INVESTIGATIVE REPORT

No Association between Infections, HLA Type and Other Transplant-related Factors and Risk of Cutaneous Squamous Cell Carcinoma in Solid Organ Transplant Recipients

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Recipients of solid organ transplants are at a markedly increased risk of cutaneous squamous cell carcinoma (SCC). We investigated potential associations between post-transplant infections, HLA type, and other transplant-related factors and risk of SCC, taking immunosuppressive treatment into account. A population-based case-control study was conducted. All patients who developed SCC during follow-up (1970–1997) were eligible as cases (*n*=207). Controls (*n*=189) were individually matched to the cases on age and calendar period of transplantation. Detailed exposure information was collected through an extensive, blinded review of medical records. Odds ratios were computed with conditional logistic regression. There were no significant associations with any infectious agents, or with number and timing of infections, specific HLA-type, donor characteristics, or other transplant characteristics and risk of post-transplant SCC. These results suggest that risk of post-transplant SCC is neither closely related to specific post-transplant infectious disorders, nor to the infectious load or specific HLA types. *Key words: carcinoma, squamous cell; case-control study; HLA antigens; infection; organ transplantation.*

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Cutaneous squamous cell carcinoma (SCC) is the most common malignancy following solid organ transplantation, affecting 20% and 80% of recipients at 20 years after transplantation in Europe and Australia, respectively (1, 2). Although the increased risk of SCC post-transplantation has been attributed largely to the immunosuppressive treatment (3–5), the underlying mechanisms are unclear. Some authors have concluded, from studies of multidrug regimens, that risk of SCC is conferred primarily by a heavy total load of drug-induced immunosuppression, rather than by carcinogenic effects of specific drugs (5, 6). We have recently presented evidence that there are important differences in risk according to specific immunosuppressive drugs (7).

An established side-effect of the pharmacologically induced immunosuppressive state of transplant patients is the increased frequency of bacterial, viral and fungal infections. The occurrence and panorama of specific infections appear to be determined by the intensity and duration of the immunosuppressive treatment (8). Specific infectious agents may also have direct carcinogenic effects (9, 10). While a role for human papillomavirus (HPV) in SCC aetiology has been investigated repeatedly (9, 10), few studies have investigated the possible role of herpes group viruses (11–16), bacterial, or fungal infections.

Previous studies have found both protective and deleterious associations between different HLA types and risk of SCC in organ transplant recipients (17–21). Expression of HLA-A3, -A11, -B27, -DR1, and -DR7 has been suggested to increase risk of non-melanoma skin cancer (NMSC) in some studies (17, 19–21), whereas other studies have reported a reduced risk with HLA-A11, and HLA-DR4 (17, 18). Hence, results are contradictory and often hampered by small sample sizes (17, 19, 20). With regard to other transplant characteristics that may be of importance for immune function, old age and female sex of the donor have been associated with reduced graft survival but not with risk of NMSC (1, 6, 22–25). Diabetic nephropathy as the cause of kidney failure has been associated with a decreased risk of post-transplant SCC in some studies (25, 26) but not in others (1, 27).

In this case-control study, nested within the well-defined nationwide Swedish organ transplantation cohort, we investigated whether bacterial, fungal or herpes group virus infections are associated with risk of SCC, while taking immunosuppressive drug treatment into account. Furthermore, we aimed to clarify whether HLA types and other transplant-related characteristics affect the risk of SCC.

METHODS

Swedish organ transplantation cohort

The Swedish organ transplantation cohort has been described previously by Adami et al. 2003 (2). Briefly, the cohort consisted of all patients without a pre-transplant history of cancer who underwent solid organ transplantation in Sweden from 1970 to 1997 and were registered in the Swedish National Patient Register ($n = 5,931$) (28). In this register, up to eight discharge diagnoses and 10 surgical codes are recorded for each patient discharge, and the coverage gradually increased from 60% in 1969 to close to 100% from 1987 onwards (28). An evaluation of the validity of the register records showed that 98% of the records had correct surgical codes (29). In Sweden, organ transplantations are performed in only 4 public university hospitals; thus, the national registration of organ transplantations is population-based. However, since 2 of the hospitals did not report to the National Patient Register before 1972, while the other two reported from 1970, a few early organ transplantations (~50) were not included (30).

