authors:	James, Laura; University of Sydney, Saglimbene, Valeria; The University of Sydney, Sydney School of Public Health Wong, Germaine; The Children's Hospital at Westmead, Centre for Kidney Research Tong, Allison; The University of Sydney, Sydney School of Public Health Luu, Laurence; The University of Sydney, Sydney School of Public Health Craig, Jonathan; Flinders University Faculty of Medicine Nursing and Health Sciences, College of Medicine and Public Health, ; The Children's Hospital at Westmead, Centre for Kidney Research Howard, Kirsten; University of Sydney, School of Public Health Howell, Martin; University of Sydney - Camperdown and Darlington Campus, School of Public Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	skin cancer, melanoma, prevention, sun protection, sun protection behaviors

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Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

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Word count (abstract): 205

Word count (body): 3593

Tables: 4 **Figures:** 5

K**ey words:** skin cancer, melanoma, prevention, sun protection, sun protection behaviors, health behavior

Authorship

LJJ, GW, AT, LL, JCC, KH, MH designed the study; LJJ, VS, LL, MH conducted the data extraction and analyses; all authors contributed to the interpretation of the analyses. LJJ drafted the manuscript; all authors contributed to the writing and review of the manuscript.

Disclosure

The authors declare no conflicts of interest.

Data availability statement

No additional data available.

Funding

LJJ is supported by the National Health and Medical Research Council (NHMRC) Better Evidence and Translation in Chronic Kidney Disease (BEAT-CKD) Program Grant (APP1092957). MH is supported by the BEAT-CKD Program Grant (APP1092957). AT is supported by the NHMRC Fellowship (APP1106716). The funding organizations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript.

Abbreviations

AZA, azathioprine

BCC, basal cell carcinoma

CNI, calcineurin inhibitors

CI, confidence intervals

MAL, methyl aminolaevulinate cream

MD, mean difference

MMF, mycophenolate mofetil

mTORI, mammalian target of rapamaycin inhibitors

NMSC, non-melanoma skin cancer

RCT, randomized controlled trial

RR, relative risk

SCC, squamous cell carcinoma

SMD, standardized mean difference

ABSTRACT

Objectives

Solid organ transplant recipients are at increased risk of skin cancer, affecting more than 50% of recipients. We aimed to determine the effectiveness of interventions for behavioral change for sun protection or skin cancer prevention in solid organ transplant recipients.

Design

Systematic review

Data sources

Electronic databases were searched from inception to January 2018.

Eligibility Criteria

We included randomized controlled trials that evaluated the effect of behavioral or pharmaceutical interventions on behavioral change or skin cancer prevention in solid organ transplant recipients.

Data extraction and synthesis

Risks of bias and evidence certainty were assessed using Cochrane and the GRADE framework.

Results

Twenty trials (n=2,295 participants) were included. It is uncertain whether behavioral interventions improve sun protection behavior (N=3, n= 414, SMD 0.89, 95% CI -0.84-2.62, I^2 =98%) and knowledge (N=4, n=489, SMD 0.50, 95% CI 0.12-0.87, $I^{2=}$ 76%) as the quality of evidence is very low. We are uncertain of the effects of mammalian target of rapamaycin inhibitors on the incidence of non-melanocytic skin cancer (N=5, n=1080, RR 0.46 95% CI 0.28-0.75, $I^{2 =}$72%) as the quality of evidence is very low.

Conclusions

Behavioral and pharmaceutical preventive interventions may improve sun protective behavior and knowledge, and reduce the incidence of non-melanocytic skin cancer, but the overall quality of the evidence is very low and insufficient to guide decision-making and clinical practice.

PROSPERO Registration number

CRD42017063962

ARTICLE SUMMARY

Strengths and limitations

- A comprehensive review conducted using methods outlined by Cochrane Collaboration including GRADE to assess risk of bias and evidence certainty
- Inclusion of a broad range of interventions, including behavioral to improve sun protection behavior and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence
- Difficulty obtaining an overall summary estimate for many outcomes due to the variability in the analytical methods and reporting in individual studies
- Unable to perform detailed subgroup analyses or assess for publication bias due to small number of studies
- Few trials included the important outcomes of skin cancer and none included melanoma or mortality.

1. INTRODUCTION

Skin cancer, including melanoma and nonmelanoma skin cancer (NMSC), is the most frequently diagnosed malignancy among solid organ transplant recipients, affecting more than 50% of post-transplantation recipients.[1 2] The cumulative incidence of NMSC increases with time after transplantation, from 5-10% at 2 years to 40-80% at 20 years.[2-4] Compared to the general population, there is a higher rate of squamous cell carcinoma (SCC) to basal cell carcinoma (BCC), with an incidence of 65 to 250 times greater than the age and gender-matched general population.[5-8] Once cancer develops, management options are limited as immunotherapy may be unsuitable as it may lead to graft rejection.[9 10] Although registry data shows improvement in survival rates of transplant recipients as a result of improved transplantation techniques and management of immunosuppression, there is a greater burden of skin cancer and cancer related mortality.[11] The excess risk of death from invasive and metastatic skin cancer, such as SCC and melanoma, are three times to nine times higher than the general population, with five-year overall survival of less than 30%.[6 12-15]

Sun exposure behaviors remain the most significant and modifiable risk factor in the prevention of skin cancers in the general population.[16] However, with the dramatic increase in skin cancers in solid organ transplant recipients, pharmaceuticals have also been used to reduce and delay the development of skin cancer.[16 17] Current recommendations for preventive strategies have often been extrapolated from guidelines in the general population, which may not be applicable to solid organ transplant recipients.[18 19] For example, frequent skin self-examination and annual to biannual total body skin examination are generally recommended for the general population.[18-20] Sun protective behaviors including use of sunscreen, protective clothing and limiting sun exposure during peak hours of high UV index days are potential measures for skin cancer prevention.[3 4 14]

Further, alteration of maintenance immunosuppression such as conversion to mammalian target of rapamaycin inhibitors (mTORi) and secondary prevention using retinoid acitretin are recommended for management of skin cancers in high risk transplant recipients.[20]

The aim of this study is determine the effectiveness of interventions that promote behavioral change and skin cancer prevention in solid organ transplant recipients.

2. METHODS

This systematic review followed a pre-specified protocol registered in PROSPERO (CRD42017063962) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[21] The study was exempt from approval from an ethics' board.

2.1 Inclusion criteria

All randomized controlled trials (RCTs) or quasi RCTs (allocated to trial arms by investigators) of interventions for skin cancer prevention (both melanoma and non-melanoma skin cancer) in solid organ transplant recipients were included. Behavioral interventions defined as any strategy used to promote sun protective behavior including passive (e.g. pamphlets), active (e.g. group workshops, counselling, dermatology clinic) and provision of sun protective equipment; and pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers, nicotinamide and oral retinoids) and studies that reported skin cancer related outcomes as their primary outcomes were included. Studies that did not report these outcomes as primary end-points were excluded. Studies of interventions for the treatment of skin cancer were excluded.

2.2 Search strategies

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from inception to November 2019 without language restriction, using search strategies designed by a specialist information manager (see Medline search strategy in Figure S1). Reference lists of included studies were also searched.

2.3 Data extraction

Titles and abstracts were reviewed by two independent authors (LJJ & LL) and those that did not meet the inclusion criteria were excluded. Full text articles were reviewed by 3 independent reviewers (LJJ, VS, LL) and any disagreements were resolved by discussion. Data on study design, geographic location, sample size, type of transplant, measurement of interventions, interventions and comparators were extracted. We sought unclear or missing information from authors where possible.

2.4 Outcome measures

The pre-specified outcome measures were incidence of precancerous and cancerous lesions, sun protection behavior (including use of sunscreen, use of protective clothing including hats and sunglasses, shade and sun avoidance), knowledge and attitude, skin self-examination, sun exposure (including skin irritation, sunburn) and biologic measures (including measurement of melanin index and sun damage assessment).

2.5 Risk of bias and quality of evidence

The risk of bias was assessed independently by LJJ and VS using the Cochrane risk of bias tool.[22] The domains included in the assessment were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, trial registration and industry involvement. Each criterion was

assigned a judgment of high, low or unclear risk of bias. Intention to treat and lost to follow up were also assessed for each study. The quality of the evidence informing summary estimates for each outcome was then assessed by LJJ using the Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines.[23]

2.6 Data synthesis and statistical analyses

Continuous outcomes were summarized as mean difference (MD) or standardized mean difference (SMD) and dichotomous outcomes as relative risk (RR). A MD/SMD greater than zero and/or a RR greater than 1 could be interpreted as favoring the intervention group relative to the control, unless specified elsewhere. Risk estimates were reported with 95% confidence intervals (CI), using random-effects meta-analysis. We considered P values <0.05 to be statistically significant. We quantified the heterogeneity using the I^2 statistic. An I^2 value of <25% was considered to represent low heterogeneity and >75% as high heterogeneity. When sufficient data were available, possible sources of heterogeneity were investigated using subgroup analysis based on pre-specified study characteristics including sample size, trial duration, setting and overall risk of bias. Funnel plots were planned to evaluate small study effects when at least ten studies were included in meta-analysis. All analyses were conducted using Review Manager version 5.3 software.

2.7 Patient and public involvement

There was no patient or public involvement.

3. RESULTS

3.1 Study selection

The literature search identified 1280 articles, of which, 1201 were excluded after abstract and title review. Full text assessment of 79 studies found 22 eligible articles for inclusion (Figure 1).

3.2 Studies characteristics

We included 22 reports of 20 RCTs, including 2,295 participants (Figure 1). The study characteristics are summarized in Table 1 and Table 2. The median number of participants was 44 (range 17 to 830) and the median follow-up duration was 10 months (range 1 day to 60 months). All studies included kidney transplant recipients, with some also including heart transplant recipients (n=1), liver, heart, pancreas, lung, heart/lung and other transplants (n=1), and lung and liver transplant recipients (n=2). In total, 15 of 21 (76%) studies provided sufficient data for the meta-analyses. Six studies did not meet final criteria for meta-analysis as they had the same sample of participants (n=1),[24] or did not provide data that was able to be meta-analyzed (n=5).[25-29]

3.3 Risk of bias and quality of the evidence

Overall studies were at low or unclear risk of bias for many domains (Figure 2; Figure S2). Random sequence generation and allocation concealment were unclear in most studies (n=12, 60%). Blinding of participants was not done in most studies (n=16, 80%) and blinding of outcome assessors was only reporting in half of the studies (n=10). Intention to treat analyses were used in 6 (30%) studies and 6 studies (30%) had a high loss to follow-up. A total of 3 (15%) studies had incomplete outcome data, and all studies were at low risk for selective reporting. Seven studies (35%) reported industry involvement in authorship, design, or data analysis, and of the 16 trials requiring trial registration, only 9 (56%) reported accordingly.

The overall quality of the evidence was very low for all outcomes (Table S1) due to limitations in study design, heterogeneity in the intervention and outcomes measures, the very small sample size of individual studies and the small number of studies for each specific outcome. Obtaining an overall summary estimate was difficult for many outcomes due to the variability in the analytical methods and reporting in individual studies. In particular, assessment of reporting of sun protection behavior and sun protection knowledge was not possible as outcomes were inconsistent and there was large diversity of interventions used (e.g. written education material versus a mobile app program). Furthermore, formal testing of publication bias was not performed due to insufficient data.

3.4 Interventions

The interventions in the included studies were grouped in three broad categories, behavioral (n=6), switch to mTOR inhibitors (n=6), and other pharmaceutical interventions (photodynamic therapy, immune response modifiers, oral retinoids and nicotinamide) (n=9). Studies of behavioral interventions used passive methods of delivery including written educational material (n=2), both written educational material and text messages (n=1), mobile app programs (n=2) and a video (n=1).

All six studies of immunosuppression compared mTORis (sirolimus) to calcineurin inhibitors (CNI) based therapies.

Four of the eight studies of other pharmaceutical interventions assessed the effect of photodynamic therapy using methyl aminolevinate creams compared to placebo (n=1), no treatment to contralateral area (n=2) or a topical immune response modifier cream (n=1). Three studies assessed oral retinoid using acitretin compared to placebo (n=1), lower dose (n=1) or a

drug free period (n=1), one study assessed nicotinamide compared to placebo and a single study assessed the benefits of topical immune response modifier compared to placebo in kidney transplant recipients.

3.5 Effect of behavioural interventions on sun protection outcomes

Sun protection behavior

Sun protection behavior, defined as hours spent outdoors per week, use of sunscreen, wearing protective clothing and seeking shade, was assessed in three trials[30-32]. Educational workbooks,[30] educational workbooks and text messages[31] and a mobile app program[32] were compared with standard care. Patients who received behavioral interventions reported improved sun protection behavior scores[30-32] (3 studies, 414 participants, SMD 0.89, 95% CI -0.84-2.62, I^2 98%) (Table 3; Figure 3). We are uncertain of the effects of behavioural interventions on sun protection behavior due to very low quality of evidence. A single trial assessed a standardised and validated educational workbook and found an improvement in the proportion of participants engaging in skin self-examination after one month (75 participants, RR 4.14, 95% CI 2.22-7.72).[33] One trial assessed a mobile app program and reported a reduction in daily hours spent outdoors among the intervention group (170 participants, MD -6.12, 95% CI -711 to -5.13).[32]

Sun protection knowledge

The effectiveness of educational workbooks, text messages, mobile app programs and videos on sun protection knowledge was assessed in 6 studies[24 28 30-33], four of which provided data for a meta-analysis. There was an improvement in knowledge scores (4 studies, 489 participants, SMD 0.50, 95% CI 0.12-0.87, I^2 76%) in the intervention group compared to standard care (Figure 4).[30-33] One study compared an interactive visual representation of the educational program with

standard information pamphlets and found that knowledge of sun protection improved among those who received the educational video.[28]

Sun protection attitude

Three studies assessed sun protective attitude after receiving an educational workbook, text messages or a mobile app program over a period of 0.5 months to 1.5 months.[31-33] Compared to standard care, there was an overall improvement in scores of concern about developing cancer (3 studies, 348 participants, SMD 1.85, 95% CI 1.59-2.11, I^2 96%).[31-33] Two studies involving 273 participants reported an improvement in scores of understanding the personal risk of skin cancer (SMD 0.61, 95% CI -0.60-1.82, I^2 96%), adherence to sun protection (SMD 0.77 95% CI -0.14-1.68, I^2 92%) and willingness or intention to change behavior (SMD 1.70, 95% CI -1.68-5.07, I^2 99%).[31 32] We are uncertain of the effects of behavioural interventions on sun protection attitude due to very low quality of evidence. A single study involving 75 participants also reported an improvement in scores of ability to recognize a potential skin cancer (MD 1.80, 95% CI 1.35-2.25), importance of skin self-examination (MD 1.05, 95% CI 0.61-1.49) and having a partner help for skin self-examination (MD 1.59, 95% CI 1.10-2.08).[33] Another single study reported an improvement in the importance of engaging in sun protection (measured using 5-point Likert scale) (101 participants, MD 7.00, 95% CI 2.94-11.06).[31]

Skin complications and biologic measures

Two trials of behavioral interventions in 271 kidney transplant recipients compared a mobile app or an educational workbook and text messages to standard care on reported skin complications and biologic measures of sun exposure.[31 32] The intervention group experienced a reduced incidence of skin irritation (a culturally relevant term for sun exposure[34]) (RR 1.00, 95% CI 0.89-1.13, I^2 95%) or sunburn (RR 3.19, 95% CI 2.47-4.10, I^2 99%). They also had a decreased melanin

index (right forearm, SMD -0.42, 95% CI -0.66 to -0.18; cheek SMD -0.25, 95% CI -0.64 to -0.15) and reduced severity of sun damage (SMD -0.13, 95% CI -0.40 to 0.13) on sun exposed areas (measured using clinical images of chronic sun damage and scored 1-10).

3.6 Effect of pharmaceutical interventions on skin cancer prevention

The incidence and responses of pre-cancerous lesions were measured only in trials of pharmaceutical interventions (Table 4). These included the switch to mTOR inhibitors (n=1),[35] photodynamic therapy (n=2)[36 37] and immune response modifiers (n=1)[38] to current treatment or placebo. The incidence of non-melanocytic skin cancers (NMSC) was assessed in nine pharmaceutical studies.[1 35 38-44] None included melanoma as an outcome.

Topical/local interventions

One trial of 14 participants compared an immune response modifier, 5% imiquimod cream with placebo and found a reduction in the incidence of skin dysplasia (RR 2.14, 95% CI 0.31-14.65), skin atypia (RR 3.00, 95% CI 0.47-19.35), and viral warts (RR 7.00, 95% CI 0.46-106.10).[38]

One Danish study of 26 kidney transplant recipients compared photodynamic therapy with no treatment and reported a relative reduction by approximately 40% in the incidence of NMSC on the treated area (RR 0.59, 95% CI 0.34-21.03, p 0.06).[44] A lower incidence of SCC was also reported in one trial comparing two areas of skin using an immune response modifier and placebo (14 participants, RR 0.09, 95% CI 0.0.01-1.70).[38] Two trials comparing photodynamic therapy to an immune response modifier or photodynamic therapy to placebo in recipients with diagnosed keratoses reported a complete response rate of 60% compared to 24% in the control group (50 participants, RR 5.03, 95% CI 0.14-176.17, I^2 85%).[36 37] We are uncertain of the effects of

photodynamic therapy on incidence of precancerous lesions due to very low quality of evidence. Further, one trial which was not included in the meta-analysis, reported a higher cumulative incidence of actinic keratosis lesions in untreated skin (63%) compared with skin treated by photodynamic therapy (28%).[27]

Systemic interventions

mTORis therapy reduced the incidence of NMSC compared to CNIs maintenance therapy (5 trials, 1082 participants, RR 0.46, 95% CI 0.28-0.75, I^2 72%) (Figure 5).[1 35 39 41 43] However evidence was limited due to short follow-up periods, variability in dosing of mTORis and significant rates of loss to follow up, and therefore we are uncertain of the effects of mTORis on skin cancer incidence due to very low quality of evidence. A single trial involving 21 patients reported a reduction in the overall incidence of SCC by 49% in the conversion arm, but reported a drop out rate of 77% and follow-up time of less than 2 years.[25] Further, a single trial which compared mTORi conversion from CNI based therapy reported a significant improvement in skin dysplasia (32 participants, RR 24.35, 95% CI 1.55-381.99).[35]

Two trials comparing an oral retinoid, acitretin, with placebo or a drug free period reported an increased lower risk of both SCCs and BCCs (46 participants, RR 0.40, 95% CI 0.19-0.85, p 0.02; RR 0.50, 95% CI 0.14-1.76)[42] or development of a new skin cancer (19 participants, RR 0.22, 95% CI 0.06-0.90). However, there were no differences in the incidence of new SCCs.[40] One trial, which was not included in the meta-analysis, showed approximately a 50% reduction in the incidence of actinic keratosis which compared a high dose to a low dose of acitretin.[26]

One Australian trial of 22 kidney transplant recipients compared nicotinamide with placebo and reported an estimated relative rate difference of 0.35 (95% CI -0.62 to 0.74), 0.67 (95% CI -0.40 to 0.90) and 0.07 (95% CI -1.51 to 0.65) for NMSC, BCCs and SCCs respectively.[29]

3.7 Subgroup analysis

Study size, trial duration, setting and risk of bias did not modify the effects of CNIs and mTORIs on skin cancer incidences (Figure S3). Sources of heterogeneity for other treatment effects could not be explored due to insufficient data.

4 DISCUSSION

Skin cancers (both non-melanoma and melanoma) are major causes of morbidity and mortality in solid organ transplant recipients. Despite this, trials of interventions aimed at preventing skin cancer in solid organ transplant recipients are few in number (20 trials), small with half comprising of 50 patients or less, of short duration (48% have <12 months follow up) and 52% do not include incidence of skin cancer as an outcome. Our review included 22 reports of 20 trials involving 2,295 transplant recipients, who were predominately kidney transplant recipients. The studies covered a broad range of interventions, including behavioral to improve sun protection behavior and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence. None of the behavioral intervention studies included precancerous lesions or skin cancer incidence as outcomes. Although interventions showed plausible improvements to sun protection behaviors, precancerous lesion responses and cancer incidence, there was considerable variability across interventions types, variability in outcomes assessed and outcome estimates. Overall, the current evidence for interventions for skin cancer prevention in solid organ transplant recipients is of very low quality and is insufficient to guide decision-making and clinical practice.

Although behavioral interventions appeared to improve sun protection attitude, knowledge and behavior, there were inconsistencies detected and none of these studies included skin cancer as an outcome. Due to limited number of studies, we were unable to compare specific behavioral interventions (e.g. mobile app vs. written education) to ascertain the most effective method of delivering sun protection education. While there may be some modest benefits in the reduction in cancer incidence (for NMSC) among solid organ transplant recipients who were converted to mTORIs compared to those on CNI maintenance, there was substantial heterogeneity across the studies that was unable to be explained by subgroup analyses. Heterogeneity may be attributed to the absence of long term follow up, large discontinuation rates owing to adverse events and variability in the doses of mTORIs. Pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers) showed a reduction in precancerous lesions compared to standard care or a comparator group. However uncertainty exists in the treatment effects and there were too few studies, interventions were incomparable, follow-up times were variable and considerable loss to follow up for some studies to conclude that the benefits are sustainable.

