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

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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 behavioural 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 randomised controlled trials that evaluated the effect of behavioural or pharmaceutical interventions on behavioural 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 Grading of Recommendations Assessment Development and Evaluation framework.

Results Twenty trials (n=2295 participants) were included. It is uncertain whether behavioural interventions improve sun protection behaviour (n=3, n=414, standardised mean difference (SMD) 0.89, 95% CI −0.84 to 2.62, I^2=98%) and knowledge (n=4, n=489, SMD 0.50, 95% CI 0.12 to 0.87, $I^{2=}$ 76%) as the quality of evidence is very low. We are uncertain of the effects of mammalian target of rapamycin inhibitors on the incidence of non-melanocytic skin cancer (n=5, n=1080, relative risk 0.46, 95% CI 0.28 to 0.75, $I^{2=}$72%) as the quality of evidence is very low.

Conclusions Behavioural and pharmaceutical preventive interventions may improve sun protective behaviour 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.

Strengths and limitations of this study

- A comprehensive review conducted using methods outlined by Cochrane Collaboration including Grading of Recommendations Assessment Development and Evaluation to assess risk of bias and evidence certainty.
- Inclusion of a broad range of interventions, including behavioural to improve sun protection behaviour 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.

INTRODUCTION

Skin cancer, including melanoma and non-melanoma 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 with 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 show 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 to nine times higher than the general population, with 5-year overall survival of <30%.[6 12–15]

Sun exposure behaviours 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 behaviours 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 (mTORis) 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 behavioural change and skin cancer prevention in solid organ transplant recipients.

METHODS

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

Inclusion criteria

All randomised controlled trials (RCTs) or quasi RCTs (allocated to trial arms by investigators) of interventions for skin cancer prevention (both melanoma and NMSC) in solid organ transplant recipients were included. Behavioural interventions defined as any strategy used to promote sun protective behaviour including passive (eg, pamphlets), active (eg, group workshops, counselling, dermatology clinic) and provision of sun protective equipment; and pharmaceutical interventions (switch to mTORis, 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 endpoints were excluded. Studies of interventions for the treatment of skin cancer were excluded.

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 online supplementary figure S1). Reference lists of included studies were also searched.

Data extraction

Titles and abstracts were reviewed by two independent authors (LJJ and LDWL) and those who did not meet the inclusion criteria were excluded. Full-text articles were reviewed by three independent reviewers (LJJ, VS, LDWL) 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.

Outcome measures

The prespecified outcome measures were incidence of precancerous and cancerous lesions, sun protection behaviour (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).

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 judgement 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]

Data synthesis and statistical analyses

Continuous outcomes were summarised as mean difference (MD) or standardised mean difference (SMD) and dichotomous outcomes as relative risk (RR). A MD/SMD greater than 0 and/or a RR greater than 1 could be interpreted as favouring the intervention group relative to the control, unless specified elsewhere. Risk estimates were reported with 95% CIs, 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 prespecified 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 10 studies were included in meta-analysis.