This study was approved by the Regional Ethics Review Board, Stockholm, Sweden (01-006).

Identification of SCC cases and controls

The identification of cases and controls has been described previously (7). The cohort of organ transplant patients was linked to the Swedish Cancer Register by employing the unique 10-digit national registration number assigned to all Swedish citizens. The seventh edition of International Classification of Diseases (ICD-7) code 191 was used for identifying incident cases with SCC. All patients who developed SCC ($n = 242$) as a first cancer diagnosis during follow-up through 31 December 1997 were selected as cases. Controls were randomly chosen from the cohort and individually matched to the cases (1:1) by age (± 5 years) and calendar period of transplantation (± 5 years). The controls were also required to be alive and free from cancer after an equal length of follow-up time as the time from first transplantation to SCC diagnosis for the corresponding case. Nineteen patients (3.9%) were excluded because they had an unregistered previous transplantation or because they died before the end of follow-up, and two patients (0.4%) developed a cancer that was not registered in the Swedish Cancer Register. From all living cases and controls ($n = 233$), we requested written, informed consent, which all but 14 patients (6%) provided. Of the 449 remaining patients, 53 (12% of which 53% were cases) were lost to follow-up since their medical records could not be located. After these exclusions, the study subjects comprised 207 cases (88% of eligible cases) and 189 controls (84% of eligible controls).

Data collection

A comprehensive protocol was designed to ensure standardized collection of information from the patient medical records. Data collection was carried out by trained personnel who were blinded to case/control status. Information, carefully recorded for all transplantations from the date of transplantation to end of follow-up, included basic characteristics (sex, age), HLA type (A, B, DR), infectious serologies of recipient and donor, vital status of donor, type of organ transplanted, cause of organ failure, post-transplant rejection episodes, immunosuppressive treatment, and infections. For post-transplant infections, we specifically recorded occurrence and date of infections with the herpes group viruses: herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV)), with hepatitis (A, B, C), and with fungi and bacteria. A bacterial infection was defined as either a positive culture (> 100,000 bacteria/ml for urinary tract infections) or antibiotic treatment of symptoms, and included both single and recurrent infections. A herpes group virus infection was based on a clinical diagnosis as noted in the medical records, with or without treatment or serological evidence of seroconversion or a significant increase in specific IgG antibodies. Hepatitis infection was determined by serological evidence. Fungal infections included infections with yeast (mainly *Candida albicans*), *Pneumocystis carinii*, and *Aspergillus* species. HLA typing methods differed between laboratories, time periods, and HLA loci, and included either serological typing or genomic typing. Information on typing method was not collected. All HLA antigen splits were standardized to their broad HLA antigen (17, 21). When only one antigen could be identified for a given locus, homozygosity was assumed (21).

Statistical analyses

A variable for the total number of infections was created by adding the numbers of herpes group virus infections, hepatitis, bacterial and fungal infections. Infections during the last 30 days prior to SCC diagnosis were censored in order to exclude infections occurring after the development of cancer. Also, we created a variable to describe occurrence of combinations of infections with bacteria, herpes group viruses, and fungi. The time from first transplantation to first infection with herpes group viruses, bacteria and fungi, respectively, was determined for all patients. Exposure variables were stratified according to the tertile distributions among controls with no infection as reference.

Correlations between variables were first tested using Spearman's correlation coefficient (r_s). Odds ratios were estimated using conditional logistic regression and served as measures of relative risk (RR). Exact logistic regression was used for exposure variables with low numbers of exposed. Associations were assessed in a univariate as well as in a multivariate conditional logistic regression model and tested for statistical significance with likelihood ratio tests. The multivariate model included adjustment for sex of the recipient and use of immunosuppressive drugs that were previously observed and reported to be associated with risk of SCC in this study, namely categories of total accumulated dose of azathioprine, cyclosporine, and corticosteroids, respectively (7). Thereafter, all exposure variables were added, one by one, to the multivariate model and tested with likelihood ratio tests for significance. Since there was no major difference between adjusted and crude results, only the adjusted results are presented. Trends in risk of SCC was tested when relevant by taking the median of the continuous exposure in each category of the categorized exposure variable, and then including the new "scored" variable in the model. Sensitivity analyses were performed for exposure variables when the proportion of missing information exceeded 15% (HLA-DR, age and sex of donor) by including all missing information in the extreme categories of each variable, one at a time, and re-analysing the data. Statistical analyses were carried out in Stata 9.0 (StataCorp., 2003, Stata Statistical Software: Release 9.0. College Station, TX, USA).

