Epidemiology of keratinocyte carcinomas after organ transplantation*

M.M. Madeleine, N.S. Patel, E.I. Plasmeijer, E.A. Engels, J.N. Bouwes Bavinck, A.E. Toland, and A.C. Green on behalf of the Keratinocyte Carcinoma Consortium (KeraCon) Immunosuppression Working Group

1Fred Hutchinson Cancer Research Center, Seattle, WA, U.S.A.
2University of South Florida, Tampa, FL, U.S.A.
3QIMR Berghofer Medical Research Institute, Queensland, Australia
4National Cancer Institute, Bethesda, MD, U.S.A.
5Leiden University Medical Centre, Leiden, the Netherlands
6The Ohio State University Medical Center, Columbus, OH, U.S.A.
7CRUK Manchester Institute and University of Manchester, Manchester Academic Health Sciences Centre, Manchester, U.K.

Linked Comment: Raymond. Br J Dermatol 2017; 177:1152–1153.

Summary

Keratinocyte carcinoma (KC) is the most common type of cancer among white populations, but it is even more common among solid organ transplant recipients (OTRs). The most frequent histological type of KC among OTRs is cutaneous squamous cell carcinoma (cSCC), followed by basal cell carcinoma, although the reverse is seen in the general population. Metastatic cSCCs are more frequent, and mortality is increased compared with immunocompetent populations. There is strong evidence that the risk of KC among OTRs rises with increasing time after transplantation and older age at transplantation, and that KC is enhanced in those with sun-damaged skin. This evidence suggests that accelerated accumulation of genetic damage from several sources leads to excess KC in OTRs. We describe international variation in KC and focus on trends in immunosuppressive regimens, the role of ultraviolet susceptibility and exposure, and the contribution of genetics to tumour development. Further epidemiological studies are needed to address gaps in our understanding of the mediation of excess KC by immunosuppressive drugs, viral infection, genetic susceptibility, timing of relevant ultraviolet exposure or some combination of these factors.

What’s already known about this topic?
- Keratinocyte carcinomas (KCs) are the most commonly occurring cancers among white solid organ transplant recipients (OTRs).
- Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) account for 90% of KCs.
- Increased risks of metastases and mortality are associated with cSCC among OTRs.
- Continued long-term studies of immunosuppressive regimens and KC incidence and mortality are needed to assess the overall impact on OTRs.

What does this study add?
- Epidemiological studies continue to uncover changes in KC trends, identify new targets for treatment or markers of progression, and strengthen strategies to stratify screening groups and identify target groups for more intense surveillance.

Nearly 120 000 organs are transplanted per year worldwide (http://www.transplant-observatory.org). The extraordinary benefits of solid organ transplantation include extended lifespan and increased quality of life. Drawbacks include
dependence on immunosuppression to maintain engraftment and an increase in cancer rates among organ transplant recipients (OTRs). Specifically, there is an approximately two- to sixfold increased risk of all types of malignancy compared with cancer rates in the general population. In this systematic review we explore the epidemiology of keratinocyte carcinoma (KC), the most common malignancy that occurs among transplant recipients in light-skinned populations.

KC comprises two main histological types, cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC), which together account for 90% of post-transplantation KC. In OTRs, as with KC in the general population, both histological types are caused mainly by excessive exposure to ultraviolet (UV) radiation and are found most often on sun-exposed skin. They also occur more often in men than in women and are more frequent with increasing age. Despite these commonalities with KC in the general population, KCs among OTRs are characterized by higher rates of cSCC than BCC, while the reverse is seen among immunocompetent populations. This excess of cSCC after transplantation suggests that unique factors associated with transplantation play an important role in promoting cSCC development among OTRs.

In this review we discuss epidemiological studies of demographic factors, transplant-related factors, UV susceptibility and exposure measures, viral aetiology and genetic variation associated with development of KC after organ transplantation. We also point out gaps in our understanding that can be addressed in future epidemiological studies of risk factors and prognosis of KC in OTRs.

Demography and demographic trends

Incidence

Studies conducted in the last 10 years reporting standardized incidence ratios (SIRs, which measure incidence relative to the general population) are summarized in Table 1, and cumulative incidences over time are summarized in Table 2. SIRs of cSCC are higher than SIRs for planning treatment and surveillance post-transplantation (Table 2).

Cumulative incidence estimates also vary somewhat by geographical location, study period and centre, but all support an excess of BCC and cSCC regardless of the type of organ transplanted. A long-term follow-up of a cohort in Sweden reported that 19% (95% CI 14–25%) of heart/lung, 18% (95% CI 12–29%) of liver and 9% (95% CI 8–9.9%) of kidney recipients had a cSCC by 20 years post-transplantation. Another large cohort study in the U.K. followed over 900 transplant recipients, for an average of approximately 10 years; the investigators reported a 30-year cumulative incidence of 65-4% for cSCC and 46-5% BCC. These long-term studies in countries with population-based data suggest that the majority of light-skinned OTRs will eventually develop cSCC, providing key information for surveillance guidelines.