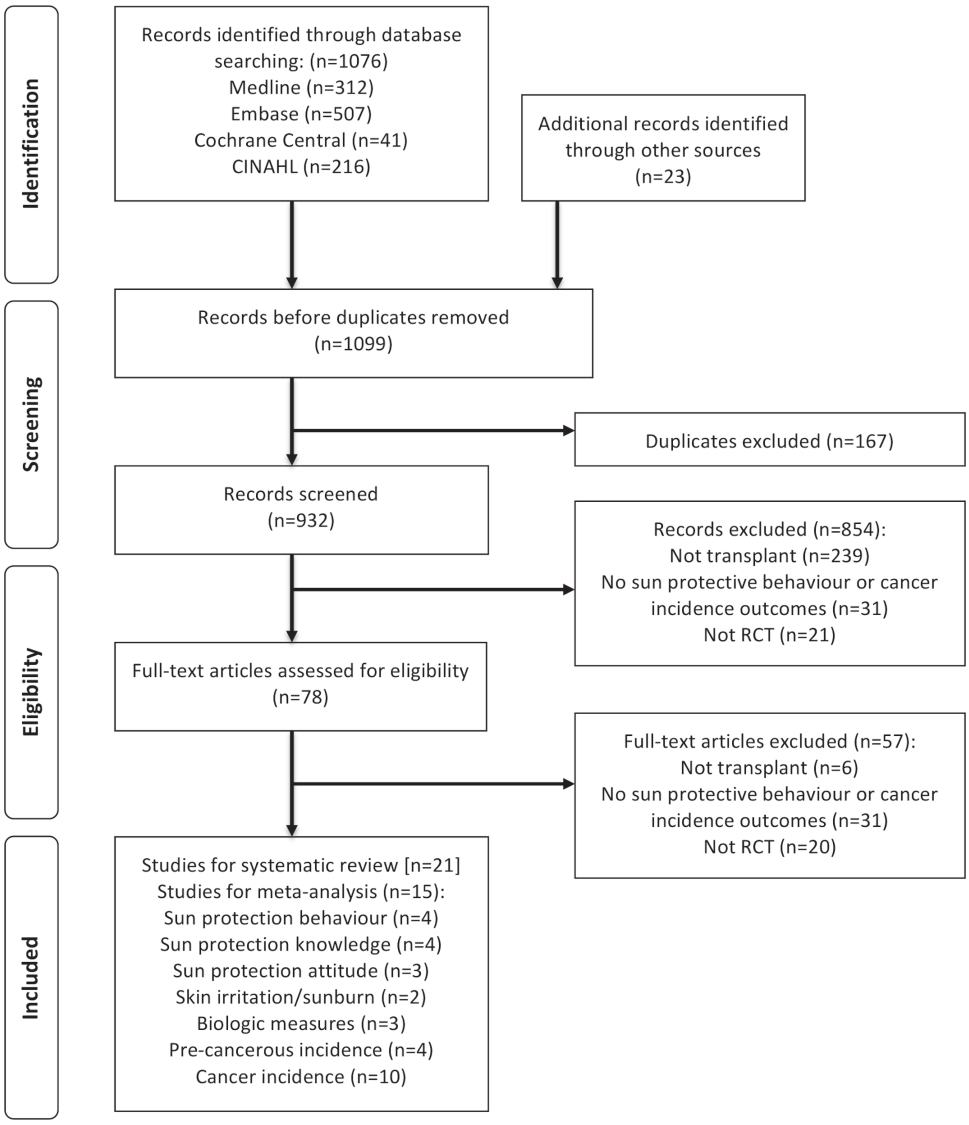

Figure 1 Study selection. RCT, randomised controlled trial.

All analyses were conducted using Review Manager V.5.3 software.

Patient and public involvement

There was no patient or public involvement.

RESULTS

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).

Studies characteristics

We included 22 reports of 20 RCTs, including 2295 participants (figure 1). The study characteristics are summarised in tables 1 and 2. The median number of participants was 44 (range 17–830) 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 (76%) of 21 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 were able to be meta-analysed (n=5).[25–29]

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; online supplementary 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 reported in half of the studies (n=10). Intention to treat analyses were used in 6 (30%) studies and 6 (30%) studies had a high loss to follow-up. A total of 3 (15%) studies had incomplete outcome data, and all studies were at low

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 centre	8 (40)
Multicentre	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)
UK	3 (15)
USA	6 (30)
Other†	1 (5)
Intervention type	
Behavioural	5 (25)
Switch to mTORis	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, USA), South Africa and South America (Argentina, Brazil, Chile).
mTORis, mammalian target of rapamaycin inhibitors.

risk for selective reporting. Seven (35%) studies 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 (online supplementary table S1) due to limitations in study design, heterogeneity in the intervention and outcome 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 behaviour and sun protection knowledge was not possible as outcomes were inconsistent and there was large diversity of interventions used (eg, written education material vs a mobile app programme). Furthermore, formal testing of publication bias was not performed due to insufficient data.

Interventions

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

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

Four of the eight studies of other pharmaceutical interventions assessed the effect of photodynamic therapy using methyl aminolevinate creams compared with 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 with placebo (n=1), lower dose (n=1) or a drug-free period (n=1), one study assessed nicotinamide

Table 2 Characteristics of individual studies

Study	N	Type of transplant	Setting	Type of intervention	Measures	Intervention	Comparator	Primary outcomes	Time (months)
Behavioural interventions (n=6)									
Clowers-Webb 2006[30]	202	Kidney, liver, heart, pancreas, lung, heart/lung, other§	Single centre, USA	Behavioural	Self-reported questionnaire	Repetitive written material	Standard care	Knowledge and behaviour	10
Robinson 2011[33]	75	Kidney	USA	Behavioural	Self-reported questionnaire	Workbook	Standard care	Knowledge and behaviour	1
Robinson 2014[31]	101	Kidney	Single centre, USA	Behavioural	Self-reported questionnaire Physical examination	Workbook Text messages	Standard care	Knowledge and behaviour	1.5
Robinson 2015[24] ‡	170	Kidney	Multicentre, USA	Behavioural	Self-reported questionnaire	Mobile app program	Standard care	Knowledge and behaviour	0.5
Robinson 2016[32]	170	Kidney	Multicentre, USA	Behavioural	Self-reported questionnaire Physical examination	Mobile app program	Standard care	Knowledge and behaviour	1.5
Trinh 2014[28] *	100	Kidney, liver, lung	Single centre, USA	Behavioural	Self-reported questionnaire	Video	Pamphlet	Knowledge	1 day
Switch to mTORis (n=7)									
Alberu 2011[39]	830	Kidney	Multicentre§	Switch to mTORis	Investigator-reported adverse events	Conversion to sirolimus	CNI	Cancer incidence	24
Campbell 2012[41]	86	Kidney	Multicentre, Australia, New Zealand, USA	Switch to mTORis	Physical examination +/– biopsy	Conversion to sirolimus	CNI	Cancer incidence	12
Carroll 2013[25] *	32	Kidney	Multicentre, UK	Switch to mTORis	Physical examination +/– biopsy	Conversion to prednisolone and sirolimus	CNI/AZA	Cancer incidence	24
Euvrard 2012[1 64]	120	Kidney	Multicentre, France	Switch to mTORis	Physical examination +/– biopsy	Conversion to sirolimus	CNI	Cancer incidence	24
Hoogendijk-van den Akker 2013[43]	155	Kidney	Multicentre, Netherlands, UK	Switch to mTORis	Physical examination +/– biopsy	Conversion to sirolimus	AZA/MMF/ CNI	Cancer incidence	24
Salgo 2010[35]	44	Kidney	Single centre, Germany	Switch to mTORis	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)									

