Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2013;42:1669–1677
doi:10.1093/ije/dys179

COHORT PROFILE

Cohort Profile: The Skin Cancer After Organ Transplant Study

Margaret M Madeleine,[1,2]* Lisa G Johnson,[1] Janet R Daling,[1,2] Stephen M Schwartz,[1,2] Joseph J Carter,[3] Daniel Berg,[4] Karen Nelson,[5] Connie L Davis[6] and Denise A Galloway[3,7]

[1]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]Department of Epidemiology, University of Washington, Seattle, WA, USA, [3]Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]Division of Dermatology, University of Washington, Seattle, WA, USA, [5]Laboratory of Immunogenetics, Puget Sound Blood Center, Seattle, WA, USA, [6]Division of Nephrology, University of Washington, Seattle, WA, USA and [7]Department of Microbiology, University of Washington, Seattle, WA, USA

*Corresponding author. Program in Epidemiology, Public Health Sciences Division M4-C308, Fred Hutchinson Cancer Research Center, PO Box 19024, Seattle, WA 98109, USA. E-mail: mmadelei@fhcrc.org

Accepted 25 September 2012

The Skin Cancer after Organ Transplant (SCOT) study was designed to investigate the link between genus beta human papillomavirus (HPV) and squamous cell skin cancer (SCSC). We focused on a population receiving immunosuppressive therapy for extended periods, transplant patients, as they are at extremely high risk for developing SCSC. Two complementary projects were conducted in the Seattle area: (i) a retrospective cohort with interview data from 2004 recipients of renal or cardiac transplants between 1995 and 2010 and (ii) a prospective cohort with interview data from 328 people on the transplant waiting lists between 2009 and 2011. Within the retrospective cohort, we developed a nested case–control study (172 cases and 337 control subjects) to assess risk of SCSC associated with markers of HPV in SCSC tumour tissue and eyebrow hair bulb DNA (HPV genotypes) and blood (HPV antibodies). In the prospective cohort, 135 participants had a 1-year post-transplant visit and 71 completed a 2-year post-transplant visit. In both arms of the cohort, we collected samples to assess markers of HPV infection such as acquisition of new types, proportion positive for each type, persistence of types at consecutive visits and number of HPV types detected. In the prospective cohort, we will also examine these HPV markers in relation to levels of cell-mediated immunity. The goal of the SCOT study is to use the data we collected to gain a more complete understanding of the role of immune suppression in HPV kinetics and of genus beta HPV types in SCSC. For more information, please contact the principal investigator through the study website: http://www.fhcrc.org/science/phs/cerc/The_SCOT_Study.html.

Why was the cohort set up?

Solid organ transplant recipients (OTR) are at a 2-fold increased risk of cancer,[1] and risk of squamous cell skin cancer (SCSC) is reportedly >50-fold.[2–4] Approximately 30% of OTR have been reported to develop SCSC within 10 years of transplant, and 70% may be affected within 20 years of transplant.[5] The established SCSC risk factors in OTR are the same as

those for SCSC in the general population, the most important of which are those that indicate sensitivity to UV light such as low pigment skin type, blue eyes, red hair and history of severe sunburn. These are also established risk factors for the most common type of skin cancer in the general population, basal cell carcinoma (SCSC). However, in the general population, the ratio of SCSC to BCC is about 1:4,[6] and in transplant recipients, this ratio is reversed and is estimated to be about 5:1.[7]

In addition to an increased risk of SCSC in OTRs, the SCSC tumours are more aggressive. Hallmarks of this behaviour include earlier age at diagnosis, more deeply invasive disease, increased risk of local recurrence, high rates of multiple primaries, increased tendency for regional and distant metastasis (5–8% of cases)[3] and higher mortality from SCSC in OTR when compared with SCSC in immune competent populations.[8–10] Some kidney OTR with aggressive SCSC have their immune suppression regimen altered to reduce the risk of SCSC progression, which may affect the functioning of their graft.[11]