Some cases and controls ($n = 71$) had lost their matched partner in the dataset due to loss to follow-up or technical errors. These subjects were joined together into new matched pairs or entered into other matched pairs if they fulfilled the original matching criteria ($n = 18$) or slightly revised matching criteria (± 10 years for age and calendar time and < 60 days difference in follow-up time) ($n = 34$) (7). Analyses were performed both with and without the additional 52 subjects, and the results were essentially unchanged, hence they were included in the final analyses.

RESULTS

Characteristics of the matched study subjects are shown in Table I. The median age at first transplantation (51 years) and the median follow-up time (6.6 years) were similar among cases and controls. Sex distribution differed between cases and controls, and male organ transplant recipients comprised 73% of the cases and 63% of the controls. Use of immunosuppressive drugs has been described elsewhere (7). In short, all patients were treated with corticosteroids in combination with either azathioprine only (23% of cases and 21% of controls) or cyclosporine only (4% of cases and 15% of controls), or in a triple treatment combination where corticosteroids were administered together with both azathioprine and cyclosporine (72% of cases and 64% of controls).

Table II presents the adjusted RRs of SCC in relation to characteristics of the recipient and donor at the first transplantation. Eighty-four percent had a single transplantation and the majority (95%) received a kidney graft. Type of transplanted organ and cause of kidney failure did not affect the risk of SCC. Likewise, donor vital status and donor age had no impact on the risk of SCC. Female sex of the donor non-significantly increased the risk of SCC two-fold (95% confidence interval (CI) 0.9–4.5).

The type and number of infections in relation to risk of SCC are shown in Table SI (available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1271). There were no statistically significant associations between any infectious

agents or groups of agents and risk of SCC. Herpes group virus infections, infections overall, or infections with the individual herpes viruses, CMV, HSV, VZV and EBV, were not associated with risk of SCC. Similarly, there was no correlation between SCC risk and hepatitis infections or fungal infections. Compared with having no bacterial infections, a history of more than six bacterial infections in the post-transplant period was associated with a relative risk of SCC of 1.5 (95% CI 0.8–3.0), in the crude analysis. Upon adjustment for immunosuppressive drug use and sex of the recipient, this risk was slightly more pronounced (RR 1.9, 95% CI 0.8–4.2). The latency times from first organ transplantation to first occurrence of bacterial, viral and fungal infections were similarly distributed among cases and controls. Of patients infected, the majority was diagnosed with the first bacterial infection within the first month, the first herpes group virus infection during months 2 to 6, and the first fungal infection later than 6 months post-transplantation.

There were no statistically significant associations between any of the HLA types tested (including HLA-A3, -A11, -B27, -DR1, -DR7 and -DR homozygosity) and risk of SCC either in the crude or the adjusted analyses (Table SII; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1271). However, HLA-DR1 was associated with a non-significant 60% increase in risk of SCC in the multivariate analyses (RR 1.6, 95% CI 0.9–3.1). Sensitivity analyses of the potential impact of missing data on the results did not essentially change the estimates relating HLA-DR types to the risk of SCC (data not shown).

Table I. *Distribution of characteristics among cutaneous squamous cell carcinoma (SCC) cases and controls*[a]

	Cases n (%)	Controls n (%)	p-value[*]
Total	207 (52)	189 (48)	
Age of recipient at transplantation			
0–19 years	4 (2)	4 (2)	
20–39 years	48 (23)	45 (24)	
40–59 years	109 (53)	103 (55)	
≥60 years	46 (22)	37 (20)	
Median (range)	51 (11–71)	51 (14–72)	0.94
Sex of recipient			
Female	56 (27)	70 (37)	
Male	151 (73)	119 (63)	0.03
Time of follow-up, years			
Median (range)	6.7 (0.7–21.3)	6.5 (0.2–21.3)	
Calendar time of first transplantation			
1971–1980	54 (26)	38 (20)	
1981–1990	116 (56)	114 (60)	
1990–1997	37 (18)	37 (20)	0.37

[a]Controls were matched to cases by age at (± 5 years), and calendar period of transplantation (± 5 years) and were further required to be alive and free of cancer at the time of the case SCC diagnosis.
[*]p-values refer to χ² tests to study the difference in distribution of characteristics between cases and controls.