Continued

Table 2 Continued

Study	N	Type of transplant	Setting	Type of intervention	Measures	Intervention	Comparator	Primary outcomes	Time (months)
Bavinck 1995[40]	44	Kidney	Multicentre, Netherlands	Oral retinoid	Physical examination +/– biopsy	Acitretin	Placebo	Cancer incidence precancerous lesion reduction	6
Brown 2005[38]	21	Kidney	Multicentre, 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	Multicentre, 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	Multicentre, 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	Multicentre, 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.
†Randomised 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, USA), South Africa and South America (Argentina, Brazil, Chile).
AZA, azathioprine; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; mTORis, mammalian target of rapamaycin inhibitors.

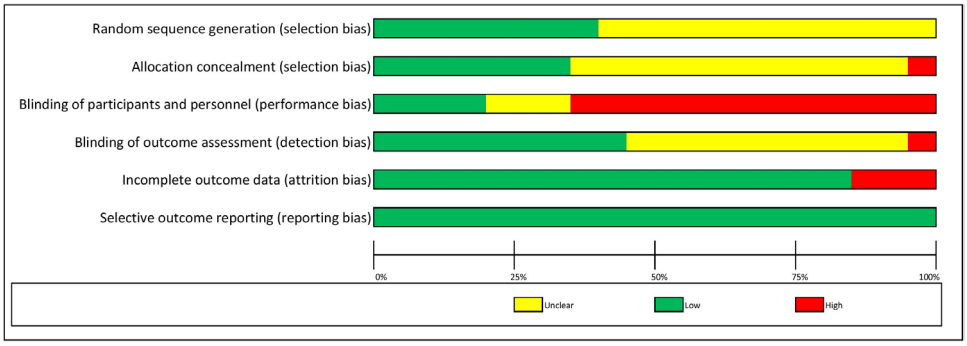

Figure 2 Risk of bias of included studies.

compared with placebo and a single study assessed the benefits of topical immune response modifier compared with placebo in kidney transplant recipients.

Effect of behavioural interventions on sun protection outcomes

Sun protection behaviour

Sun protection behaviour, 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 behavioural interventions reported improved sun protection behaviour scores[30–32] (3 studies, 414 participants, SMD 0.89, 95% CI −0.84 to 2.62, I^2 98%, table 3; figure 3). We are uncertain of the effects of behavioural interventions on sun protection behaviour 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 1 month (75 participants, RR 4.14, 95% CI 2.22 to 7.72).[33] One trial assessed a mobile app programme 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 programmes and videos on sun protection knowledge was assessed in six 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 to 0.87, I^2 76%) in the intervention group compared with standard care (figure 4).[30–33] One study compared an interactive visual representation of the educational programme 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 programme over a period of 0.5 months to 1.5 months.[31–33] Compared with 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 to 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 to 1.82, I^2 96%), adherence to sun protection (SMD 0.77, 95% CI −0.14 to 1.68, I^2 92%) and willingness or intention to change behaviour (SMD 1.70, 95% CI −1.68 to 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 recognise a potential skin cancer (MD 1.80, 95% CI 1.35 to 2.25), importance of skin self-examination (MD 1.05, 95% CI 0.61 to 1.49) and having a partner help for skin self-examination (MD 1.59, 95% CI 1.10 to 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 to 11.06).[31]

Skin complications and biologic measures

Two trials of behavioural 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 to 1.13, I^2 95%) or sunburn (RR 3.19, 95% CI 2.47 to 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).

