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SPECIAL SECTION PAPER

Cancer incidence and risk factors after solid organ transplantation

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Iatrogenic immunosuppression is a unique setting for investigating immune-related mechanisms of carcinogenesis. Solid organ transplant recipients have a 3-fold excess risk of cancer relative to the age- and sex-matched general population. Population-based studies utilizing cancer registry records indicate that a wide range of cancers, mostly those with a viral etiology, occur at excess rates. To date, cancer risk has predominantly been examined in adult kidney transplant recipients in Western countries. It is yet to be established whether a similar incidence profile exists in the long-term for other solid organ, pediatric and non-Western transplant recipients. The cancer incidence profile before and after kidney transplantation strongly suggests a relatively minor contribution by both preexisting cancer risk factors and the conditions underlying end-stage kidney disease, and points to a causal role for immunosuppression. Within-cohort risk factor analyses have largely been performed on cohorts with voluntary cancer notification, and very few have incorporated biomarkers of the level of immunosuppression, the current receipt of immunosuppressive agents, or genetic risk factors. Because of their markedly high risk of certain cancers, findings from comprehensive studies in transplant recipients have the potential to raise new avenues for investigation into causal mechanisms and preventive measures against immune-related and infectious causes of cancer.
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A wide-ranging excess risk of cancer after solid organ transplantation has been increasingly recognized over recent decades as advances in medicine have extended the life of transplant recipients. Malignancy is now a leading cause of patient death with graft function,[1–3] an outcome that can predominantly be attributed to the iatrogenic immunosuppression required to avoid rejection of the transplanted organ. Solid organ transplantation provides a unique setting for the identification of cancers under immunological control, and for examination of the risk factors for their development. Knowledge of the range of increased cancers and the magnitude of the increased risks is important in developing appropriate prevention and early detection programs for patients undergoing long-term immunosuppression. In addition, comparison of cancer incidence and risk factors between populations with different forms of immune system impairment offers insight into carcinogenic mechanisms that has ramifications for cancer control not only in these populations but also in the general community.

This review focuses on the cancer incidence profile in solid organ transplant recipients, and the established and emerging risk factors for 5 cancers that occur at increased rates.

Cancer incidence after solid organ transplantation

Shortly after the widespread introduction of solid organ transplantation, it became apparent that immune suppression was associated with a strikingly increased risk of a few cancers, including nonmelanoma skin cancer (NMSC) and non-Hodgkin lymphoma (NHL).[4] Since that time, studies have been largely inconsistent with respect to the range of cancers for which risk is increased, though the majority of studies have been based on relatively small clinical cohorts or transplant registry cohorts without registry-based ascertainment of incident cancers. Findings from such studies are potentially biased because the transplant cohort was not population based and because the cancers were identified through clinical records, and not the same process as that employed for cancers in the reference population. In a truly unbiased study, all transplanted patients from a well-defined geographic region over a specified calendar period would be identified, cancers in the cohort and general population would be ascertained using identical methods and risk would be calculated relative to the cancer incidence in individuals of the same age and sex in that region over the same period of time. The advent of data linkage between population-based registers has not only allowed larger studies of transplant recipients with longer follow-up but has also enabled an unbiased means of cancer ascertainment with systematic coding of incident malignancies in both the cohort and general population.[5–15]

Which cancers are increased in incidence?

A meta-analysis of 5 population-based studies published before March 2007 demonstrated a 3-fold increased risk of cancer in solid organ transplant recipients compared with the general population matched for age, sex and calendar period.[16] A total of 31,977 transplant recipients, predominantly kidney, were included in the analysis, and the mean follow-up per recipient ranged from 6.8 to 8.5 years. Incidence was significantly increased for 23 of the 28 types of cancer examined, most of which have a known or suspected infectious cause (Fig. 1). Also increased in incidence were cancers with no known infectious cause to date, including colorectal, kidney, bladder and thyroid cancer, multiple myeloma, leukemia and melanoma. Twenty of these cancers were also increased in incidence in a meta-analysis of cancer registry-based studies of people immunosuppressed due to infection with human immunodeficiency virus (HIV; $n = 444{,}172$).[16] This shared cancer incidence profile suggests a broad role for the immune system in the prevention of cancer.