Many malignancies that occur in high excess in OTR are attributable to viruses that thrive in the setting of immune suppression, such as Epstein Barr virus-associated non-Hodgkin lymphomas, hepatitis viruses and liver cancers and human papillomavirus (HPV)-related anogenital cancers. SCSC may also be related to a virus. Initial evidence pointed to HPV as a candidate virus in SCSC, as HPV was found in patients with a rare autosomal recessive disease, epidermodysplasia verruciformis.[12] Epidermodysplasia verruciformis patients present with immune dysfunction and disseminated skin lesions that resemble warts. About one-third of these patients develop SCSC on sun-exposed areas of their skin, and genus beta HPV types have been detected in >90% of SCSC tumours in these patients.[12] Recent studies suggest various mechanisms by which beta HPV types might be involved in SCSC carcinogenesis. These viruses have been shown to block apoptosis by interfering with the Bak protein in sun-damaged epithelial cells, allowing damaged cells to accumulate.[13,14] In another study, beta HPV5 and beta HPV8 E6 proteins were found to interact with p300, promoting its instability.[15] Together, these studies add to the evidence in support of a role for HPV in SCSC.

The Skin Cancer after Organ Transplant (SCOT) study was designed to investigate the putative link between beta HPV and SCSC in the context of immune suppression, and with the understanding that UV exposure is likely the key initiator of SCSC. Our over-arching goal was to provide evidence that would establish a role for beta HPV in SCSC development. If a definitive link between genus beta HPV and SCSC can be established, it might lead to new approaches to prevention and treatment of SCSC in both transplant patients and members of the general population.

To achieve these goals, we conducted two related studies in the Seattle area: (i) a large retrospective cohort study with a nested case–control study conducted among kidney and heart transplant recipients who received their transplants between 1995 and 2010 and (ii) a prospective longitudinal cohort study among OTR that enrolled adults on the kidney and heart transplant waiting lists to examine viral kinetics in a longitudinal study, with data collected pre-transplant and 1 and 2 years post-transplant. The study goals were to assess markers of beta HPV from SCSC tumour tissue, eyebrow hair samples or serum samples for evidence of genus beta HPVs. Further, interview information on sun sensitivity and exposure history, medication use, genetic predisposition and other factors will be examined as cofactors of an association between beta HPV and SCSC.

Who is in the cohort?

The SCOT study cohort enrolled renal and cardiac transplant recipients in the Seattle area: a retrospective cohort ($n = 2004$) transplanted between 1995 and 2010 and a prospective cohort ($n = 328$) transplanted between 2009 and 2011. Within the retrospective cohort, we developed a nested case–control study (172 cases and 337 control subjects) to assess risk of SCSC associated with markers of HPV in SCSC tumour tissue and hair follicles and blood. All study protocols and documents were approved by institutional review boards, and no monetary inducements were provided for joining the study.

Retrospective cohort

Using data from the transplant centres, we mailed a letter of approach, an informed consent document and a 4-page questionnaire to the 2731 transplant recipients who had been transplanted between 1995 and 2010 and were not known to have died as of the start of study recruitment (April 2008). To find potential participants for whom the address from the transplant centre was no longer accurate, we searched state and federal data sources, such as Washington state drivers' licence and electoral rolls and internet sources. We enrolled 2004 (73.4%) OTR in the SCOT cohort study.

Inclusion criteria for the retrospective cohort were having a first kidney, kidney and pancreas or heart transplant at one of the three transplant centres in Seattle between 1995 and 2010; having an intact graft for at least 3 months; being $\geqslant$18 years of age as of the date of transplant; having no history of a SCSC diagnosis before transplant; able to communicate in English and being a resident of Washington, Idaho, Alaska, Montana or Wyoming at the time of transplant. Transplant recipients may have received more than one transplant during the study period as long as their graft functioned for at least 3 months.

Table 1 Characteristics of SCOT study OTR compared with all kidney, kidney/pancreas and heart transplants at Seattle area transplant institutions, 1995–2010

Characteristics	SCOT Participants ($n=2004$)	OPTN[a] 1995–2010 ($n=4112$)
Age at transplant		
18–49	1013 (50.5)	2063 (50.2)
50–64	787 (39.2)	1582 (38.5)
65+	204 (10.2)	466 (11.3)
Year of transplant		
1995–99	426 (21.3)	1143 (27.7)
2000–04	691 (34.5)	1405 (34.2)
2005–10	887 (44.3)	1564 (38.0)
Sex		
Male	1184 (59.1)	2526 (61.4)
Female	820 (40.9)	1586 (38.6)
Organ transplanted		
Kidney	1601 (79.9)	3373 (82.0)
Heart	213 (10.6)	377 (9.2)
Pancreas	190 (9.5)	362 (8.8)
Type of donor		
Living	600 (33.6)	1354 (32.9)
Living related	359 (20.0)	NA
Living unrelated	244 (13.6)	NA
Deceased	970 (54.2)	2758 (67.1)
Unknown	218 (12.2)	0 (0.0)

[a]Publicly available data from the US Department of Health and Human Services, OPTN, (http://optn.transplant.hrsa.gov/), to which transplant centres in the USA are obligated to report all transplant surgeries; relationship status for the living donors was not available (NA) from OPTN.

