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, I²=98%) and knowledge (n=4, n=489, SMD 0.50, 95% CI 0.12 to 0.87, I²=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, I²=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.

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 rapamycin inhibitors (mTORis) and secondary prevention using retinoid actretin 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.

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 I² statistic. An I² 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.
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), or did not provide data that were able to be meta-analysed (n=5).

**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) |

*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 rapamycin inhibitors.
### Table 2 Characteristics of individual studies

| Study                        | N   | Type of transplant | Setting                              | Type of intervention | Measures                  | Intervention                          | Comparator               | Primary outcomes       | Time (months) |
|------------------------------|-----|--------------------|-------------------------------------|----------------------|---------------------------|---------------------------------------|--------------------------|------------------------|-----------------|
| **Behavioural interventions**|     |                    |                                     |                      |                           |                                       |                          |                        |                 |
| Clowers-Webb 2006            | 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                | 75  | Kidney             | USA                                 | Behavioural          | Self-reported questionnaire | Workbook                             | Standard care           | Knowledge and behaviour | 1               |
| Robinson 2014                | 101 | Kidney             | Single centre, USA                  | Behavioural          | Self-reported questionnaire | Workbook, Text messages              | Standard care           | Knowledge and behaviour | 1.5             |
| Robinson 2015                | 170 | Kidney             | Multicentre, USA                    | Behavioural          | Self-reported questionnaire | Mobile app program                   | Standard care           | Knowledge and behaviour | 0.5             |
| Robinson 2016                | 170 | Kidney             | Multicentre, USA                    | Behavioural          | Self-reported questionnaire | Mobile app program                   | Standard care           | Knowledge and behaviour | 1.5             |
| Trinh 2014                   | 100 | Kidney, liver, lung | Single centre, USA                  | Behavioural          | Self-reported questionnaire | Video                                | Pamphlet                | Knowledge            | 1 day           |
| **Switch to mTORis**         |     |                    |                                     |                      |                           |                                       |                          |                        |                 |
| Alberu 2011                  | 830 | Kidney             | Multicentre§                         | Switch to mTORis     | Investigator-reported adverse events | Conversion to sirolimus            | CNI                      | Cancer incidence     | 24              |
| Campbell 2012                | 86  | Kidney             | Multicentre, Australia, New Zealand, USA | Switch to mTORis | Physical examination +/- biopsy | Conversion to sirolimus            | CNI                      | Cancer incidence     | 12              |
| Carroll 2013                 | 32  | Kidney             | Multicentre, UK                     | Switch to mTORis     | Physical examination +/- biopsy | Conversion to prednisolone and sirolimus | CNI/AZA                | Cancer incidence     | 24              |
| Euvrard 2012                 | 120 | Kidney             | Multicentre, France                 | Switch to mTORis     | Physical examination +/- biopsy | Conversion to sirolimus            | CNI                      | Cancer incidence     | 24              |
| Hoogendijk-van den Akker 2013| 155 | Kidney             | Multicentre, Netherlands, UK        | Switch to mTORis     | Physical examination +/- biopsy | Conversion to sirolimus            | AZA/MMF/CNI             | Cancer incidence     | 24              |
| Salgo 2010                   | 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** |   |                    |                                     |                      |                           |                                       |                          |                        |                 |
|                             |     |                    |                                     |                      |                           |                                       |                          |                        |                 |