The established virus-related cancers that are increased in transplant recipients include Kaposi sarcoma (human herpes virus 8, HHV8), which occurs at a rate of several hundred times than seen in the general population, NHL and Hodgkin lymphoma (Epstein-Barr virus), liver cancer (hepatitis C and hepatitis B virus) and cancer of the cervix, vulva/vagina, penis, anus and oral cavity and pharynx (human papillomavirus, HPV; Fig. 1). The markedly increased risk of these cancers is believed to arise from impaired

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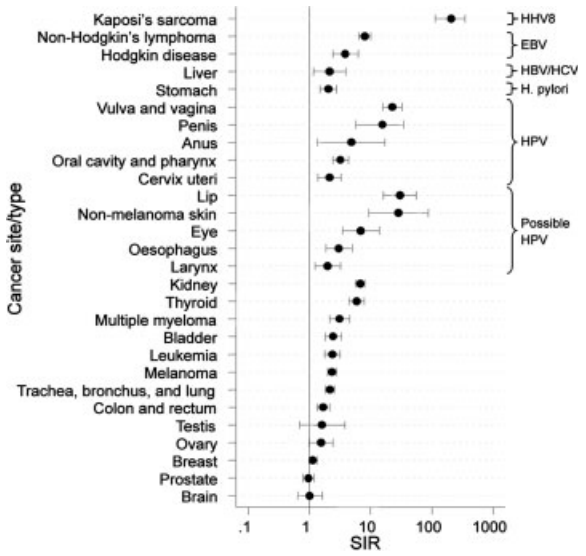

Figure 1 – Site-specific meta-SIRs for population-based studies of solid organ transplant recipients. [Modified from Lancet, 370, Grulich et al., 59–67. Copyright Elsevier (2007).[16]]

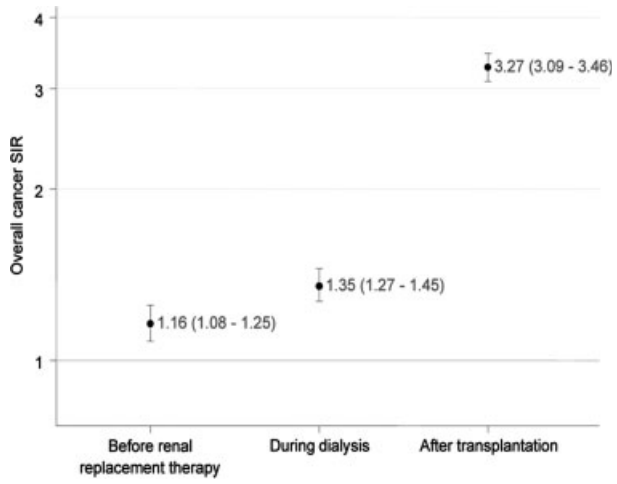

Figure 2 – Overall risk of cancer—Excluding nonmelanoma skin cancer, polymorphic post-transplant lymphoproliferative disorder and cancers known to cause end-stage renal disease (multiple myeloma and cancer of the kidney and urinary tract)—for an Australian population-based cohort of end-stage kidney disease patients by period of follow-up: prior to renal replacement therapy (dialysis or transplantation), during dialysis and after transplantation.

immune control of viral oncogenes, but the precise biological mechanisms of neoplastic progression are not yet understood. Given that some of these viruses are ubiquitous, the role of cofactors, including host, behavioral and transplantation-related factors, cannot be underestimated.

Which cancers are not increased in incidence?

Breast, prostate, ovarian, brain and testicular cancers were not increased in incidence in transplant recipients,[16] a finding that appears to refute the case for a viral cause for a large proportion of these cancers. However, there is some evidence that rates of screening for nonskin cancer in this population may be lower than that for the general population,[17] thereby decreasing the opportunity for the discovery of asymptomatic, screen-detected malignancies. In addition, prostate-specific antigen (PSA) testing in men with chronic renal dysfunction is unreliable, because of impaired clearance of the antigen,[18] but possibly also because of a direct effect of specific immunosuppressive agents.[19] As a result, PSA testing may be less likely to be utilized in kidney transplant recipients,[20] resulting in lower rates of screen-detected, asymptomatic prostate cancer. The interpretation of mammograms is also problematic because of the increased frequency of breast calcification associated with end-stage renal disease,[21] and higher rates of benign adenomas that may be associated with exposure to cyclosporine A.[22] Nevertheless, the fact that there was also no increase in incidence of breast, prostate and ovarian cancer in people with HIV/AIDS[16] provides some reassurance that rates of these cancers are truly not increased and that this finding is not an artifact of bias in ascertainment.

