REVIEW

Skin cancer in organ transplant recipients: More than the immune system

Lee Wheless, PhD,[a,b,c] Sarah Jacks, BA,[b,c] Kathryn Anne Mooneyham Potter, BS,[b,c] Brian C. Leach, MD,[c] and Joel Cook, MD[c]
Charleston, South Carolina

Organ transplant recipients (OTRs) are at increased risk of developing nonmelanoma skin cancers. This has long been thought to be caused by immunosuppression and viral infection. However, skin cancer risk among individuals with AIDS or iatrogenic immunodeficiency does not approach the levels seen in OTRs, suggesting other factors play a critical role in oncogenesis. In clinical trials of OTRs, switching from calcineurin inhibitors to mammalian target of rapamycin inhibitors consistently led to a significant reduction in the risk of developing new skin cancers. New evidence suggests calcineurin inhibitors interfere with p53 signaling and nucleotide excision repair. These two pathways are associated with nonmelanoma skin cancer, and squamous cell carcinoma in particular. This finding may help explain the predominance of squamous cell carcinoma over basal cell carcinoma in this population. Mammalian target of rapamycin inhibitors do not appear to impact these pathways. Immunosuppression, viral infection, and impaired DNA repair and p53 signaling all interact in OTRs to create a phenotype of extreme risk for nonmelanoma skin cancer. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.02.039.)

Key words: calcineurin inhibitors; immunosuppression; mammalian target of rapamycin inhibitors; oncogenic viruses; organ transplant recipients; skin cancer.

The extreme risk of nonmelanoma skin cancer (NMSC) among organ transplant recipients (OTRs) is well known.[1-6] Because of risks reported to be increased 20- to 100-fold, the dogma has become that immunosuppression is a risk factor for NMSC.[7,8] Recent findings suggest, however, there is more to the risk of NMSC in OTRs than just immunosuppression.[9-11] Several recent reviews have expertly summarized individual topics in article, such as the role of oncogenic viruses or classes of immunosuppressants on NMSC risk, but none has examined the risk factors as they interact in OTRs to contribute to the elevated NMSC risk.[9-14] This review aims to synthesize the epidemiologic, clinical, and basic science evidence that suggest that immunosuppression by itself is not the cause of the extreme risk of NMSC, but rather the combination of immunosuppression, viral infection, and the mechanism of action of the immunosuppressive medications all contribute to the risk of skin cancer in OTRs.

Abbreviations used:

BCC:	basal cell carcinoma
CI:	confidence interval
CNI:	calcineurin inhibitor
HPV:	human papillomavirus
mTOR:	mammalian target of rapamycin
NER:	nucleotide excision repair
NMSC:	nonmelanoma skin cancer
OTR:	organ transplant recipient
SCC:	squamous cell carcinoma
UV:	ultraviolet
UVR:	ultraviolet radiation

SKIN CANCER IN OTRs

OTRs are at extreme risk for NMSC, with many institutions devoting specialty clinics to the care of this population.[1,2,9] For example, a

From the Departments of Public Health Sciences,[a] Medicine,[b] and Dermatology and Dermatologic Surgery,[c] Medical University of South Carolina.

Supported by funding from the National Institutes of Health National Institute of General Medical Sciences grant T32GM008716 (Dr Wheless).
Conflicts of interest: None declared.
Accepted for publication February 11, 2014.

Reprint requests: Brian C. Leach, MD, Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina, 135 Rutledge Ave, MSC 578, PO Box 250578, Charleston, SC 29425. E-mail: leachb@musc.edu.