Mortality

A recent review reports that mortality rates for KC in the general population, dominated by cSCC, are 0-5 and 0-4 per 100 000 in developed and developing countries, respectively. Much higher mortality rates were reported in a study of transplant recipients in the U.S.A., with a cSCC-specific mortality rate of 4.9 per 100 000. KC-specific mortality among OTRs in the U.S.A. was reported as 11% for BCC, 18% for cSCC and 15% for both. A U.K. study of all OTRs reported that seven of 26 OTRs (27%) with more than 10 diagnosed skin cancers died of their

Table 1: Standardized incidence ratios (95% confidence intervals) of keratinocyte cancer (KC), basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) among organ transplant recipients

| Study               | Outcome | Location | KTR       | LiTR     | HTR       | LuTR     |
|---------------------|---------|----------|-----------|----------|-----------|----------|
| Chapman 2013       | KC      | Finland  | 39.2 (29.3–51.4) | 34.0 (17.0–60.6) | 16.1 (13.1–19.6) | 6.4 (4.6–9.2) |
| Chapman 2013       | Sweden  | 57.7 (51.0–65.1) |          |          |          |          |
| Chapman 2013       | U.K.    | 16.6 (15.9–17.3) | 6.6 (5.8–7.5) | 18.5 (16.9–20.3) | 16.1 (13.1–19.6) |          |
| Jensen 2010        | cSCC    | Denmark  | 81 (68–96) | 60 (27–113) | 113 (74–166) | 65 (28–128) |
| Jensen 2010        | BCC     | Denmark  | 6.9 (5.8–8.1) | 4.6 (2.1–8.7) | 5.6 (3.1–9.5) | 4.1 (1.7–8.5) |
| Krynitz 2013       | cSCC    | Sweden   | 53 (46–61) | 15 (7.2–28) | 67 (46–94) |          |
| Krynitz 2013       | ≤ 5 years |           |          |          |          |          |
| Krynitz 2013       | 5–9 years |           |          |          |          |          |
| Krynitz 2013       | 10–19 years |         |          |          |          |          |
| Krynitz 2013       | ≥ 20 years |          |          |          |          |          |

KTR, kidney transplant recipient; LiTR, liver transplant recipient; HTR, heart transplant recipient; LuTR, lung transplant recipient. *Heart and lung transplant recipients.

© 2017 British Association of Dermatologists

British Journal of Dermatology (2017) 177, pp1208–1216
In a US registry-based study of nearly 500,000 OTRs (all organ types), patients aged ≥50 years at the time of transplantation were at higher risk of dying from cSCC than those aged <50 years at transplantation (hazard ratio 2.8, 95% CI 1.9–4.0).

An international study of OTRs with metastatic skin cancer followed 68 patients treated between 1989 and 2001, among whom the majority (n = 62) had metastatic cSCC. The study reported that among the 68 OTRs with metastatic skin cancers, 34 died, 23 with metastatic skin cancer, compared with 34 alive at the end of the study, 14 with disease. In a large single-centre study in France that followed 188 OTRs, 10 developed metastatic cSCC and seven died of disease. The exact reason for the comparatively high rate of mortality from cSCC in OTRs compared with the general population is unknown. It is likely that aggressive cSCC in OTRs is attributable to a combination of factors such as increased frequency of cSCC leading to genetic instability, carcinogenic immunotherapies, prior UV damage and a blunted immune response to tumour antigens due to underlying disease, immunosuppression and older age.

Geography

Proximity to the equator and susceptibility to cumulative sun damage explain part of the worldwide variability in KC incidence among OTRs. Thus, higher rates of KC are reported in white OTRs in low-latitude Australia compared with Europe or the U.S.A. The lowest rates are reported for OTRs from Africa, East Asia and India. Taken together, these data point to the protective effect of darker skin pigmentation (also see ‘UV susceptibility’ below). This is illustrated by the much less significant burden of KC among Asian OTRs. A Japanese study of 1744 kidney transplant recipients (KTRs) with 12,982 person-years of observation reported only one cSCC. Similarly, a review of cancer registry data of 283 Taiwanese KTRs from 1981 to 2002 and a retrospective review of 569 Chinese liver transplant recipients failed to reveal even a single KC. A low incidence of KC has also been reported in liver transplant recipients in Korea, with only two skin cancers out of 44 de novo cancers.