Cancer incidence before and after kidney transplantation

A recent population-based cohort study of Australian patients with end-stage kidney disease examined the cancer incidence profile in the 5-year period prior to kidney failure, during dialysis and after transplantation.[10] The standardized incidence ratio (SIR) for any cancer (excluding nonmelanoma skin cancer (NMSC), polymorphic post-transplant lymphoproliferative disorder (PTLD), and cancers known to cause end-stage kidney disease) increased significantly across these 3 periods, from 1.16 (95% CI 1.08–1.25), to 1.35 (95% CI 1.27–1.45), and 3.27 (95% CI 3.09–3.46), respectively (Fig. 2).

The widespread excess risk of cancer after transplantation compared with the preceding periods seen in this study strongly implicates immunosuppression; it is unlikely to be driven by factors related to end-stage kidney disease or dialysis, nor to a greater prevalence of preexisting cancer risk factors in this population compared with the general population. However, there are sites for which the increased cancer risk may relate to factors that are unique to patients with end-stage kidney disease, rather than being related to immune suppression. This is particularly the case for multiple myeloma and cancer of the kidney, bladder and thyroid, as the incidence of these cancers is increased in patients with chronic end-stage kidney disease prior to kidney transplantation,[10] and rates of the latter 3 cancers are not increased in people with HIV-related immunosuppression.[16]

Other risk factors related to transplantation but not dialysis are antigenic stimulation from the graft, donor-derived transmission of cancer and the donor-derived transmission of oncogenic virus. The contribution of chronic antigenic stimulation by transplanted organs is uncertain. The risk of a donor having an undetected malignancy that is transmitted by organ transplantation to the recipient has been examined and found to be very low, between 0.012 and 0.025%[23] and 0.20%.[24] Donor Epstein-Barr virus has been detected in neoplastic-B-cells of recipient origin, and while the mechanism by which this occurs is not known, it has been assumed to be the transmission of cell-free virus.[25] However, there is emerging evidence that HHV-8-infected hematopoietic cells in some post-transplant Kaposi sarcomas are of donor origin,[26,27] but these findings have yet to be confirmed in large-scale studies.

Kidney transplantation also provides a unique setting that examines cancer incidence after the withdrawal or reduction of immunosuppression upon graft failure and the reinstitution of dialysis. A recent analysis, in the same cohort of Australian kidney transplant recipients, has shown that lip cancer risk after transplantation is strongly related to the current receipt of immunosuppression.[28] The SIR for lip cancer during all periods of dialysis subsequent to transplant failure (SIR 2.16, 95% CI 0.05–12.05) was significantly lower than during periods of transplant function (SIR 52.26, 95% CI 45.27–60.02, $p = 0.001$), and was comparable with that observed during the period of dialysis prior to transplantation (SIR 3.44, 95% CI 2.23–5.08, $p = 0.649$). The complete and rapid reversal of risk upon graft failure strongly suggests a causal role for immunosuppression. It is also consistent with the regression of

some of the other immune-related tumors upon cessation of immunosuppression including NMSC, Kaposi sarcoma and polymorphic PTLD.[29,30]

Studies based on long-term follow-up indicate that cancer risk remains substantially elevated up to 10 years after kidney transplantation.[10,11] However, the precise pattern over time is somewhat uncertain, with one cancer registry-based study reporting a significant increase in risk with increasing number of years post-transplantation,[10] and another indicating a reduction in risk over time.[11] Moreover, incidence trends over time differ by cancer type and are therefore more informative with respect to etiology when they are restricted to individual cancers. In addition, risk for kidney transplant recipients should be censored at graft failure and the withdrawal or reduction of immunosuppression. Compared with the general population, the risk of NMSC in an Irish cohort of kidney transplant recipients was increased at all periods post-transplant, markedly so after the second year and with a late peak, around 8 years post-transplantation.[9] Most studies of the pattern of NHL risk over time since transplantation have demonstrated an early peak and a decline thereafter.[11,13,14,31,32] However, data from the Collaborative Transplant Study indicate that incidence 10 years after transplantation remains substantially elevated.[32]