Published online April 8, 2014.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.02.039

population-based study in Sweden observed a standardized incidence ratio of 121 (95% confidence interval [CI] 116-127) among OTRs compared with the general population.[15] A multiethnic cohort in the United Kingdom observed a 26% 10-year incidence of NMSC in OTRs, and a 15% incidence among those of African ancestry, a group that otherwise would be at low risk of ultraviolet (UV) radiation (UVR)-induced cancers.[16] The lower incidence among those with darker pigmentation suggests that UVR still plays a significant role in the development of these cancers. Fitzpatrick skin type and sun exposure are independently associated with skin cancer risk among OTRs.[9,17,18]

CAPSULE SUMMARY

- Organ transplant recipients are at greatly increased risk of basal and squamous cell carcinoma.
- Immunosuppression, viral infection, and calcineurin inhibition all contribute to increased skin cancer risk in organ transplant recipients.
- Calcineurin inhibitors carry a greater skin cancer risk than other regimens because of impaired p53 signaling and nucleotide excision repair.

The paradigm has been that the immunosuppression required to keep the body from rejecting the transplanted organ also impairs immune surveillance, thereby allowing tumor cells to proliferate unchecked.[7] The fact that cumulative dosage of cyclosporine and other immunosuppressants is independently associated with risk of noncutaneous cancers in OTRs tends to support this theory.[19,20] The best example of the association between immunosuppression and increased skin cancer risk comes from patients with HIV and AIDS.

SKIN CANCER IN PATIENTS WITH HIV AND AIDS

The role of the immune system in cancer prevention is highlighted by the increased cancer risk among patients with AIDS, particularly among cancers caused by infectious agents.[12] A meta-analysis showed that compared with the general population, the standardized incidence ratio of Kaposi sarcoma among OTRs was 208 (95% CI 114-349), whereas among patients with AIDS it was 3640 (95% CI 3326-3976).[12] The risks of cervical cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and liver cancer, all of which have known viral etiologic contributions, were greater among patients with AIDS than OTRs. The lower incidence of AIDS-defining cancers among OTRs suggests greater residual immune function than in individuals with AIDS. It therefore seems logical that greater immune function should translate into a lesser risk of virally mediated neoplasia.[12] Viral effects aside, if immunosuppression itself were the major contributor to NMSC risk, it would logically follow that patients with AIDS would experience a greater increased risk of skin cancer than OTRs.[12] This was not observed. Rather, the risk of NMSC among patients with AIDS was 4.11 (95% CI 1.08-16.6), whereas among OTRs it was 28.62 (95% CI 9.39-87.2).

In another study, patients with HIV developed NMSC at an adjusted rate ratio of 2.1 (95% CI 1.9-2.3).[21] When stratified by most recent CD4 levels, squamous cell carcinoma (SCC) risk was increased among those with CD4 less than 200/mm^3 compared with those with CD4 more than 500/mm^3, whereas there was no difference for basal cell carcinoma (BCC). As with Kaposi sarcoma and human herpesvirus-8, the stronger association between immune function and SCC could be consistent with an infectious cause, an example of which could be certain strains of human papillomavirus (HPV), which are found in a subset of SCCs.[11]

SKIN CANCER AND ONCOGENIC VIRUSES

The association between multiple cancers and HPV is well established.[13,22,23] The role of HPV in cutaneous SCC, and BCC, is less clear, although recent studies have found more significant associations.[11,13,24-28] Immunosuppressed populations have higher rates of HPV infection, and in the absence of large prospective studies, it is difficult to identify whether the immunosuppression or the viral infection is the etiologic factor.[11,13,26,28] Further clouding the picture is the stronger association between the two in those with a greater sensitivity to UVR.[29] The strongest associations between HPV and NMSC, and SCC in particular have had odds ratios or relative risks less than 4.0,[29] with most others reporting point estimates of these measures to be less than 2.0.[11,13,25,28] The large number of HPV serotypes and differences in measuring infection have made it difficult to draw firm conclusions regarding a causal association.[11,13,27,30] As OTRs are increasingly vaccinated against HPV, it remains to be seen whether there will be a decrease in NMSC rates in this population.[31] The ongoing Skin Cancer after Organ Transplant Study will provide the first prospective evidence of HPV acquisition and association with NMSC, with results not expected for several years.[32]