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HLA Antigen Frequencies in Renal Transplant Recipients and Non-immunosuppressed Patients with Non-melanoma Skin Cancer

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An increased frequency of human leukocyte antigen (HLA)-DR1 was found in 49 non-immunosuppressed patients with non-melanoma skin cancer (NMSC), being highest in patients under the age of 60 with multiple squamous cell carcinomas (SCC). Of 266 patients receiving long-term immunosuppression following renal transplantation 46 (17%) were found to have NMSC. No increase in HLA-DR1 was found in renal transplant recipients (RTR) with non-melanoma skin cancer (RTR+C) when compared with matched renal transplant recipients without skin cancer (matched RTR−C), or when compared with healthy controls. There was an increased frequency of DQw2 in RTR+C, most pronounced in RTR with SCC (61.9% compared with 18.75% in matched RTR−C), giving a relative risk of 13.98. We found statistically significant differences in the frequency of a number of HLA antigens on comparing RTR+C with healthy controls, but none of these differences were found when we compared RTR+C against matched RTR−C.
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INTRODUCTION

NON-MELANOMA SKIN CANCERS (NMSC) are among the most common form of cancer with a study in 1970 giving a prevalence of 1.9% in the population over 21 years of age in Great Britain [1]. The incidence appears to be increasing, with a 60–70% increase observed between 1973 and 1987 [2]. In the general population basal cell carcinoma (BCC) occurs five times more frequently than squamous cell carcinoma (SCC) [3]. Factors implicated in the development of NMSC include increasing age, ultraviolet radiation (UVR), fair skin and cigarette smoking [4]. On the basis of clinical and epidemiological evidence it is clear that UVR is the predominant causal factor in human cutaneous carcinogenesis [5]. The prevalence of skin cancer correlates inversely with the depth of skin pigmentation and with the geographic latitude away from the equator [6]. More than 90% of NMSC in whites occur on sun-exposed skin, and they occur more frequently in individuals who receive greater sun exposure [7].

Interest has now focused on the role of host immunity in the response to skin tumours. Abnormalities of cell-mediated immunity have been reported in patients with multiple BCC [8] and SCC [9]. Further compelling evidence for the role of host immunity in NMSC comes from reports of greatly increased numbers of NMSC in renal transplant recipients (RTR) who receive long-term immunosuppression [10, 11]. In particular the incidence of SCC is raised, SCC outnumbering BCC by a ratio of 1.6–1 [11], in contrast to non-immunosuppressed patients [3]. There is increasing evidence to suggest that the human papillomavirus (HPV) is implicated in the development of SCC in allograft recipients [12]. The incidence of warts is greatly increased in transplant recipients compared with the normal population [10]. The warts tend to be flat and very numerous and may resemble the lesions of epidermodysplasia verruciformis (EV), a rare condition in which an oncogenic role for HPV in the development of multiple skin cancers is well established [13]. HPV DNA has been found in SCC from small numbers of patients [12, 14]. Other malignancies which occur more frequently in RTR include a number of non-Hodgkin B-cell lymphoproliferative syndromes, associated with evidence of Epstein–Barr virus (EBV) infection [15], and cervical carcinoma and carcinoma of the vulva and perineum, both associated with HPV infection [16], suggesting that failure to eliminate certain viruses is an important factor in oncogenesis in these patients.

There is increasing evidence that immunogenetic factors may be relevant in the development of NMSC, with recent studies indicating that susceptibility to the immunosuppressive effects of UVB may be genetically determined [17]. Studies of non-immunosuppressed patients from America [18] and Sardinia [19] have shown an association of non-melanoma skin cancer with HLA-DR1. In Southern Australia this association with human leukocyte antigen (HLA)-DR1 was confirmed in patients with multiple basal cell carcinomas, but at a lower relative risk [20]. HLA antigens may play an important role in host defences against viruses as well as in control of the development and spread of tumours. HLA-associated susceptibility exists for several kinds of virus-related malignancies including Kaposi's sarcoma (HLA-DR5) [21] and Burkitt's lymphoma (HLA-A1, -B12 and -DR7) [22]. A negative association of HLA-A11 and virus-related carcinoma of the cervix has been reported [23],

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and the same negative association has been demonstrated in renal transplant patients with skin cancer in The Netherlands [24].

We investigated the HLA antigens in 49 non-immunosuppressed skin cancer patients to determine whether the association with HLA-DR1 also occurred in the Caucasoid population living in East London. We also investigated the association with HLA type in 46 renal transplant recipients who had been diagnosed as having NMSC during a population study of patients attending the Renal Transplant Clinic at the Royal London Hospital, to determine (a) whether this group also show a positive association with HAL-DR1, and (b) whether we could confirm the negative association with HLA-A11 reported from Holland [24].

MATERIALS AND METHODS

Non-immunosuppressed patients

The subjects were consecutive patients seen in the clinic on one particular day a week. Every patient had at least one BCC or SCC, examined and identified by a pathologist, in order to confirm the clinical diagnosis. Questionnaires were completed for each patient. These included such details as tumour history, date and place of birth, occupational and recreational UVR exposure and arsenic exposure.