Pediatric organ transplant recipients

The bulk of cancer registry-based incidence data come from adult transplant recipients. Site-specific cancer SIRs have not been separately reported for pediatric patients, other than for NHL. The risk of NHL after liver transplantation is strikingly higher in children compared with adults; SIR 123 (95% CI 3.12–686) for recipients aged less than 17 years, 55.7 (95% CI 6.74–201) for ages 17–39 years and 9.42 (95% CI 3.06–22.0) for ages 40+ years.[13] This same study reported an SIR for all cancers combined of 18.1 (95% CI 2.19–65.5) for children, 5.77 (95% CI 1.87–13.5) for adults 17–39 years and 2.27 (95% CI 1.55–3.20) for those aged 40+ years.

Clinic-based studies of pediatric organ transplant recipients have also reported a significant excess risk of cancer, and a consistent excess risk of PTLD, particularly EBV-positive B-cell NHL.[33,34] In contrast to the profile of incident cancers observed in nontransplanted children[35] where leukemia, central nervous system tumors and lymphomas predominate, malignancies with a viral etiology may also prevail in pediatric transplant recipients. For instance, incident cancers in pediatric patients reported to the Israel Penn International Transplant Tumor Registry included, in order of decreasing frequency, NHL, NMSC, Kaposi sarcoma, soft tissue sarcoma, and anogenital, thyroid, urinary, and liver cancer, leukemia, melanoma and brain cancer.[36]

Non-kidney organ transplant recipients

Ninety seven percent of transplant recipients in the meta-analysis of registry-based studies received a kidney graft.[16] Since that time, an additional 3 studies have been reported, bringing the total to 4 population-based registry-based studies of all-cancer incidence in non-kidney transplant recipients.[8,12–14] The largest (n = 2,034) of these, conducted in Canadian liver transplant recipients, reported an increased risk of NHL and colorectal cancer.[14] An increased risk of NHL and NMSC was observed in a study of Finnish liver (n = 540) transplant recipients,[13] while an increased risk of lymphoma/leukemia, head and neck cancer (predominantly lip cancer) and lung cancer was reported in Australian cardiothoracic transplant recipients (n = 907).[12] Adami *et al*.[8] also reported site-specific SIRs in their study of liver (n = 394), heart (n = 236), lung (n = 117), pancreas (n = 26) and multiple organ (n = 154) recipients in Sweden; excess risk was observed for NHL, NMSC and stomach cancer for all non-kidney recipients combined. The apparently reduced range of cancers occurring at statistically significant excess risk compared with kidney transplant recipients is noteworthy, but may simply be related to the smaller cohort sizes and shorter follow-up times for the non-kidney studies (Table I).

Findings from studies without registry-based cancer ascertainment include an inconsistent excess risk of colon cancer, oropharyngeal and liver and lung cancer after liver transplantation.[37–43] In one investigation, rates of oropharyngeal, genitourinary and pulmonary cancer were significantly increased in alcoholic, but not in nonalcoholic, liver transplant recipients,[41] a finding repeated for oropharyngeal and laryngeal cancers in another single-centre study.[43] An increased risk of colon cancer after liver transplantation has also been attributed to a higher than background rate of ulcerative colitis in association with primary sclerosing cholangitis, an indication for liver transplantation.[38,39] A similar situation exists for cirrhosis secondary to chronic hepatitis C virus (HCV) infection and liver cancer risk in liver transplant recipients. A very large study based on the United States Scientific Registry of Transplant Recipients (SRTR) found an increased risk of liver cancer for liver transplant recipients (SIR 3.4, 95% CI 2.4–4.6) but not for non-liver transplant recipients (SIR 0.8, 95% CI 0.5–1.0).[42] The pattern of cancer incidence after non-kidney transplantation is contentious, but the varying indications for transplantation offer great potential for systematically examining the risk determinants. Indeed, the SRTR study identified hepatitis B surface antigen, HCV antibody and diabetes mellitus as independently associated with risk of liver cancer in non-liver transplant recipients, and age at transplantation, male sex, HCV antibody and diabetes mellitus as risk factors for liver cancer in liver transplant recipients.[42]