Continued
| Study            | N | Type of transplant | Setting                  | Type of intervention              | Measures                                      | Intervention   | Comparator   | Primary outcomes                                                                 | Time (months) |
|------------------|---|--------------------|--------------------------|----------------------------------|----------------------------------------------|----------------|-------------|---------------------------------------------------------------------------------|---------------|
| Bavinck 1995     | 44| Kidney             | Multicentre, Netherlands | Oral retinoid                    | Physical examination +/- biopsy              | Acitretin      | Placebo     | Cancer incidence, precancerous lesion reduction                                 | 6             |
| Brown 2005       | 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        | 22| Kidney             | Single centre, Australia | Nicotinamide                     | Physical examination                       | Nicotinamide   | Placebo     | Cancer incidence                                                              | 6             |
| de Sevaux 2003   | 26| Kidney             | Single centre, Netherlands | Oral retinoid                    | Physical examination +/- biopsy             | High dose acitretin, Low dose acitretin      | Cancer and precancerous incidence | 12            |
| Dragieva 2004    | 17| Kidney, heart      | Single centre, Switzerland | Photodynamic therapy             | Physical examination +/- biopsy, Clinical photographs | Methyl aminolevulinate cream | Placebo     | Precancerous lesion response                                                    | 4             |
| George 2002      | 23| Kidney             | Multicentre, Australia   | Oral retinoid                    | Physical examination, Annual radiological evaluation | Acitretin      | Drug-free period | Cancer incidence                                                              | 24            |
| Togsverd-Bo 2015 | 25| Kidney             | Single centre, Denmark   | Photodynamic therapy             | Physical examination                       | Methyl aminolevulinate cream | No treatment contralateral area | Actinic keratosis incidence                                                      | 36            |
| Togsverd-Bo 2017 | 35| Kidney, lung, liver| Multicentre, Denmark and Sweden | Photodynamic therapy             | Physical examination                       | Methyl aminolevulinate cream, 5% Imiquimoid cream | Actinic keratosis lesion response | 6             |
| Wulf 2006        | 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; mTORs, mammalian target of rapamycin inhibitors.
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 messages31 and a mobile app program32 were compared with standard care. Patients who received behavioural interventions reported improved sun protection behaviour scores30–32 (3 studies, 414 participants, SMD 0.89, 95% CI −0.84 to 2.62, I² 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, I² 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.32

**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, I² 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, I² 96%), adherence to sun protection (SMD 0.77, 95% CI −0.14 to 1.68, I² 92%) and willingness or intention to change behaviour (SMD 1.70, 95% CI −1.68 to 5.07, I² 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 exposure34 (RR 1.00, 95% CI 0.89 to 1.13, I² 95%) or sunburn (RR 3.19, 95% CI 2.47 to 4.10, I² 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* | | | | |
| 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** | | | | | | | | |
| 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% | Workbook and text messages, mobile app programme | Standard care |
| Willingness/intention to change behaviour | 2 | 273 | 1.70 (−1.68 to 5.07) | 0.32 | 99% | Workbook and text messages, mobile app programme | Standard care |
| 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 |
| **Complications** | | | | | | | | |
| 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 | Workbook | Standard care |
| Importance of partner help for skin self-examination | 1 | 75 | 1.59 (1.10 to 2.08) | <0.001 | N/A | Workbook | Standard care |
| **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% | Workbook and text messages, mobile app programme | Standard care |
| Sunburn (past week) | | | | | | | | |
| None | 2 | 271 | 3.19 (2.47 to 4.10) | <0.001 | 99% | Workbook and text messages, mobile app programme | Standard care |
| >1 | 2 | 271 | 2.68 (1.81 to 3.96) | <0.002 | 95% | Workbook and text messages, mobile app programme | Standard care |

Continued
modifiers (n=1)\textsuperscript{38} to current treatment or placebo. The incidence of NMSCs was assessed in nine pharmaceutical studies.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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).\textsuperscript{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\textsuperscript{2} 85%).\textsuperscript{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%).\textsuperscript{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\textsuperscript{2} 72%, figure 5).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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)\textsuperscript{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.\textsuperscript{40} One trial, which was not included in the meta-analysis, showed approximately a 50% reduction in the incidence

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### Table 3  Continued

| Outcome | Studies | Participants | Weighted MD/SMD (95% CI) | RR | P | i\textsuperscript{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 0.16)† | 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.

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**Figure 3**  Behavioural interventions—sun protection behaviour (general).
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
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 factors47 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     | I² | 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 178.17) | 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** | | | | | | | |
| SCC incidence | 1 | 14* | 0.59 (0.34 to 1.03) | 0.06 | N/A | MAL | No treatment |
| **Immune response modifiers (n=1)** | | | | | | | |
| 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 | 1 | 14* | 0.09 (0.01 to 1.70) | 0.11 | N/A | Imiquimod 5% cream | Placebo |
| **Oral retinoids (n=2)** | | | | | | | |
| Decreased incidence: | | | | | | | |
| >1 SCC | 1 | 46* | 0.40 (0.19 to 0.85) | 0.02 | N/A | Acitretin | 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 rapamycin inhibitors; 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. On the contrary, overall mortality is higher and discontinuation following adverse events is more common in patients who receive mTORi therapy. Several RCTs showed a higher rate of patients reporting adverse events or drug discontinuation with sirolimus, demonstrating concern of its clinical usefulness. 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, 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, were less likely to use sunscreen and that patients have to perceive skin cancer as being an important risk to be motivated to change behaviour.

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.

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. 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.
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. 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 behaviour, 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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LJJ, GW, AT, LDWL, JC, KH and MH designed the study. LJJ, VS, LDWL and 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.

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