Based on publicly available data from the US Department of Health and Human Services, Organ Procurement and Transplantation Network (OPTN), (http://optn.transplant.hrsa.gov/), there were 4112 adult heart, kidney or kidney and pancreas transplant recipients at the three transplant centres during the study period. These data suggest that we were able to identify ~81% ($n=3317$) of potentially eligible cohort members. In Table 1, we compare the SCOT study participants' transplant characteristics with data available from the OPTN website for our transplant centres to gauge the representativeness of our study to the local OTR population, and the groups are generally similar.

The main reasons for non-response were death before contact (18%), death after attempted recruitment (2%), loss to follow-up/untraceable (11%) and refusal to participate (9%) (Table 2). Of the 2004 enrolled cohort members, 1180 participants (43%) returned the 4-page mailed questionnaire by mail and 824 participants (30%) filled out the same questionnaire over the phone. In Table 2, loss to follow-up over time is described for those who died before the study started, who were not traceable or who refused contact. Although no information is available on these OTR, Table 1 suggests that the patients who were followed are representative of all patients in the study catchment who were reported to OPTN.

Nested case–control study of SCSC

The nested case–control study design allows us to accurately estimate relative risk for the whole cohort, but is efficient because it focuses on all cases and a matched subset of the cohort as control subjects. Cases were identified by reviewing pathology reports from potential case subjects who reported a skin biopsy after transplant. We confirmed 195 SCSC cases nested within the cohort. Among those 195 cases, 172 (88%) agreed to participate in the nested case–control study. We selected control subjects from among the retrospective cohort participants.

Control subjects were matched to cases on the following factors: time since transplant (exact number of months), age at transplant (±5 years), year of transplant (±2 years), organ transplanted, hospital, donor type (living versus deceased), gender and race (White versus non-White). When necessary, matching factors were prioritized, and highest priority was given to time since transplant, organ transplanted and sex. We enrolled 337 participants as control subjects, which was 81% of the total number of control subjects approached.

Prospective cohort

The prospective cohort was identified from the local transplant waiting lists starting in 2009. Inclusion criteria were as follows: being a resident of one of six counties in the Seattle metropolitan area (King, Pierce, Snohomish, Skagit, Whatcom and Thurston), being on the heart or kidney transplant list in 2009 through 2011 and being $\geqslant 25$ years of age. We contacted 636 eligible participants by mail and asked them to fill out a 4-page questionnaire. We recruited 328 participants who completed a short in-person interview and donated blood and eyebrow samples. Among the 328 prospective SCOT study cohort members, 201 (61%) received a transplant (as of March 2012). Among them, 135 (67%) had a 1-year post-transplant study visit and 71 (53%) had a 2-year post-transplant visit; thus, 71 OTR had three longitudinal study visits. In addition, study participants who did not receive a transplant were asked to return annual 4-page questionnaires to ascertain whether these patients remained eligible for the study.

Table 2 SCOT study cohort enrolment by transplant year

Transplant year	Eligible *n*	Non-cases *n* (%)	Cases *n* (%)	Died *n* (%)	Untraceable *n* (%)	Refused *n* (%)
1995–99	934	331 (17.2)	73 (37.4)	365 (55.4)	106 (29.0)	59 (20.5)
2000–04	1174	597 (33.0)	84 (43.1)	246 (37.3)	161 (44.0)	86 (29.9)
2005–10	1183	881 (48.7)	38 (19.5)	48 (7.3)	99 (27.0)	117 (40.6)
Total	3317[a]	1809	195[b]	659	366[a]	288[a]

[a]The number eligible for the study that had not died as of the start of data collection was 2731, which was used as the denominator for the response proportion of 73.2%; we did not have information on transplant year for 26 refusers.
[b]Of the 195 confirmed cases, 172 (88.2%) agreed to participate in the case–control study.