There is some evidence that the risk of other cancers may also vary by the type of organ transplanted. For instance, the age-adjusted incidence of NMSC is 3 times higher in heart transplant recipients than kidney transplant recipients,[44] and large differences have been noted for NHL. In an analysis of physician-notified cancers in organ recipients in the Collaborative Transplant Study, the risk of NHL during the first year post-transplantation was strikingly higher in combined heart-lung and lung recipients compared with recipients of other organs.[45] At 5-years post-transplant, the differences remained, with the highest risk for heart-lung transplant recipients (relative risk (RR) 239.5; relative to the expected incidence in the nontransplanted population), then lung (RR 58.6), pancreas (RR 34.9), liver (RR 29.9), heart (RR 27.6) and cadaver kidney (RR 12.6). Within age strata, the differences remained, with the relative risk consistently highest for heart, then liver and kidney transplant recipients. A greater risk of NHL for non-kidney compared with kidney transplant recipients is supported by cancer registry based-data (Table I), but stratification by age and period of follow-up is required for unconfounded estimates of risk relative to the general population.

Variation in cancer risk between recipients of different organs is thought to arise from differences in the intensity of immunosuppression; compared with kidney recipients, heart recipients are more likely to receive anti-lymphocyte antibody induction and a higher dose of immunosuppression.[31,45] It also reflects, but is not fully explained by, the larger proportion of pediatric recipients of heart and liver transplants,[31,45] and future comparisons should adjust for recipient age, duration of follow-up and other confounders. Interestingly, cases of NHL in lung/heart-lung and heart transplant recipients reported in the Collaborative Transplant Study were preferentially localized in the lung, those of liver recipients were in the liver, but the kidney was not the predominant location for recipients of kidney transplantations. It has been hypothesized that this pattern may correlate with the amount of lymphoid tissue in the transplanted organ.[46]

Non-Caucasian organ transplant recipients

Almost all cancer registry based-data on transplant recipients comes from Western countries with predominantly Caucasian populations, specifically Australia, Canada, Sweden, Finland, Denmark and Ireland. A recent cancer registry-based study of 283 kidney transplant recipients from a centre in southern Taiwan reported an overall cancer SIR of 4.6 (95% CI 2.8–6.5), and a significant excess risk of cancer of the renal tract, bladder, liver

TABLE I – RISK OF NON-HODGKIN LYMPHOMA IN CANCER REGISTRY-BASED STUDIES OF SOLID ORGAN TRANSPLANT RECIPIENTS, BY ORGAN SITE

Transplanted organ(s)	Country	Number of recipients	Proportion pediatric	Mean follow-up (yrs)	SIR for non-Hodgkin lymphoma (95% CI)
Kidney	Denmark[5]	1,821	n/a	7.9	Men 6.35 (2.32–13.82); Women 3.87 (0.43–13.96)
	Sweden[8]	5,004	n/a	3.7	3.8 (2.5–5.6)
	Finland[6]	2,890	4.3% <16 years of age	7.2	4.75 (2.17–9.01)
	Australia[10]	10,180	4.4% <20 years of age	8.5	9.86 (8.37–11.54)
	Canada[11]	11,155	8.8% <20 years of age	7.4	8.8 (7.4–10.5)
Liver	Finland[13]	540	14% <17 years of age	6.0	13.9 (6.01–27.4)
	Canada[14]	2,034	12.8% <10 years of age	4.5	20.8 (14.9–28.3)
Heart/heart-lung	Australia[12]	905	n/a	5.3	26.2 (n/a)
Liver/heart/lung/pancreas	Sweden[8]	931	n/a	3.7	37.3 (22.1–59.1)

n/a, not available.

and skin over a mean follow-up of 6.6 years.[47] Data from clinic-based studies of organ transplant recipients in Asian and middle-Eastern countries have not supported a broad-ranging excess of cancer,[48–50] but interpretation is again hindered by small cohort sizes, short follow-up time and an absence of data on cancer incidence relative to the general population. Should a different cancer incidence profile exist for non-Caucasian populations, it may indicate genetic variation in response to infection in the long-term immune suppressed, or it may reflect variation in the population prevalence of infection with oncogenic viruses and the background cancer incidence rates.