Previous systematic reviews have evaluated the impact of behavioral interventions on skin cancer prevention in the general population,[45] and concluded that computer programs may increase sun protective behaviors, and 'appearance-focused' interventions may decrease sun tanning and UV exposure in adolescents and young women, respectively. Reviews conducted in other populations at high-risk including outdoor workers,[46] family history, personal history and phenotypic factors[47] have found similar improvement in sun protective behaviors, including use of sunscreen, as well as a decreased incidence of keratoses. A systematic review of the benefits and harms of oral

retinoids for the prevention of skin cancer among high risk transplant recipients led to inconclusive results on the effect of acitretin due to the small number of included trials.[48]

Despite the inclusion of all interventions aimed at the prevention of skin cancer in solid organ transplant recipients and the comprehensive systematic search for eligible studies, there are some potential limitations. Due to the heterogeneity of the studies, the high risk of bias, the potential for reporting bias and imprecision in the point estimates of individual studies, there is a high degree of uncertainty in the estimate of the effect of skin cancer prevention interventions. All studies of behavioral interventions were undertaken in United States, with 4 by the same authors, whilst most pharmacological intervention studies were conducted in Europe. There were also large discontinuation rates owing to adverse events in trials of mTORIs. Further, given the small number of studies included in the meta-analysis, we were unable to perform any detailed subgroup analyses to explore heterogeneity or assess for publication bias. While we were unable to show and assess publication bias using standard statistical tests, we would suggest the observed heterogeneity may also be attributed to potential publication and reporting biases. It is difficult to quantify the extent of such bias in this review, but one would expect research with 'positive' findings that indicate an intervention works, such as behavioral interventions improve sun protection, are more likely to be published more than one, in high impact journals and more likely to be cited. Finally, few trials included patient important outcomes associated with skin cancer and none included melanoma or mortality.

The use of pharmaceutical and immunosuppression therapy remains complex. Not only has mTORI therapy shown benefits in lowering the risk of skin cancer, early conversion to mTORI therapy from CNIs has also shown promising effects in reducing cancer rates.[49 50]On the contrary, overall mortality is higher and discontinuation following adverse events is more common in patients who

receive mTORI therapy.[49 50] Several RCTs showed a higher rate of patients reporting adverse events or drug discontinuation with sirolimus,[1 41 43] demonstrating concern of its clinical usefulness.[49] Nicotinamide may also offer benefits to reducing skin cancer incidence by 20% and is relatively safe with minimal side effects. The protective effect of nicotinamide on skin cancer incidence in kidney transplant recipients is currently being explored in a phase 3 randomised controlled trial.

Although behavioral change is a simple strategy, long-term adherence remains challenging. While behavioral counseling has been shown to increase sun protective behaviors in non-transplant populations,[45] there is no direct evidence to show that the behavioral change led to a reduction in morbidity and mortality. Previous studies have suggested that transplant recipients do not practice sun protective behaviors regularly,[51-53] were less likely to use sunscreen[54] and that patients have to perceive skin cancer as being an important risk to be motivated to change behavior.[55 56] However, studies on risk perception of transplant recipients remain conflicting. Given this complexity and the observed inconsistencies in the existing trials, process evaluations including facilitators and barriers to behavioral change should be included in future trials. Such evaluations could include the use of qualitative methodology to support the trial design, ascertain the perspectives of participants on the intervention and evaluate the implementation.[57 58]

We suggest that further strategies for skin cancer prevention in transplant recipients require a multifaceted and individualized approach. Transplant recipients are likely to benefit from early implementation of education, particularly before transplantation occurs and recipients may be preoccupied with other health needs related to transplantation. Although recipients understand the importance of ongoing education for the ability to self-manage their disease, they may experience difficulty in concentrating and learning new knowledge, and are often unable to look

beyond their graft and the anxiety/fear of graft loss.[59-61] Interventions should be integrated into routine appointments and tailored to meet the individual needs of patients. This would be best achieved through a shared decision-making approach to identify the patient's preferences and priorities and thereby enhance the likelihood of success of self-management and prevention.[62]

Additional large-scale and high-quality RCTs are needed to demonstrate the effectiveness of interventions used to prevent skin cancer in transplant recipients in terms of patient important outcomes, in particular morbidity and mortality associated with skin cancer. Determining patient's preferences for prevention and management of skin cancer are also warranted to ensure interventions and outcomes for trials are relevant to patient needs and priorities and better support patient-centered treatment decisions.[63] Evidence of the efficacy of sun protective behavior interventions need to be strengthened, with use of measures that are homogenous, reliable and validated.

Preventative measures including behavioral, switch to mTOR inhibitors and other pharmaceuticals may improve skin cancer outcomes for solid organ transplant recipients. However, the overall quality of evidence is of very low and insufficient to guide decision-making and clinical practice. Future robust studies that are well powered, have long-term follow up, and use clinical and patient important outcome measures in a consistent manner are required to therefore optimize outcomes for solid organ transplant recipients.

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Table 1. Characteristics of included studies (n=20)

Characteristics	N (%)
Type of transplant	
Kidney	16 (80)
Multiple*	4 (20)
Sex	
≥ 50% Male	18 (90)
< 50% Male	1 (5)
Not specified	1 (5)
Age (mean)	
< 60	10 (50)
≥ 60	5 (25)
Not specified	5 (25)
Sample size	
10 – 50	11 (55)
50 – 100	3 (15)
100 – 200	4 (20)
>200	2 (10)
Setting	
Single center	8 (40)
Multi center	11 (55)
Not specified	1 (5)
Country of origin	
Australia	3 (15)
Denmark	4 (20)
France	1 (5)
Germany	1 (5)
Netherlands	2 (10)
New Zealand	2 (10)
Switzerland	1 (5)
Sweden	1 (5)
United Kingdom	3 (15)
United States	6 (30)
Other†	1 (5)
Intervention Type	
Behavioral	5 (25)
Switch to mTOR inhibitors	6 (30)
Photodynamic therapy	4 (20)
Oral retinoid	3 (15)
Nictotinamide	1 (5)
Topical immune response modifier	1 (5)
Duration of follow up	
<12 months	9 (45)
12 months	4 (20)
24 months	5 (25)
>24 months	1 (5)
Not specified	1 (5)
Year of publication	
1995 – 1999	1 (5)
2000 – 2004	3 (15)
2005 – 2009	4 (20)
2010 – 2014	8 (40)
2015 – 2017	4 (20)

* Kidney, liver and lung (n=2); kidney and heart (n=1); Kidney and multiple other types (n=1) – see text

† 111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Table 2. Characteristics of individual studies

Study	N	Type of transplant	Setting	Type of intervention	Measures	Intervention	Comparator	Primary outcomes	Time (mths)
Behavioral interventions (n=6)									
Clowers-Webb 2006[30]	202	Kidney, liver, heart, pancreas, lung, heart/lung, other§	Single centre, United States	Behavioral	Self-reported questionnaire	Repetitive written material	Standard care	Knowledge & behavior	10
Robinson 2011[33]	75	Kidney	United States	Behavioral	Self-reported questionnaire	Workbook	Standard care	Knowledge & behavior	1
Robinson 2014[31]	101	Kidney	Single centre, United States	Behavioral	Self-reported questionnaire Physical examination	Workbook Text messages	Standard care	Knowledge & behavior	1.5
Robinson 2015[24]‡	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire	Mobile app program	Standard care	Knowledge & behavior	0.5
Robinson 2016[32]	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire Physical examination	Mobile app program	Standard care	Knowledge & behavior	1.5
Trinh 2014[28]*	100	Kidney, liver, lung	Single centre, United States	Behavioral	Self-reported questionnaire	Video	Pamphlet	Knowledge	1 day
Switch to mTOR inhibitors (n=7)									
Alberu 2011[39]	830	Kidney	Multi centre§	Switch to mTOR inhibitors	Investigator reported adverse events	Conversion to sirolimus	CNI	Cancer incidence	24
Campbell 2012[41]	86	Kidney	Multi centre, Australia, New Zealand, United States	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	12
Carroll 2013[25]*	32	Kidney	Multi centre, UK	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to prednisolone & sirolimus	CNI/AZA	Cancer incidence	24
Euvrard 2012[1 64]	120	Kidney	Multi centre, France	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	24
Hoogendijk-van den Akker	155	Kidney	Multi centre, Netherlands, UK	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	AZA/MMF/ CNI	Cancer incidence	24

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2013[43]									
Salgo 2010[35]	44	Kidney	Single centre, Germany	Switch to mTOR inhibitors	Physical examination +/- biopsy Clinical photographs	Conversion to sirolimus and prednisone	AZA/MMF/ CNI	Precancerous skin dysplasia incidence	12
Pharmaceutical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); nicotinamide (n=1); 5% imiquimod cream (n=1)									
Bavinck 1995[40]	44	Kidney	Multi centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	Acitretin	Placebo	Cancer incidence precancerous lesion reduction	6
Brown 2005[38]	21	Kidney	Multi centre, UK	Topical immune response modifier cream	Physical examination +/- biopsy Clinical mapping and photographs	5% Imiquimod cream	Placebo	Reduction of precancerous lesions	4
Chen 2016[29]*	22	Kidney	Single centre, Australia	Nicotinamide	Physical examination	Nicotinamide	Placebo	Cancer incidence	6
de Sevaux 2003[26]*	26	Kidney	Single centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	High dose acitretin	Low dose acitretin	Cancer and precancerous incidence	12
Dragieva 2004[36]	17	Kidney, heart	Single centre, Switzerland	Photodynamic therapy	Physical examination +/- biopsy Clinical photographs	Methyl aminolevulinate cream	Placebo	Precancerous lesion response	4
George 2002[42]	23	Kidney	Multi centre, Australia	Oral retinoid	Physical examination Annual radiological evaluation	Acitretin	Drug free period	Cancer incidence	24
Togsverd-Bo 2015[27]*†	25	Kidney	Single centre, Denmark	Photodynamic therapy	Physical examination Clinical photographs	Methyl aminolevulinate cream	No treatment contralateral area	Actinic keratosis incidence	36
Togsverd-Bo 2017[37]†	35	Kidney, lung, liver	Multi-centre, Denmark and Sweden	Photodynamic therapy	Physical examination Questionnaire/Diary	Methyl aminolevulinate cream	5% imiquimoid cream	Actinic keratosis lesion response	6

Wulf 2006[44†]	27	Kidney	Multi centre, Denmark and Netherlands	Photodynamic therapy	Clinical mapping and photographs	Methyl aminolevulinate cream	No treatment contralateral area	Cancer incidence	12

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

‡Excluded from analyses – same participants as Robinson 2016

§111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Abbreviations: CNI, Calcineurin inhibitor; AZA. Azathioprine; MMF, Mycophenolate mofetil

Table 3. Effect of behavioral interventions on sun protection outcomes

Outcome	Studies	Participants	Weighted MD[a]/SMD[b] [95% CI]	Relative risk	P	I^2	Intervention	Comparator
BEHAVIORALINTERVENTION (n=5)								
SUN PROTECTION BEHAVIOR								
General sun protection behavior	3	414	0.89 [-0.84, 2.62]		0.31	98%	Workbook, text messages, mobile app program	Standard care
Skin self-examination								
1 month after visit	1	75		4.14 [2.22, 7.72]	<0.001	□0.	Workbook	Standard care
If checked, concerned	1	42		6.43 [0.42, 98.58]	0.18	□□□		
If concerned, saw dermatologist	1	12		Not estimable[c]		□□□		
Decrease daily hours outdoors	1	170	-6.12 [-7.11, -5.13][d]		<0.001	□□□	Mobile app program	Standard care
SUN PROTECTION KNOWLEDGE	4	489	0.50 [0.12, 0.87]		0.01	76%	Workbook, text messages, mobile app program	Standard care
SUN PROTECTION ATTITUDE								
Concern about developing skin cancer	3	348	1.88 [0.96, 2.80]		<0.001	92%	Workbook, text messages, mobile app program	Standard care
Recognise personal risk	2	273	0.61 [-0.60, 1.82]		0.32	96%	Workbook and text messages, mobile app program	Standard care
Confidence in ability to perform sun protection	2	273	0.77 [-0.14, 1.68]		0.10	92%		
Willingness/intention to change behavior	2	273	1.70 [-1.68, 5.07]		0.32	99%		
Knowledge of significance of skin cancer, relevance of sun protection, risk of having a tan	1	101	7.00 [2.94, 11.06]		0.001	□□□	Workbook and text messages	Standard care
Confidence in ability to recognise a skin cancer	1	75	1.80 [1.35, 2.25]		<0.001	□□□	Workbook	Standard care
Importance of skin self-examination	1	75	1.05 [0.61, 1.49]		<0.001	□□□		
Importance of partner help for skin self-examination	1	75	1.59 [1.10, 2.08]		<0.001	□□□		

COMPLICATIONS							
Skin irritation							
None	2	271		1.00 [0.89, 1.13]	0.95	95%	Workbook and text messages, mobile app program	Standard care
> 1	2	271		0.77 [0.43, 1.36]	0.36	89%		
Sunburn (past week)							
None	2	271		3.19 [2.47, 4.10]	<0.001	99%		
> 1	2	271		2.68 [1.81, 3.96]	<0.001	95%		
BIOLOGIC MEASURES							
Melanin index - RU arm (sun protected	2	271	0.12 [-0.12, 0.35]		0.34	0%	Workbook and text messages, mobile app program	Standard care
Melanin index - R forearm (sun exposed)	2	271	-0.42 [-0.66, -0.18][d]		0.001	0%		
Cheek (sun exposed)	2	271	-0.25 [-0.64, 0.15][d]		0.22	61%		
Sun damage assessment - R forearm	2	271	-0.13 [-0.40, 0.13][d]		0.33	16%		

[a]Mean difference
[b]Standardised mean difference
[c]Unable to estimate due to absence of comparator group
[d]Reduction of outcome of interest represents an improvement

Table 4. Effect of pharmaceutical interventions on skin cancer prevention

Outcome	Studies	Participants	Relative risk	P	I^2	Intervention	Comparator
SWITH TO mTOR INHIBITORS (n=5)							
PRE-CANCEROUS LESIONS							
Skin dysplasia							
Any improvement	1	32	24.35 [1.55, 381.99]	0.02	□.0	Sirolimus	CNI[b]
Unchanged	1	32	0.85 [0.28, 2.61]	0.78	□□□		
Any worsening	1	32	0.04 [0.00, 0.66]	0.02	□□□		
CANCEROUS LESIONS							
SCC[d]/BCC[e] incidence	5	1082	0.46 [0.28, 0.75]	0.002	72%	Sirolimus	CNI
≥1 SCC	1	53	0.64 (0.35, 1.17)	0.15	N/A		
Skin cancer (excluding SCC)	1	53	0.74 (0.49, 1.14)	0.17	N/A		
Skin cancer (including SCC)	1	53	0.85 (0.61, 1.17)	0.32	N/A		
Skin cancer with BCC	1	53	0.89 (0.45, 1.78)	0.75	N/A		
PHOTODYNAMIC THERAPY (n=3)							
PRE-CANCEROUS LESIONS							
Actinic keratosis reduction (1-2 sessions)							
Complete response	2	50[a]	5.03 [0.14, 176.17]	0.37	85%	MAL[c]	Placebo, Imiquimod 5% cream
Partial response	1	17[a]	7.00 [0.39, 125.99]	0.19	N/A	MAL	Placebo
No reduction	1	17[a]	0.09 [0.02, 0.40]	0.002	N/A		
CANCEROUS LESIONS	1	26[a]	0.59 [0.34, 1.03]	0.06	N/A	MAL	No treatment
IMMUNE RESPONSE MODIFIERS (n=1)							
PRE-CANCEROUS LESIONS							
Reduced skin atypia	1	14[a]	3.00 [0.47, 19.35]	0.25	N/A	Imiquimod 5% cream	Placebo
Reduced dysplasia	1	14[a]	2.14 [0.31, 14.65]	0.44	N/A		
Reduced keratoses	1	14[a]	2.14 [0.31, 14.65]	0.44	N/A		
Reduced no. viral warts	1	14[a]	7.00 [0.46, 106.10]	0.16	N/A		

CANCEROUS LESIONS							
SCC incidence							
Treated (cream vs. placebo)	1	14[a]	0.09 [0.01, 1.70]	0.11	N/A	Imiquimod 5% cream	Placebo
Untreated (control site)	1	14[a]	0.43 [0.08, 2.37]	0.33	N/A		
ORAL RETINOIDS (n=2)							
CANCEROUS LESIONS							
Decreased incidence:							
> 1 SCC	1	46[a]	0.40 [0.19, 0.85]	0.02	N/A	Acitretin	Drug free period
> 1 BCC	1	46[a]	0.50 [0.14, 1.76]	0.28	N/A		
New skin cancer	1	19[a]	0.22 [0.06, 0.90]	0.03	N/A	Acitretin	Placebo

[a]Control is the contralateral or similar area of skin on the same participant
[b]Calcineurin inhibitor
[c]Methyl aminolaevulinate cream
[d]Squamous cell carcinoma
[e]Basal cell carcinoma

Figure legends

Figure 1. Study selection

Figure 2. Risk of bias of included studies

Figure 3. Behavioral interventions – Sun protection behavior (general)

Figure 4. Behavioral interventions – Sun protection knowledge

Figure 5. Switch to mTOR inhibitors – Non melanoma skin cancer incidence

Figure 1. PRISMA Flowchart

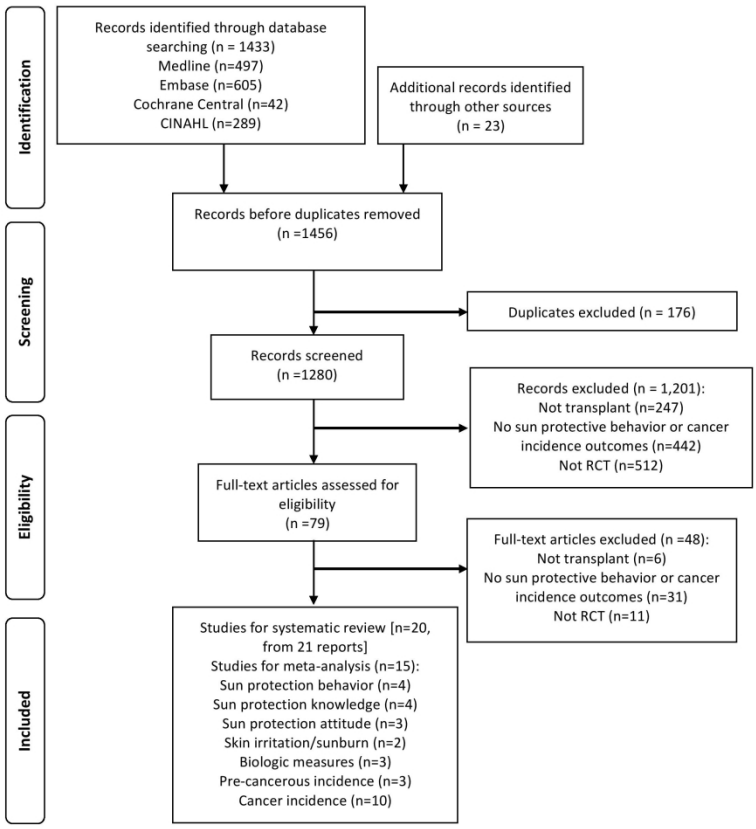

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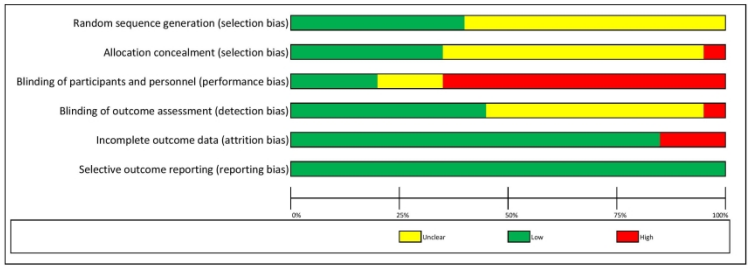
Figure 2. Risk of bias in included studies



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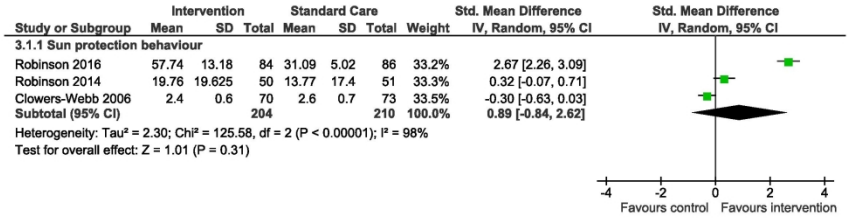

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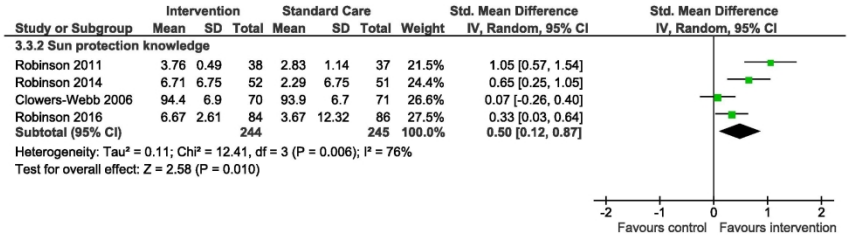

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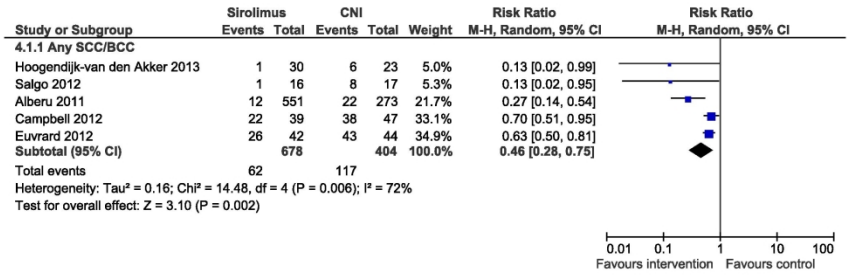