Second keratinocyte carcinoma tumours

In the general population, the risk of developing second KC tumours was 50% at 5 years after a first KC. This high rate of second KC primaries is even more elevated among OTRs. In the U.K. long-term cohort study of OTRs, 66% of those with KC developed multiple tumours. In a US study of 166 lung transplant recipients, 80% developed a second cSCC an average of 4 years after the initial cSCC. A study in the Netherlands reported that 72% of KTRs developed a second KC 5 years after transplantation, with similarly high rates of second cSCCs in other studies of KTRs.

Age at transplantation

Age at transplantation is an independent risk factor in the development of KC. Many studies have reported that older
age at transplantation is significantly correlated with KC development, likely due to higher levels of UV exposure prior to transplantation leading to more cumulative genetic damage.

**Transplantation-related factors**

**Maintenance immunosuppression**

Immunosuppression is a key causal cofactor for KC among those OTRs susceptible to UV-induced skin damage. Long duration of induced immunosuppression post-transplantation to maintain grafts results in not just years of a depressed immune response but also a longer duration of exposure to potentially carcinogenic medications. Azathioprine, one of the first drugs used to maintain graft function, interrupts rapidly dividing cells, including synthesis of immune cells, and is most often associated with increased risk of KC. In the setting of significant ultraviolet A exposure, azathioprine has been found to be mutagenic. Ciclosporin, a calcineurin inhibitor, is another medication used to prevent graft rejection post-transplantation. It was introduced in the 1980s to supplement azathioprine-based regimens, and can disrupt nucleotide excision repair and increase sensitization to UV damage. Through its action on the transforming growth factor-β pathway, ciclosporin has been found both to increase phenotypic changes in cells and to increase tumour invasiveness.

The KC risk profile of drugs introduced to post-transplantation medication regimens in more recent years has not yet been well characterized. Mycophenolate mofetil and mycophenolate sodium are nucleotide inhibitors introduced in 1995 and 2004, respectively, to replace azathioprine. Limited data provide evidence for a role of these mycophenolic acid preparations in reducing KC risk compared with other immunosuppressive medications. Likewise, tacrolimus is a calcineurin inhibitor introduced to replace ciclosporin in 1994. Data from a meta-analysis of randomized trials comparing overall cancer rates according to choice of calcineurin inhibitor demonstrated no difference between tacrolimus and ciclosporin, but more recent data suggest lower skin cancer risk associated with tacrolimus. Changing clinical practice will require pooling data from longitudinal projects that keep track of major changes in the maintenance regimen over time post-transplantation.

**Newer drugs**

Mammalian target of rapamycin pathway inhibitors like sirolimus and everolimus may have anticancer properties, and have been studied in OTRs although side-effects have discouraged wide-scale adoption. A multicentre trial that switched individuals using calcineurin inhibitors to sirolimus observed a decreased risk of second cSCC compared with the usual-treatment calcineurin inhibitor group in a trial among KTRs. A single-institution study found that sirolimus did not reduce risk of skin cancers after lung transplantation in a US study.

**Immunosuppression by type of organ transplanted**

The average level of immunosuppression post-transplantation varies by the type of organ transplanted. The highest levels of long-term immunosuppression are required for heart/lung transplants, followed by kidney, and lowest for liver. Also, lower levels of immunosuppression are reported with organs from living compared with deceased donors, and by level of mismatch between donors and recipients. These relative levels of immunosuppression correlate with rates of KC by organ type, for both incidence and mortality. Higher levels of immunosuppression are associated with higher risk of KC, and therefore immunosuppression is lowered when possible as part of treatment for aggressive KC.

**Ultraviolet susceptibility and exposure**

**Measures of ultraviolet susceptibility**

Studies in the last 5 years have used a variety of measures of UV susceptibility in KC among OTRs (Table 3). The most common measure of skin susceptibility to the harmful effects of UV has been a self-reported tendency to sunburn or develop a tan after acute sun exposure, classified according to the Fitzpatrick six-point phototype scale. The Fitzpatrick scale ranges from I, skin that always burns without tanning, to VI, black skin.

An investigation at Northwestern University, Illinois, of 63 liver recipients and 620 kidney recipients reported that Fitzpatrick skin types I and II were independently associated with the development of KC. They also found that the duration of time until an incident KC was greater in patients with higher Fitzpatrick skin types. Similarly, an investigation of US transplant patients demonstrated a cSCC accrual of 14% among nonwhite OTRs (eight of 58) compared with 65% among white OTRs (61 of 94). BCC was also diagnosed more frequently among white vs. nonwhite OTRs: 28% (26 of 94) vs. 2% (one of 58). Indeed, all recent studies show higher skin cancer and cSCC risk in OTRs with fair skin (phototypes I–II), or have shown a tendency towards higher numbers of new cSCCs compared with those with dark skin phototypes, irrespective of the organ type (Table 3). Positive associations were also seen with light hair and light eye colour.