There is some noncancer registry-based evidence that the cancer risk profile does vary for Caucasian and non-Caucasian transplant recipients. Consistent with risk in the general population, there were no cases of NMSC in non-white kidney transplant recipients in South Africa over an average of 6.3 years.[51] In the same population, the frequency of Kaposi sarcoma was 7-fold higher in non-white compared with white kidney transplant recipients,[52] corresponding to the 7-fold difference in infection by human herpesvirus type 8 (HHV-8) in these sub-populations.[53] Data from the United States Organ Procurement and Tissue Network also support an association between HHV-8 infection and post-transplantation Kaposi sarcoma, with a significantly higher incidence in non-US citizens compared with US citizens, in particular, those from the Middle East.[54]

Risk factors for cancer after solid organ transplantation

The following summarizes the current state of knowledge on the key risk factors for 5 cancers that occur at excess rates after solid organ transplantation. Most data are derived from hospital-based cohorts, without registry-based cancer ascertainment and comprises classical epidemiological and hitherto limited biomolecular measures. The potential for a direct contribution by immunosuppressive agents to cancer risk, independent of their effect on immunosuppression *per se,* is a controversial issue. Several agents have been implicated in experimental data, but these findings have not been widely confirmed in epidemiological studies. However, few clinical trials have been sufficiently powered to examine malignancy as an outcome, and other epidemiological studies have utilized poor measures of exposure. For instance, most large-scale analyses are based on agents received at the time of transplantation or shortly afterward, not accounting for the common practice of switching between agents,[55] and are thereby open to exposure misclassification. Interpretation is further complicated by the fact that the actual level of immunosuppression can vary between patients on the same drug regimen[56]; as yet there are no population-based analyses of risk in association with biomarkers for the extent of immunosuppression.

Nonmelanoma skin cancer

NMSC is the most common malignancy in adult Caucasian solid organ transplant recipients. As for immune competent individuals, prior exposure to solar ultraviolet radiation (UVR) is a principal risk factor, with squamous cell carcinomas (SCCs) most likely to occur at sun exposed body sites and in recipients with a history of high sun exposure.[57–59] Related host factors include greater age at transplantation and male sex, fair phenotype[60] and certain genetic polymorphisms, several of which are believed to be related to skin type.[61] In one comprehensive investigation, the strongest independent risk factor for post-transplantation NMSC was pretransplantation NMSC.[59]

Transplantation-related risk factors include both the intensity and the duration of immunosuppressive treatment. In a retrospective cohort study, the use of 3 compared with 2 immunosuppressive agents increased the incidence of NMSC from 29 to 48 cases per 1,000 person years and decreased the time to NMSC development.[62] A randomized clinical trial of normal-dose compared with low-dose cyclosporine in kidney transplant recipients over a mean of 6.5 years showed a significantly reduced incidence of NMSC, their precursor lesions and warts in the low-dose group.[63] In addition, a lower average CD4 T-cell count was associated with increased risk of NMSC in one prospective study.[64] Although an association with various measures of the intensity of immunosuppression has not been a consistent finding, there is universal agreement that the incidence of NMSC increases with increasing time after transplantation.[9,56,59,65]

Independent of their immunosuppressive effects, there is laboratory evidence that azathioprine and cyclosporine have direct biological effects capable of enhancing UVR-related carcinogenesis. Azathioprine sensitizes DNA to ultraviolet A radiation,[66] reducing the minimal erythema dose in skin cells of treated patients,[67,68] while cyclosporine inhibits DNA repair and apoptosis in ultraviolet B radiation-exposed human keratinocytes.[69,70] However, exposure to either of these agents has not been consistently associated with an increased risk of NMSC.

Infection by cutaneous human papillomavirus (HPV) subtypes, specifically of the epidermodysplasia verruciformis (EV) or beta genus (HPV5,8), has been associated with SCC development in the immunocompetent,[71] probably in association with exposure to solar UVR.[72] Transplant recipients have a greater prevalence of beta HPV infection in SCC than nontransplant recipients,[73] particularly multiple beta HPV types,[74] in addition to a greater prevalence of cutaneous warts and a copredilection of warts and SCC for sun-exposed body sites.[57,60,75] Thus, the etiology of NMSC in transplant recipients is multifactorial and includes solar UVR, genetic predisposition, immunosuppressive factors and possibly HPV infection.