How often have they been followed up?

Table 3 describes the timing of sample and data collection for the retrospective cohort, nested case–control study and prospective study that together make up the SCOT study. The study began active data collection in April 2008 and completed data collection in March 2012. Of the 2004 members enrolled in the retrospective cohort who completed the initial questionnaire, 1708 patients completed the first annual follow-up questionnaire (85%) and 1407 completed a second follow-up questionnaire (70%). For the nested case–control study, participants were followed annually during the data collection period with short mailed questionnaires after they completed the long, in-person interview. For the prospective cohort, 328 participants were enrolled from the waiting lists between 2009 and 2011. A longer in-person interview was conducted at 1 year post-transplant ($n = 135$ completed) and a short in-person interview was completed at 2-year post-transplant time point ($n = 71$ completed).

Median follow-up time for participants in the retrospective cohort was 84.4 months (SD 49.9) from transplant to last contact. In the nested case–control study, median time from transplant to reference date (diagnosis or similar date for control subjects) was 63.8 months for control subjects (SD 38.1) and 64.7 months for cases (SD 38.3). Median follow-up time for the prospective cohort was 15.5 months (SD 6.4) from transplant to last contact.

What has been measured?

Questionnaires

The retrospective and prospective cohort members received annual 4-page follow-up questionnaires during the study (April 2008–March 2012). The initial questionnaire asked about any full body skin examinations by a dermatologist, skin conditions and skin biopsies as well as information on graft status, skin type and demographics. Annual short questionnaires repeated these questions and added additional questions on UV exposure, medication history and other health conditions (Table 3).

A more detailed, in-person interview was given to all participants in the nested case–control study and was also used as the first follow-up questionnaire (at the 1-year post-transplant visit) in the prospective cohort. The longer questionnaire focused on residence history; history of UV exposure; skin type; use of sunscreen and tanning devices; general medication history, including transplant medications; non-steroidal anti-inflammatory use and use of steroids; family history of cancer; comorbidities including any personal history of cancer, history of diabetes, time on dialysis, indication for transplant, sexual history, active and passive smoking history, reproductive history, body size, race and grandparents' countries of origin.

Laboratory assays

Our molecular biology laboratory developed type-specific antibody and DNA genotyping assays for genus beta HPV types. The beta HPV serological assays developed to the L1 proteins of the various beta HPV types allow us to examine risk of SCSC associated with specific beta HPV types in the entire cohort. All OTR have a blood sample stored at the time of transplant, and we retrieved serum from study participants who consented. Those participating in the nested case–control study had a second blood sample drawn (serum, plasma, buffy coat) at the time of the in-person interview. We also are able to examine whether antibodies to several of the human polyomaviruses (PyV, e.g. Merkel cell PyV, KIPyV, JCPyV, BKV, WUPyV, HPyV6, HPyV7) are associated with SCSC.[16]

In the nested case–control study, we plan to examine beta HPV genotypes in eyebrow hairs collected at the time of the in-person interview, as hair follicles are potentially a reservoir for genus beta HPV,[17] and the forehead is a sun exposed area where SCSC commonly occurs. We also plan to assay HPV genotypes in stored SCSC tumour tissue that we have retrieved for cases ($n = 125/172$) and compare those with beta HPV types found in eyebrow hairs.

As a measure of immune suppression, we collected whole blood for the ImmuKnow assay (Cylex), which