**Measures of ultraviolet exposure**

Measures of cumulative UV exposure have ranged from a focus on geographical location to indices of occupational sun exposure. Other exposure variables used include residential history, sun avoidance, use of sunscreen and clinical elastosis of the neck (a sign of chronic photodamage).

The relationship of UV exposure to cSCC in OTRs is not as clear as for general populations, suggesting a need for further research into UV exposure among OTRs. In one Australian cross-sectional study, native-born OTRs had twice the prevalence of cSCC of those born elsewhere, while clinical elastosis of the neck was not convincingly associated with cSCC.
Table 3  Studies of ultraviolet (UV) exposure and keratinocyte carcinomas (KCs) in organ transplant recipients

| Study          | Country | Years of study | Study design                  | Study population | KCs reported | UV exposure and sensitivity variable | Risk estimates |
|---------------|---------|----------------|-------------------------------|------------------|--------------|-------------------------------------|----------------|
| Ng 2014\textsuperscript{43} | Australia | 2004–2009 | Prospective follow-up study | 142 KTR          | 253 cSCC, 88 BCC | Skin phototype                       | Accrual (± SD)\textsuperscript{a} |
|               |         |               |                               |                  |              | I 1.26 ± 0.70                        | 2.41 ± 0.49     |
|               |         |               |                               |                  |              | II 0.60 ± 1.40                       | 0.40 ± 1.75     |
|               |         |               |                               |                  |              | III 0.60 ± 1.40                      | 0.40 ± 1.75     |
|               |         |               |                               |                  |              | IV 0.60 ± 1.40                       | 0.40 ± 1.75     |
|               |         |               |                               |                  |              | Occupational sun                      | Accrual (± SD)\textsuperscript{a} |
| Bernat Garcia | Spain   | 1996–2010     | Prospective + retrospective follow-up study | 289 KTR          | 41 cSCC, 91 BCC, 25 Bowen | Phototype                             | HR (95% CI)\textsuperscript{b} |
| 2013\textsuperscript{45} |         |               |                               |                  |              | I–II 1 (ref)                          | 0.5–0.27–0.92   |
|               |         |               |                               |                  |              | III 1 (ref)                           | 0.5–0.27–0.92   |
|               |         |               |                               |                  |              | IV 1 (ref)                            | 0.5–0.27–0.92   |
|               |         |               |                               |                  |              | V 1 (ref)                             | 0.5–0.27–0.92   |
| Gogia 2013\textsuperscript{56} | U.S.A. | 2004–2008 | Retrospective follow-up study | 556 KTR/LiTR/PTR/HTR/LuTR/HLuTR/HKTR | 317 cSCC | Fitzpatrick skin type                 | HR (95% CI)\textsuperscript{b} |
|               |         |               |                               |                  |              | I 3.47 (1.46–8.28)                    | 2.63 (1.16–5.92) |
|               |         |               |                               |                  |              | II 2.63 (1.16–5.92)                   | 2.79 (1.24–6.30) |
|               |         |               |                               |                  |              | III 2.07 (0.91–4.70)                  | 1.58 (0.66–3.81) |
|               |         |               |                               |                  |              | IV 1 (ref)                            | 1 (ref)          |
|               |         |               |                               |                  |              | V 1 (ref)                             | 1 (ref)          |
| Ducroux 2014\textsuperscript{44} | France | 1996–2008 | Retrospective follow-up study | 371 LiTR          | 50 KC (cSCC and/or BCC) | Skin type                             | OR (95% CI)\textsuperscript{b} |
|               |         |               |                               |                  |              | I–III 10.91 (1.45–81.77)              | 1 (ref)         |
|               |         |               |                               |                  |              | IV–VI 1 (ref)                         | 1 (ref)         |
|               |         |               |                               |                  |              | Hair colour                           | OR (95% CI)\textsuperscript{b} |
|               |         |               |                               |                  |              | Red or blond                          | 3.58 (1.35–8.25) |
|               |         |               |                               |                  |              | Black or brown                        | 1 (ref)         |