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Figure S1. Search Strategy

1. exp Neoplasms, Basal Cell/
2. basal cell carcinoma.ti,ab.
3. exp Neoplasms, Squamous Cell/
4. squamous cell carcinoma.ti,ab.
5. nonmelanom*.ti,ab.
6. non melanom*.ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Melanoma/
9. melanoma*.ti,ab.
10. Skin Neoplasms/
11. skin cancer*.ti,ab.
12. 8 or 9 or 10 or 11
13. 7 or 12
14. exp Organ Transplantation/
15. solid organ transplant*.mp.
16. transplant recipient*.tw.
17. exp Immunosuppression/
18. Immunocompromised Host/
19. 14 or 15 or 16 or 17 or 18
20. 13 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. Clinical Trials as Topic/
26. randomly.ab.
27. (crossover or cross-over).tw.
28. trial.ti.
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Animals/ not (animals/ and Humans/)

31. 29 not 30

32. 20 and 31

Figure S2. Risk of bias and key findings in individual studies

Study, year	Random sequence generation	Allocation concealment	Blinding participants & personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Intervention & comparator	Outcome RR/MD/SMD (95% CI)
Behavioral Interventions (n=6)								
Clowers-Webb 2006[30]	Unclear	Unclear	High	Unclear	High	Low	Repetitive written material vs. standard care	General behavior SMD -0.30 (-0.63, 0.03) Knowledge SMD 0.07 (-0.26, 0.40)
Robinson 2011[33]	Unclear	Unclear	Unclear	Unclear	Low	Low	Workbook vs. standard care	Skin self examination (1 month) RR 4.14 (2.22, 7.72) Knowledge SMD 1.05 (0.57, 1.54) Concern about developing cancer SMD 0.95 (0.47, 1.43) Confidence to recognize cancer MD 1.80 (1.35, 2.25) Importance of skin self-examination MD 1.05 (0.61, 1.49) Importance of partner to help for skin self-examination MD 1.59 (1.10, 2.08)
Robinson 2014[31]	Low	Low	High	Low	Low	Low	Workbook & text messages vs. standard care	General behavior SMD 0.32 (-0.07, 0.71) Knowledge SMD 0.65 (0.25, 1.05) Concern about developing cancer SMD 2.73 (2.19, 3.27) Recognize personal risk SMD -0.01 (0.40, 0.38) Confidence in sun protection SMD 0.30 (-0.09, 0.68) Willingness/intention to change behaviour SMD -0.02 (-0.41, 0.36) Importance of skin cancer/sun protection/having a tan MD 7.00 (2.94, 11.06) Skin irritation none RR 1.37 (1.16, 1.63) Skin irritation >1 RR 0.15 (0.03, 0.61) Sunburn none RR 1.30 (1.12, 1.52) Sunburn >1 RR 0.17 (0.04, 0.72) Melanin index - RU arm (sun protected) SMD 0.23

								(-0.17, 0.62) Melanin index - R forearm (sun exposed) SMD -0.37 (-0.76, 0.02) Cheek (sun exposed) SMD -0.03 (-0.42, 0.36) Sun damage assessment - R forearm SMD -0.30 (-0.69, 0.09)
Robinson 2016[32]	Unclear	Low	High	Low	Low	Low	Mobile app program vs. standard care	General behavior SMD 2.67 (2.26, 3.09) Daily hours outdoors MD -6.12 (-7.11, -5.13) Knowledge SMD 0.33 (0.03, 0.64) Concern about developing cancer SMD 1.97 (1.61, 2.34) Recognize personal risk SMD 1.22 (0.90, 1.55) Confidence in sun protection SMD 1.23 (0.09, 1.56) Willingness/intention to change behaviour SMD 3.42 (2.94, 3.89) Skin irritation none RR 0.82 (0.69, 0.96) Skin irritation >1 RR 1.64 (0.79, 3.40) Sunburn none RR 40.44 (10.27, 159.27) Sunburn >1 RR 4.83 (2.95, 7.90) Melanin index - RU arm (sun protected) SMD 0.05 (-0.25, 0.35) Melanin index - R forearm (sun exposed) SMD -0.46 (-0.76, -0.15) Cheek (sun exposed) SMD -0.43 (-0.73, -0.12) Sun damage assessment - R forearm SMD -0.02 (-0.33, 0.28)
Trinh 2014[28*]	Low	Unclear	Unclear	Unclear	Low	Low	Video vs. pamphlet	
Switch to mTOR inhibitors (n=6)								
Alberu 2011[39]	Low	Unclear	High	High	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.27 (0.14, 0.54)
Campbell 2009[41]	Low	Low	High	Low	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.70 (0.51, 0.95)
Carroll 2013[25*]	Unclear	Unclear	High	Low	Low	Low	Sirolimus vs. CNI/AZA	
Euvrard 2012[1]	Unclear	Unclear	High	Unclear	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.63 (0.50, 0.81)

Hoogendijk-van den Akker 2013[43]	Unclear	Low	High	Low	High	Low	SIrolimus vs CNI/MMF/AZA	Cancer incidence RR 0.13 (0.02, 0.99)
Salgo 2010[35]	Unclear	Unclear	High	Low	High	Low	SIrolimus vs CNI/MMF/AZA	Cancer incidence RR 0.13 (0.02, 0.95) Skin dysplasia Any improvement RR 24.35 (1.55, 381.99) Unchanged RR 0.85 (0.28, 2.61) Any worsening RR 0.04 (0.00, 0.66)
Pharmacetical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); 5% imiquimod cream (n=1)								
Bavinck 1995[40]	Unclear	Unclear	Low	Unclear	Low	Low	Acitretin vs. placebo	Cancer incidence RR 0.22 (0.06, 0.90)
Brown 2005[38]	Unclear	Unclear	Low	Low	Low	Low	5% Imiquimod cream vs. placebo	Cancer incidence SCC treated RR 0.09 (0.01, 1.70) SCC untreated RR 0.43 (0.08, 2.37) Reduced skin atypia RR 3.00 (0.47, 19.35) Reduced dysplasia RR 2.14 (0.31, 14.65) Reduced keratosis RR 2.14 (0.31, 14.65) Reduced no. viral warts RR 07.00 (0.46, 106.10)
Chen 2016[29]	Low	Unclear	Low	Low	Low	Low	Nicotinamide vs. placebo	
de Sevaux 2003[26]	Unclear	Low	High	Unclear	Low	Low	High dose acitretin vs. low dose acitretin	
Dragieva 2004[36]	Unclear	Unclear	Low	Unclear	Low	Low	Methyl aminolevulinate cream vs. placebo	Actinic keratosis reduction Complete response RR 27.00 (1.73, 420.67) Partial reduction RR 7.00 (0.39, 125.99) No reduction RR 0.09 (0.02, 0.40)
George 2002[42]	Unclear	Unclear	High	Unclear	Low	Low	Acitretin vs. drug free period	Cancer incidence >1 SCC RR 0.40 (0.19, 0.85) >1 BCC RR 0.50 (0.14, 1.76)
Togsverd-Bo 2015[27*†]	Low	Low	Unclear	Low	Low	Low	Methyl aminolevulinate cream vs. no treatment	

Togsverd-Bo 2017[37†]	Low	Low	High	Unclear	Low	Low	Methyl aminolevulinate cream vs.5% Imiquimod cream	Actinic keratosis reduction Complete response RR 1.42 (0.81, 2.48)
Wulf 2006[44†]	Low	High	High	Low	Low	Low	Methyl aminolevulinate cream vs. no treatment	Cancer incidence RR 0.59 (0.34, 1.03)

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

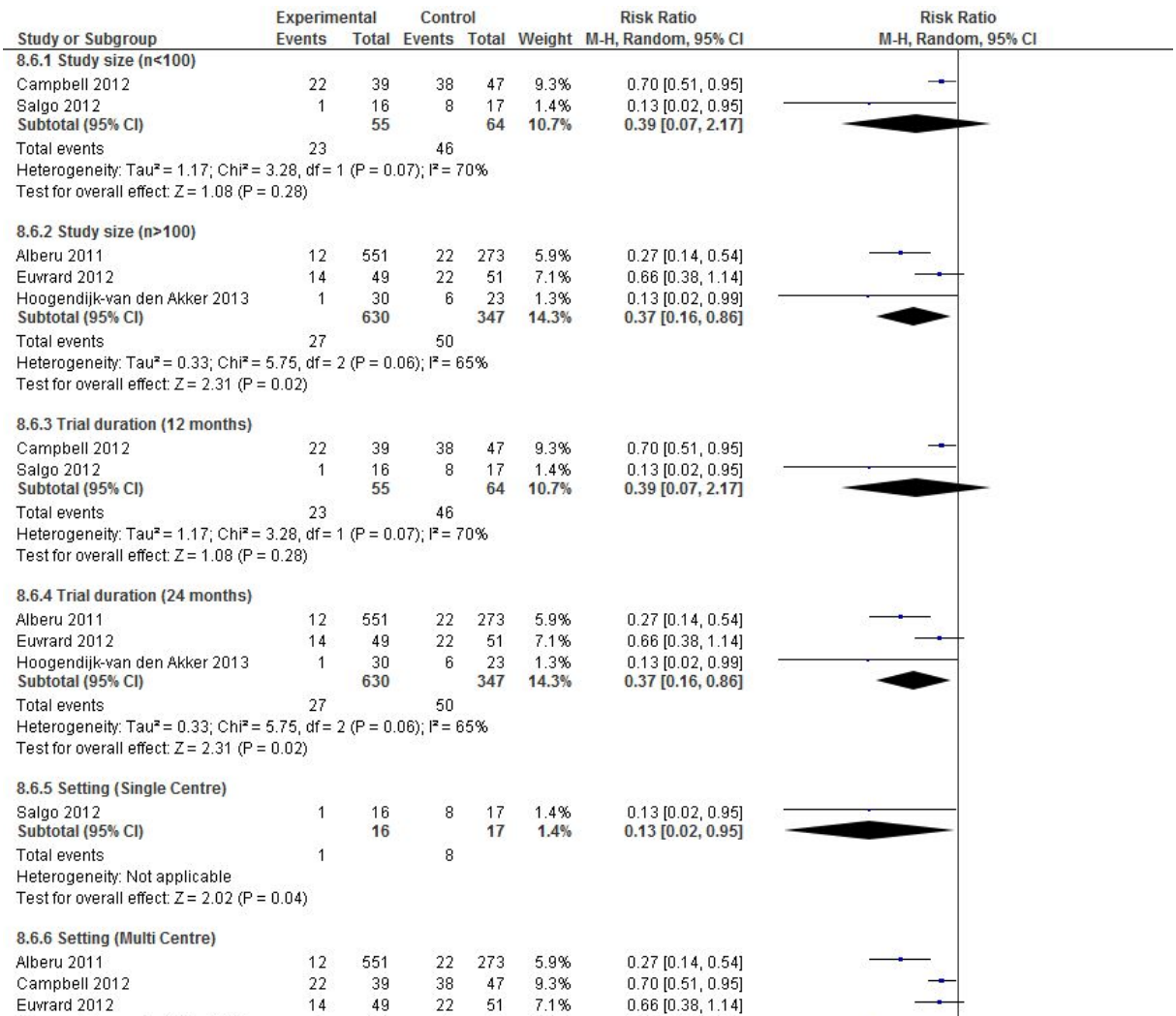
‡Excluded from analyses – same participants as Robinson 2016

Table S1. Assessment of quality of studies using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

Quality of assessment (Decrease in quality score)						
Number of studies	**Risk of bias/Quality of evidence**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality**
Sun protection behavior						
35 RCTs[24 30-33]	**Serious study limitations (-1)** Randomisation unclear[24 30 32 33] Participants not blinded or well described[24 30-33] Concealment of allocation not described.[30 33]	**Important inconsistency (-1)** Analysed in subgroups. heterogeneity (I^2=99%)[30-32]	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (2 weeks to 10 months) Same sample of participants[24 32]	**Serious imprecision (-1)** Small sample size, CIs crosses the null	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection knowledge						
6 RCTs[24 28 30-33]	**Serious limitations (-1)** Randomisation unclear[24 30 32 33] Participants not blinded or well described[24 28 30-33] Concealment of allocation not described[28 33]	**Important inconsistency (-1)** Heterogeneity (I^2 85%)	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (1 day to 10 months) Same sample[24 32]	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection attitude						
4 RCTs[24 31-33]	**Serious limitations (-1)** Randomisation unclear[24 32 33] Participants not blinded or well described[24 31-33] Concealment of allocation	**Important inconsistency (-1)** Wide variation in the effect estimates, heterogeneity (I^2 97%).	**Indirectness (-1)** Diverse interventions (written vs. electronic), Similar duration. Same sample[24 32]	**Serious imprecision (-1)** Small sample size, small number of events	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**

	not described[32 33]					
Complications (skin irritation, sunburn)						
2 RCTs[31 32]	**Serious limitations (-1)** Participants not blinded[31 32]	**Important inconsistency (-1)** Heterogeneity (I^2=95-99%) Analysed in subgroups. Similar effect estimates.	**Indirectness (-1)** Diverse interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Biologic measures (melanin index, sun damage)						
2 RCTs[31 32]	**Serious limitations (-1)** Randomisation unclear[32] Participants not blinded[31 32]	**Important inconsistency (-1)** Analysed in subgroups. Heterogeneity (I^2 60%)	**Indirectness (-1)** Different interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Pre-cancerous incidence						
4 RCTs [27 35-38]	**Serious limitations (-1)** Randomisation or allocation unclear[35 36 38] Participants not blinded or well described[27 35-38]	**Important inconsistency (-1)** Analysed in subgroups.	**Indirectness (-1)** Diverse interventions, varying duration	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**
Cancer incidence						
10 RCTs [1 29 35 38-44]	**Serious limitations (-1)** Randomisation unclear[1 40 42 43] Allocation concealment not used or unclear[1 29 39 40 42 44] Participants not blinded.[1 35 39 41-44]	**Important inconsistency (-1)** Majority of participants came from 1 study[39] Small sample[1 29 35 38 40-44]	**Indirectness (-1)** Diverse interventions (immunosuppression, photodynamic therapy, immune response modifier, retinoid, nicotinamide), varying duration	**Serious imprecision (-1)** Majority of participants from one trial (n=551), small number of events	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**

Figure S3. Subgroup analyses of immunosuppression conversion interventions on skin cancer incidence



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029265.R2
Article Type:	Original research
Date Submitted by the Author:	29-Jan-2020
Complete List of Authors:	James, Laura; University of Sydney, Saglimbene, Valeria; The University of Sydney, Sydney School of Public Health Wong, Germaine; The Children's Hospital at Westmead, Centre for Kidney Research Tong, Allison; The University of Sydney, Sydney School of Public Health Luu, Laurence; The University of Sydney, Sydney School of Public Health Craig, Jonathan; Flinders University Faculty of Medicine Nursing and Health Sciences, College of Medicine and Public Health, ; The Children's Hospital at Westmead, Centre for Kidney Research Howard, Kirsten; University of Sydney, School of Public Health Howell, Martin; University of Sydney - Camperdown and Darlington Campus, School of Public Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	skin cancer, melanoma, prevention, sun protection, sun protection behaviors

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Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

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Word count (abstract): 205

Word count (body): 3593

Tables: 4 **Figures:** 5

K**ey words:** skin cancer, melanoma, prevention, sun protection, sun protection behaviors, health behavior

Authorship

LJJ, GW, AT, LL, JCC, KH, MH designed the study; LJJ, VS, LL, MH conducted the data extraction and analyses; all authors contributed to the interpretation of the analyses. LJJ drafted the manuscript; all authors contributed to the writing and review of the manuscript.

Disclosure

The authors declare no conflicts of interest.

Data availability statement

No additional data available.

Funding

LJJ is supported by the National Health and Medical Research Council (NHMRC) Better Evidence and Translation in Chronic Kidney Disease (BEAT-CKD) Program Grant (APP1092957). MH is supported by the BEAT-CKD Program Grant (APP1092957). AT is supported by the NHMRC Fellowship (APP1106716). The funding organizations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript.

Abbreviations

AZA, azathioprine

BCC, basal cell carcinoma

CNI, calcineurin inhibitors

CI, confidence intervals

MAL, methyl aminolaevulinate cream

MD, mean difference

MMF, mycophenolate mofetil

mTORI, mammalian target of rapamaycin inhibitors

NMSC, non-melanoma skin cancer

RCT, randomized controlled trial

RR, relative risk

SCC, squamous cell carcinoma

SMD, standardized mean difference

ABSTRACT

Objectives

Solid organ transplant recipients are at increased risk of skin cancer, affecting more than 50% of recipients. We aimed to determine the effectiveness of interventions for behavioral change for sun protection or skin cancer prevention in solid organ transplant recipients.

Design

Systematic review

Data sources

Electronic databases were searched from inception to November 2019.

Eligibility Criteria

We included randomized controlled trials that evaluated the effect of behavioral or pharmaceutical interventions on behavioral change or skin cancer prevention in solid organ transplant recipients.

Data extraction and synthesis

Risks of bias and evidence certainty were assessed using Cochrane and the GRADE framework.

Results

Twenty trials (n=2,295 participants) were included. It is uncertain whether behavioral interventions improve sun protection behavior (N=3, n= 414, SMD 0.89, 95% CI -0.84-2.62, I^2 =98%) and knowledge (N=4, n=489, SMD 0.50, 95% CI 0.12-0.87, $I^{2=}$ 76%) as the quality of evidence

is very low. We are uncertain of the effects of mammalian target of rapamaycin inhibitors on the incidence of non-melanocytic skin cancer (N=5, n=1080, RR 0.46 95% CI 0.28-0.75, I^2 =72%) as the quality of evidence is very low.

Conclusions

Behavioral and pharmaceutical preventive interventions may improve sun protective behavior and knowledge, and reduce the incidence of non-melanocytic skin cancer, but the overall quality of the evidence is very low and insufficient to guide decision-making and clinical practice.

PROSPERO Registration number

CRD42017063962

ARTICLE SUMMARY

Strengths and limitations

- A comprehensive review conducted using methods outlined by Cochrane Collaboration including GRADE to assess risk of bias and evidence certainty
- Inclusion of a broad range of interventions, including behavioral to improve sun protection behavior and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence
- Difficulty obtaining an overall summary estimate for many outcomes due to the variability in the analytical methods and reporting in individual studies
- Unable to perform detailed subgroup analyses or assess for publication bias due to small number of studies
- Few trials included the important outcomes of skin cancer and none included melanoma or mortality.

1. INTRODUCTION

Skin cancer, including melanoma and nonmelanoma skin cancer (NMSC), is the most frequently diagnosed malignancy among solid organ transplant recipients, affecting more than 50% of post-transplantation recipients.[1 2] The cumulative incidence of NMSC increases with time after transplantation, from 5-10% at 2 years to 40-80% at 20 years.[2-4] Compared to the general population, there is a higher rate of squamous cell carcinoma (SCC) to basal cell carcinoma (BCC), with an incidence of 65 to 250 times greater than the age and gender-matched general population.[5-8] Once cancer develops, management options are limited as immunotherapy may be unsuitable as it may lead to graft rejection.[9 10] Although registry data shows improvement in survival rates of transplant recipients as a result of improved transplantation techniques and management of immunosuppression, there is a greater burden of skin cancer and cancer related mortality.[11] The excess risk of death from invasive and metastatic skin cancer, such as SCC and melanoma, are three times to nine times higher than the general population, with five-year overall survival of less than 30%.[6 12-15]

Sun exposure behaviors remain the most significant and modifiable risk factor in the prevention of skin cancers in the general population.[16] However, with the dramatic increase in skin cancers in solid organ transplant recipients, pharmaceuticals have also been used to reduce and delay the development of skin cancer.[16 17] Current recommendations for preventive strategies have often been extrapolated from guidelines in the general population, which may not be applicable to solid organ transplant recipients.[18 19] For example, frequent skin self-examination and annual to biannual total body skin examination are generally recommended for the general population.[18-20] Sun protective behaviors including use of sunscreen, protective clothing and limiting sun exposure during peak hours of high UV index days are potential measures for skin cancer prevention.[3 4 14]

Further, alteration of maintenance immunosuppression such as conversion to mammalian target of rapamaycin inhibitors (mTORi) and secondary prevention using retinoid acitretin are recommended for management of skin cancers in high risk transplant recipients.[20]

The aim of this study is determine the effectiveness of interventions that promote behavioral change and skin cancer prevention in solid organ transplant recipients.

2. METHODS

This systematic review followed a pre-specified protocol registered in PROSPERO (CRD42017063962) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[21] The study was exempt from approval from an ethics' board.

2.1 Inclusion criteria

All randomized controlled trials (RCTs) or quasi RCTs (allocated to trial arms by investigators) of interventions for skin cancer prevention (both melanoma and non-melanoma skin cancer) in solid organ transplant recipients were included. Behavioral interventions defined as any strategy used to promote sun protective behavior including passive (e.g. pamphlets), active (e.g. group workshops, counselling, dermatology clinic) and provision of sun protective equipment; and pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers, nicotinamide and oral retinoids) and studies that reported skin cancer related outcomes as their primary outcomes were included. Studies that did not report these outcomes as primary end-points were excluded. Studies of interventions for the treatment of skin cancer were excluded.

2.2 Search strategies

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from inception to November 2019 without language restriction, using search strategies designed by a specialist information manager (see Medline search strategy in Figure S1). Reference lists of included studies were also searched.

2.3 Data extraction

Titles and abstracts were reviewed by two independent authors (LJJ & LL) and those that did not meet the inclusion criteria were excluded. Full text articles were reviewed by 3 independent reviewers (LJJ, VS, LL) and any disagreements were resolved by discussion. Data on study design, geographic location, sample size, type of transplant, measurement of interventions, interventions and comparators were extracted. We sought unclear or missing information from authors where possible.