Lip cancer

The risk of lip cancer after solid organ transplantation is 30 times that of the general population (Fig. 1).[16] Despite this markedly high risk, examination of the risk determinants in this population is limited to a single cohort study. A cancer registry-based study ascertained 203 cases of squamous cell carcinoma of the lip in an Australian cohort of 8,162 kidney transplant recipients.[28] On account of the strong association with currency of immunosuppression previously noted in this article, the risk factor analyses

were restricted to the period of first transplant function. During first transplant function, cancer of the lower lip ($n = 180$) was independently associated with increasing year of age (IRR 1.03, 95% CI 1.02–1.05), greater time since transplantation ($p < 0.001$), smoking (IRR 2.13, 95% CI 1.12–4.07) and current use of azathioprine (IRR 2.67, 95% CI 1.39–5.15) or cyclosporine (IRR 1.63, 95% CI 1.00–2.65). Risk of lip cancer was not increased in those exposed to lymphocyte depleting antibody. Female sex (IRR 0.29, 95% CI 0.18–0.46) and non-Australian/New Zealand country of birth ($p = 0.006$), surrogate indices of reduced exposure to solar UVR, were significantly protective. An association with UV exposure was also implicated by the predilection for the lower lip, the part of the lip which receives the greatest dose of solar UV radiation.

A history of smoking and exposure to solar ultraviolet radiation appear to increase lip cancer risk in both the immunocompetent and the iatrogenically immunosuppressed. In the immunosuppressed, lip cancer risk also appears to be positively associated with the currency, duration and the type of immunosuppression. As predicted for NMSC, in addition to their immunosuppressive effects, azathioprine and cyclosporine may exert direct carcinogenic effects that impact lip cancer development. Such a relationship is supported by the ~10-fold higher risk of both lip cancer and NMSC in transplant recipients compared with people with HIV infection.[16] Therefore, exposure to solar UVR, potentiated by the use of specific immunosuppressive agents, may be causally associated with lip cancer in this setting. The role of HPV infection is unclear, but it may interact with solar UVR to increase lip cancer risk, as proposed for NMSC in the immunocompetent.[72]

Post-transplant lymphoproliferative disorders

Increased risk for PTLD following organ transplantation is well documented. PTLD ranges from the often regressive hyperplasia, to polymorphic lesions, and the rarely regressive malignant monomorphic B and T-cell NHL and Hodgkin lymphoma.[76] It has been unequivocally established that EBV infection is causally associated with NHL in immunosuppressed individuals, with NHL arising as a result of reduced lymphocyte regulation, a lack of control of the oncogenic virus by EBV-specific CD8+ cytotoxic T-cells, and proliferation of EBV-infected B cells.[77] Indeed, the majority of PTLD lesions are EBV-positive, and PTLD risk is highest in those undergoing primary EBV infection, such as children.[78] Biomarkers related to the host immune response to EBV infection are emerging as potential risk factors, especially interleukin (IL)-6, which promotes the growth of EBV-transformed cells *in vitro*,[79] and dysregulated expression of genetic mutations which confer a proliferative B-cell growth advantage, the protooncogenes c-myc and B cell lymphoma (BCL)-6,[80] have been implicated. An increased risk in association with infection by hepatitis C virus has also been suggested by some but not all studies.[81] An etiological role for cytomegalovirus (CMV) infection is unlikely given the lack of association between PTLD risk and the receipt of CMV antiviral drugs in a large multicentre study.[82]

NHL has long been recognized as an immune-related neoplasm,[4] and examination of incidence patterns and risk factors across immune deficient populations strongly implicates the intensity of immunosuppression. In transplant recipients, an increased risk of PTLD is observed in association with receipt of potent T-cell depleting antibody[31,83,84] and by the regression of some lesions upon reduction of immunosuppression.[85] Risk of NHL was inversely correlated with CD4 T-cell count in a small prospective study of PTLD ($n = 10$),[86] consistent with similar data in people with HIV-related immunosuppression. Despite *in vitro* evidence that predicts a positive association with exposure to calcineurin inhibitors, risk factor analyses to date have been inconclusive.[45,87] In contrast, a reduced risk of PTLD in association with the use of antiproliferative agents, particularly mycophenolate, has been noted in some studies,[84,87] and may be supported by their inhibitory effects on B-cell proliferation.