(continued)
| Study | Country | Years of study | Study design | Study population | KCs reported | UV exposure and sensitivity variable | Risk estimates |
|-------|---------|----------------|--------------|------------------|--------------|-------------------------------------|----------------|
| Savoia 2011 | Italy | 1997–2010 | Retrospective follow-up study | 282 KTR | 99 skin cancer (23 with SCC) | Use of sunscreen | HR (95% CI)<sup>b</sup> |
|         |         |                |              |                  |              | Yes | 1 (ref) |
|         |         |                |              |                  |              | No | 1.25 (0.56–2.79) |
|         |         |                |              |                  |              | Born in Australia | PR (95% CI)<sup>c</sup> |
|         |         |                |              |                  |              | No | 1 (ref) |
|         |         |                |              |                  |              | Yes | 2.38 (1.28–4.42) |
| Iannacone 2016 | Australia | 2012–2014 | Cross-sectional study | 295 KTR, 214 LiTR | 41 cSCC, 50 BCC, 77 Bowen | Natural complexion | PR (95% CI)<sup>c</sup> |
|         |         |                |              |                  |              | Olive/medium | 1 (ref) |
|         |         |                |              |                  |              | Fair | 1.61 (1.07–2.43) |
|         |         |                |              |                  |              | Skin reaction in sun | PR (95% CI)<sup>c</sup> |
|         |         |                |              |                  |              | Only tan | 1 (ref) |
|         |         |                |              |                  |              | Burn then tan | 1.14 (0.70–1.87) |
|         |         |                |              |                  |              | Always burn | 1.62 (0.96–2.25) |
|         |         |                |              |                  |              | Elastosis of neck | PR (95% CI)<sup>c</sup> |
|         |         |                |              |                  |              | None/mild | 1 (ref) |
|         |         |                |              |                  |              | Moderate/high | 1.33 (0.87–2.05) |
|         |         |                |              |                  |              | Job | HR (95% CI)<sup>b</sup> |
|         |         |                |              |                  |              | Indoor | 1 (ref) |
|         |         |                |              |                  |              | Outdoor | 0.48 (0.12–1.91) |

BCC, basal cell carcinoma; cSCC, squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; ref, reference value; PR, prevalence ratio; KTR, kidney transplant; LiTR, liver transplant; PTR, pancreas transplant; HTR, heart transplant; HKTR, heart–kidney transplant; HLuTR, heart–lung transplant. <sup>c</sup>cSCC only, <sup>all</sup> all skin cancers combined, <sup>b</sup>BCC and cSCC combined.
Oriential sun exposure was inversely associated in some studies, but positively in another (Table 3). In several of these studies, potential confounding factors were not assessed, and thus confounding could explain differences in results.

Most of the more recently published studies of KC risk in relation to UV exposure have been retrospective cohort studies in KTRs (Table 3). Also, UV exposure has usually been solar as opposed to artificial UV (indoors tanning). Most outcomes studied were ‘all KCs combined’, with a minority looking at cSCC alone. Reviews that summarized KC studies in OTRs in the previous decade consistently found fair skin and high sun exposure to be risk factors for the development of KC along with a variety of secondary factors. Future studies of patterns of UV exposure and risk of KC must be specific about the histological type(s) of KC that develop after transplantation.

Viral aetiology and replication

In addition to its intended beneficial effects, immunosuppressive therapy is also associated with increased susceptibility to virus-associated cancers in OTRs, including non-Hodgkin lymphoma (sevenfold SIR, associated with Epstein–Barr virus infection), Kaposis sarcoma (61-fold SIR, associated with human herpesvirus 8) and liver cancer (11-fold SIR, commonly caused by persistent infection with hepatitis B or C virus). Given that all OTR studies have reported greatly increased SIRs for KC (Table 1), a potential viral aetiology for KC is described in more detail in the accompanying review on pathogenesis.

The leading candidate viruses in prior studies of OTRs are cutaneous types of human papillomavirus (HPV). Despite rigorous study designs and occasional significant findings for HPV types, studies of associations between HPV and KC among OTRs are so far inconclusive. Larger studies with pooled samples and harmonized laboratory techniques may increase the specificity of the associations. Alternatively, undetected HPV types, or indeed other viruses, may account for the associations. Taken together, the epidemiological data support a possible but not definitive role for a cutaneous HPV virus in the aetiology of KC, supporting the need for further studies.

Genetic variation: germline genetic risk factors

A limited number of genetic studies have been performed in OTRs, and most studies were small in size, which may decrease reproducibility as the effect size for most confirmed genetic associations is < 1.5. As in the general population, variants in pigment-related genes, such as MC1R, were associated with an approximately twofold increased risk for cSCC. A second study evaluated the impact of genetic variants in eight pigmentation-related genes on time to first cSCC post-transplant. That study reported that the rs12203592 T allele in IRF4, a gene important in melanin synthesis, was associated with an increased hazard ratio for time to first cSCC, and the rs16891982 C allele in SLC45A2, which encodes a melanosome transport-associated protein, was associated with decreased risk of cSCC. These findings persisted after adjusting for skin, hair and eye colour, suggesting that the effects of the melanin genes extend beyond phototype.