2.4 Outcome measures

The pre-specified outcome measures were incidence of precancerous and cancerous lesions, sun protection behavior (including use of sunscreen, use of protective clothing including hats and sunglasses, shade and sun avoidance), knowledge and attitude, skin self-examination, sun exposure (including skin irritation, sunburn) and biologic measures (including measurement of melanin index and sun damage assessment).

2.5 Risk of bias and quality of evidence

The risk of bias was assessed independently by LJJ and VS using the Cochrane risk of bias tool.[22] The domains included in the assessment were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, trial registration and industry involvement. Each criterion was

assigned a judgment of high, low or unclear risk of bias. Intention to treat and lost to follow up were also assessed for each study. The quality of the evidence informing summary estimates for each outcome was then assessed by LJJ using the Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines.[23]

2.6 Data synthesis and statistical analyses

Continuous outcomes were summarized as mean difference (MD) or standardized mean difference (SMD) and dichotomous outcomes as relative risk (RR). A MD/SMD greater than zero and/or a RR greater than 1 could be interpreted as favoring the intervention group relative to the control, unless specified elsewhere. Risk estimates were reported with 95% confidence intervals (CI), using random-effects meta-analysis. We quantified the heterogeneity using the I^2 statistic. An I^2 value of <25% was considered to represent low heterogeneity and >75% as high heterogeneity. When sufficient data were available, possible sources of heterogeneity were investigated using subgroup analysis based on pre-specified study characteristics including sample size, trial duration, setting and overall risk of bias. Funnel plots were planned to evaluate small study effects when at least ten studies were included in meta-analysis. All analyses were conducted using Review Manager version 5.3 software.

2.7 Patient and public involvement

There was no patient or public involvement.

3. RESULTS

3.1 Study selection

The literature search identified 1280 articles, of which, 1201 were excluded after abstract and title review. Full text assessment of 79 studies found 22 eligible articles for inclusion (Figure 1).

3.2 Studies characteristics

We included 22 reports of 20 RCTs, including 2,295 participants (Figure 1). The study characteristics are summarized in Table 1 and Table 2. The median number of participants was 44 (range 17 to 830) and the median follow-up duration was 10 months (range 1 day to 60 months). All studies included kidney transplant recipients, with some also including heart transplant recipients (n=1), liver, heart, pancreas, lung, heart/lung and other transplants (n=1), and lung and liver transplant recipients (n=2). In total, 15 of 21 (76%) studies provided sufficient data for the meta-analyses. Six studies did not meet final criteria for meta-analysis as they had the same sample of participants (n=1),[24] or did not provide data that was able to be meta-analyzed (n=5).[25-29]

3.3 Risk of bias and quality of the evidence

Overall studies had either high or unclear risk of bias for at least one domain (Figure 2; Figure S2). Random sequence generation and allocation concealment were unclear in most studies (n=12, 60%). Blinding of participants was not done in most studies (n=16, 80%) and blinding of outcome assessors was only reporting in half of the studies (n=10). Intention to treat analyses were used in 6 (30%) studies and 6 studies (30%) had a high loss to follow-up. A total of 3 (15%) studies had incomplete outcome data, and all studies were at low risk for selective reporting. Seven studies (35%) reported industry involvement in authorship, design, or data analysis, and of the 16 trials requiring trial registration, only 9 (56%) reported accordingly.

The overall quality of the evidence was very low for all outcomes (Table S1) due to limitations in study design, heterogeneity in the intervention and outcomes measures, the very small sample size of individual studies and the small number of studies for each specific outcome. Obtaining an

overall summary estimate was difficult for many outcomes due to the variability in the analytical methods and reporting in individual studies. In particular, assessment of reporting of sun protection behavior and sun protection knowledge was not possible as outcomes were inconsistent and there was large diversity of interventions used (e.g. written education material versus a mobile app program). Furthermore, formal testing of publication bias was not performed due to insufficient data.

3.4 Interventions

The interventions in the included studies were grouped in three broad categories, behavioral (n=6), switch to mTOR inhibitors (n=6), and other pharmaceutical interventions (photodynamic therapy, immune response modifiers, oral retinoids and nicotinamide) (n=9). Studies of behavioral interventions used passive methods of delivery including written educational material (n=2), both written educational material and text messages (n=1), mobile app programs (n=2) and a video (n=1).

All six studies of immunosuppression compared mTORis (sirolimus) to calcineurin inhibitors (CNI) based therapies.

Four of the eight studies of other pharmaceutical interventions assessed the effect of photodynamic therapy using methyl aminolevinate creams compared to placebo (n=1), no treatment to contralateral area (n=2) or a topical immune response modifier cream (n=1). Three studies assessed oral retinoid using acitretin compared to placebo (n=1), lower dose (n=1) or a drug free period (n=1), one study assessed nicotinamide compared to placebo and a single study assessed the benefits of topical immune response modifier compared to placebo in kidney transplant recipients.

3.5 Effect of behavioural interventions on sun protection outcomes

Sun protection behavior

Sun protection behavior, defined as hours spent outdoors per week, use of sunscreen, wearing protective clothing and seeking shade, was assessed in three trials[30-32]. Educational workbooks,[30] educational workbooks and text messages[31] and a mobile app program[32] were compared with standard care. Patients who received behavioral interventions reported improved sun protection behavior scores[30-32] (3 studies, 414 participants, SMD 0.89, 95% CI -0.84-2.62, I^2 98%) (Table 3; Figure 3). We are uncertain of the effects of behavioural interventions on sun protection behavior due to very low quality of evidence. A single trial assessed a standardised and validated educational workbook and found an improvement in the proportion of participants engaging in skin self-examination after one month (75 participants, RR 4.14, 95% CI 2.22-7.72).[33] One trial assessed a mobile app program and reported a reduction in daily hours spent outdoors among the intervention group (170 participants, MD -6.12, 95% CI -711 to -5.13).[32]

Sun protection knowledge

The effectiveness of educational workbooks, text messages, mobile app programs and videos on sun protection knowledge was assessed in 6 studies[24 28 30-33], four of which provided data for a meta-analysis. There was an improvement in knowledge scores (4 studies, 489 participants, SMD 0.50, 95% CI 0.12-0.87, I^2 76%) in the intervention group compared to standard care (Figure 4).[30-33] One study compared an interactive visual representation of the educational program with standard information pamphlets and found that knowledge of sun protection improved among those who received the educational video.[28]

Sun protection attitude

Three studies assessed sun protective attitude after receiving an educational workbook, text messages or a mobile app program over a period of 0.5 months to 1.5 months.[31-33] Compared to standard care, there was an overall improvement in scores of concern about developing cancer (3 studies, 348 participants, SMD 1.85, 95% CI 1.59-2.11, I^2 96%).[31-33] Two studies involving 273 participants reported an improvement in scores of understanding the personal risk of skin cancer (SMD 0.61, 95% CI -0.60-1.82, I^2 96%), adherence to sun protection (SMD 0.77 95% CI -0.14-1.68, I^2 92%) and willingness or intention to change behavior (SMD 1.70, 95% CI -1.68-5.07, I^2 99%).[31 32] We are uncertain of the effects of behavioural interventions on sun protection attitude due to very low quality of evidence. A single study involving 75 participants also reported an improvement in scores of ability to recognize a potential skin cancer (MD 1.80, 95% CI 1.35-2.25), importance of skin self-examination (MD 1.05, 95% CI 0.61-1.49) and having a partner help for skin self-examination (MD 1.59, 95% CI 1.10-2.08).[33] Another single study reported an improvement in the importance of engaging in sun protection (measured using 5-point Likert scale) (101 participants, MD 7.00, 95% CI 2.94-11.06).[31]

Skin complications and biologic measures

Two trials of behavioral interventions in 271 kidney transplant recipients compared a mobile app or an educational workbook and text messages to standard care on reported skin complications and biologic measures of sun exposure.[31 32] The intervention group experienced a reduced incidence of skin irritation (a culturally relevant term for sun exposure[34]) (RR 1.00, 95% CI 0.89-1.13, I^2 95%) or sunburn (RR 3.19, 95% CI 2.47-4.10, I^2 99%). They also had a decreased melanin index (right forearm, SMD -0.42, 95% CI -0.66 to -0.18; cheek SMD -0.25, 95% CI -0.64 to -0.15) and reduced severity of sun damage (SMD -0.13, 95% CI -0.40 to 0.13) on sun exposed areas (measured using clinical images of chronic sun damage and scored 1-10).

3.6 Effect of pharmaceutical interventions on skin cancer prevention

The incidence and responses of pre-cancerous lesions were measured only in trials of pharmaceutical interventions (Table 4). These included the switch to mTOR inhibitors (n=1),[35] photodynamic therapy (n=2)[36 37] and immune response modifiers (n=1)[38] to current treatment or placebo. The incidence of non-melanocytic skin cancers (NMSC) was assessed in nine pharmaceutical studies.[1 35 38-44] None included melanoma as an outcome.

Topical/local interventions

One trial of 14 participants compared an immune response modifier, 5% imiquimod cream with placebo and found a reduction in the incidence of skin dysplasia (RR 2.14, 95% CI 0.31-14.65), skin atypia (RR 3.00, 95% CI 0.47-19.35), and viral warts (RR 7.00, 95% CI 0.46-106.10).[38]

One Danish study of 26 kidney transplant recipients compared photodynamic therapy with no treatment and reported a relative reduction by approximately 40% in the incidence of NMSC on the treated area (RR 0.59, 95% CI 0.34-21.03, p 0.06).[44] A lower incidence of SCC was also reported in one trial comparing two areas of skin using an immune response modifier and placebo (14 participants, RR 0.09, 95% CI 0.0.01-1.70).[38] Two trials comparing photodynamic therapy to an immune response modifier or photodynamic therapy to placebo in recipients with diagnosed keratoses reported a complete response rate of 60% compared to 24% in the control group (50 participants, RR 5.03, 95% CI 0.14-176.17, I^2 85%).[36 37] We are uncertain of the effects of photodynamic therapy on incidence of precancerous lesions due to very low quality of evidence. Further, one trial which was not included in the meta-analysis, reported a higher cumulative

incidence of actinic keratosis lesions in untreated skin (63%) compared with skin treated by photodynamic therapy (28%).[27]

Systemic interventions

mTORis therapy reduced the incidence of NMSC compared to CNIs maintenance therapy (5 trials, 1082 participants, RR 0.46, 95% CI 0.28-0.75, I^2 72%) (Figure 5).[1 35 39 41 43] However evidence was limited due to short follow-up periods, variability in dosing of mTORis and significant rates of loss to follow up, and therefore we are uncertain of the effects of mTORis on skin cancer incidence due to very low quality of evidence. A single trial involving 21 patients reported a reduction in the overall incidence of SCC by 49% in the conversion arm, but reported a drop out rate of 77% and follow-up time of less than 2 years.[25] Further, a single trial which compared mTORi conversion from CNI based therapy reported a significant improvement in skin dysplasia (32 participants, RR 24.35, 95% CI 1.55-381.99).[35]

Two trials comparing an oral retinoid, acitretin, with placebo or a drug free period reported an increased lower risk of both SCCs and BCCs (46 participants, RR 0.40, 95% CI 0.19-0.85, p 0.02; RR 0.50, 95% CI 0.14-1.76)[42] or development of a new skin cancer (19 participants, RR 0.22, 95% CI 0.06-0.90). However, there were no differences in the incidence of new SCCs.[40] One trial, which was not included in the meta-analysis, showed approximately a 50% reduction in the incidence of actinic keratosis which compared a high dose to a low dose of acitretin.[26]

One Australian trial of 22 kidney transplant recipients compared nicotinamide with placebo and reported an estimated relative rate difference of 0.35 (95% CI -0.62 to 0.74), 0.67 (95% CI -0.40 to 0.90) and 0.07 (95% CI -1.51 to 0.65) for NMSC, BCCs and SCCs respectively.[29]

3.7 Subgroup analysis

Study size, trial duration, setting and risk of bias did not modify the effects of CNIs and mTORIs on skin cancer incidences (Figure S3). Sources of heterogeneity for other treatment effects could not be explored due to insufficient data.

4 DISCUSSION

Skin cancers (both non-melanoma and melanoma) are major causes of morbidity and mortality in solid organ transplant recipients. Despite this, trials of interventions aimed at preventing skin cancer in solid organ transplant recipients are few in number (20 trials), small with half comprising of 50 patients or less, of short duration (48% have <12 months follow up) and 52% do not include incidence of skin cancer as an outcome. Our review included 22 reports of 20 trials involving 2,295 transplant recipients, who were predominately kidney transplant recipients. The studies covered a broad range of interventions, including behavioral to improve sun protection behavior and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence. None of the behavioral intervention studies included precancerous lesions or skin cancer incidence as outcomes. Although interventions showed plausible improvements to sun protection behaviors, precancerous lesion responses and cancer incidence, there was considerable variability across interventions types, variability in outcomes assessed and outcome estimates. Overall, the current evidence for interventions for skin cancer prevention in solid organ transplant recipients is of very low quality and is insufficient to guide decision-making and clinical practice.

Although behavioral interventions appeared to improve sun protection attitude, knowledge and behavior, there were inconsistencies detected and none of these studies included skin cancer as

an outcome. Due to limited number of studies, we were unable to compare specific behavioral interventions (e.g. mobile app vs. written education) to ascertain the most effective method of delivering sun protection education. While there may be some modest benefits in the reduction in cancer incidence (for NMSC) among solid organ transplant recipients who were converted to mTORIs compared to those on CNI maintenance, there was substantial heterogeneity across the studies that was unable to be explained by subgroup analyses. Heterogeneity may be attributed to the absence of long term follow up, large discontinuation rates owing to adverse events and variability in the doses of mTORIs. Pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers) showed a reduction in precancerous lesions compared to standard care or a comparator group. However uncertainty exists in the treatment effects and there were too few studies, interventions were incomparable, follow-up times were variable and considerable loss to follow up for some studies to conclude that the benefits are sustainable.

Previous systematic reviews have evaluated the impact of behavioral interventions on skin cancer prevention in the general population,[45] and concluded that computer programs may increase sun protective behaviors, and 'appearance-focused' interventions may decrease sun tanning and UV exposure in adolescents and young women, respectively. Reviews conducted in other populations at high-risk including outdoor workers,[46] family history, personal history and phenotypic factors[47] have found similar improvement in sun protective behaviors, including use of sunscreen, as well as a decreased incidence of keratoses. A systematic review of the benefits and harms of oral retinoids for the prevention of skin cancer among high risk transplant recipients led to inconclusive results on the effect of acitretin due to the small number of included trials.[48]

Despite the inclusion of all interventions aimed at the prevention of skin cancer in solid organ transplant recipients and the comprehensive systematic search for eligible studies, there are some potential limitations. Due to the heterogeneity of the studies, the high risk of bias, the potential for reporting bias and imprecision in the point estimates of individual studies, there is a high degree of uncertainty in the estimate of the effect of skin cancer prevention interventions. All studies of behavioral interventions were undertaken in United States, with 4 by the same authors, whilst most pharmacological intervention studies were conducted in Europe. There were also large discontinuation rates owing to adverse events in trials of mTORIs. Further, given the small number of studies included in the meta-analysis, we were unable to perform any detailed subgroup analyses to explore heterogeneity or assess for publication bias. While we were unable to show and assess publication bias using standard statistical tests, we would suggest the observed heterogeneity may also be attributed to potential publication and reporting biases. It is difficult to quantify the extent of such bias in this review, but one would expect research with 'positive' findings that indicate an intervention works, such as behavioral interventions improve sun protection, are more likely to be published more than one, in high impact journals and more likely to be cited. Finally, few trials included patient important outcomes associated with skin cancer and none included melanoma or mortality.

The use of pharmaceutical and immunosuppression therapy remains complex. Not only has mTORI therapy shown benefits in lowering the risk of skin cancer, early conversion to mTORI therapy from CNIs has also shown promising effects in reducing cancer rates.[49 50]On the contrary, overall mortality is higher and discontinuation following adverse events is more common in patients who receive mTORI therapy.[49 50] Several RCTs showed a higher rate of patients reporting adverse events or drug discontinuation with sirolimus,[1 41 43] demonstrating concern of its clinical usefulness.[49] Nicotinamide may also offer benefits to reducing skin cancer incidence by 20% and is

relatively safe with minimal side effects. The protective effect of nicotinamide on skin cancer incidence in kidney transplant recipients is currently being explored in a phase 3 randomised controlled trial.

Although behavioral change is a simple strategy, long-term adherence remains challenging. While behavioral counseling has been shown to increase sun protective behaviors in non-transplant populations,[45] there is no direct evidence to show that the behavioral change led to a reduction in morbidity and mortality. Previous studies have suggested that transplant recipients do not practice sun protective behaviors regularly,[51-53] were less likely to use sunscreen[54] and that patients have to perceive skin cancer as being an important risk to be motivated to change behavior.[55 56] However, studies on risk perception of transplant recipients remain conflicting. Given this complexity and the observed inconsistencies in the existing trials, process evaluations including facilitators and barriers to behavioral change should be included in future trials. Such evaluations could include the use of qualitative methodology to support the trial design, ascertain the perspectives of participants on the intervention and evaluate the implementation.[57 58]

We suggest that further strategies for skin cancer prevention in transplant recipients require a multifaceted and individualized approach. Transplant recipients are likely to benefit from early implementation of education, particularly before transplantation occurs and recipients may be preoccupied with other health needs related to transplantation. Although recipients understand the importance of ongoing education for the ability to self-manage their disease, they may experience difficulty in concentrating and learning new knowledge, and are often unable to look beyond their graft and the anxiety/fear of graft loss.[59-61] Interventions should be integrated into routine appointments and tailored to meet the individual needs of patients. This would be best

achieved through a shared decision-making approach to identify the patient's preferences and priorities and thereby enhance the likelihood of success of self-management and prevention.[62]

Additional large-scale and high-quality RCTs are needed to demonstrate the effectiveness of interventions used to prevent skin cancer in transplant recipients in terms of patient important outcomes, in particular morbidity and mortality associated with skin cancer. Determining patient's preferences for prevention and management of skin cancer are also warranted to ensure interventions and outcomes for trials are relevant to patient needs and priorities and better support patient-centered treatment decisions.[63] Evidence of the efficacy of sun protective behavior interventions need to be strengthened, with use of measures that are homogenous, reliable and validated.

Preventative measures including behavioral, switch to mTOR inhibitors and other pharmaceuticals may improve skin cancer outcomes for solid organ transplant recipients. However, the overall quality of evidence is of very low and insufficient to guide decision-making and clinical practice. Future robust studies that are well powered, have long-term follow up, and use clinical and patient important outcome measures in a consistent manner are required to therefore optimize outcomes for solid organ transplant recipients.

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Table 1. Characteristics of included studies (n=20)

Characteristics	N (%)
Type of transplant	
Kidney	16 (80)
Multiple*	4 (20)
Sex	
≥ 50% Male	18 (90)
< 50% Male	1 (5)
Not specified	1 (5)
Age (mean)	
< 60	10 (50)
≥ 60	5 (25)
Not specified	5 (25)
Sample size	
10 – 50	11 (55)
50 – 100	3 (15)
100 – 200	4 (20)
>200	2 (10)
Setting	
Single center	8 (40)
Multi center	11 (55)
Not specified	1 (5)
Country of origin	
Australia	3 (15)
Denmark	4 (20)
France	1 (5)
Germany	1 (5)
Netherlands	2 (10)
New Zealand	2 (10)
Switzerland	1 (5)
Sweden	1 (5)
United Kingdom	3 (15)
United States	6 (30)
Other†	1 (5)
Intervention Type	
Behavioral	5 (25)
Switch to mTOR inhibitors	6 (30)
Photodynamic therapy	4 (20)
Oral retinoid	3 (15)
Nictotinamide	1 (5)
Topical immune response modifier	1 (5)
Duration of follow up	
<12 months	9 (45)
12 months	4 (20)
24 months	5 (25)
>24 months	1 (5)
Not specified	1 (5)
Year of publication	
1995 – 1999	1 (5)
2000 – 2004	3 (15)
2005 – 2009	4 (20)
2010 – 2014	8 (40)
2015 – 2017	4 (20)

* Kidney, liver and lung (n=2); kidney and heart (n=1); Kidney and multiple other types (n=1) – see text

† 111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Table 2. Characteristics of individual studies

Study	N	Type of transplant	Setting	Type of intervention	Measures	Intervention	Comparator	Primary outcomes	Time (mths)
Behavioral interventions (n=6)									
Clowers-Webb 2006[30]	202	Kidney, liver, heart, pancreas, lung, heart/lung, other§	Single centre, United States	Behavioral	Self-reported questionnaire	Repetitive written material	Standard care	Knowledge & behavior	10
Robinson 2011[33]	75	Kidney	United States	Behavioral	Self-reported questionnaire	Workbook	Standard care	Knowledge & behavior	1
Robinson 2014[31]	101	Kidney	Single centre, United States	Behavioral	Self-reported questionnaire Physical examination	Workbook Text messages	Standard care	Knowledge & behavior	1.5
Robinson 2015[24]‡	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire	Mobile app program	Standard care	Knowledge & behavior	0.5
Robinson 2016[32]	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire Physical examination	Mobile app program	Standard care	Knowledge & behavior	1.5
Trinh 2014[28]*	100	Kidney, liver, lung	Single centre, United States	Behavioral	Self-reported questionnaire	Video	Pamphlet	Knowledge	1 day
Switch to mTOR inhibitors (n=7)									
Alberu 2011[39]	830	Kidney	Multi centre§	Switch to mTOR inhibitors	Investigator reported adverse events	Conversion to sirolimus	CNI	Cancer incidence	24
Campbell 2012[41]	86	Kidney	Multi centre, Australia, New Zealand, United States	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	12
Carroll 2013[25]*	32	Kidney	Multi centre, UK	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to prednisolone & sirolimus	CNI/AZA	Cancer incidence	24
Euvrard 2012[1 64]	120	Kidney	Multi centre, France	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	24
Hoogendijk-van den Akker	155	Kidney	Multi centre, Netherlands, UK	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	AZA/MMF/ CNI	Cancer incidence	24