DISCUSSION

In this population-based case-control study of skin cancer among organ transplant recipients we found no significant relationships between post-transplant infectious load and risk of SCC. Specific herpes group virus infections, hepatitis, or fungal infections were not associated with risk of SCC, although a moderate increase in risk with more than six bacterial infections cannot be excluded. There was no detectable association with number of transplantations, type of organ transplanted, cause of kidney failure, donor characteristics, or HLA types and risk of SCC.

The increased risk of SCC post-transplantation has been attributed to the immunosuppression achieved with immunosuppressive drugs (3–5). It has been suggested that the risk is related to a high total immunosuppressive drug load (5, 6, 31), which is also associated with a high risk of post-transplant infections (8, 32). There is, to our knowledge, no previous study that has investigated potential associations between infectious burden, bacterial or fungal infections, or hepatitis and risk of post-transplant SCC. With regard to infections with

Table II. *Relative risks[a] (RRs) of cutaneous squamous cell carcinoma (SCC) after organ transplantation in relation to characteristics of the first transplantation and of the first donor*

	Cases n (%)	Controls n (%)	Adjusted RR[a,b] (95% CI)	p-value*
Number of transplantations				
1	171 (83)	161 (85)	Ref	
2–4	36 (17)	28 (15)	0.9 (0.4–1.8)	0.74
Type of organ				
Kidney	199 (96)	178 (94)	Ref	
Liver	5 (2)	3 (2)	1.0 (0.1–7.9)[d]	1.00
Heart	3 (1)	6 (3)	0.3 (0.02–2.1)[d]	0.31
Lung	0 (0)	2 (1)	0.3 (0.0–10.7)[d]	0.43
Cause of kidney failure[c]				
Chronic glomerulonephritis	93 (47)	80 (45)	Ref	
Diabetic nephropathy	24 (12)	22 (12)	0.7 (0.3–1.7)	0.44
Polycystic kidney disease	31 (16)	30 (17)	0.6 (0.3–1.2)	0.16
Other kidney disease	49 (25)	45 (25)	0.8 (0.4–1.4)	0.43
Donor status				
Deceased donor	157 (76)	147 (78)	Ref	
Alive donor (related and unrelated)	49 (24)	42 (22)	0.8 (0.4–1.4)	0.35
Donor age				
<19 years	19 (9)	16 (8)	Ref	
20–39 years	45 (22)	55 (29)	1.0 (0.3–2.8)	
40–59 years	72 (35)	71 (38)	1.3 (0.5–3.5)	
≥60 years	37 (18)	22 (12)	1.7 (0.5–5.7)	0.66
Missing (%)	(16)	(13)		
Donor sex				
Male	72 (35)	73 (39)	Ref	
Female	64 (31)	60 (32)	2.0 (0.9–4.5)	0.10
Missing (%)	(34)	(30)		

Controls were matched to cases by age (± 5 years) and calendar period of transplantation (± 5 years) and were further required to be alive and free of cancer at the time of the case SCC diagnosis.

[a]Relative risks were estimated by odds ratios and 95% confidence intervals (CI) using multivariate conditional logistic regression models.

[b]Estimates adjusted for sex of the recipient and total accumulated dose of azathioprine, cyclosporine and corticosteroids.

[c]Restricted to kidney transplant recipients.

[d]RRs and 95% CI were estimated using exact logistic regression due to low number of exposed. The multivariate exact logistic regression model was only adjusted for sex and accumulated dose of azathioprine.

*Statistical significance (p-value) was estimated with likelihood ratio tests.

herpes group viruses, which have the ability to establish chronic/latent infections by modulating the immune response (33), there are a few reports of the presence of HSV and CMV DNA in SCC lesions in non-transplant individuals (12–14, 34) and EBV DNA in such lesions in heart transplant recipients (16). However, our results do not support an association between HSV, EBV, CMV or VZV infection and risk of post-transplant SCC, which is in line with other studies (11, 14, 15). Several studies have also investigated the potential aetiological role of HPV in SCC (9, 10). Although there is some evidence of a role for HPV in the development of SCC, an association has not been established (9, 10).