Table 3 SCOT study cohort profile

Study timing (n enrolled)	Biomarkers, samples	Inclusion criteria/data measurements
Retrospective cohort		Kidney and heart recipients ($n = 2004$), transplanted 1995–2010
Letter of approach (2008–11) ($n = 2004$)	None	First mailed questionnaire: • Skin conditions, dermatologist visits, biopsy since transplant • Organ status, skin type, race, smoking
First follow-up—12 months later ($n = 1708$)	Stored pre-transplant serum samples (1995–2010)	Second questionnaire mailed 12 months after initial contact • Update of initial questionnaire • Current medications, organ status and dialysis Release for access to stored pre-transplant serum
Second follow-up—12 months thereafter ($n = 1407$)	None	Third questionnaire mailed 12 months after second contact • Update of prior questionnaires • Tanning lamp exposure, NSAID use, cancer history Medical records release
Nested case–control study		Nested within cohort (172 SCSC cases and 337 control subjects)
Interview after pathology report confirmation of SCSC or selection as matched control (2008–11)($n = 172$ cases, 337 control subjects)	• Stored pre-transplant serum (1995–2010) • Peripheral blood drawn: serum, WBCs, plasma • Eyebrow hairs • Tumour tissue • Light meter	Cases with histologically confirmed incident SCSC; control subjects matched on potential confounders Detailed in-person interview • Sun exposure history, medications, health history • Blood and eyebrow hair samples collected • Tumour tissue release and collection for SCSC cases • Sun reflectance on exposed and unexposed skin Medical records release Release for access to stored pre-transplant serum
Annual follow-up (under retrospective cohort)	None	Mailed questionnaires • Update of prior questionnaire • Self-reported current medications • Questions on tanning, NSAID use, cancer history
Prospective cohort		Organ transplant waiting listed 2009–11 ($n = 328$)
First study visit before transplant (2008–11)($n = 328$)	• Peripheral blood drawn pre-transplant: serum, WBCs, plasma, whole blood • Eyebrow hairs	Short in-person interview (4-page) • Sun exposure history, medication history, health history • Blood and hair samples collected by interviewer Medical records release Whole blood collected in heparin tube for immune assay

(continued)

Table 3 Continued

Study timing (*n* enrolled)	Biomarkers, samples	Inclusion criteria/data measurements
Second study visit, 12 months post-transplant($n=135$)	• Peripheral blood drawn: serum, WBCs, plasma, whole blood • Eyebrow hairs • Light meter	Detailed in-person interview • Sun exposure history, medications, health history • Blood and eyebrow hair samples collected • Tumour tissue release and collection for SCSC cases • Sun reflectance on exposed and unexposed skin Whole blood collected in heparin tube for immune assay
Second follow-up at 24 months post-transplant($n=71$)	• Peripheral blood drawn pre-transplant: serum, WBCs, plasma, whole blood • Eyebrow hairs	In-person short interview (4-page) and sample collection • Update of prior questionnaires • Pap testing history, current immunosuppressive and steroid use, medication use for skin conditions Whole blood collected in heparin tube for immune assay

is a global immune function test that measures lymphocyte stimulation after incubation with a mitogen (PHA) by assessing generation of ATP. These assays are run using samples collected from the prospective cohort participants at the pre-transplant study visit and at 1- and 2-year post-transplant study visit.

Light meter

We use a CR-400 Konica Minolta light meter to assess sun reflectance on the back of the hand and on the less sun-exposed ventral forearm for all patients in the nested case–control and longitudinal studies to characterize skin colour, including indices of erythema and melanin content of the skin through light reflectance. The light meter will also provide an objective measure of skin colour changes over the time course of the prospective cohort.

What has it found? Key findings and publications

Results from the nested case–control study are summarized in Table 4. Men were more predominant in the case group (76.7%) than the cohort overall (59.1%), though control subjects were matched to cases on sex, making the groups comparable. The groups were also very similar with respect to time since transplant. Using conditional logistic regression analysis, we found that measures of sensitivity to UV light resulted in excess risk of SCSC with blue (but not green) eye colour, light hair, sunburn (including history of blistering burns) and resistance to tanning were significantly related to SCSC.

In the retrospective cohort, only 54% of patients reported having had a full-body examination by a dermatologist, despite recommendations by most transplant physicians that OTR have yearly dermatological screenings. The proportion of OTR with SCSC who reported screening was higher (87%) than that in the cohort overall, as was the proportion of matched control subjects who reported dermatological screening (62%). In the nested case–control study, high rates of insurance coverage were reported, as expected, for >90% of participants. Nearly all participants reported that their insurance plan did cover dermatology services (98.2%).

What are the main strengths and weaknesses?