Other candidate genes were hypothesized to be important in KC risk among OTRs. Due to the link between immune system suppression and increased KC risk, human leucocyte antigen alleles that activate acquired T-cell responses were assessed for their potential impact. Additional candidate gene polymorphism studies have not yet yielded convincing associations. These include KC risk linked to TP53 polymorphisms associated with UV damage, variants in detoxifying enzymes such as glutathione S-transferase, and CYPIA1 polymorphisms associated with drug metabolism. In short, larger studies are needed to clarify the genetic associations and to allow for adjustment for potential confounding factors.

Future studies may warrant examining drug–gene interactions for OTRs. For example, a recent report suggests that the excess risk of cSCC observed in individuals with lung transplants who take voriconazole may be related to having two copies of a CYP2C19 rapid-metabolizing allele. This finding adds to the data supporting excess risk in these patients being due to the photosensitizing properties of the drug. The implications of such drug–gene interaction studies may be particularly important for highly medicated OTRs.

Future studies

The epidemiological evidence in OTRs strongly supports an excess of cSCC compared with BCC, and higher mortality associated with cSCC after transplantation, but the aetiology that drives these differences is unclear. Future studies may comprehensively assess the direct impact of specific immunosuppressive drugs, patterns in UV exposure before and after transplantation, or a role for cutaneous viruses, but these remain areas that require careful and collaborative epidemiological study.

Challenges for such future studies include collecting data in a standardized way across studies in different geographical locations, preferably in longitudinal cohort settings with harmonized data collection instruments. Such studies need to evaluate best approaches to measuring UV exposure, and changes over time in immunosuppressive medication use. Studies of cutaneous viruses, such as HPV, will need to standardize their approach to DNA and serological testing of the same samples across laboratories. As multiple KC tumours and the potential for metastatic disease have been noted, an important aspect of future studies will be continued surveillance over time to assess risk factors for aggressive KC after transplantation.

Key ongoing large surveillance studies are methodologically challenging but important for assessing the epidemiology of multiple primary KCs. Consortia that include studies of OTRs and immunocompetent individuals will facilitate sharing data across research groups so that future epidemiological studies are well positioned to contribute to a more definitive understanding of the excess risk of KC among OTRs. Such findings may enhance surveillance and provide new treatment targets for KC.
Conclusions

This review highlights the importance of assessing KC risk by histological type, and highlights that the common cofactors, such as UV exposure and level of immunosuppression, cannot be overlooked. We find that the risk of KC after organ transplantation is generally higher among those whose skin is susceptible to photodamage and who have a prolonged immunosuppression history. Thus, OTRs with the highest reported history of sun damage before transplantation have the most KCs. In addition, older age at transplantation, time since transplantation, and type of organ transplanted are likely surrogates for accumulated UV damage and the level or duration of immunosuppression.

Acknowledgments

The KeraCon Immunosuppression Working Group (Sarah Arron, Maryam Asgari, Maria Blomberg, Jan Nico Bouwes Bavinck, Eric Engels, Adele Green, Catherine Harwood, Günther Hofbauer, Margaret M. Madeleine, Priya Nagarajan, Luigi Naldi, Nishit Patel, Charlotte Proby and Amanda Ewart Toland) helped to conceive this study and provided detailed feedback on this review.