Effect of pharmaceutical interventions on skin cancer prevention

The incidence and responses of precancerous lesions were measured only in trials of pharmaceutical interventions (table 4). These included the switch to mTORis (n=1),[35] photodynamic therapy (n=2)[36 37] and immune response

Table 3 Effect of behavioural interventions on sun protection outcomes

Outcome	Studies	Participants	Weighted MD/SMD (95% CI)	RR	P	I^2	Intervention	Comparator
Behavioural intervention (n=5)								
Sun protection behaviour								
General sun protection behaviour	3	414	0.89 (–0.84 to 2.62)		0.31	98%	Workbook, text messages, mobile app programme	Standard care
Skin self-examination								
1 month after visit	1	75		4.14 (2.22 to 7.72)	<0.001	N 0.	Workbook	Standard care
If checked, concerned	1	42		6.43 (0.42 to 98.58)	0.18	N/A		
If concerned, saw dermatologist	1	12		Not estimable*		N/A		
Decrease daily hours outdoors	1	170	–6.12 (–7.11 to –5.13)†		<0.001	N/A	Mobile app programme	Standard care
Sun protection knowledge	4	489	0.50 (0.12 to 0.87)		0.01	76%	Workbook, text messages, mobile app programme	Standard care
Sun protection attitude								
Concern about developing skin cancer	3	348	1.88 (0.96 to 2.80)		<0.001	92%	Workbook, text messages, mobile app programme	Standard care
Recognise personal risk	2	273	0.61 (–0.60 to 1.82)		0.32	96%	Workbook and text messages, mobile app programme	Standard care
Confidence in ability to perform sun protection	2	273	0.77 (–0.14 to 1.68)		0.10	92%		
Willingness/intention to change behaviour	2	273	1.70 (–1.68 to 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 to 11.06)		0.001	N/A	Workbook and text messages	Standard care
Confidence in ability to recognise a skin cancer	1	75	1.80 (1.35 to 2.25)		<0.001	N/A	Workbook	Standard care
Importance of skin self-examination	1	75	1.05 (0.61 to 1.49)		<0.001	N/A		
Importance of partner help for skin self-examination	1	75	1.59 (1.10 to 2.08)		<0.001	N/A		
Complications								
Skin irritation								
None	2	271		1.00 (0.89 to 1.13)	0.95	95%	Workbook and text messages, mobile app programme	Standard care
>1	2	271		0.77 (0.43 to 1.36)	0.36	89%		
Sunburn (past week)								
None	2	271		3.19 (2.47 to 4.10)	<0.001	99%		
>1	2	271		2.68 (1.81 to 3.96)	<0.002	95%		
Biologic measures								

Continued

Table 3 Continued

Outcome	Studies	Participants	Weighted MD/SMD (95% CI)	RR	P	I^2	Intervention	Comparator
Melanin index— RU arm (sun protected	2	271	0.12 (–0.12 to 0.35)		0.34	0%	Workbook and text messages, mobile app programme	Standard care
Melanin index—R forearm (sun exposed)	2	271	–0.42 (–0.66 to -0.18)†		0.001	0%		
Cheek (sun exposed)	2	271	–0.25 (–0.64 to 0.15)†		0.22	61%		
Sun damage assessment—R forearm	2	271	–0.13 (–0.40 to 0.13)†		0.33	16%		

*Unable to estimate due to absence of comparator group.
†Reduction of outcome of interest represents an improvement.
MD, mean difference; SMD, standardised mean difference.

modifiers (n=1)[38] to current treatment or placebo. The incidence of NMSCs 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 to 14.65), skin atypia (RR 3.00, 95% CI 0.47 to 19.35), and viral warts (RR 7.00, 95% CI 0.46 to 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 to 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 to 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 with 24% in the control group (50 participants, RR 5.03, 95% CI 0.14 to 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 with CNIs maintenance therapy (5 trials, 1082 participants, RR 0.46, 95% CI 0.28 to 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 to 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 to 0.85, p 0.02; RR 0.50, 95% CI 0.14 to 1.76)[42] or development of a new skin cancer (19 participants, RR 0.22, 95% CI 0.06 to 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

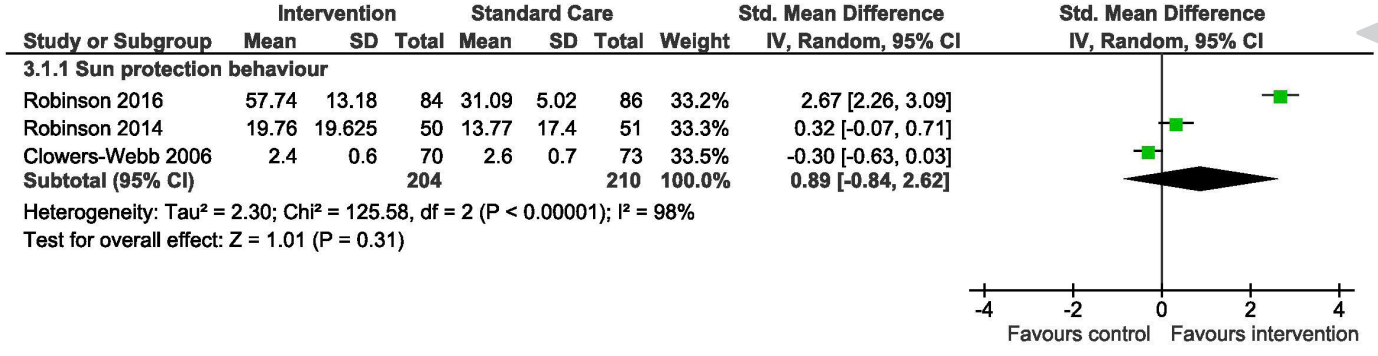

Figure 3 Behaviouralinterventions—sun protection behaviour (general).