A major strength of the SCOT study is that blood specimens were available from the immediate pre-transplant period for all participants in the study. This will allow us to evaluate associations between pre-diagnostic serum markers of viral infection and subsequent risk of SCSC in the nested case–control study. In the prospective study, which

Table 4 Characteristics associated with the risk of SCSC in the SCOT nested case–control study

Characteristics	Control subjects ($n = 337$) n (%)	Cases ($n = 172$) n (%)	OR[a] (95% CI)
Sex			
Male	257 (76.3)	132 (76.7)	
Female	80 (23.7)	40 (23.3)	
Time from transplant to reference (years)			
0 to <2	44 (13.1)	22 (12.8)	
2 to <5	136 (40.4)	69 (40.1)	
5 to <10	125 (37.1)	63 (36.6)	
10+	32 (9.5)	18 (10.5)	
Eye colour			
Brown	105 (31.2)	31 (18.0)	Ref
Hazel	54 (16.0)	30 (17.4)	1.8 (0.9–3.3)
Green	46 (13.6)	15 (8.7)	1.2 (0.6–2.5)
Blue	132 (39.2)	96 (55.8)	2.6 (1.5–4.3)
Hair colour			
Brown or black	287 (85.2)	126 (73.3)	Ref
Blonde or red	50 (14.8)	46 (26.7)	2.3 (1.4–3.8)
Reaction to initial sun in summer (burning)			
None	92 (27.3)	26 (15.1)	Ref
Mild	172 (51.0)	89 (51.7)	1.8 (1.1–3.1)
Burn then tan	59 (17.5)	45 (26.2)	3.1 (1.6–5.9)
Burn with blistering	14 (4.2)	12 (7.0)	3.9 (1.5–10.1)
Repeated sun exposure (tanning)			
Very tanned	112 (33.2)	29 (16.9)	Ref
Moderately tanned	139 (41.2)	80 (46.5)	2.2 (1.3–3.7)
Mildly tanned	68 (20.2)	49 (28.5)	2.8 (1.6–5.0)
Burned only	18 (5.3)	14 (8.1)	3.0 (1.2–7.4)
No. blistering sunburns			
None	93 (40.3)	48 (36.4)	Ref
1–2	98 (42.4)	43 (32.6)	0.8 (0.4–1.4)
3+	40 (17.3)	41 (31.1)	2.4 (1.2–4.8)
Used a tanning lamp/sun lamp			
Never	268 (79.5)	133 (77.3)	Ref
Ever	69 (20.5)	39 (22.7)	1.2 (0.7–1.9)

[a]Odds ratios and confidence intervals generated using conditional logistic regression accounting for matched case–control pairs and adjusted for linear age at reference to account for possible residual confounding by grouped age-matching. Matching factors for the case–control study: time since transplant, age at transplant, year of transplant, organ transplanted, hospital, donor type, sex and race.

collected blood longitudinally at three time points, we will explore the changes in serological response to HPV (and HPV genotype from eyebrow hairs), in relation to level of immune suppression as measured. These stored samples may also be useful for future testing.

In the nested case–control study, we collected additional sera at the time of the in-person interview and will be able to assess the impact of changes in beta HPV serology between the pre-transplant and interview blood draws. Furthermore, the case–control study has been matched carefully on a number of variables such as age at transplant, time since transplant and year of transplant, to limit confounding by these factors. We have also obtained medical records releases from study participants, which will allow us to explore ancillary hypotheses.

A limitation of the study is that the nested case–control study has retrospective ascertainment (for the transplant years 1995–2008); thus, although blood samples were drawn pre-transplant and at the time of the interview, we will not have blood samples collected during the post-transplant period before SCSC treatment. This may influence measurement of the HPV markers, as treatment could affect the levels of circulating antibody.

Other measures such as sun exposure history and immune suppression medication, may be differential for cases compared with control subjects owing to potential risk of SCSC. Fortunately, the blood draw for all pre-transplant will be available to examine risk of primary SCSC associated with pre-diagnostic serum markers.

The SCOT study appears to be representative of the renal and cardiac transplant recipients in the US Northwest, and may therefore be generalizable to other OTR populations in the USA. We were able to ascertain the number of transplant surgeries conducted in our catchment area using publicly available data from the US OPTN (http://optn.transplant.hrsa.gov/). Indeed, a motivation for this study is that, as there is an increasing epidemic of SCSC in the general population of the USA,[18] this study may be important to understanding mechanisms of SCSC development that extend beyond this high risk and most adversely affected population.

Can I get hold of the data? Where can I find out more?