Blood samples were collected from each patient. Half were separated under sterile conditions for transformation into B-lymphoid lines, while the rest were separated into B- and T-lymphocytes using Dyna-beads coated with a pan-B cell monoclonal antibody. The residues from the density gradients were also saved for DNA preparation. Typing for HLA-DR and HLA-DQ antigens was carried out using the standard National Institutes of Health method [25], using carboxy-fluorescein diacetate. The HLA antigen frequencies were compared with a random control panel of 108 healthy individuals from the same ethnic background. Relative risks were calculated according to Woolf's method using Haldane's modified formula for small numbers [26].

Immunosuppressed patients

All patients attending the renal transplant clinic at the Royal London Hospital were examined by a dermatologist over a period of 2 years. A standard questionnaire was used, similar to that used for the non-immunosuppressed patients. High UVR exposure was documented if the patient worked outdoors for more than 5 years, or had lived for more than 6 months in a tropical or subtropical country. Skin type was assessed using the criteria described by Fitzpatrick [27]. All lesions thought to be malignant or premalignant were excised and examined histologically. The HLA type was known from tissue typing preceding transplantation. Some patients who had no HLA Class II data were retyped [28]. The HLA antigen frequencies of RTR with NMSC (RTR+C) were compared with those of RTR matched for age and duration of transplantation without NMSC (matched RTR−C), and also with a control panel of healthy patients. Relative risks were calculated according to Woolf's method using Haldane's modified formula for small numbers [26].

RESULTS

Non-immunosuppressed patients

49 patients (25 male and 24 female) with histologically documented BCC or SCC were HLA-DR typed. All were non-Jewish Caucasoid. Details of the tumours are listed in Table 1. The proportion of patients with BCC was higher than those with SCC, being approximately 3.5:1. The male:female ratio was 1:1.

Table 1. Details of NMSC in non-immunosuppressed patients

		Mean age of onset (years)	Number of tumours
Number of patients			
Total	49		
Male	25		
Female	24		
Number of patients with BCC			
Total	42		236
Single	15	58.5	
Multiple	27	58.4	Mean per patient: 8 Range: 2–40
Number of patients with SCC			
Total	12		95
Single	3	75	
Multiple	9*	60	Mean per patient: 8 Range: 2–30

*5 patients with multiple squamous cell carcinomas (SCC) also had basal cell carcinoma (BCC).

5 patients had lived in a tropical or sub-tropical country for more than 1 year, and 7 had worked for more than 5 years out of doors in the U.K. 1 patient had had a thymectomy for myasthenia gravis at the age of 24 years. 1 patient had had radiotherapy to the thigh for treatment of sarcoma, and three recalled exposure to Parrish's chemical food (known to contain arsenic) in childhood, though the quantities were unknown. One had been treated with arsenic for chorea.

Analysis of HLA class II antigens indicates an overall increase in DR1 for the entire patient group (Table 2). The frequency of DR1 was highest in the subgroup of patients under 60 years of age with multiple SCC, giving a relative risk of 4.5. However, as this was a small group of 5 patients the increased risk did not reach a significant level. No other antigen was consistently raised. DR2 was non-significantly decreased in all the subgroups.

Immunosuppressed patients

The questionnaire was completed and examination was carried out on 266 renal transplant recipients (174 male, 92 female). This represents 95% of the transplant population attending this hospital. The mean duration of transplantation was 4.4 years, and the mean age of the patients at the time of examination was 47 years. Patients transplanted before 1986 receive maintenance immunosuppression with prednisolone (10 mg/day) and azathi-

Table 2. Non-immunosuppressed patients with skin cancer. Frequency of DR 1 and relative risk

		DR 1			
Diagnosis	No. of patients	No. of patients	(%)	Relative risk	χ^2
Controls	108	14	(13)	—	
All patients	49	12	(24.5)	2.2	2.46
All BCC	42	10	(23.8)	2.1	1.9
All SCC	12	3	(25)	2.4	0.49
Multiple SCC under 60 years	5	2	(40.0)	4.5	1.08

SCC, Squamous cell carcinoma; BCC, basal cell carcinoma.

Table 3. Details of NMSC in renal transplant recipients

			Mean age (years)	Number of tumours
Total number of patients	266	Male 174 Female 92	47	—
Total number of patients with NMSC	46	Male 32 Female 14	47	—
Number of patients with BCC				
Total	27*		48	Mean number: 4
Single	20			Range: 2–8
Multiple	7			
Number of patients with SCC				
Total	27*		47	Mean number: 5
Single	12			Range: 2–15
Multiple	15			

*8 patients had both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).
NMSC, Non-melanoma skin cancer.

Table 4. Percentages of RTR with warts and NMSC (absolute numbers in parentheses) in the group as a whole, in all patients transplanted for more than 5 years, and in patients with skin types I or II tranpslanted for more than 5 years.