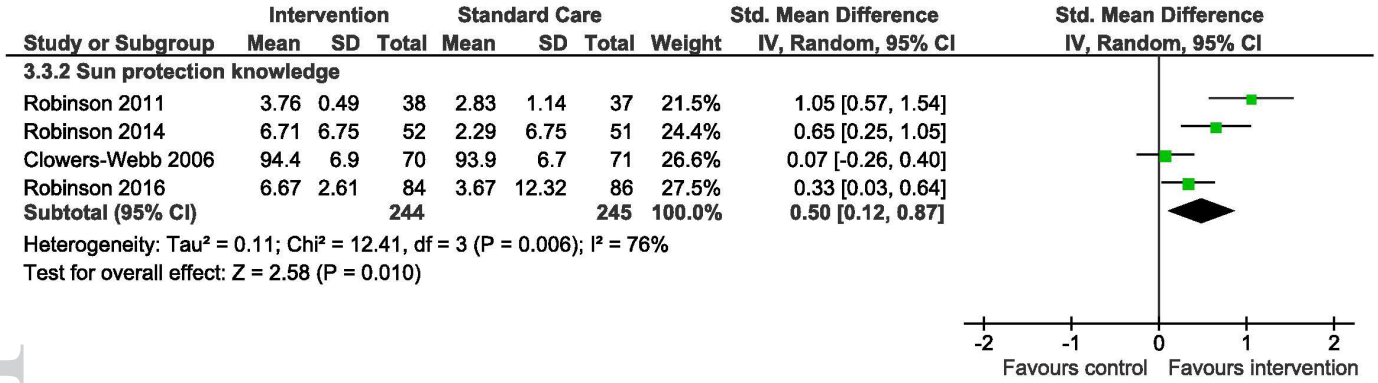

Figure 4 Behaviouralinterventions—sun protection knowledge.

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]

Subgroup analysis

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

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 2295 transplant recipients, who were predominately kidney transplant recipients. The studies covered a broad range of interventions, including behavioural to improve sun protection behaviour and pharmaceutical (immunosuppression, photodynamic therapy, oral retinoid, nicotinamide and topical immune response modifiers) to evaluate precancerous lesion response and cancer incidence. None of the behavioural intervention studies included precancerous lesions or skin cancer incidence as outcomes. Although interventions showed plausible improvements to sun protection behaviours, precancerous lesion responses and cancer incidence, there was considerable variability across intervention 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 behavioural interventions appeared to improve sun protection attitude, knowledge and behaviour, 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 behavioural interventions (eg, 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 with 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 mTORis, photodynamic therapy, immune response modifiers) showed a reduction in precancerous lesions compared with 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 behavioural interventions on skin cancer prevention in the general population,[45] and concluded that computer programmes may increase sun protective behaviours, 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 behaviours, 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]

Table 4 Effect of pharmaceutical interventions on skin cancer prevention

Outcome	Studies	Participants	Relative risk	P	I^2	Intervention	Comparator
Switch to mTORis (n=5)							
Precancerous lesions							
Skin dysplasia							
Any improvement	1	32	24.35 (1.55 to 381.99)	0.02	N/A	Sirolimus	CNI
Unchanged	1	32	0.85 (0.28 to 2.61)	0.78	N/A		
Any worsening	1	32	0.04 (0.00 to 0.66)	0.02	N/A		
Cancerous lesions							
SCC /BCC incidence	5	1082	0.46 (0.28 to 0.75)	0.002	72%	Sirolimus	CNI
≥1 SCC	1	53	0.64 (0.35 to 1.17)	0.15	N/A		
Skin cancer (excluding SCC)	1	53	0.74 (0.49 to 1.14)	0.17	N/A		
Skin cancer (including SCC)	1	53	0.85 (0.61 to 1.17)	0.32	N/A		
Skin cancer with BCC	1	53	0.89 (0.45 to 1.78)	0.75	N/A		
Photodynamic therapy (n=3)							
Precancerous lesions							
Actinic keratosis reduction (1–2 sessions)							
Complete response	2	50*	5.03 (0.14 to 176.17)	0.37	85%	MAL	Placebo to imiquimod 5% cream
Partial response	1	17*	7.00 (0.39 to 125.99)	0.19	N/A	MAL	Placebo
No reduction	1	17*	0.09 (0.02 to 0.40)	0.002	N/A		
Cancerous lesions	1	26*	0.59 (0.34 to 1.03)	0.06	N/A	MAL	No treatment
Immune response modifiers (n=1)							
Precancerous lesions							
Reduced skin atypia	1	14*	3.00 (0.47 to 19.35)	0.25	N/A	Imiquimod 5% cream	Placebo
Reduced dysplasia	1	14*	2.14 (0.31 to 14.65)	0.44	N/A		
Reduced keratoses	1	14*	2.14 (0.31 to 14.65)	0.44	N/A		
Reduced number of viral warts	1	14*	7.00 (0.46 to 106.10)	0.16	N/A		
Cancerous lesions							
SCC incidence							
Treated (cream vs placebo)	1	14*	0.09 (0.01 to 1.70)	0.11	N/A	Imiquimod 5% cream	Placebo
Untreated (control site)	1	14*	0.43 (0.08 to 2.37)	0.33	N/A		
Oral retinoids (n=2)							
Cancerous lesions							
Decreased incidence:							
>1 SCC	1	46*	0.40 (0.19 to 0.85)	0.02	N/A	Acitetrin	Drug-free period
>1 BCC	1	46*	0.50 (0.14 to 1.76)	0.28	N/A		
New skin cancer	1	19*	0.22 (0.06 to 0.90)	0.03	N/A	Acitretin	Placebo