We welcome development of new collaborations to address additional compelling hypotheses in the SCOT study cohort, dependent on ethics board (institutional review board) approval. We request a short research proposal that should include information on the hypothesis, timeline, methods and budget. Approval of the proposal depends on the topic and quality of the proposal. We hope to collaborate with other researchers with similar data to expand our ability to address key scientific questions. One area of particular interest to us, genetic variation in key pathways that may affect development of SCSC, would benefit greatly from multicentre efforts to increase sample size. For more information, please contact us through the study website: http://www.fhcrc.org/science/phs/cerc/The_SCOT_Study.html, or contact the SCOT study principal investigator, Dr Margaret Madeleine, at 1-206-667-4630 or scot@fhcrc.org.

Funding

This work was supported by the National Cancer Institute at the National Institutes of Health [grant number P01 CA042792]. The funding mechanism is a Program Project grant (P01 CA042792, Denise Galloway, PI), with projects including an epidemiological study of skin cancer after organ transplant (Margaret Madeleine, PI) as well as projects focused on the immunogenetics of HPV-related cancers (Stephen Schwartz, PI), and the molecular mechanisms of genus beta HPV E6 and E7 proteins (Denise Galloway, PI).

Conflicts of interest: None declared.

KEY MESSAGES

- The proportion of solid organ transplants in the Seattle area with SCSC was 4.5% among kidney transplants and 8.5% among heart transplants at 5 years and 7.8 and 15.5% at 10 years, respectively.
- The incidence of SCSC among transplant recipients in this cohort is lower than prior reports and may reflect changes in the medications used to supress graft rejection.
- Only 54% of transplant recipients in this cohort (545/2004) reported seeing a dermatologist, despite advice to do so.

Acknowledgements

We would like to acknowledge our appreciation of the transplant recipients who contributed generously of their time to this study, our colleagues at the transplant hospital, and the study coordinators Joia Hicks and Nancy Blythe. This study was part of an interdisciplinary collaboration to examine the role of HPV in cancer aetiology.

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] Penn I. The problem of cancer in organ transplant recipients: an overview. *Transplant Sci* 1994;**4:**23–32.

[3] Euvrard 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.

[4] Jensen P, Hansen S, Moller B *et al*. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* 1999;**40:**177–86.
[5] Carroll RP, Segundo DS, Hollowood K *et al*. Immune phenotype predicts risk for posttransplantation squamous cell carcinoma. *J Am Soc Nephrol* 2010;**21:**713–22.
[6] Thomas VD, Aasi SZ, Wilson LD, Leffell DJ. Cancer of the skin. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds). *Cancer: Principles and Practice of Oncology*. 8th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2008, pp. 1863–87.
[7] Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. *J Am Acad Dermatol* 1999;**40:**27–34.
[8] Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol* 2002;**47:**1–17.
[9] Smith KJ, Hamza S, Skelton H. Histologic features in primary cutaneous squamous cell carcinomas in immunocompromised patients focusing on organ transplant patients. *Dermatol Surg* 2004;**30:**634–41.
[10] Brewer JD, Colegio OR, Phillips PK *et al*. Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol* 2009;**145:**1391–96.
[11] Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol* 2002;**47:**1–17.
[12] Orth G, Favre M, Breitburd F. Epidermodysplasia verruciformis: a model for the role of papillomaviruses in human cancer. In: Essex M, Todaro G, zur Hausen H (eds). *Viruses in Naturally Occurring Cancer*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1980, pp. 259–82.
[13] Jackson S, Harwood C, Thomas M, Banks L, Storey A. Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. *Genes Dev* 2000;**14:**3065–73.
[14] Underbrink MP, Howie HL, Bedard KM, Koop JI, Galloway DA. E6 proteins from multiple human betapapillomavirus types degrade Bak and protect keratinocytes from apoptosis after UVB irradiation. *J Virol* 2008;**82:**10408–17.
[15] Howie HL, Koop JI, Weese J *et al*. Beta-HPV 5 and 8 E6 promote p300 degradation by blocking AKT/p300 association. *PLoS Pathog* 2011;**7:**e1002211.
[16] Paulson KG, Carter JJ, Johnson LG *et al*. Antibodies to merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients. *Cancer Res* 2010;**70:**8388–97.
[17] Boxman IL, Berkhout RJ, Mulder LH *et al*. Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers. *J Invest Dermatol* 1997;**108:**712–15.
[18] Rogers HW, Weinstock MA, Harris AR *et al*. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol* 2010;**146:**283–87.