NHL that lacks detectable EBV DNA occurs in 23–42% of cases[88,89] and also occurs to excess, particularly late after transplantation. It has been hypothesized that these lymphomas may be similar to those observed in the immunocompetent.[90–93] The etiology of these NHLs is unknown and impaired immune surveillance, chronic antigenic B cell stimulation from the graft or an uncommon infectious agent and chronically impaired immunoregulation have been advanced as causal explanations.[91–94] Gene expression studies that build on the preliminary comparisons of EBV-positive and EBV-negative PTLD, and B-cell NHL in the immunocompetent and HIV-immunosuppressed,[95] may prove enlightening.

Lung cancer

Risk of lung cancer in transplant recipients is moderately increased relative to the general population.[16] Although no risk factor analyses have been performed in renal transplant recipients, a novel study of single-lung versus bilateral-lung transplant recipients matched for underlying disease, smoking history and age identified a significant 5-fold increased risk of primary lung cancer for recipients of single-lungs.[96] In all single-lung recipients, the primary cancer arose in the native lung. This finding is consistent with the observation that HIV infection is associated with an increased risk of lung cancer, independent of smoking history.[97] The possibility of an infectious agent playing a role in some lung cancers is intriguing,[98] particularly in the setting of immunosuppression.

Cutaneous melanoma

Risk of cutaneous melanoma in solid organ transplant recipients is 2.3 times that of the general population (Fig. 1).[16] However, population-based studies have had limited capacity to examine risk factors because of the small numbers of incident cases, and the association with the duration, extent and type of immunosuppression is unknown. The largest ($n = 246$) noncancer registry-based analysis of kidney transplant recipients did not report or control for duration of immunosuppression, and was unable to examine the association with exposure to specific immunosuppressive agents.[99] In multivariate analysis, melanoma risk was significantly increased with increasing year of age at transplantation, and decreased in female recipients and Black recipients, implicating a role for past exposure to solar UVR, a risk factor in immunocompetent hosts.

Acquired melanocytic nevi, markers of a propensity for melanocytic proliferation, occur in excess in pediatric and adult transplant recipients,[100,101] and there is some histopathological evidence that melanomas in transplant recipients may preferentially evolve from precursor nevi.[102] Although excess melanocytic nevi have also been observed in people with HIV infection,[103] the increased risk of melanoma in the HIV population is much lower (meta-SIR 1.24),[16] raising the possibility of detection bias of asymptomatic melanomas in the transplanted population due to surveillance for NMSC. Nevertheless, the highly antigenic properties of melanomas[104] and the systemic immunosuppressive effects of solar UVR[105] support a role for immune function. The setting of iatrogenic immunosuppression offers a model in which to examine the complex interaction between environment and host immune function and genetic profile in the genesis of this neoplasm.

Conclusions

The risk of cancer is strikingly increased after solid organ transplantation. Cancer registry-based studies show that a large number of cancers, mostly those associated with oncogenic viruses, occur at increased rates relative to the general population. The complex suite of risk factors for malignancy in the setting of iatrogenic immunosuppression is currently incompletely understood. However, the weight of available evidence supports an etiological role for both the intensity and the duration of immunosuppression,

infection by viral agents, host genetic susceptibility and other factors such as age, and established carcinogenic exposures including sun exposure and tobacco smoking. There is also emerging evidence for a direct effect of immunosuppressive agents for certain cancers. Importantly, risk factors vary by cancer site, strongly arguing against analyses that assess risk for all cancers combined.

Transplant recipients offer an exceptional model for examining the risk factors for immune-related cancers. Prospective cohort studies with biospecimen collection will advance our understanding of the role of immune function in the carcinogenic process. Insight into the independent and related effects of long-term depressed immunosurveillance, infection by and reactivation of oncogenic viruses, antigenic stimulation, impaired immunoregulation, ageing, host genetic factors and the direct effects of immunosuppressive agents will inform preventative measures for this high-risk population and possibly the wider general population.

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