References

1. Engels EA, Pfeiffer RM, Fraumeni JF Jr et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011; 306:1891–901.
2. Adam J, Gabel H, Lindelof B et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2003; 89:1221–7.
3. Krynsitz B, Edgren G, Lindelof B et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—a Swedish population-based study. Int J Cancer 2013; 132:1429–38.
4. Euwraard S, Kanitakis J, Cludry A. Skin cancers after organ transplantation. N Engl J Med 2003; 348:1681–91.
5. Moloney FJ, Comber H, O’Lorcain P et al. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol 2006; 154:498–504.
6. Jensen AO, Svaerke C, Farask D et al. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. Acta Derm Venereol 2010; 90:474–9.
7. 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.
8. Boyers LN, Karimkhanzi C, Naghavi M et al. Global mortality from conditions with skin manifestations. J Am Acad Dermatol 2014; 71:1137–43.
9. Garrett GL, Lowenstein SE, Singer JP et al. Trends of skin mortality after transplantation in the United States: 1987 to 2013. J Am Acad Dermatol 2016; 75:106–12.
10. Buell JF, Hanaway MJ, Thomas M et al. Skin cancer following transplantation: the Israel Penn International Transplant Tumor Registry experience. Transplant Proc 2005; 37:962–3.
11. Martinez JC, Odely 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.
12. Euwraard S, Kanitakis J, Decullier E et al. Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. Transplantation 2006; 81:1093–100.
13. Proby CM, Wisgerhof HC, Casabonne D et al. The epidemiology of transplant-associated keratinocyte cancers in different geographical regions. Cancer Treat Res 2009; 146:75–95.
14. Hoshiba Y, Tsukuma H, Yasunaga Y et al. Cancer risk after renal transplantation in Japan. Int J Cancer 1997; 71:517–20.
15. Feng WW, Wang TN, Chen HC et al. Malignancies after renal transplantation in southern Taiwan: experience in one centre. BJU Int 2007; 99:825–9.
16. Yu S, Gao F, Yu J et al. De novo cancers following liver transplantation: a single center experience in China. PLOS ONE 2014; 9:e85651.
17. Park HW, Hwang S, Ahn CS et al. De novo malignancies after liver transplantation: incidence comparison with the Korean cancer registry. Transplant Proc 2012; 44:802–5.
18. Karagas MR, Stukel TA, Greenberg ER et al. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. Skin Cancer Prevention Study Group. JAMA 1992; 267:3303–10.
19. Rashitak S, Dierkhising RA, Kremers WK et al. Incidence and risk factors for skin cancer following lung transplantation. J Am Acad Dermatol 2015; 72:92–8.
20. Wisgerhof HC, Edelbroek JR, de Fijter JW et al. Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. Transplantation 2010; 89:1231–8.
21. Mackenzie KA, Wells JE, Lynn KL et al. First and subsequent non-melanoma skin cancers: incidence and predictors in a population of New Zealand renal transplant recipients. Nephrol Dial Transplant 2010; 25:300–6.
22. Magruder JT, Crawford TC, Grimm J et al. Risk factors for de novo malignancy following lung transplantation. Am J Transplant 2017; 17:227–38.
23. Sanders ML, Karnes JH, Denny JC et al. Clinical and genetic factors associated with cutaneous squamous cell carcinoma in kidney and heart transplant recipients. Transplant Direct 2015; 1:e113.
24. Helmy S, Marschalek J, Bader Y et al. Risk factors for de novo malignancies in women after kidney transplantation: a multicenter transversal study. Int J Gynecol Cancer 2016; 26:967–70.
25. Kaufmann RA, Oberholzer PA, Cazzaniga S et al. Epithelial skin cancers after kidney transplantation: a retrospective single-centre study of 376 recipients. Eur J Dermatol 2016; 26:265–70.
26. Kuschel C, Kai-Martin T, Schubert S et al. Skin cancer in organ transplant recipients: effects of immunosuppressive medications on DNA repair. Exp Dermatol 2011; 20:2–6.
27. Jiayd Z, Olsen CM, Burke MT et al. Azathioprine and risk of skin cancer in organ transplant recipients: systematic review and meta-analysis. Am J Transplant 2016; 16:3490–503.
28. O’Donovan P, Perrett CM, Zhang X et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Soma 2005; 309:1871–4.
29. Han W, Soltani K, Ming M, He YY. Deregulation of XPC and CypA by cyclosporin A: an immunosuppression-independent mechanism of skin carcinogenesis. Cancer Prev Res (Phila) 2012; 5:1155–62.
30. Hojo M, Morimoto T, Maluccio M et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 1999; 397:530–4.
31. Coghll AE, Johnson LG, Berg D et al. Immunosuppressive medications and squamous cell skin carcinoma: nested case-control study.
Keratinocyte carcinomas after organ transplantation, M.M. Madeleine et al.