*Control is the contralateral or similar area of skin on the same participant.
BCC, basal cell carcinoma; CNI, calcineurin inhibitor; MAL, methyl aminolaevulinate; mTORis, mammalian target of rapamaycin inhibitors; SCC, squamous cell carcinoma.

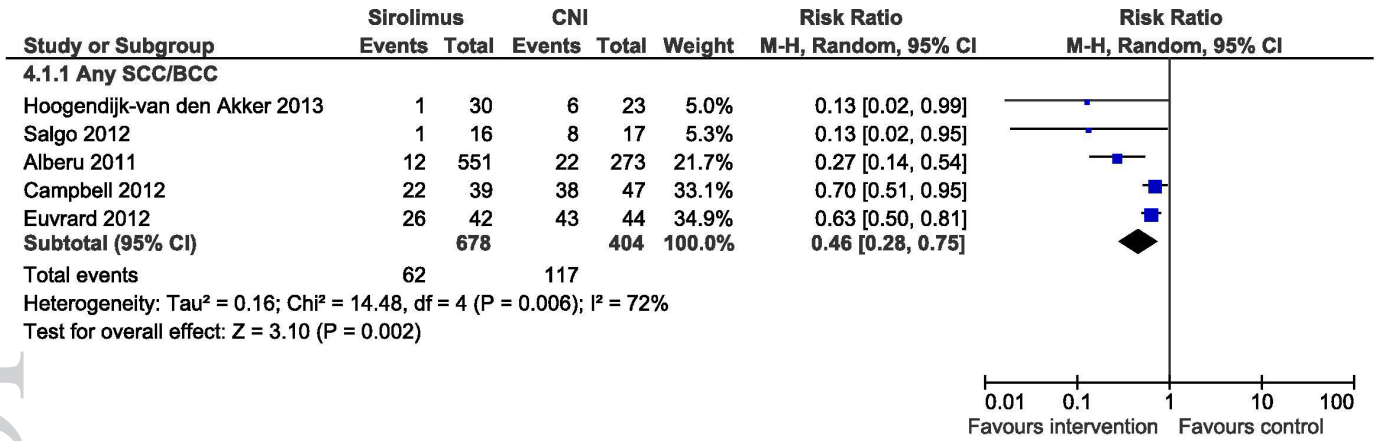

Figure 5 Switch to mTORis—NMSC incidence. BCC, basal cell carcinoma; mTORis, mammalian target of rapamaycin inhibitors; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma.

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 behavioural interventions were undertaken in USA, with four by the same authors, while 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 behavioural 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 III RCT.

Although behavioural change is a simple strategy, long-term adherence remains challenging.

While behavioural counselling has been shown to increase sun protective behaviours in non-transplant populations,[45] there is no direct evidence to show that the behavioural change led to a reduction in morbidity and mortality. Previous studies have suggested that transplant recipients do not practice sun protective behaviours 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 behaviour.[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 behavioural 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 individualised 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 is also warranted to ensure interventions and outcomes for trials are relevant to patient needs and priorities and better support patient-centred treatment decisions.[63] Evidence of the efficacy of sun protective behaviour interventions need to be strengthened, with use of measures that are homogeneous, reliable and validated.

Preventative measures including behavioural, switch to mTORis and other pharmaceuticals may improve skin cancer outcomes for solid organ transplant recipients. However, the overall quality of evidence is 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 optimise outcomes for solid organ transplant recipients.