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2013[43]									
Salgo 2010[35]	44	Kidney	Single centre, Germany	Switch to mTOR inhibitors	Physical examination +/- biopsy Clinical photographs	Conversion to sirolimus and prednisone	AZA/MMF/ CNI	Precancerous skin dysplasia incidence	12
Pharmaceutical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); nicotinamide (n=1); 5% imiquimod cream (n=1)									
Bavinck 1995[40]	44	Kidney	Multi centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	Acitretin	Placebo	Cancer incidence precancerous lesion reduction	6
Brown 2005[38]	21	Kidney	Multi centre, UK	Topical immune response modifier cream	Physical examination +/- biopsy Clinical mapping and photographs	5% Imiquimod cream	Placebo	Reduction of precancerous lesions	4
Chen 2016[29]*	22	Kidney	Single centre, Australia	Nicotinamide	Physical examination	Nicotinamide	Placebo	Cancer incidence	6
de Sevaux 2003[26]*	26	Kidney	Single centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	High dose acitretin	Low dose acitretin	Cancer and precancerous incidence	12
Dragieva 2004[36]	17	Kidney, heart	Single centre, Switzerland	Photodynamic therapy	Physical examination +/- biopsy Clinical photographs	Methyl aminolevulinate cream	Placebo	Precancerous lesion response	4
George 2002[42]	23	Kidney	Multi centre, Australia	Oral retinoid	Physical examination Annual radiological evaluation	Acitretin	Drug free period	Cancer incidence	24
Togsverd-Bo 2015[27]*†	25	Kidney	Single centre, Denmark	Photodynamic therapy	Physical examination Clinical photographs	Methyl aminolevulinate cream	No treatment contralateral area	Actinic keratosis incidence	36
Togsverd-Bo 2017[37]†	35	Kidney, lung, liver	Multi-centre, Denmark and Sweden	Photodynamic therapy	Physical examination Questionnaire/Diary	Methyl aminolevulinate cream	5% imiquimoid cream	Actinic keratosis lesion response	6

Wulf 2006[44†]	27	Kidney	Multi centre, Denmark and Netherlands	Photodynamic therapy	Clinical mapping and photographs	Methyl aminolevulinate cream	No treatment contralateral area	Cancer incidence	12

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

‡Excluded from analyses – same participants as Robinson 2016

§111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Abbreviations: CNI, Calcineurin inhibitor; AZA. Azathioprine; MMF, Mycophenolate mofetil

Table 3. Effect of behavioral interventions on sun protection outcomes

Outcome	Studies	Participants	Weighted MD[a]/SMD[b] [95% CI]	Relative risk	P	I^2	Intervention	Comparator
BEHAVIORALINTERVENTION (n=5)								
SUN PROTECTION BEHAVIOR								
General sun protection behavior	3	414	0.89 [-0.84, 2.62]		0.31	98%	Workbook, text messages, mobile app program	Standard care
Skin self-examination								
1 month after visit	1	75		4.14 [2.22, 7.72]	<0.001	□0.	Workbook	Standard care
If checked, concerned	1	42		6.43 [0.42, 98.58]	0.18	□□□		
If concerned, saw dermatologist	1	12		Not estimable[c]		□□□		
Decrease daily hours outdoors	1	170	-6.12 [-7.11, -5.13][d]		<0.001	□□□	Mobile app program	Standard care
SUN PROTECTION KNOWLEDGE	4	489	0.50 [0.12, 0.87]		0.01	76%	Workbook, text messages, mobile app program	Standard care
SUN PROTECTION ATTITUDE								
Concern about developing skin cancer	3	348	1.88 [0.96, 2.80]		<0.001	92%	Workbook, text messages, mobile app program	Standard care
Recognise personal risk	2	273	0.61 [-0.60, 1.82]		0.32	96%	Workbook and text messages, mobile app program	Standard care
Confidence in ability to perform sun protection	2	273	0.77 [-0.14, 1.68]		0.10	92%		
Willingness/intention to change behavior	2	273	1.70 [-1.68, 5.07]		0.32	99%		
Knowledge of significance of skin cancer, relevance of sun protection, risk of having a tan	1	101	7.00 [2.94, 11.06]		0.001	□□□	Workbook and text messages	Standard care
Confidence in ability to recognise a skin cancer	1	75	1.80 [1.35, 2.25]		<0.001	□□□	Workbook	Standard care
Importance of skin self-examination	1	75	1.05 [0.61, 1.49]		<0.001	□□□		
Importance of partner help for skin self-examination	1	75	1.59 [1.10, 2.08]		<0.001	□□□		

COMPLICATIONS							
Skin irritation							
None	2	271		1.00 [0.89, 1.13]	0.95	95%	Workbook and text messages, mobile app program	Standard care
> 1	2	271		0.77 [0.43, 1.36]	0.36	89%		
Sunburn (past week)							
None	2	271		3.19 [2.47, 4.10]	<0.001	99%		
> 1	2	271		2.68 [1.81, 3.96]	<0.001	95%		
BIOLOGIC MEASURES							
Melanin index - RU arm (sun protected	2	271	0.12 [-0.12, 0.35]		0.34	0%	Workbook and text messages, mobile app program	Standard care
Melanin index - R forearm (sun exposed)	2	271	-0.42 [-0.66, -0.18][d]		0.001	0%		
Cheek (sun exposed)	2	271	-0.25 [-0.64, 0.15][d]		0.22	61%		
Sun damage assessment - R forearm	2	271	-0.13 [-0.40, 0.13][d]		0.33	16%		

[a]Mean difference
[b]Standardised mean difference
[c]Unable to estimate due to absence of comparator group
[d]Reduction of outcome of interest represents an improvement

Table 4. Effect of pharmaceutical interventions on skin cancer prevention

Outcome	Studies	Participants	Relative risk	P	I^2	Intervention	Comparator
SWITH TO mTOR INHIBITORS (n=5)							
PRE-CANCEROUS LESIONS							
Skin dysplasia							
Any improvement	1	32	24.35 [1.55, 381.99]	0.02	□.0	Sirolimus	CNI[b]
Unchanged	1	32	0.85 [0.28, 2.61]	0.78	□□□		
Any worsening	1	32	0.04 [0.00, 0.66]	0.02	□□□		
CANCEROUS LESIONS							
SCC[d]/BCC[e] incidence	5	1082	0.46 [0.28, 0.75]	0.002	72%	Sirolimus	CNI
≥1 SCC	1	53	0.64 (0.35, 1.17)	0.15	N/A		
Skin cancer (excluding SCC)	1	53	0.74 (0.49, 1.14)	0.17	N/A		
Skin cancer (including SCC)	1	53	0.85 (0.61, 1.17)	0.32	N/A		
Skin cancer with BCC	1	53	0.89 (0.45, 1.78)	0.75	N/A		
PHOTODYNAMIC THERAPY (n=3)							
PRE-CANCEROUS LESIONS							
Actinic keratosis reduction (1-2 sessions)							
Complete response	2	50[a]	5.03 [0.14, 176.17]	0.37	85%	MAL[c]	Placebo, Imiquimod 5% cream
Partial response	1	17[a]	7.00 [0.39, 125.99]	0.19	N/A	MAL	Placebo
No reduction	1	17[a]	0.09 [0.02, 0.40]	0.002	N/A		
CANCEROUS LESIONS	1	26[a]	0.59 [0.34, 1.03]	0.06	N/A	MAL	No treatment
IMMUNE RESPONSE MODIFIERS (n=1)							
PRE-CANCEROUS LESIONS							
Reduced skin atypia	1	14[a]	3.00 [0.47, 19.35]	0.25	N/A	Imiquimod 5% cream	Placebo
Reduced dysplasia	1	14[a]	2.14 [0.31, 14.65]	0.44	N/A		
Reduced keratoses	1	14[a]	2.14 [0.31, 14.65]	0.44	N/A		
Reduced no. viral warts	1	14[a]	7.00 [0.46, 106.10]	0.16	N/A		

CANCEROUS LESIONS							
SCC incidence							
Treated (cream vs. placebo)	1	14[a]	0.09 [0.01, 1.70]	0.11	N/A	Imiquimod 5% cream	Placebo
Untreated (control site)	1	14[a]	0.43 [0.08, 2.37]	0.33	N/A		
ORAL RETINOIDS (n=2)							
CANCEROUS LESIONS							
Decreased incidence:							
> 1 SCC	1	46[a]	0.40 [0.19, 0.85]	0.02	N/A	Acitretin	Drug free period
> 1 BCC	1	46[a]	0.50 [0.14, 1.76]	0.28	N/A		
New skin cancer	1	19[a]	0.22 [0.06, 0.90]	0.03	N/A	Acitretin	Placebo

[a]Control is the contralateral or similar area of skin on the same participant
[b]Calcineurin inhibitor
[c]Methyl aminolaevulinate cream
[d]Squamous cell carcinoma
[e]Basal cell carcinoma

Figure legends

Figure 1. Study selection

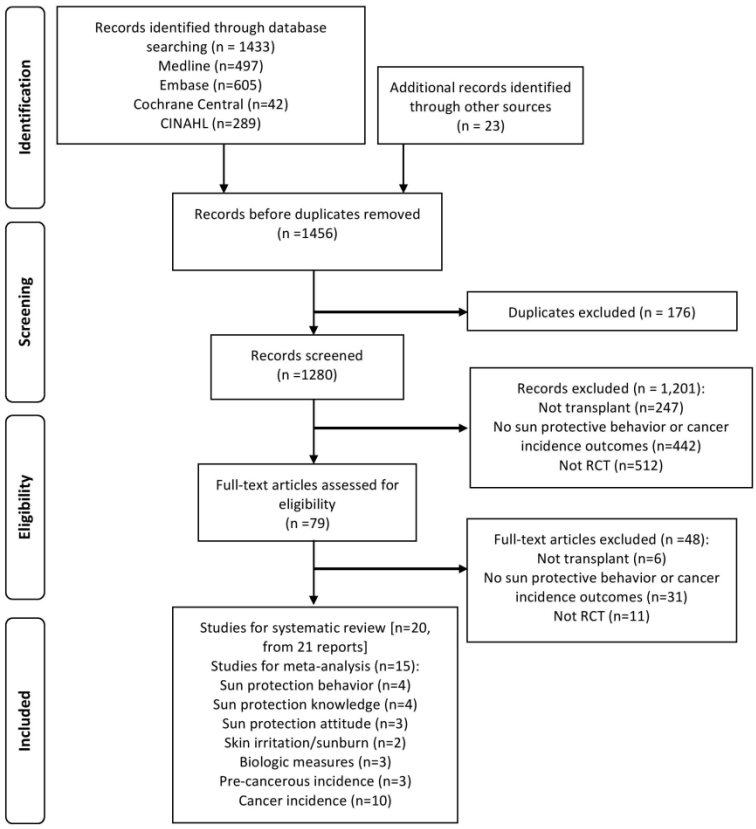
Figure 2. Risk of bias of included studies

Figure 3. Behavioral interventions – Sun protection behavior (general)

Figure 4. Behavioral interventions – Sun protection knowledge

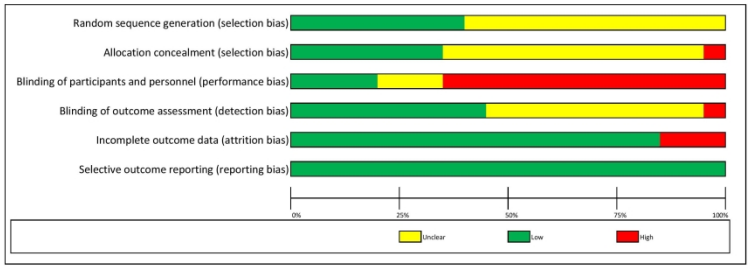
Figure 5. Switch to mTOR inhibitors – Non melanoma skin cancer incidence

Figure 1. PRISMA Flowchart



209x297mm (300 x 300 DPI)

Figure 2. Risk of bias in included studies



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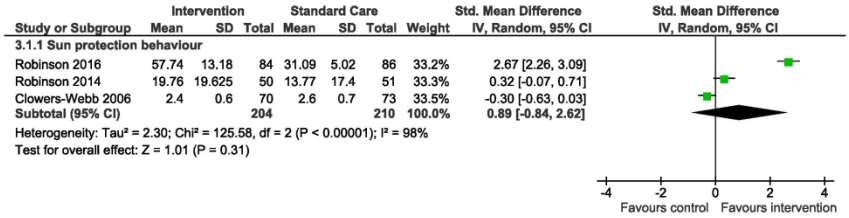

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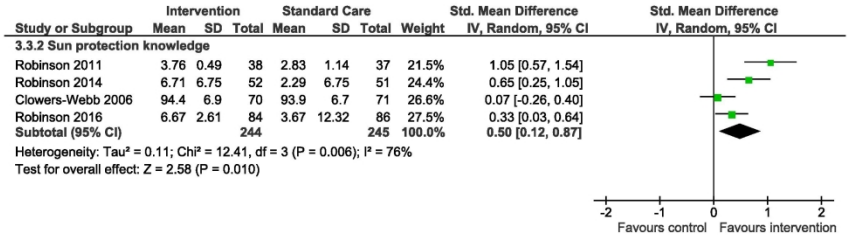

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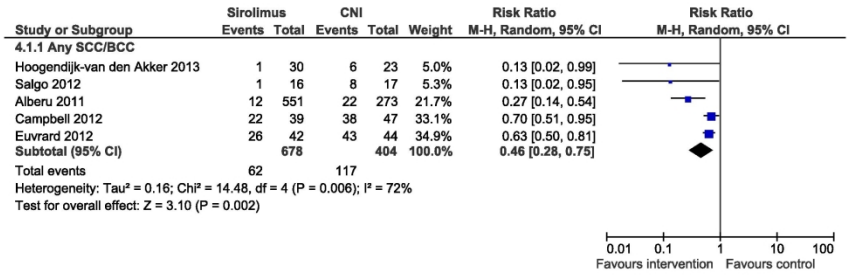

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Figure S1. Search Strategy

1. exp Neoplasms, Basal Cell/
2. basal cell carcinoma.ti,ab.
3. exp Neoplasms, Squamous Cell/
4. squamous cell carcinoma.ti,ab.
5. nonmelanom*.ti,ab.
6. non melanom*.ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Melanoma/
9. melanoma*.ti,ab.
10. Skin Neoplasms/
11. skin cancer*.ti,ab.
12. 8 or 9 or 10 or 11
13. 7 or 12
14. exp Organ Transplantation/
15. solid organ transplant*.mp.
16. transplant recipient*.tw.
17. exp Immunosuppression/
18. Immunocompromised Host/
19. 14 or 15 or 16 or 17 or 18
20. 13 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. Clinical Trials as Topic/
26. randomly.ab.
27. (crossover or cross-over).tw.
28. trial.ti.
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Animals/ not (animals/ and Humans/)

31. 29 not 30

32. 20 and 31

Figure S2. Risk of bias and key findings in individual studies

Study, year	Random sequence generation	Allocation concealment	Blinding participants & personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Intervention & comparator	Outcome RR/MD/SMD (95% CI)
Behavioral Interventions (n=6)								
Clowers-Webb 2006[30]	Unclear	Unclear	High	Unclear	High	Low	Repetitive written material vs. standard care	General behavior SMD -0.30 (-0.63, 0.03) Knowledge SMD 0.07 (-0.26, 0.40)
Robinson 2011[33]	Unclear	Unclear	Unclear	Unclear	Low	Low	Workbook vs. standard care	Skin self examination (1 month) RR 4.14 (2.22, 7.72) Knowledge SMD 1.05 (0.57, 1.54) Concern about developing cancer SMD 0.95 (0.47, 1.43) Confidence to recognize cancer MD 1.80 (1.35, 2.25) Importance of skin self-examination MD 1.05 (0.61, 1.49) Importance of partner to help for skin self-examination MD 1.59 (1.10, 2.08)
Robinson 2014[31]	Low	Low	High	Low	Low	Low	Workbook & text messages vs. standard care	General behavior SMD 0.32 (-0.07, 0.71) Knowledge SMD 0.65 (0.25, 1.05) Concern about developing cancer SMD 2.73 (2.19, 3.27) Recognize personal risk SMD -0.01 (0.40, 0.38) Confidence in sun protection SMD 0.30 (-0.09, 0.68) Willingness/intention to change behaviour SMD -0.02 (-0.41, 0.36) Importance of skin cancer/sun protection/having a tan MD 7.00 (2.94, 11.06) Skin irritation none RR 1.37 (1.16, 1.63) Skin irritation >1 RR 0.15 (0.03, 0.61) Sunburn none RR 1.30 (1.12, 1.52) Sunburn >1 RR 0.17 (0.04, 0.72) Melanin index - RU arm (sun protected) SMD 0.23

								(-0.17, 0.62) Melanin index - R forearm (sun exposed) SMD -0.37 (-0.76, 0.02) Cheek (sun exposed) SMD -0.03 (-0.42, 0.36) Sun damage assessment - R forearm SMD -0.30 (-0.69, 0.09)
Robinson 2016[32]	Unclear	Low	High	Low	Low	Low	Mobile app program vs. standard care	General behavior SMD 2.67 (2.26, 3.09) Daily hours outdoors MD -6.12 (-7.11, -5.13) Knowledge SMD 0.33 (0.03, 0.64) Concern about developing cancer SMD 1.97 (1.61, 2.34) Recognize personal risk SMD 1.22 (0.90, 1.55) Confidence in sun protection SMD 1.23 (0.09, 1.56) Willingness/intention to change behaviour SMD 3.42 (2.94, 3.89) Skin irritation none RR 0.82 (0.69, 0.96) Skin irritation >1 RR 1.64 (0.79, 3.40) Sunburn none RR 40.44 (10.27, 159.27) Sunburn >1 RR 4.83 (2.95, 7.90) Melanin index - RU arm (sun protected) SMD 0.05 (-0.25, 0.35) Melanin index - R forearm (sun exposed) SMD -0.46 (-0.76, -0.15) Cheek (sun exposed) SMD -0.43 (-0.73, -0.12) Sun damage assessment - R forearm SMD -0.02 (-0.33, 0.28)
Trinh 2014[28*]	Low	Unclear	Unclear	Unclear	Low	Low	Video vs. pamphlet	
Switch to mTOR inhibitors (n=6)								
Alberu 2011[39]	Low	Unclear	High	High	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.27 (0.14, 0.54)
Campbell 2009[41]	Low	Low	High	Low	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.70 (0.51, 0.95)
Carroll 2013[25*]	Unclear	Unclear	High	Low	Low	Low	Sirolimus vs. CNI/AZA	
Euvrard 2012[1]	Unclear	Unclear	High	Unclear	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.63 (0.50, 0.81)

Hoogendijk-van den Akker 2013[43]	Unclear	Low	High	Low	High	Low	SIrolimus vs CNI/MMF/AZA	Cancer incidence RR 0.13 (0.02, 0.99)
Salgo 2010[35]	Unclear	Unclear	High	Low	High	Low	SIrolimus vs CNI/MMF/AZA	Cancer incidence RR 0.13 (0.02, 0.95) Skin dysplasia Any improvement RR 24.35 (1.55, 381.99) Unchanged RR 0.85 (0.28, 2.61) Any worsening RR 0.04 (0.00, 0.66)
Pharmacetical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); 5% imiquimod cream (n=1)								
Bavinck 1995[40]	Unclear	Unclear	Low	Unclear	Low	Low	Acitretin vs. placebo	Cancer incidence RR 0.22 (0.06, 0.90)
Brown 2005[38]	Unclear	Unclear	Low	Low	Low	Low	5% Imiquimod cream vs. placebo	Cancer incidence SCC treated RR 0.09 (0.01, 1.70) SCC untreated RR 0.43 (0.08, 2.37) Reduced skin atypia RR 3.00 (0.47, 19.35) Reduced dysplasia RR 2.14 (0.31, 14.65) Reduced keratosis RR 2.14 (0.31, 14.65) Reduced no. viral warts RR 07.00 (0.46, 106.10)
Chen 2016[29]	Low	Unclear	Low	Low	Low	Low	Nicotinamide vs. placebo	
de Sevaux 2003[26]	Unclear	Low	High	Unclear	Low	Low	High dose acitretin vs. low dose acitretin	
Dragieva 2004[36]	Unclear	Unclear	Low	Unclear	Low	Low	Methyl aminolevulinate cream vs. placebo	Actinic keratosis reduction Complete response RR 27.00 (1.73, 420.67) Partial reduction RR 7.00 (0.39, 125.99) No reduction RR 0.09 (0.02, 0.40)
George 2002[42]	Unclear	Unclear	High	Unclear	Low	Low	Acitretin vs. drug free period	Cancer incidence >1 SCC RR 0.40 (0.19, 0.85) >1 BCC RR 0.50 (0.14, 1.76)
Togsverd-Bo 2015[27*†]	Low	Low	Unclear	Low	Low	Low	Methyl aminolevulinate cream vs. no treatment	

Togsverd-Bo 2017[37†]	Low	Low	High	Unclear	Low	Low	Methyl aminolevulinate cream vs.5% Imiquimod cream	Actinic keratosis reduction Complete response RR 1.42 (0.81, 2.48)
Wulf 2006[44†]	Low	High	High	Low	Low	Low	Methyl aminolevulinate cream vs. no treatment	Cancer incidence RR 0.59 (0.34, 1.03)