Previous observations supporting the immunosuppressive load theory with regard to post-transplant malignancies, include the increased frequency of oncogenic virus-associated tumours, e.g. non-Hodgkin's lymphoma (2, 35–37), and the regression of tumours, such as lymphomas, upon lowering doses of immunosuppressive drugs (38, 39). However, SCC usually do not develop during the period of most intense immunosuppression, i.e. month 2 to 6 post-transplantation,

but later. Likewise, HPV infections that previously have been implicated in SCC aetiology commonly do not emerge until after the first 6-month period post-transplantation (8). This indicates that risk of SCC is not primarily driven by the biologically achieved *level* of immunosuppression but rather by a mechanism driven by the *chronicity* of the immunosuppressive therapy. In addition, we recently presented evidence that the risk of SCC is associated with specific drug use rather than with high drug doses in general (7). While azathioprine treatment increased the risk of SCC considerably, use of corticosteroids had a smaller effect and cyclosporine treatment was not associated with risk of SCC (7).

The lack of an association between number of transplantations, cause of kidney failure, and donor characteristics are in line with most previous studies (1, 6, 24, 27, 36). Discrepant results with regard to diabetic nephropathy and risk of skin cancer could be due to variations in the composition of skin malignancies studied, or suboptimal control for potential confounders (25, 26).

HLA have an important role in the detection of malignant cells and in the activation of the cellular immune

response directed at such cells. In previous studies in organ transplant recipients, expression of specific HLA types have been reported to have both protective (-A11, -DR4) and deleterious (-A3, -B27, -DR1, -DR7) effects on the risk of NMSC (17–21). We explored the effect of the HLA types that previously have been connected with risk of SCC, but found no significant associations between specific HLA types and risk of SCC. This is in line with other studies that have not been able to confirm these associations (6, 19, 20). These conflicting results could be due to population differences, suboptimal quality in HLA typing, grouping of different skin carcinomas (20), multiple testing, or chance, since some previous studies were hampered by small size (17, 19, 20).

The strengths of this study include the population-based nature of the Swedish transplantation cohort, the detailed collection of exposure information, the long follow-up, the matching for relevant confounding factors, and the adjustment for accumulated doses of immunosuppressive drugs. However, we were not able to adjust for sun exposure, constitutional characteristics or HPV infection. A previous study in the same organ transplant population found an increased risk of SCC in patients with skin type 1–2, blond hair and viral warts (HPV infection), but there was no association with sun exposure (40). However, since frequent sun exposure and HPV infection would, if anything, be expected to be positively associated with frequency of other infections as well as with SCC risk, our null results between infectious burden and specific infectious types and risk of SCC do not indicate any major problem of such confounding. Infections were not ranked according to severity in this study and therefore did not contribute information about the immunosuppressive level of the patients. Even though our protocol was designed to capture all infections we cannot exclude that some infections might have been missed due to inter-doctor variations, different treatment traditions or patient disparities in reporting symptoms. This might have caused non-differential misclassification bias that could have hidden a small impact on the risk of SCC from infections. However, it is unlikely that such bias concealed any substantial effect. Also, we were unable to account for the potential influence of the use of medical devices in causing infections during inpatient care, but we have no reason to believe that it differs between cases and controls. Likewise, we had no information on the HLA typing method used, which might have influenced the quality of the HLA data and diluted the true effect. Some missing data on HLA-DR types and donor characteristics limit the certainty of conclusions drawn from these analyses. Lastly, some time has passed since this study was conducted, and the treatment protocols have changed and newer immunosuppressive regimens are now the standard treatment. However, this should not affect our results, since our primary aim in this study was to investigate the risk of SCC in relation to infections, HLA and other transplant-related factors in immunosuppressed patients, and not the role of specific immunosuppressive drugs.

In conclusion, we did not observe an association between infectious burden or infections with specific microorganisms, and risk of SCC. This study does not rule out a contribution of impaired immune surveillance and susceptibility to infections with oncogenic viruses to the increased risk of SCC post-transplantation, but it adds to the evidence that there are additional important factors in skin carcinogenesis. One possible mechanism that needs further research is the biologic interaction between ultraviolet radiation, immunosuppressive drugs, and HPV-inhibited apoptosis.

ACKNOWLEDGEMENTS

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