within the Skin Cancer after Organ Transplant (SCOT) cohort. Am J Transplant 2016; 16:565–73.
32 Webster AC, Woodroffe RC, Taylor RS et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BJM 2005; 331:810–2.
33 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.
34 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.
35 Campbell SB, Walker R, Tai SS et al. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for non-melanoma skin cancer. Am J Transplant 2012; 12:1146–56.
36 Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. Cancer Med 2015; 4:1448–59.
37 Colegio OR, Hanlon A, Olasz EB et al. Sirolimus reduces cutaneous squamous cell carcinomas in transplantation recipients. J Clin Oncol 2013; 31:3297–8.
38 Bostami RT, Ojo AO, Wolfe RA et al. Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant recipients. Am J Transplant 2004; 4:87–93.
39 Hampton T. Skin cancer’s ranks rise: immunosuppression to blame. JAMA 2005; 294:1476–80.
40 Zwald F, Brown M, eds. Advances in Transplant Dermatology: Clinical and Practical Implications. New York: Springer, 2015.
41 Buoy AG, Yoo S, Alam M et al. Distribution of skin type and skin cancer in organ transplant recipients. Arch Dermatol 2010; 146:344–6.
42 Ruiz de Luzuriaga AM, Hsieh C. Yearly burden of skin cancer in non-Caucasian and Caucasian solid-organ transplant recipients. J Clin Aesthet Dermatol 2015; 8:16–19.
43 Ng JC, Cumming S, Leung V et al. Accrual of non-melanoma skin cancer in renal-transplant recipients: experience of a Victorian tertiary referral institution. Australas J Dermatol 2014; 55:43–8.
44 Ducroux E, Bouillot O, Orcampo MA et al. Skin cancers after liver transplantation: retrospective single-center study on 371 recipients. Transplantation 2014; 98:335–40.
45 Bernat Garcia J, Morales Suarez-Varela M, Vilata JI et al. Risk factors for non-melanoma skin cancer in kidney transplant patients in a Spanish population in the Mediterranean region. Acta Derm Venereol 2013; 93:422–7.
46 Iannaccone MR, Sinnya S, Pandeya N et al. Prevalence of skin cancer and related skin tumors in high-risk kidney and liver transplant recipients in Queensland, Australia. J Invest Dermatol 2016; 136:1382–6.
47 Savoia P, Stroppiana E, Cavaliere G et al. Skin cancers and other cutaneous diseases in renal transplant recipients: a single Italian center observational study. Eur J Dermatol 2011; 21:242–7.
48 Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011; 65:263–79.
49 Mudigonda T, Pearce DJ, Yentzer BA et al. The economic impact of non-melanoma skin cancer: a review. J Natl Compr Canc Netw 2010; 8:888–96.
50 Harwood CA, Toland AE, Proby CM et al. The pathogenesis of cutaneous squamous cell carcinoma in organ transplant recipients. Br J Dermatol 2017; in press.
51 Proby CM, Harwood CA, Neale RE et al. A case–control study of beta-papillomavirus infection and cutaneous squamous cell carcinoma in organ transplant recipients. Am J Transplant 2011; 11:1498–508.
52 Casabonne D, Lally A, Mitchell L et al. A case–control study of cutaneous squamous cell carcinoma among Caucasian organ transplant recipients: the role of antibodies against human papillomavirus and other risk factors. Int J Cancer 2009; 125:1935–45.
53 Madeleine MM, Carter JJ, Johnson LG et al. Risk of squamous cell skin cancer after organ transplant associated with antibodies to cutaneous papillomaviruses, polyomaviruses, and TMC6/8 (EVER1/2) variants. Cancer Med 2014; 3:1440–7.
54 Andreason PA, Nymoen DA, Kjaerheim K et al. Susceptibility to cutaneous squamous cell carcinoma in renal transplant recipients associates with genes regulating melanogenesis independent of their role in pigmentation. Biomark Cancer 2013; 5:41–7.
55 Asgari MM, Wang W, Ioannidis NM et al. Identification of susceptibility loci for cutaneous squamous cell carcinoma. J Invest Dermatol 2016; 136:930–7.
56 Bouwes Bavinck JN, Claas FH, Hardie DR et al. Relation between HLA antigens and skin cancer in renal transplant recipients in Queensland, Australia. J Invest Dermatol 1997; 108:708–11.
57 Bouwes Bavinck JN, Kootte AM, van der Woude FJ et al. On a possible protective effect of HLA-A11 against skin cancer and keratotic skin lesions in renal transplant recipients. J Invest Dermatol 1991; 97:269–72.
58 Cairney-Remonnay S, Humbley O, Mougin C et al. TP53 polymorphism of exon 4 at codon 72 in cutaneous squamous cell carcinoma and benign epithelial lesions of renal transplant recipients and immunocompetent individuals: lack of correlation with human papillomavirus status. J Invest Dermatol 2002; 118:1026–31.
59 Lira MG, Provezza L, Malerba G et al. Glutathione S-transferase and CYPIA1 gene polymorphisms and non-melanoma skin cancer risk in Italian transplanted patients. Exp Dermatol 2006; 15:958–65.
60 Williams K, Arron ST. Association of CYP2C19 *17/*17 genotype with the risk of voriconazole-associated squamous cell carcinoma. JAMA Dermatol 2016; 152:719–20.
61 Vadrnerka A, Nguyen MH, Mitsani D et al. Voriconazole exposure and geographic location are independent risk factors for squamous cell carcinoma of the skin among lung transplant recipients. J Heart Lung Transplant 2010; 29:1240–4.
62 Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. Cold Spring Harb Perspect Med 2013; 3:a015677.
63 Fortina AB, Caforio AL, Piasecko S et al. Skin cancer in heart transplant recipients: frequency and risk factor analysis. J Heart Lung Transplant 2000; 19:249–55.
64 Haagmans EB, Hagens VE, Schaapveld M et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001; 34:84–91.
65 Ramsay HM, Fryer AA, Hawley CM et al. Non-melanoma skin cancer risk in the Queensland renal transplantation population. Br J Dermatol 2002; 147:950–6.
66 Gogia R, Bunstock M, Hirose R et al. Fitzpatrick skin phototype is an independent predictor of squamous cell carcinoma risk after solid organ transplantation. J Am Acad Dermatol 2013; 68:585–91.