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

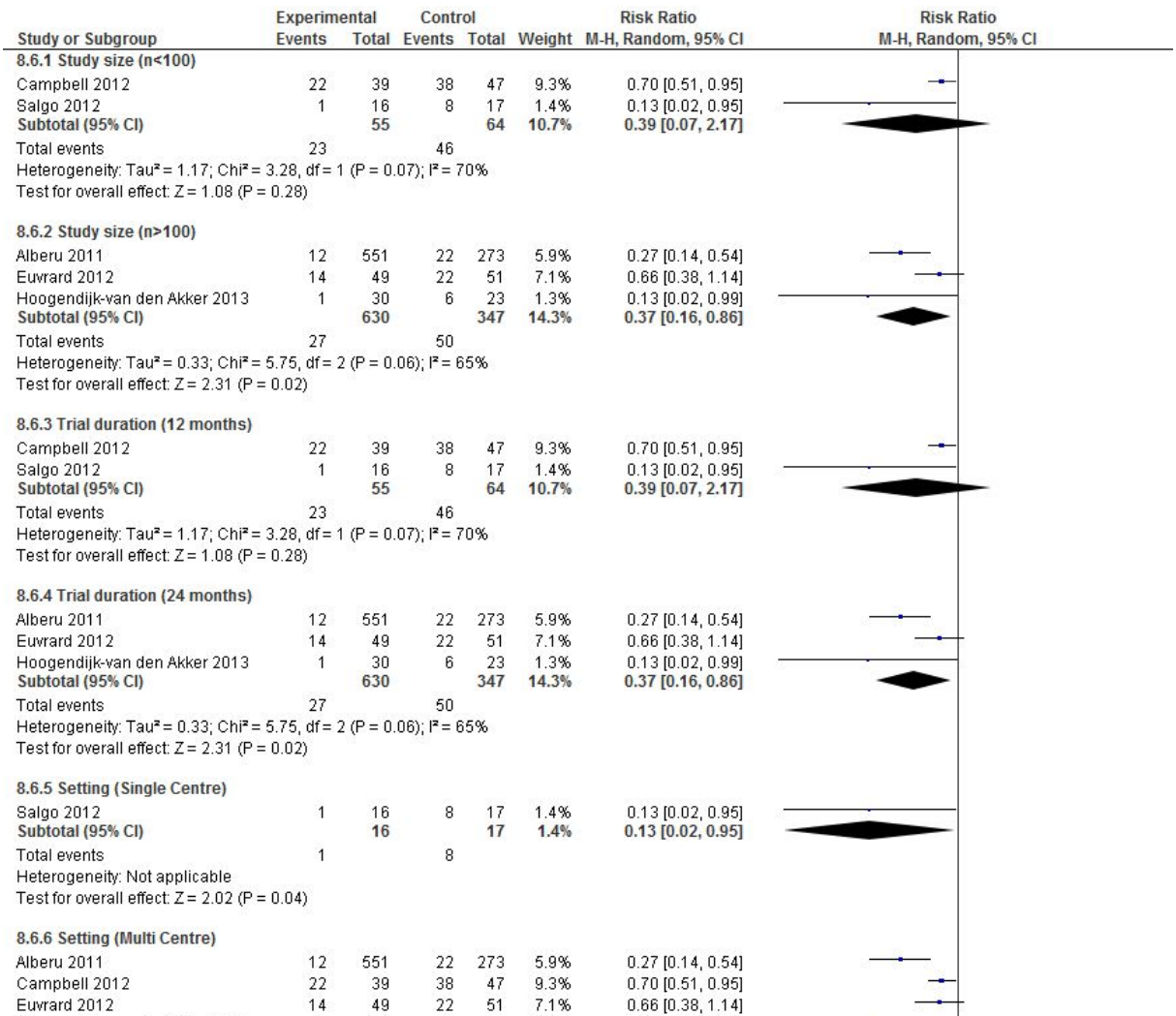
‡Excluded from analyses – same participants as Robinson 2016

Table S1. Assessment of quality of studies using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

Quality of assessment (Decrease in quality score)						
Number of studies	**Risk of bias/Quality of evidence**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality**
Sun protection behavior						
35 RCTs[24 30-33]	**Serious study limitations (-1)** Randomisation unclear[24 30 32 33] Participants not blinded or well described[24 30-33] Concealment of allocation not described.[30 33]	**Important inconsistency (-1)** Analysed in subgroups. heterogeneity (I^2=99%)[30-32]	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (2 weeks to 10 months) Same sample of participants[24 32]	**Serious imprecision (-1)** Small sample size, CIs crosses the null	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection knowledge						
6 RCTs[24 28 30-33]	**Serious limitations (-1)** Randomisation unclear[24 30 32 33] Participants not blinded or well described[24 28 30-33] Concealment of allocation not described[28 33]	**Important inconsistency (-1)** Heterogeneity (I^2 85%)	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (1 day to 10 months) Same sample[24 32]	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection attitude						
4 RCTs[24 31-33]	**Serious limitations (-1)** Randomisation unclear[24 32 33] Participants not blinded or well described[24 31-33] Concealment of allocation	**Important inconsistency (-1)** Wide variation in the effect estimates, heterogeneity (I^2 97%).	**Indirectness (-1)** Diverse interventions (written vs. electronic), Similar duration. Same sample[24 32]	**Serious imprecision (-1)** Small sample size, small number of events	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**

	not described[32 33]					
Complications (skin irritation, sunburn)						
2 RCTs[31 32]	**Serious limitations (-1)** Participants not blinded[31 32]	**Important inconsistency (-1)** Heterogeneity (I^2=95-99%) Analysed in subgroups. Similar effect estimates.	**Indirectness (-1)** Diverse interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Biologic measures (melanin index, sun damage)						
2 RCTs[31 32]	**Serious limitations (-1)** Randomisation unclear[32] Participants not blinded[31 32]	**Important inconsistency (-1)** Analysed in subgroups. Heterogeneity (I^2 60%)	**Indirectness (-1)** Different interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Pre-cancerous incidence						
4 RCTs [27 35-38]	**Serious limitations (-1)** Randomisation or allocation unclear[35 36 38] Participants not blinded or well described[27 35-38]	**Important inconsistency (-1)** Analysed in subgroups.	**Indirectness (-1)** Diverse interventions, varying duration	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**
Cancer incidence						
10 RCTs [1 29 35 38-44]	**Serious limitations (-1)** Randomisation unclear[1 40 42 43] Allocation concealment not used or unclear[1 29 39 40 42 44] Participants not blinded.[1 35 39 41-44]	**Important inconsistency (-1)** Majority of participants came from 1 study[39] Small sample[1 29 35 38 40-44]	**Indirectness (-1)** Diverse interventions (immunosuppression, photodynamic therapy, immune response modifier, retinoid, nicotinamide), varying duration	**Serious imprecision (-1)** Majority of participants from one trial (n=551), small number of events	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**

Figure S3. Subgroup analyses of immunosuppression conversion interventions on skin cancer incidence



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029265.R3
Article Type:	Original research
Date Submitted by the Author:	20-Mar-2020
Complete List of Authors:	James, Laura; University of Sydney, Saglimbene, Valeria; The University of Sydney, Sydney School of Public Health Wong, Germaine; The Children's Hospital at Westmead, Centre for Kidney Research Tong, Allison; The University of Sydney, Sydney School of Public Health Luu, Laurence; The University of Sydney, Sydney School of Public Health Craig, Jonathan; Flinders University Faculty of Medicine Nursing and Health Sciences, College of Medicine and Public Health, ; The Children's Hospital at Westmead, Centre for Kidney Research Howard, Kirsten; University of Sydney, School of Public Health Howell, Martin; University of Sydney - Camperdown and Darlington Campus, School of Public Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	skin cancer, melanoma, prevention, sun protection, sun protection behaviors

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Behavioral and pharmaceutical interventions for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

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Word count (abstract): 205

Word count (body): 3593

Tables: 4 **Figures:** 5

K**ey words:** skin cancer, melanoma, prevention, sun protection, sun protection behaviors, health behavior

Authorship

LJJ, GW, AT, LL, JCC, KH, MH designed the study; LJJ, VS, LL, MH conducted the data extraction and analyses; all authors contributed to the interpretation of the analyses. LJJ drafted the manuscript; all authors contributed to the writing and review of the manuscript.

Disclosure

The authors declare no conflicts of interest.

Data availability statement

No additional data available.

Funding

LJJ is supported by the National Health and Medical Research Council (NHMRC) Better Evidence and Translation in Chronic Kidney Disease (BEAT-CKD) Program Grant (APP1092957). MH is supported by the BEAT-CKD Program Grant (APP1092957). AT is supported by the NHMRC Fellowship (APP1106716). The funding organizations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript.

Abbreviations

AZA, azathioprine

BCC, basal cell carcinoma

CNI, calcineurin inhibitors

CI, confidence intervals

MAL, methyl aminolaevulinate cream

MD, mean difference

MMF, mycophenolate mofetil

mTORI, mammalian target of rapamaycin inhibitors

NMSC, non-melanoma skin cancer

RCT, randomized controlled trial

RR, relative risk

SCC, squamous cell carcinoma

SMD, standardized mean difference

ABSTRACT

Objectives

Solid organ transplant recipients are at increased risk of skin cancer, affecting more than 50% of recipients. We aimed to determine the effectiveness of interventions for behavioral change for sun protection or skin cancer prevention in solid organ transplant recipients.

Design

Systematic review

Data sources

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from inception to November 2019.

Eligibility Criteria

We included randomized controlled trials that evaluated the effect of behavioral or pharmaceutical interventions on behavioral change or skin cancer prevention in solid organ transplant recipients.

Data extraction and synthesis

Risks of bias and evidence certainty were assessed using Cochrane and the GRADE framework.

Results

Twenty trials (n=2,295 participants) were included. It is uncertain whether behavioral interventions improve sun protection behavior (N=3, n= 414, SMD 0.89, 95% CI -0.84-2.62, I^2

=98%) and knowledge (N=4, n=489, SMD 0.50, 95% CI 0.12-0.87, $I^{2=}$ 76%) as the quality of evidence is very low. We are uncertain of the effects of mammalian target of rapamaycin inhibitors on the incidence of non-melanocytic skin cancer (N=5, n=1080, RR 0.46 95% CI 0.28-0.75, $I^{2=}$72%) as the quality of evidence is very low.

Conclusions

Behavioral and pharmaceutical preventive interventions may improve sun protective behavior and knowledge, and reduce the incidence of non-melanocytic skin cancer, but the overall quality of the evidence is very low and insufficient to guide decision-making and clinical practice.

PROSPERO Registration number

CRD42017063962

ARTICLE SUMMARY

Strengths and limitations

- A comprehensive review conducted using methods outlined by Cochrane Collaboration including GRADE to assess risk of bias and evidence certainty
- Inclusion of a broad range of interventions, including behavioral to improve sun protection behavior and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence
- Difficulty obtaining an overall summary estimate for many outcomes due to the variability in the analytical methods and reporting in individual studies
- Unable to perform detailed subgroup analyses or assess for publication bias due to small number of studies
- Few trials included the important outcomes of skin cancer and none included melanoma or mortality.

1. INTRODUCTION

Skin cancer, including melanoma and nonmelanoma skin cancer (NMSC), is the most frequently diagnosed malignancy among solid organ transplant recipients, affecting more than 50% of post-transplantation recipients.[1 2] The cumulative incidence of NMSC increases with time after transplantation, from 5-10% at 2 years to 40-80% at 20 years.[2-4] Compared to the general population, there is a higher rate of squamous cell carcinoma (SCC) to basal cell carcinoma (BCC), with an incidence of 65 to 250 times greater than the age and gender-matched general population.[5-8] Once cancer develops, management options are limited as immunotherapy may be unsuitable as it may lead to graft rejection.[9 10] Although registry data shows improvement in survival rates of transplant recipients as a result of improved transplantation techniques and management of immunosuppression, there is a greater burden of skin cancer and cancer related mortality.[11] The excess risk of death from invasive and metastatic skin cancer, such as SCC and melanoma, are three times to nine times higher than the general population, with five-year overall survival of less than 30%.[6 12-15]

Sun exposure behaviors remain the most significant and modifiable risk factor in the prevention of skin cancers in the general population.[16] However, with the dramatic increase in skin cancers in solid organ transplant recipients, pharmaceuticals have also been used to reduce and delay the development of skin cancer.[16 17] Current recommendations for preventive strategies have often been extrapolated from guidelines in the general population, which may not be applicable to solid organ transplant recipients.[18 19] For example, frequent skin self-examination and annual to biannual total body skin examination are generally recommended for the general population.[18-20] Sun protective behaviors including use of sunscreen, protective clothing and limiting sun exposure during peak hours of high UV index days are potential measures for skin cancer prevention.[3 4 14]

Further, alteration of maintenance immunosuppression such as conversion to mammalian target of rapamaycin inhibitors (mTORi) and secondary prevention using retinoid acitretin are recommended for management of skin cancers in high risk transplant recipients.[20]

The aim of this study is determine the effectiveness of interventions that promote behavioral change and skin cancer prevention in solid organ transplant recipients.

2. METHODS

This systematic review followed a pre-specified protocol registered in PROSPERO (CRD42017063962) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[21] The study was exempt from approval from an ethics' board.

2.1 Inclusion criteria

All randomized controlled trials (RCTs) or quasi RCTs (allocated to trial arms by investigators) of interventions for skin cancer prevention (both melanoma and non-melanoma skin cancer) in solid organ transplant recipients were included. Behavioral interventions defined as any strategy used to promote sun protective behavior including passive (e.g. pamphlets), active (e.g. group workshops, counselling, dermatology clinic) and provision of sun protective equipment; and pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers, nicotinamide and oral retinoids) and studies that reported skin cancer related outcomes as their primary outcomes were included. Studies that did not report these outcomes as primary end-points were excluded. Studies of interventions for the treatment of skin cancer were excluded.

2.2 Search strategies

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from inception to November 2019 without language restriction, using search strategies designed by a specialist information manager (see Medline search strategy in Figure S1). Reference lists of included studies were also searched.

2.3 Data extraction

Titles and abstracts were reviewed by two independent authors (LJJ & LL) and those that did not meet the inclusion criteria were excluded. Full text articles were reviewed by 3 independent reviewers (LJJ, VS, LL) and any disagreements were resolved by discussion. Data on study design, geographic location, sample size, type of transplant, measurement of interventions, interventions and comparators were extracted. We sought unclear or missing information from authors where possible.

2.4 Outcome measures

The pre-specified outcome measures were incidence of precancerous and cancerous lesions, sun protection behavior (including use of sunscreen, use of protective clothing including hats and sunglasses, shade and sun avoidance), knowledge and attitude, skin self-examination, sun exposure (including skin irritation, sunburn) and biologic measures (including measurement of melanin index and sun damage assessment).

2.5 Risk of bias and quality of evidence

The risk of bias was assessed independently by LJJ and VS using the Cochrane risk of bias tool.[22] The domains included in the assessment were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, trial registration and industry involvement. Each criterion was

assigned a judgment of high, low or unclear risk of bias. Intention to treat and lost to follow up were also assessed for each study. The quality of the evidence informing summary estimates for each outcome was then assessed by LJJ using the Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines.[23]

2.6 Data synthesis and statistical analyses

Continuous outcomes were summarized as mean difference (MD) or standardized mean difference (SMD) and dichotomous outcomes as relative risk (RR). A MD/SMD greater than zero and/or a RR greater than 1 could be interpreted as favoring the intervention group relative to the control, unless specified elsewhere. Risk estimates were reported with 95% confidence intervals (CI), using random-effects meta-analysis. We quantified the heterogeneity using the I^2 statistic. An I^2 value of <25% was considered to represent low heterogeneity and >75% as high heterogeneity. When sufficient data were available, possible sources of heterogeneity were investigated using subgroup analysis based on pre-specified study characteristics including sample size, trial duration, setting and overall risk of bias. Funnel plots were planned to evaluate small study effects when at least ten studies were included in meta-analysis. All analyses were conducted using Review Manager version 5.3 software.

2.7 Patient and public involvement

There was no patient or public involvement.

3. RESULTS

3.1 Study selection

The literature search identified 1280 articles, of which, 1201 were excluded after abstract and title review. Full text assessment of 79 studies found 22 eligible articles for inclusion (Figure 1).

3.2 Studies characteristics

We included 22 reports of 20 RCTs, including 2,295 participants (Figure 1). The study characteristics are summarized in Table 1 and Table 2. The median number of participants was 44 (range 17 to 830) and the median follow-up duration was 10 months (range 1 day to 60 months). All studies included kidney transplant recipients, with some also including heart transplant recipients (n=1), liver, heart, pancreas, lung, heart/lung and other transplants (n=1), and lung and liver transplant recipients (n=2). In total, 15 of 21 (76%) studies provided sufficient data for the meta-analyses. Six studies did not meet final criteria for meta-analysis as they had the same sample of participants (n=1),[24] or did not provide data that was able to be meta-analyzed (n=5).[25-29]

3.3 Risk of bias and quality of the evidence

Overall studies had either high or unclear risk of bias for at least one domain (Figure 2; Figure S2). Random sequence generation and allocation concealment were unclear in most studies (n=12, 60%). Blinding of participants was not done in most studies (n=16, 80%) and blinding of outcome assessors was only reporting in half of the studies (n=10). Intention to treat analyses were used in 6 (30%) studies and 6 studies (30%) had a high loss to follow-up. A total of 3 (15%) studies had incomplete outcome data, and all studies were at low risk for selective reporting. Seven studies (35%) reported industry involvement in authorship, design, or data analysis, and of the 16 trials requiring trial registration, only 9 (56%) reported accordingly.

The overall quality of the evidence was very low for all outcomes (Table S1) due to limitations in study design, heterogeneity in the intervention and outcomes measures, the very small sample size of individual studies and the small number of studies for each specific outcome. Obtaining an

overall summary estimate was difficult for many outcomes due to the variability in the analytical methods and reporting in individual studies. In particular, assessment of reporting of sun protection behavior and sun protection knowledge was not possible as outcomes were inconsistent and there was large diversity of interventions used (e.g. written education material versus a mobile app program). Furthermore, formal testing of publication bias was not performed due to insufficient data.

3.4 Interventions

The interventions in the included studies were grouped in three broad categories, behavioral (n=6), switch to mTOR inhibitors (n=6), and other pharmaceutical interventions (photodynamic therapy, immune response modifiers, oral retinoids and nicotinamide) (n=9). Studies of behavioral interventions used passive methods of delivery including written educational material (n=2), both written educational material and text messages (n=1), mobile app programs (n=2) and a video (n=1).

All six studies of immunosuppression compared mTORis (sirolimus) to calcineurin inhibitors (CNI) based therapies.

Four of the eight studies of other pharmaceutical interventions assessed the effect of photodynamic therapy using methyl aminolevinate creams compared to placebo (n=1), no treatment to contralateral area (n=2) or a topical immune response modifier cream (n=1). Three studies assessed oral retinoid using acitretin compared to placebo (n=1), lower dose (n=1) or a drug free period (n=1), one study assessed nicotinamide compared to placebo and a single study assessed the benefits of topical immune response modifier compared to placebo in kidney transplant recipients.

3.5 Effect of behavioural interventions on sun protection outcomes

Sun protection behavior

Sun protection behavior, defined as hours spent outdoors per week, use of sunscreen, wearing protective clothing and seeking shade, was assessed in three trials[30-32]. Educational workbooks,[30] educational workbooks and text messages[31] and a mobile app program[32] were compared with standard care. Patients who received behavioral interventions reported improved sun protection behavior scores[30-32] (3 studies, 414 participants, SMD 0.89, 95% CI -0.84-2.62, I^2 98%) (Table 3; Figure 3). We are uncertain of the effects of behavioural interventions on sun protection behavior due to very low quality of evidence. A single trial assessed a standardised and validated educational workbook and found an improvement in the proportion of participants engaging in skin self-examination after one month (75 participants, RR 4.14, 95% CI 2.22-7.72).[33] One trial assessed a mobile app program and reported a reduction in daily hours spent outdoors among the intervention group (170 participants, MD -6.12, 95% CI -711 to -5.13).[32]

Sun protection knowledge

The effectiveness of educational workbooks, text messages, mobile app programs and videos on sun protection knowledge was assessed in 6 studies[24 28 30-33], four of which provided data for a meta-analysis. There was an improvement in knowledge scores (4 studies, 489 participants, SMD 0.50, 95% CI 0.12-0.87, I^2 76%) in the intervention group compared to standard care (Figure 4).[30-33] One study compared an interactive visual representation of the educational program with standard information pamphlets and found that knowledge of sun protection improved among those who received the educational video.[28]

Sun protection attitude

Three studies assessed sun protective attitude after receiving an educational workbook, text messages or a mobile app program over a period of 0.5 months to 1.5 months.[31-33] Compared to standard care, there was an overall improvement in scores of concern about developing cancer (3 studies, 348 participants, SMD 1.85, 95% CI 1.59-2.11, I^2 96%).[31-33] Two studies involving 273 participants reported an improvement in scores of understanding the personal risk of skin cancer (SMD 0.61, 95% CI -0.60-1.82, I^2 96%), adherence to sun protection (SMD 0.77 95% CI -0.14-1.68, I^2 92%) and willingness or intention to change behavior (SMD 1.70, 95% CI -1.68-5.07, I^2 99%).[31 32] We are uncertain of the effects of behavioural interventions on sun protection attitude due to very low quality of evidence. A single study involving 75 participants also reported an improvement in scores of ability to recognize a potential skin cancer (MD 1.80, 95% CI 1.35-2.25), importance of skin self-examination (MD 1.05, 95% CI 0.61-1.49) and having a partner help for skin self-examination (MD 1.59, 95% CI 1.10-2.08).[33] Another single study reported an improvement in the importance of engaging in sun protection (measured using 5-point Likert scale) (101 participants, MD 7.00, 95% CI 2.94-11.06).[31]

Skin complications and biologic measures

Two trials of behavioral interventions in 271 kidney transplant recipients compared a mobile app or an educational workbook and text messages to standard care on reported skin complications and biologic measures of sun exposure.[31 32] The intervention group experienced a reduced incidence of skin irritation (a culturally relevant term for sun exposure[34]) (RR 1.00, 95% CI 0.89-1.13, I^2 95%) or sunburn (RR 3.19, 95% CI 2.47-4.10, I^2 99%). They also had a decreased melanin index (right forearm, SMD -0.42, 95% CI -0.66 to -0.18; cheek SMD -0.25, 95% CI -0.64 to -0.15) and reduced severity of sun damage (SMD -0.13, 95% CI -0.40 to 0.13) on sun exposed areas (measured using clinical images of chronic sun damage and scored 1-10).