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REFERENCES

1 Euvrard S, Morelon E, Rostaing L, *et al*. Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med* 2012;367:329–39.
2 Harwood CA, Mesher D, McGregor JM, *et al*. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant* 2013;13:119–29.
3 Ramsay HM, Fryer AA, Hawley CM, *et al*. Non-Melanoma skin cancer risk in the Queensland renal transplant population. *Br J Dermatol* 2002;147:950–6.
4 Ulrich C, Kanitakis J, Stockfleth E, *et al*. Skin cancer in organ transplant recipients--where do we stand today? *Am J Transplant* 2008;8:2192–8.
5 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003;348:1681–91.
6 Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol* 2002;47:1–20.
7 Garrett GL, Blanc PD, Boscardin J, *et al*. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. *JAMA Dermatol* 2017;153:296–303.
8 Green AC, Olsen CM. Increased risk of melanoma in organ transplant recipients: systematic review and meta-analysis of cohort studies. *Acta Derm Venereol* 2015;95:923–7.
9 Abdel-Wahab N, Safa H, Abudayyeh A, *et al*. Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature. *J Immunother Cancer* 2019;7:106.
10 Hassan NA, Abudayyeh A, Shah M, *et al*. The outcome of checkpoint inhibitor therapy in patients with cancer and solid organ transplant: a systematic review of the literature. *J Clin Oncol* 2018.
11 Au EH, Chapman JR, Craig JC, *et al*. Overall and site-specific cancer mortality in patients on dialysis and after kidney transplant. *J Am Soc Nephrol* 2019;30:471–80.
12 Martinez J-C, Otley CC, Stasko T, *et al*. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. *Arch Dermatol* 2003;139:301–6.
13 Registry A. *38Th report, chapter 10: cancer*. Adelaide, Australia.: Australia and New Zealand Dialysis and Transplant Registry, 2016.
14 Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. *Cold Spring Harb Perspect Med* 2013;3:a015677.
15 Garrett GL, Lowenstein SE, Singer JP, *et al*. Trends of skin cancer mortality after transplantation in the United States: 1987 to 2013. *J Am Acad Dermatol* 2016;75:106–12.
16 Ibrahim SF, Brown MD. Tanning and cutaneous malignancy. *Dermatol Surg* 2008;34:460–74.
17 Kovach BT, Sams HH, Stasko T. Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005;19:726–34.
18 Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: what is the evidence? *Clin J Am Soc Nephrol* 2008;3:S87–100.
19 Acuna SA, Huang JW, Scott AL, *et al*. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. *Am J Transplant* 2017;17:103–14.
20 Chadban SJ, Barraclough KA, Campbell SB, *et al*. KHA-CARI guideline: KHA-CARI adaptation of the KDIGO clinical practice guideline for the care of kidney transplant recipients. *Nephrology* 2012;17:204–14.
21 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
22 Julian PTH, Sally G. *Cochrane Handbook for systematic reviews of interventions*. Chichester, West Sussex ; Hoboken NJ: John Wiley & Sons, 2008.
23 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
24 Robinson JK, Friedewald JJ, Desai A, *et al*. Response across the health-literacy spectrum of kidney transplant recipients to a sun-protection education program delivered on tablet computers: randomized controlled trial. *JMIR Cancer* 2015;1:e8.
25 Carroll RP, Hester J, Wood KJ, *et al*. Conversion to sirolimus in kidney transplant recipients with squamous cell cancer and changes in immune phenotype. *Nephrol Dial Transplant* 2013;28:462–5.
26 de Sévaux RGL, Smit JV, de Jong EMGJ, *et al*. Acitretin treatment of premalignant and malignant skin disorders in renal transplant recipients: clinical effects of a randomized trial comparing two doses of acitretin. *J Am Acad Dermatol* 2003;49:407–12.