3.6 Effect of pharmaceutical interventions on skin cancer prevention

The incidence and responses of pre-cancerous lesions were measured only in trials of pharmaceutical interventions (Table 4). These included the switch to mTOR inhibitors (n=1),[35] photodynamic therapy (n=2)[36 37] and immune response modifiers (n=1)[38] to current treatment or placebo. The incidence of non-melanocytic skin cancers (NMSC) was assessed in nine pharmaceutical studies.[1 35 38-44] None included melanoma as an outcome.

Topical/local interventions

One trial of 14 participants compared an immune response modifier, 5% imiquimod cream with placebo and found a reduction in the incidence of skin dysplasia (RR 2.14, 95% CI 0.31-14.65), skin atypia (RR 3.00, 95% CI 0.47-19.35), and viral warts (RR 7.00, 95% CI 0.46-106.10).[38]

One Danish study of 26 kidney transplant recipients compared photodynamic therapy with no treatment and reported a relative reduction by approximately 40% in the incidence of NMSC on the treated area (RR 0.59, 95% CI 0.34-21.03, p 0.06).[44] A lower incidence of SCC was also reported in one trial comparing two areas of skin using an immune response modifier and placebo (14 participants, RR 0.09, 95% CI 0.0.01-1.70).[38] Two trials comparing photodynamic therapy to an immune response modifier or photodynamic therapy to placebo in recipients with diagnosed keratoses reported a complete response rate of 60% compared to 24% in the control group (50 participants, RR 5.03, 95% CI 0.14-176.17, I^2 85%).[36 37] We are uncertain of the effects of photodynamic therapy on incidence of precancerous lesions due to very low quality of evidence. Further, one trial which was not included in the meta-analysis, reported a higher cumulative

incidence of actinic keratosis lesions in untreated skin (63%) compared with skin treated by photodynamic therapy (28%).[27]

Systemic interventions

mTORis therapy reduced the incidence of NMSC compared to CNIs maintenance therapy (5 trials, 1082 participants, RR 0.46, 95% CI 0.28-0.75, I^2 72%) (Figure 5).[1 35 39 41 43] However evidence was limited due to short follow-up periods, variability in dosing of mTORis and significant rates of loss to follow up, and therefore we are uncertain of the effects of mTORis on skin cancer incidence due to very low quality of evidence. A single trial involving 21 patients reported a reduction in the overall incidence of SCC by 49% in the conversion arm, but reported a drop out rate of 77% and follow-up time of less than 2 years.[25] Further, a single trial which compared mTORi conversion from CNI based therapy reported a significant improvement in skin dysplasia (32 participants, RR 24.35, 95% CI 1.55-381.99).[35]

Two trials comparing an oral retinoid, acitretin, with placebo or a drug free period reported an increased lower risk of both SCCs and BCCs (46 participants, RR 0.40, 95% CI 0.19-0.85, p 0.02; RR 0.50, 95% CI 0.14-1.76)[42] or development of a new skin cancer (19 participants, RR 0.22, 95% CI 0.06-0.90). However, there were no differences in the incidence of new SCCs.[40] One trial, which was not included in the meta-analysis, showed approximately a 50% reduction in the incidence of actinic keratosis which compared a high dose to a low dose of acitretin.[26]

One Australian trial of 22 kidney transplant recipients compared nicotinamide with placebo and reported an estimated relative rate difference of 0.35 (95% CI -0.62 to 0.74), 0.67 (95% CI -0.40 to 0.90) and 0.07 (95% CI -1.51 to 0.65) for NMSC, BCCs and SCCs respectively.[29]

3.7 Subgroup analysis

Study size, trial duration, setting and risk of bias did not modify the effects of CNIs and mTORIs on skin cancer incidences (Figure S3). Sources of heterogeneity for other treatment effects could not be explored due to insufficient data.

4 DISCUSSION

Skin cancers (both non-melanoma and melanoma) are major causes of morbidity and mortality in solid organ transplant recipients. Despite this, trials of interventions aimed at preventing skin cancer in solid organ transplant recipients are few in number (20 trials), small with half comprising of 50 patients or less, of short duration (48% have <12 months follow up) and 52% do not include incidence of skin cancer as an outcome. Our review included 22 reports of 20 trials involving 2,295 transplant recipients, who were predominately kidney transplant recipients. The studies covered a broad range of interventions, including behavioral to improve sun protection behavior and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence. None of the behavioral intervention studies included precancerous lesions or skin cancer incidence as outcomes. Although interventions showed plausible improvements to sun protection behaviors, precancerous lesion responses and cancer incidence, there was considerable variability across interventions types, variability in outcomes assessed and outcome estimates. Overall, the current evidence for interventions for skin cancer prevention in solid organ transplant recipients is of very low quality and is insufficient to guide decision-making and clinical practice.

Although behavioral interventions appeared to improve sun protection attitude, knowledge and behavior, there were inconsistencies detected and none of these studies included skin cancer as

an outcome. Due to limited number of studies, we were unable to compare specific behavioral interventions (e.g. mobile app vs. written education) to ascertain the most effective method of delivering sun protection education. While there may be some modest benefits in the reduction in cancer incidence (for NMSC) among solid organ transplant recipients who were converted to mTORIs compared to those on CNI maintenance, there was substantial heterogeneity across the studies that was unable to be explained by subgroup analyses. Heterogeneity may be attributed to the absence of long term follow up, large discontinuation rates owing to adverse events and variability in the doses of mTORIs. Pharmaceutical interventions (switch to mTOR inhibitors, photodynamic therapy, immune response modifiers) showed a reduction in precancerous lesions compared to standard care or a comparator group. However uncertainty exists in the treatment effects and there were too few studies, interventions were incomparable, follow-up times were variable and considerable loss to follow up for some studies to conclude that the benefits are sustainable.

Previous systematic reviews have evaluated the impact of behavioral interventions on skin cancer prevention in the general population,[45] and concluded that computer programs may increase sun protective behaviors, and 'appearance-focused' interventions may decrease sun tanning and UV exposure in adolescents and young women, respectively. Reviews conducted in other populations at high-risk including outdoor workers,[46] family history, personal history and phenotypic factors[47] have found similar improvement in sun protective behaviors, including use of sunscreen, as well as a decreased incidence of keratoses. A systematic review of the benefits and harms of oral retinoids for the prevention of skin cancer among high risk transplant recipients led to inconclusive results on the effect of acitretin due to the small number of included trials.[48]

Despite the inclusion of all interventions aimed at the prevention of skin cancer in solid organ transplant recipients and the comprehensive systematic search for eligible studies, there are some potential limitations. Due to the heterogeneity of the studies, the high risk of bias, the potential for reporting bias and imprecision in the point estimates of individual studies, there is a high degree of uncertainty in the estimate of the effect of skin cancer prevention interventions. All studies of behavioral interventions were undertaken in United States, with 4 by the same authors, whilst most pharmacological intervention studies were conducted in Europe. There were also large discontinuation rates owing to adverse events in trials of mTORIs. Further, given the small number of studies included in the meta-analysis, we were unable to perform any detailed subgroup analyses to explore heterogeneity or assess for publication bias. While we were unable to show and assess publication bias using standard statistical tests, we would suggest the observed heterogeneity may also be attributed to potential publication and reporting biases. It is difficult to quantify the extent of such bias in this review, but one would expect research with 'positive' findings that indicate an intervention works, such as behavioral interventions improve sun protection, are more likely to be published more than one, in high impact journals and more likely to be cited. Finally, few trials included patient important outcomes associated with skin cancer and none included melanoma or mortality.

The use of pharmaceutical and immunosuppression therapy remains complex. Not only has mTORI therapy shown benefits in lowering the risk of skin cancer, early conversion to mTORI therapy from CNIs has also shown promising effects in reducing cancer rates.[49 50]On the contrary, overall mortality is higher and discontinuation following adverse events is more common in patients who receive mTORI therapy.[49 50] Several RCTs showed a higher rate of patients reporting adverse events or drug discontinuation with sirolimus,[1 41 43] demonstrating concern of its clinical usefulness.[49] Nicotinamide may also offer benefits to reducing skin cancer incidence by 20% and is

relatively safe with minimal side effects. The protective effect of nicotinamide on skin cancer incidence in kidney transplant recipients is currently being explored in a phase 3 randomised controlled trial.

Although behavioral change is a simple strategy, long-term adherence remains challenging. While behavioral counseling has been shown to increase sun protective behaviors in non-transplant populations,[45] there is no direct evidence to show that the behavioral change led to a reduction in morbidity and mortality. Previous studies have suggested that transplant recipients do not practice sun protective behaviors regularly,[51-53] were less likely to use sunscreen[54] and that patients have to perceive skin cancer as being an important risk to be motivated to change behavior.[55 56] However, studies on risk perception of transplant recipients remain conflicting. Given this complexity and the observed inconsistencies in the existing trials, process evaluations including facilitators and barriers to behavioral change should be included in future trials. Such evaluations could include the use of qualitative methodology to support the trial design, ascertain the perspectives of participants on the intervention and evaluate the implementation.[57 58]

We suggest that further strategies for skin cancer prevention in transplant recipients require a multifaceted and individualized approach. Transplant recipients are likely to benefit from early implementation of education, particularly before transplantation occurs and recipients may be preoccupied with other health needs related to transplantation. Although recipients understand the importance of ongoing education for the ability to self-manage their disease, they may experience difficulty in concentrating and learning new knowledge, and are often unable to look beyond their graft and the anxiety/fear of graft loss.[59-61] Interventions should be integrated into routine appointments and tailored to meet the individual needs of patients. This would be best

achieved through a shared decision-making approach to identify the patient's preferences and priorities and thereby enhance the likelihood of success of self-management and prevention.[62]

Additional large-scale and high-quality RCTs are needed to demonstrate the effectiveness of interventions used to prevent skin cancer in transplant recipients in terms of patient important outcomes, in particular morbidity and mortality associated with skin cancer. Determining patient's preferences for prevention and management of skin cancer are also warranted to ensure interventions and outcomes for trials are relevant to patient needs and priorities and better support patient-centered treatment decisions.[63] Evidence of the efficacy of sun protective behavior interventions need to be strengthened, with use of measures that are homogenous, reliable and validated.

Preventative measures including behavioral, switch to mTOR inhibitors and other pharmaceuticals may improve skin cancer outcomes for solid organ transplant recipients. However, the overall quality of evidence is of very low and insufficient to guide decision-making and clinical practice. Future robust studies that are well powered, have long-term follow up, and use clinical and patient important outcome measures in a consistent manner are required to therefore optimize outcomes for solid organ transplant recipients.

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Table 1. Characteristics of included studies (n=20)

Characteristics	N (%)
Type of transplant	
Kidney	16 (80)
Multiple*	4 (20)
Sex	
≥ 50% Male	18 (90)
< 50% Male	1 (5)
Not specified	1 (5)
Age (mean)	
< 60	10 (50)
≥ 60	5 (25)
Not specified	5 (25)
Sample size	
10 – 50	11 (55)
50 – 100	3 (15)
100 – 200	4 (20)
>200	2 (10)
Setting	
Single center	8 (40)
Multi center	11 (55)
Not specified	1 (5)
Country of origin	
Australia	3 (15)
Denmark	4 (20)
France	1 (5)
Germany	1 (5)
Netherlands	2 (10)
New Zealand	2 (10)
Switzerland	1 (5)
Sweden	1 (5)
United Kingdom	3 (15)
United States	6 (30)
Other†	1 (5)
Intervention Type	
Behavioral	5 (25)
Switch to mTOR inhibitors	6 (30)
Photodynamic therapy	4 (20)
Oral retinoid	3 (15)
Nictotinamide	1 (5)
Topical immune response modifier	1 (5)
Duration of follow up	
<12 months	9 (45)
12 months	4 (20)
24 months	5 (25)
>24 months	1 (5)
Not specified	1 (5)
Year of publication	
1995 – 1999	1 (5)
2000 – 2004	3 (15)
2005 – 2009	4 (20)
2010 – 2014	8 (40)
2015 – 2017	4 (20)

* Kidney, liver and lung (n=2); kidney and heart (n=1); Kidney and multiple other types (n=1) – see text

† 111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Table 2. Characteristics of individual studies

Study	N	Type of transplant	Setting	Type of intervention	Measures	Intervention	Comparator	Primary outcomes	Time (mths)
Behavioral interventions (n=6)									
Clowers-Webb 2006[30]	202	Kidney, liver, heart, pancreas, lung, heart/lung, other§	Single centre, United States	Behavioral	Self-reported questionnaire	Repetitive written material	Standard care	Knowledge & behavior	10
Robinson 2011[33]	75	Kidney	United States	Behavioral	Self-reported questionnaire	Workbook	Standard care	Knowledge & behavior	1
Robinson 2014[31]	101	Kidney	Single centre, United States	Behavioral	Self-reported questionnaire Physical examination	Workbook Text messages	Standard care	Knowledge & behavior	1.5
Robinson 2015[24]‡	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire	Mobile app program	Standard care	Knowledge & behavior	0.5
Robinson 2016[32]	170	Kidney	Multi-centre, United States	Behavioral	Self-reported questionnaire Physical examination	Mobile app program	Standard care	Knowledge & behavior	1.5
Trinh 2014[28]*	100	Kidney, liver, lung	Single centre, United States	Behavioral	Self-reported questionnaire	Video	Pamphlet	Knowledge	1 day
Switch to mTOR inhibitors (n=7)									
Alberu 2011[39]	830	Kidney	Multi centre§	Switch to mTOR inhibitors	Investigator reported adverse events	Conversion to sirolimus	CNI	Cancer incidence	24
Campbell 2012[41]	86	Kidney	Multi centre, Australia, New Zealand, United States	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	12
Carroll 2013[25]*	32	Kidney	Multi centre, UK	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to prednisolone & sirolimus	CNI/AZA	Cancer incidence	24
Euvrard 2012[1 64]	120	Kidney	Multi centre, France	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	CNI	Cancer incidence	24
Hoogendijk-van den Akker	155	Kidney	Multi centre, Netherlands, UK	Switch to mTOR inhibitors	Physical examination +/- biopsy	Conversion to sirolimus	AZA/MMF/ CNI	Cancer incidence	24

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2013[43]									
Salgo 2010[35]	44	Kidney	Single centre, Germany	Switch to mTOR inhibitors	Physical examination +/- biopsy Clinical photographs	Conversion to sirolimus and prednisone	AZA/MMF/ CNI	Precancerous skin dysplasia incidence	12
Pharmaceutical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); nicotinamide (n=1); 5% imiquimod cream (n=1)									
Bavinck 1995[40]	44	Kidney	Multi centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	Acitretin	Placebo	Cancer incidence precancerous lesion reduction	6
Brown 2005[38]	21	Kidney	Multi centre, UK	Topical immune response modifier cream	Physical examination +/- biopsy Clinical mapping and photographs	5% Imiquimod cream	Placebo	Reduction of precancerous lesions	4
Chen 2016[29]*	22	Kidney	Single centre, Australia	Nicotinamide	Physical examination	Nicotinamide	Placebo	Cancer incidence	6
de Sevaux 2003[26]*	26	Kidney	Single centre, Netherlands	Oral retinoid	Physical examination +/- biopsy	High dose acitretin	Low dose acitretin	Cancer and precancerous incidence	12
Dragieva 2004[36]	17	Kidney, heart	Single centre, Switzerland	Photodynamic therapy	Physical examination +/- biopsy Clinical photographs	Methyl aminolevulinate cream	Placebo	Precancerous lesion response	4
George 2002[42]	23	Kidney	Multi centre, Australia	Oral retinoid	Physical examination Annual radiological evaluation	Acitretin	Drug free period	Cancer incidence	24
Togsverd-Bo 2015[27]*†	25	Kidney	Single centre, Denmark	Photodynamic therapy	Physical examination Clinical photographs	Methyl aminolevulinate cream	No treatment contralateral area	Actinic keratosis incidence	36
Togsverd-Bo 2017[37]†	35	Kidney, lung, liver	Multi-centre, Denmark and Sweden	Photodynamic therapy	Physical examination Questionnaire/Diary	Methyl aminolevulinate cream	5% imiquimoid cream	Actinic keratosis lesion response	6

Wulf 2006[44†]	27	Kidney	Multi centre, Denmark and Netherlands	Photodynamic therapy	Clinical mapping and photographs	Methyl aminolevulinate cream	No treatment contralateral area	Cancer incidence	12

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

‡Excluded from analyses – same participants as Robinson 2016

§111 centres in Asia, Australia, Europe, the Middle East, North America (Canada, Mexico, United States), South Africa, and South America (Argentina, Brazil, Chile

Abbreviations: CNI, Calcineurin inhibitor; AZA. Azathioprine; MMF, Mycophenolate mofetil

Table 3. Effect of behavioral interventions on sun protection outcomes

Outcome	Studies	Participants	Weighted MD[a]/SMD[b] [95% CI]	Relative risk	P	I^2	Intervention	Comparator
BEHAVIORALINTERVENTION (n=5)								
SUN PROTECTION BEHAVIOR								
General sun protection behavior	3	414	0.89 [-0.84, 2.62]		0.31	98%	Workbook, text messages, mobile app program	Standard care
Skin self-examination								
1 month after visit	1	75		4.14 [2.22, 7.72]	<0.001	□0.	Workbook	Standard care
If checked, concerned	1	42		6.43 [0.42, 98.58]	0.18	□□□		
If concerned, saw dermatologist	1	12		Not estimable[c]		□□□		
Decrease daily hours outdoors	1	170	-6.12 [-7.11, -5.13][d]		<0.001	□□□	Mobile app program	Standard care
SUN PROTECTION KNOWLEDGE	4	489	0.50 [0.12, 0.87]		0.01	76%	Workbook, text messages, mobile app program	Standard care
SUN PROTECTION ATTITUDE								
Concern about developing skin cancer	3	348	1.88 [0.96, 2.80]		<0.001	92%	Workbook, text messages, mobile app program	Standard care
Recognise personal risk	2	273	0.61 [-0.60, 1.82]		0.32	96%	Workbook and text messages, mobile app program	Standard care
Confidence in ability to perform sun protection	2	273	0.77 [-0.14, 1.68]		0.10	92%		
Willingness/intention to change behavior	2	273	1.70 [-1.68, 5.07]		0.32	99%		
Knowledge of significance of skin cancer, relevance of sun protection, risk of having a tan	1	101	7.00 [2.94, 11.06]		0.001	□□□	Workbook and text messages	Standard care
Confidence in ability to recognise a skin cancer	1	75	1.80 [1.35, 2.25]		<0.001	□□□	Workbook	Standard care
Importance of skin self-examination	1	75	1.05 [0.61, 1.49]		<0.001	□□□		
Importance of partner help for skin self-examination	1	75	1.59 [1.10, 2.08]		<0.001	□□□		

COMPLICATIONS							
Skin irritation							
None	2	271		1.00 [0.89, 1.13]	0.95	95%	Workbook and text messages, mobile app program	Standard care
> 1	2	271		0.77 [0.43, 1.36]	0.36	89%		
Sunburn (past week)							
None	2	271		3.19 [2.47, 4.10]	<0.001	99%		
> 1	2	271		2.68 [1.81, 3.96]	<0.001	95%		
BIOLOGIC MEASURES							
Melanin index - RU arm (sun protected	2	271	0.12 [-0.12, 0.35]		0.34	0%	Workbook and text messages, mobile app program	Standard care
Melanin index - R forearm (sun exposed)	2	271	-0.42 [-0.66, -0.18][d]		0.001	0%		
Cheek (sun exposed)	2	271	-0.25 [-0.64, 0.15][d]		0.22	61%		
Sun damage assessment - R forearm	2	271	-0.13 [-0.40, 0.13][d]		0.33	16%		

[a]Mean difference
[b]Standardised mean difference
[c]Unable to estimate due to absence of comparator group
[d]Reduction of outcome of interest represents an improvement

Table 4. Effect of pharmaceutical interventions on skin cancer prevention

Outcome	Studies	Participants	Relative risk	P	I^2	Intervention	Comparator
SWITH TO mTOR INHIBITORS (n=5)							
PRE-CANCEROUS LESIONS							
Skin dysplasia							
Any improvement	1	32	24.35 [1.55, 381.99]	0.02	□.0	Sirolimus	CNI[b]
Unchanged	1	32	0.85 [0.28, 2.61]	0.78	□□□		
Any worsening	1	32	0.04 [0.00, 0.66]	0.02	□□□		
CANCEROUS LESIONS							
SCC[d]/BCC[e] incidence	5	1082	0.46 [0.28, 0.75]	0.002	72%	Sirolimus	CNI
≥1 SCC	1	53	0.64 (0.35, 1.17)	0.15	N/A		
Skin cancer (excluding SCC)	1	53	0.74 (0.49, 1.14)	0.17	N/A		
Skin cancer (including SCC)	1	53	0.85 (0.61, 1.17)	0.32	N/A		
Skin cancer with BCC	1	53	0.89 (0.45, 1.78)	0.75	N/A		
PHOTODYNAMIC THERAPY (n=3)							
PRE-CANCEROUS LESIONS							
Actinic keratosis reduction (1-2 sessions)							
Complete response	2	50[a]	5.03 [0.14, 176.17]	0.37	85%	MAL[c]	Placebo, Imiquimod 5% cream
Partial response	1	17[a]	7.00 [0.39, 125.99]	0.19	N/A	MAL	Placebo
No reduction	1	17[a]	0.09 [0.02, 0.40]	0.002	N/A		
CANCEROUS LESIONS	1	26[a]	0.59 [0.34, 1.03]	0.06	N/A	MAL	No treatment
IMMUNE RESPONSE MODIFIERS (n=1)							
PRE-CANCEROUS LESIONS							
Reduced skin atypia	1	14[a]	3.00 [0.47, 19.35]	0.25	N/A	Imiquimod 5% cream	Placebo
Reduced dysplasia	1	14[a]	2.14 [0.31, 14.65]	0.44	N/A		
Reduced keratoses	1	14[a]	2.14 [0.31, 14.65]	0.44	N/A		
Reduced no. viral warts	1	14[a]	7.00 [0.46, 106.10]	0.16	N/A		

CANCEROUS LESIONS							
SCC incidence							
Treated (cream vs. placebo)	1	14[a]	0.09 [0.01, 1.70]	0.11	N/A	Imiquimod 5% cream	Placebo
Untreated (control site)	1	14[a]	0.43 [0.08, 2.37]	0.33	N/A		
ORAL RETINOIDS (n=2)							
CANCEROUS LESIONS							
Decreased incidence:							
> 1 SCC	1	46[a]	0.40 [0.19, 0.85]	0.02	N/A	Acitretin	Drug free period
> 1 BCC	1	46[a]	0.50 [0.14, 1.76]	0.28	N/A		
New skin cancer	1	19[a]	0.22 [0.06, 0.90]	0.03	N/A	Acitretin	Placebo

[a]Control is the contralateral or similar area of skin on the same participant
[b]Calcineurin inhibitor
[c]Methyl aminolaevulinate cream
[d]Squamous cell carcinoma
[e]Basal cell carcinoma

Figure legends

Figure 1. Study selection

Figure 2. Risk of bias of included studies

Figure 3. Behavioral interventions – Sun protection behavior (general)

Figure 4. Behavioral interventions – Sun protection knowledge

Figure 5. Switch to mTOR inhibitors – Non melanoma skin cancer incidence

Figure 1. PRISMA Flowchart

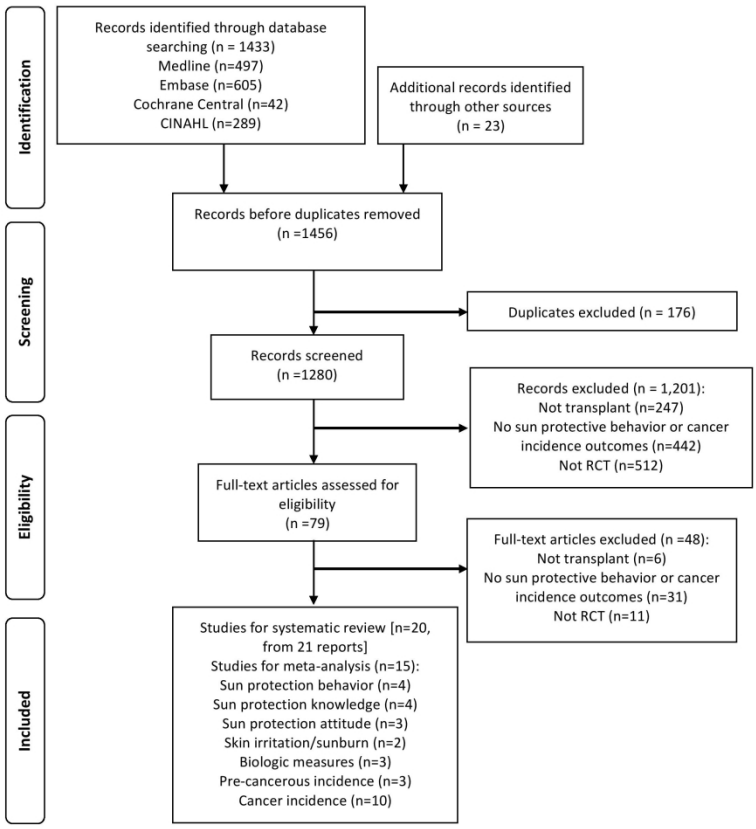

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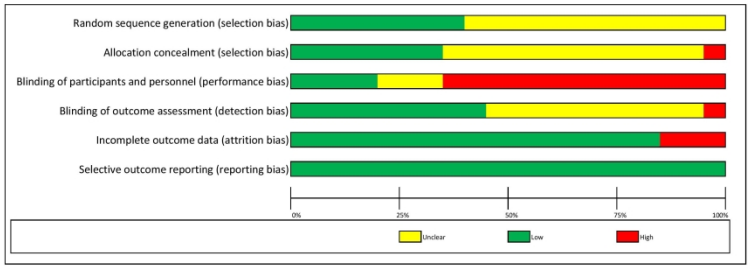
Figure 2. Risk of bias in included studies



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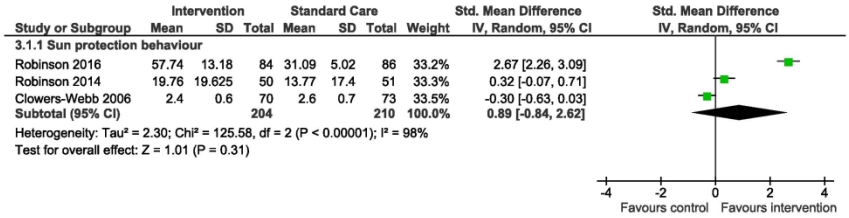

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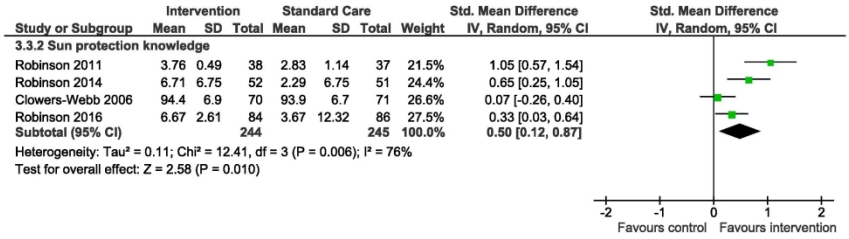

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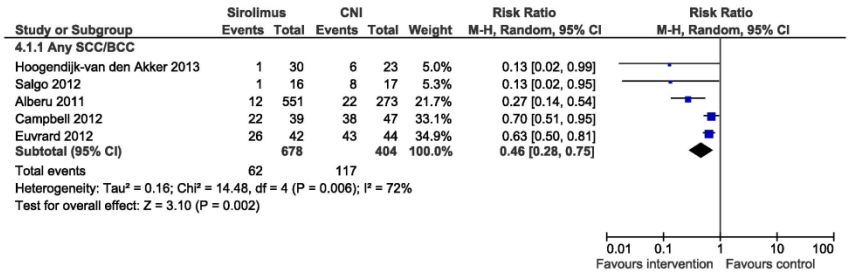

209x279mm (300 x 300 DPI)

Figure S1. Search Strategy

1. exp Neoplasms, Basal Cell/
2. basal cell carcinoma.ti,ab.
3. exp Neoplasms, Squamous Cell/
4. squamous cell carcinoma.ti,ab.
5. nonmelanom*.ti,ab.
6. non melanom*.ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Melanoma/
9. melanoma*.ti,ab.
10. Skin Neoplasms/
11. skin cancer*.ti,ab.
12. 8 or 9 or 10 or 11
13. 7 or 12
14. exp Organ Transplantation/
15. solid organ transplant*.mp.
16. transplant recipient*.tw.
17. exp Immunosuppression/
18. Immunocompromised Host/
19. 14 or 15 or 16 or 17 or 18
20. 13 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. Clinical Trials as Topic/
26. randomly.ab.
27. (crossover or cross-over).tw.
28. trial.ti.
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Animals/ not (animals/ and Humans/)

31. 29 not 30

32. 20 and 31

Figure S2. Risk of bias and key findings in individual studies

Study, year	Random sequence generation	Allocation concealment	Blinding participants & personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Intervention & comparator	Outcome RR/MD/SMD (95% CI)
Behavioral Interventions (n=6)								
Clowers-Webb 2006[30]	Unclear	Unclear	High	Unclear	High	Low	Repetitive written material vs. standard care	General behavior SMD -0.30 (-0.63, 0.03) Knowledge SMD 0.07 (-0.26, 0.40)
Robinson 2011[33]	Unclear	Unclear	Unclear	Unclear	Low	Low	Workbook vs. standard care	Skin self examination (1 month) RR 4.14 (2.22, 7.72) Knowledge SMD 1.05 (0.57, 1.54) Concern about developing cancer SMD 0.95 (0.47, 1.43) Confidence to recognize cancer MD 1.80 (1.35, 2.25) Importance of skin self-examination MD 1.05 (0.61, 1.49) Importance of partner to help for skin self-examination MD 1.59 (1.10, 2.08)
Robinson 2014[31]	Low	Low	High	Low	Low	Low	Workbook & text messages vs. standard care	General behavior SMD 0.32 (-0.07, 0.71) Knowledge SMD 0.65 (0.25, 1.05) Concern about developing cancer SMD 2.73 (2.19, 3.27) Recognize personal risk SMD -0.01 (0.40, 0.38) Confidence in sun protection SMD 0.30 (-0.09, 0.68) Willingness/intention to change behaviour SMD -0.02 (-0.41, 0.36) Importance of skin cancer/sun protection/having a tan MD 7.00 (2.94, 11.06) Skin irritation none RR 1.37 (1.16, 1.63) Skin irritation >1 RR 0.15 (0.03, 0.61) Sunburn none RR 1.30 (1.12, 1.52) Sunburn >1 RR 0.17 (0.04, 0.72) Melanin index - RU arm (sun protected) SMD 0.23

								(-0.17, 0.62) Melanin index - R forearm (sun exposed) SMD -0.37 (-0.76, 0.02) Cheek (sun exposed) SMD -0.03 (-0.42, 0.36) Sun damage assessment - R forearm SMD -0.30 (-0.69, 0.09)
Robinson 2016[32]	Unclear	Low	High	Low	Low	Low	Mobile app program vs. standard care	General behavior SMD 2.67 (2.26, 3.09) Daily hours outdoors MD -6.12 (-7.11, -5.13) Knowledge SMD 0.33 (0.03, 0.64) Concern about developing cancer SMD 1.97 (1.61, 2.34) Recognize personal risk SMD 1.22 (0.90, 1.55) Confidence in sun protection SMD 1.23 (0.09, 1.56) Willingness/intention to change behaviour SMD 3.42 (2.94, 3.89) Skin irritation none RR 0.82 (0.69, 0.96) Skin irritation >1 RR 1.64 (0.79, 3.40) Sunburn none RR 40.44 (10.27, 159.27) Sunburn >1 RR 4.83 (2.95, 7.90) Melanin index - RU arm (sun protected) SMD 0.05 (-0.25, 0.35) Melanin index - R forearm (sun exposed) SMD -0.46 (-0.76, -0.15) Cheek (sun exposed) SMD -0.43 (-0.73, -0.12) Sun damage assessment - R forearm SMD -0.02 (-0.33, 0.28)
Trinh 2014[28*]	Low	Unclear	Unclear	Unclear	Low	Low	Video vs. pamphlet	
Switch to mTOR inhibitors (n=6)								
Alberu 2011[39]	Low	Unclear	High	High	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.27 (0.14, 0.54)
Campbell 2009[41]	Low	Low	High	Low	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.70 (0.51, 0.95)
Carroll 2013[25*]	Unclear	Unclear	High	Low	Low	Low	Sirolimus vs. CNI/AZA	
Euvrard 2012[1]	Unclear	Unclear	High	Unclear	Low	Low	Sirolimus vs. CNI	Cancer incidence RR 0.63 (0.50, 0.81)

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Hoogendijk-van den Akker 2013[43]	Unclear	Low	High	Low	High	Low	SIrolimus vs CNI/MMF/AZA	Cancer incidence RR 0.13 (0.02, 0.99)
Salgo 2010[35]	Unclear	Unclear	High	Low	High	Low	SIrolimus vs CNI/MMF/AZA	Cancer incidence RR 0.13 (0.02, 0.95) Skin dysplasia Any improvement RR 24.35 (1.55, 381.99) Unchanged RR 0.85 (0.28, 2.61) Any worsening RR 0.04 (0.00, 0.66)
Pharmacetical interventions – Photodynamic therapy (n=4); oral retinoids (n=3); 5% imiquimod cream (n=1)								
Bavinck 1995[40]	Unclear	Unclear	Low	Unclear	Low	Low	Acitretin vs. placebo	Cancer incidence RR 0.22 (0.06, 0.90)
Brown 2005[38]	Unclear	Unclear	Low	Low	Low	Low	5% Imiquimod cream vs. placebo	Cancer incidence SCC treated RR 0.09 (0.01, 1.70) SCC untreated RR 0.43 (0.08, 2.37) Reduced skin atypia RR 3.00 (0.47, 19.35) Reduced dysplasia RR 2.14 (0.31, 14.65) Reduced keratosis RR 2.14 (0.31, 14.65) Reduced no. viral warts RR 07.00 (0.46, 106.10)
Chen 2016[29]	Low	Unclear	Low	Low	Low	Low	Nicotinamide vs. placebo	
de Sevaux 2003[26]	Unclear	Low	High	Unclear	Low	Low	High dose acitretin vs. low dose acitretin	
Dragieva 2004[36]	Unclear	Unclear	Low	Unclear	Low	Low	Methyl aminolevulinate cream vs. placebo	Actinic keratosis reduction Complete response RR 27.00 (1.73, 420.67) Partial reduction RR 7.00 (0.39, 125.99) No reduction RR 0.09 (0.02, 0.40)
George 2002[42]	Unclear	Unclear	High	Unclear	Low	Low	Acitretin vs. drug free period	Cancer incidence >1 SCC RR 0.40 (0.19, 0.85) >1 BCC RR 0.50 (0.14, 1.76)
Togsverd-Bo 2015[27*†]	Low	Low	Unclear	Low	Low	Low	Methyl aminolevulinate cream vs. no treatment	

Togsverd-Bo 2017[37†]	Low	Low	High	Unclear	Low	Low	Methyl aminolevulinate cream vs.5% Imiquimod cream	Actinic keratosis reduction Complete response RR 1.42 (0.81, 2.48)
Wulf 2006[44†]	Low	High	High	Low	Low	Low	Methyl aminolevulinate cream vs. no treatment	Cancer incidence RR 0.59 (0.34, 1.03)

*Excluded from analyses – no meaningful data to extract

†Randomized controlled areas of skin on individuals

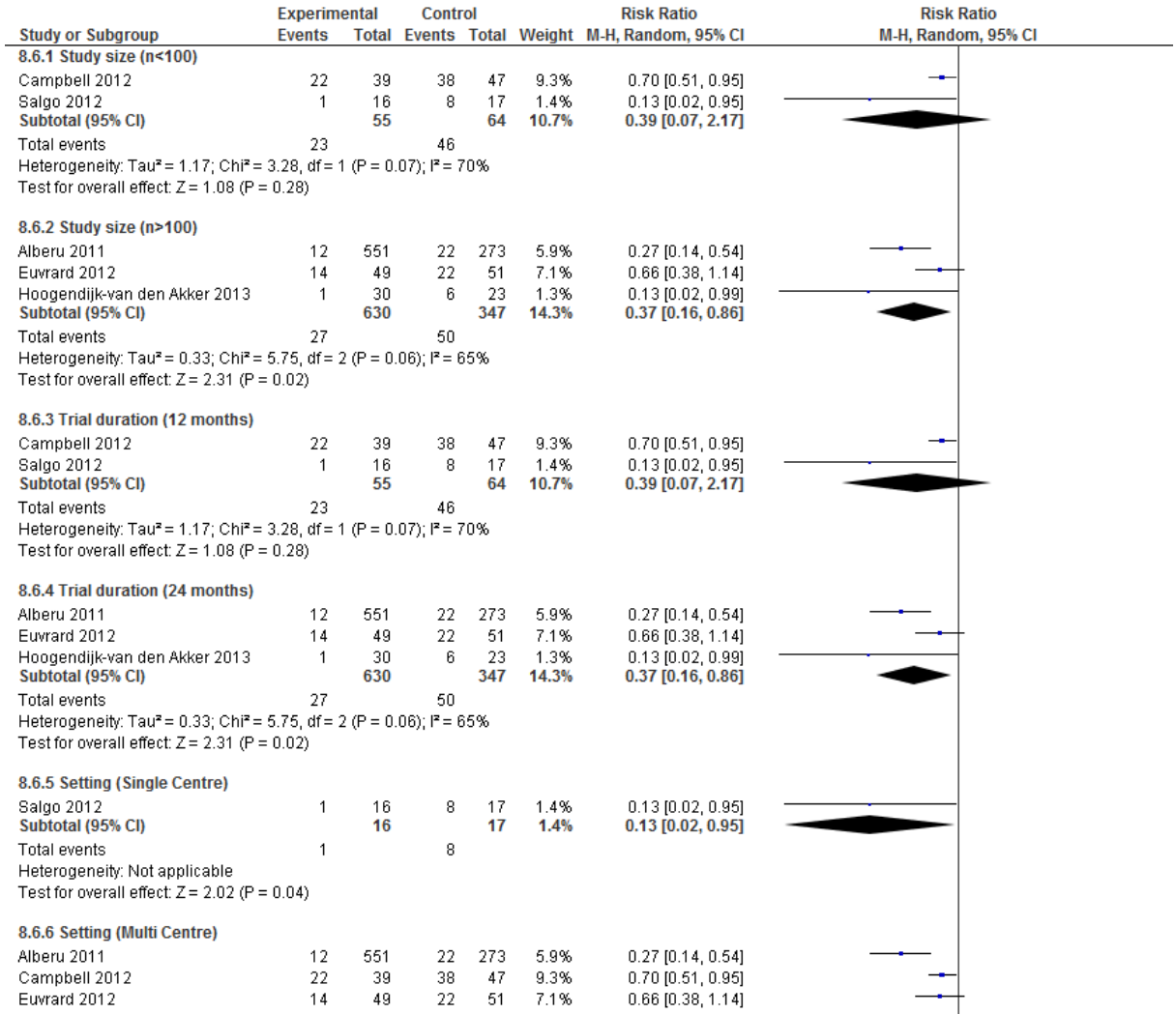
‡Excluded from analyses – same participants as Robinson 2016

Table S1. Assessment of quality of studies using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

Number of studies	Quality of assessment (Decrease in quality score) Risk of bias/Quality of evidence	Inconsistency	Indirectness	Imprecision	Publication bias	Quality
Sun protection behavior						
35 RCTs[24 30-33]	**Serious study limitations (-1)** Randomisation unclear[24 30 32 33] Participants not blinded or well described[24 30-33] Concealment of allocation not described.[30 33]	**Important inconsistency (-1)** Analysed in subgroups. heterogeneity (I^2=99%)[30-32]	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (2 weeks to 10 months) Same sample of participants[24 32]	**Serious imprecision (-1)** Small sample size, CIs crosses the null	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection knowledge						
6 RCTs[24 28 30-33]	**Serious limitations (-1)** Randomisation unclear[24 30 32 33] Participants not blinded or well described[24 28 30-33] Concealment of allocation not described[28 33]	**Important inconsistency (-1)** Heterogeneity (I^2 85%)	**Indirectness (-1)** Diverse interventions (written vs. electronic), varying duration (1 day to 10 months) Same sample[24 32]	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity	**Very low**
Sun protection attitude						
4 RCTs[24 31-33]	**Serious limitations (-1)** Randomisation unclear[24 32 33] Participants not blinded or well described[24 31-33] Concealment of allocation	**Important inconsistency (-1)** Wide variation in the effect estimates, heterogeneity (I^2 97%).	**Indirectness (-1)** Diverse interventions (written vs. electronic), Similar duration. Same sample[24 32]	**Serious imprecision (-1)** Small sample size, small number of events	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**

	not described[32 33]					
Complications (skin irritation, sunburn)						
2 RCTs[31 32]	**Serious limitations (-1)** Participants not blinded[31 32]	**Important inconsistency (-1)** Heterogeneity (I^2=95-99%) Analysed in subgroups. Similar effect estimates.	**Indirectness (-1)** Diverse interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Biologic measures (melanin index, sun damage)						
2 RCTs[31 32]	**Serious limitations (-1)** Randomisation unclear[32] Participants not blinded[31 32]	**Important inconsistency (-1)** Analysed in subgroups. Heterogeneity (I^2 60%)	**Indirectness (-1)** Different interventions (written vs. electronic), similar duration.	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Small number of studies, large heterogeneity.	**Very low**
Pre-cancerous incidence						
4 RCTs [27 35-38]	**Serious limitations (-1)** Randomisation or allocation unclear[35 36 38] Participants not blinded or well described[27 35-38]	**Important inconsistency (-1)** Analysed in subgroups.	**Indirectness (-1)** Diverse interventions, varying duration	**Serious imprecision (-1)** Small sample size	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**
Cancer incidence						
10 RCTs[1 29 35 38-44]	**Serious limitations (-1)** Randomisation unclear[1 40 42 43] Allocation concealment not used or unclear[1 29 39 40 42 44] Participants not blinded.[1 35 39 41-44]	**Important inconsistency (-1)** Majority of participants came from 1 study[39] Small sample[1 29 35 38 40-44]	**Indirectness (-1)** Diverse interventions (immunosuppression, photodynamic therapy, immune response modifier, retinoid, nicotinamide), varying duration	**Serious imprecision (-1)** Majority of participants from one trial (n=551), small number of events	**Uncertain** Unable to determine. Large heterogeneity.	**Very low**

Figure S3. Subgroup analyses of immunosuppression conversion interventions on skin cancer incidence



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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