27 Togsverd-Bo K, Omland SH, Wulf HC, *et al*. Primary prevention of skin dysplasia in renal transplant recipients with photodynamic therapy: a randomized controlled trial. *Am J Transplant* 2015;15:2986–90.
28 Trinh N, Novice K, Lekakh O, *et al*. Use of a brief educational video administered by a portable video device to improve skin cancer knowledge in the outpatient transplant population. *Dermatol Surg* 2014;40:1233–9.
29 Chen AC, Martin AJ, Dalziell RA, *et al*. A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients. *Br J Dermatol* 2016;175:1073–5.
30 Clowers-Webb HE, Christenson LJ, Phillips PK, *et al*. Educational outcomes regarding skin cancer in organ transplant recipients: randomized intervention of intensive vs standard education. *Arch Dermatol* 2006;142:712–8.
31 Robinson JK, Guevara Y, Gaber R, *et al*. Efficacy of a sun protection workbook for kidney transplant recipients: a randomized controlled trial of a culturally sensitive educational intervention. *Am J Transplant* 2014;14:2821–9.
32 Robinson JK, Friedewald JJ, Desai A, *et al*. A randomized controlled trial of a mobile medical APP for kidney transplant recipients: effect on use of sun protection. *Transplant Direct* 2016;2:1.
33 Robinson JK, Turrisi R, Mallett KA, *et al*. Efficacy of an educational intervention with kidney transplant recipients to promote skin self-examination for squamous cell carcinoma detection. *Arch Dermatol* 2011;147:689–95.
34 Robinson JK, Joshi KM, Ortiz S, *et al*. Melanoma knowledge, perception, and awareness in ethnic minorities in Chicago: recommendations regarding education. *Psychooncology* 2011;20:313–20.
35 Salgo R, Gossmann J, Schöfer H, fer H, *et al*. Switch to a sirolimus-based immunosuppression in long-term renal transplant recipients: reduced rate of (pre-)malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. *Am J Transplant* 2010;10:1385–93.
36 Dragieva G, Prinz BM, Hafner J, *et al*. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol* 2004;151:196–200.
37 Togsverd-Bo K, Halldin C, Sandberg C, *et al*. Photodynamic therapy is more effective than imiquimod for actinic keratosis in organ transplant recipients: a randomized Intraindividual controlled trial. *Br J Dermatol* 2018;178:903–9.
38 Brown VL, Atkins CL, Ghali L, *et al*. Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial. *Arch Dermatol* 2005;141:985–93.
39 Alberú J, Pascoe MD, Campistol JM, *et al*. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the convert trial. *Transplantation* 2011;92:303–10.
40 Bavinck JN, Tieben LM, Van der Woude FJ, *et al*. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;13:1933–8.
41 Campbell SB, Walker R, Tai SS, *et al*. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. *Am J Transplant* 2012;12:1146–56.
42 George R, Weightman W, Russ GR, *et al*. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. *Australas J Dermatol* 2002;43:269–73.
43 Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, *et al*. Two-Year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol* 2013;31:1317–23.
44 Wulf HC, Pavel S, Stender I, *et al*. Topical photodynamic therapy for prevention of new skin lesions in renal transplant recipients. *Acta Derm Venereol* 2006;86:25–8.
45 Lin JS, Eder M, Weinmann S. Behavioral counseling to prevent skin cancer: a systematic review for the U.S. preventive services Task force. *Ann Intern Med* 2011;154:190–201.
46 Horsham C, Auster J, Sendall MC, *et al*. Interventions to decrease skin cancer risk in outdoor workers: update to a 2007 systematic review. *BMC Res Notes* 2014;7:10.
47 Wu YP, Aspinwall LG, Conn BM, *et al*. A systematic review of interventions to improve adherence to melanoma preventive behaviors for individuals at elevated risk. *Prev Med* 2016;88:153–67.
48 Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005;152:518–23.
49 Howard MD, Su JC, Chong AH. Skin cancer following solid organ transplantation: a review of risk factors and models of care. *Am J Clin Dermatol* 2018;19:585–97.
50 Lim WH, Eris J, Kanellis J, *et al*. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *Am J Transplant* 2014;14:2106–19.
51 Iannacone MR, Pandeya N, Isbel N, *et al*. Sun protection behavior in organ transplant recipients in Queensland, Australia. *Dermatology* 2015;231:360–6.
52 Imko-Walczuk B, Graczyk M, Korban M, *et al*. Impact of skin cancer awareness on prophylactic behavior among renal transplant recipients. *Transplant Proc* 2016;48:1526–31.
53 Thomas BR, Barnabas A, Agarwal K, *et al*. Patient perception of skin-cancer prevention and risk after liver transplantation. *Clin Exp Dermatol* 2013;38:851–6.
54 Robinson JK, Rigel DS. Sun protection attitudes and behaviors of solid-organ transplant recipients. *Dermatol Surg* 2004;30:610–5.
55 Robinson JK, Friedewald J, Gordon EJ. Perceptions of risk of developing skin cancer for diverse Audiences: enhancing relevance of sun protection to reduce the risk. *J Cancer Educ* 2016;31:153–7.
56 Skiveren J, Mortensen EL, Haedersdal M. Sun protective behaviour in renal transplant recipients. A qualitative study based on individual interviews and the health belief model. *J Dermatolog Treat* 2010;21:331–6.
57 Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *BMJ* 2009;339:b3496.
58 Oakley A, Strange V, Bonell C, *et al*. Process evaluation in randomised controlled trials of complex interventions. *BMJ* 2006;332:413–6.
59 Buldukoglu K, Kulakac O, Kececioglu N, *et al*. Recipients' perceptions of their transplanted kidneys. *Transplantation* 2005;80:471–6.
60 Jamieson NJ, Hanson CS, Josephson MA, *et al*. Motivations, challenges, and attitudes to self-management in kidney transplant recipients: a systematic review of qualitative studies. *Am J Kidney Dis* 2016;67:461–78.
61 Urstad KH, Wahl AK, Andersen MH, *et al*. Renal recipients' educational experiences in the early post-operative phase--a qualitative study. *Scand J Caring Sci* 2012;26:635–42.
62 Gordon EJ, Butt Z, Jensen SE, *et al*. Opportunities for shared decision making in kidney transplantation. *Am J Transplant* 2013;13:1149–58.
63 O'Hare AM, Rodriguez RA, Bowling CB. Caring for patients with kidney disease: shifting the paradigm from evidence-based medicine to patient-centered care. *Nephrol Dial Transplant* 2016;31:368–75.
64 Dantal J, Morelon E, Rostaing L, *et al*. Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results. *J Clin Oncol* 2018;36:2612–20.