	All RTR (n = 266)		Transplant > 5 years (n = 94)		Transplant > 5 years, skin types I and II (n = 60)	
	No.	%	No.	%	No.	%
No warts or NMSC	103	38.72	10	10.63	6	10.00
BCC only	2	0.75	0		0	
BCC + warts	17	6.39	12	12.76	8	13.33
SCC only	2	0.75	0		0	
SCC + warts	17	6.39	11	11.70	10	16.67
BCC+SCC+warts	8	3.00	6	6.38	6	10.00
Warts only	116	43.60	55	58.51	30	50.00

RTR, Renal transplant rate; NMSC, non-melanoma skin cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

oprine (1.5 mg/kg/day). Those transplanted since 1986 receive in addition cyclosporin A at a dosage which produces a whole blood concentration of 100–200 ng/ml. 38 patients (14.4%) were of skin type I, 106 (43%) skin type II, 75 (28%) skin type III, 10 (3.7%) skin type IV, 18 (6.8%) skin type V, and 11 (4.1%) skin type VI. By December 1991, 46 patients (17%) had developed one or more NMSC (Table 3). The frequency of NMSC increased with duration of transplantation and was greatest in patients with skin types I and II (Table 4). All but 4 of the patients with NMSC had warts (91%). The mean age of patients at the time of diagnosis of SCC was 47 years and at the time of diagnosis of BCC was 48 years. All except one of the tumours (a peri-anal SCC) were on sun-exposed sites. Numbers of SCC ranged from 1 to 15 per patient, and of BCC from 1 to 8 per patient. 1 patient with a BCC developed Kaposi's sarcoma and a lentigo maligna melanoma. 2 patients, neither of whom had SCC or BCC, had superficial spreading melanoma.

Analysis of HLA types of the RTR with SCC compared with RTR−C matched for age and duration of transplantation, revealed a significant increase in DQw2 (relative risk 7.04, χ^2 13.98, P = 0.001) (Table 5). There was no increase in the frequency of DR1 in RTR+C as a whole, or in the sub-group of patients wth SCC (Table 5). The frequencies of HLA-A11 and of HLA-A3 in our group of 46 RTR+C were not significantly different from the frequencies of 46 RTR−C matched for age and duration of transplant (Table 5), or from a group of 108 healthy controls. Comparison of RTR+C and healthy controls revealed significant differences in the frequencies of 11 antigens, but these differences were not apparent in comparisons of RTR+C with matched RTR−C. None of the patients with melanoma were positive for DQw2.

DISCUSSION

This study lends support to the association of DR1 with NMSC in non-immunosuppressed patients as previously suggested [18–20], though the association in our patients was more pronounced for SCC than for BCC, and the relative risk was lower than in Sardinia (3.02) [19] and in non-Irish and non-Ashkenazi whites in New York (4.08) [18], and similar to the relative risk of 2.1 in the Southern Australian study [20]. These differences in relative risk possibly reflect the influence of other factors relevant to cutaneous carcinogenesis, such as UVB irradiation or arsenic ingestion, which may tend to over-ride the effect of HLA type. It is of interest that in our study 5 patients had lived in the tropics or subtropics, 4 had been exposed to arsenic, and 1 to therapeutic X-irradiation. Of these 10 patients, only 2 were positive for DR1. Similarly, in the Australian study,

Table 5. Frequencies of DQw2, DR1, A11 and A3 in RTR+SCC and RTR+C as a whole, compared with RTR−C matched for age and duration of transplantation

	DQw2			DR1			A11			A3		
	% (No.)	RR	χ^2	% (No.)	RR	χ^2	% (No.)	RR	χ^2	% (No.)	RR	χ^2
RTR+SCC	61.9 (21)	7.04	13.98**	16.7 (24)	0.83	0.09	7.41 (27)	0.44	0.84	37.0 (27)	1.60	0.62
All RTR+C	46.0 (37)	3.60	7.78*	20.9 (43)	1.09	0.03	10.9 (46)	0.68	0.38	23.9 (46)	0.86	0.09
Matched RTR−C	18.8 (32)			19.5 (41)			15.2 (46)			26.7 (45)		

No. = Number of patients tested; RR = relative risk.
RTR, Renal transplant recipients; SCC, squamous cell carcinoma; C, skin cancer.
*P = 0.01 Value corrected for number of antigens tested = 0.16.
** P = 0.001 Value corrected for the number of antigens tested = 0.016.

it seems likely that the high levels of exposure to UVB in fair-skinned individuals would lead to a relative diminution in the influence of DR1, leading to a lower relative risk for this type. How DR1 might exert an influence is unknown. It would be of interest to see whether there is an association between DR1 and susceptibility to the immunosuppressive effects of UVB as assessed by effects on development of contact hypersensitivity [17].

This study also confirms the previously reported high incidence of NMSC in RTR, although our series shows a ratio of SCC:BCC of 1:1, in contrast with other studies which show ratios in the region of 1.6:1 [11]. It is possible that this difference arises from the design of our study, involving the examination of patients who were not aware of having a cutaneous problem. 9 of the 19 patients with BCC and 4 of the 19 with SCC were found by examining patients in the transplant clinic whilst they were waiting to see the nephrologist. All of these patients had previously failed to attend appointments for routine examination in the dermatology clinic.

In contrast with non-immunosuppressed patients, RTR+C did not show an increase in frequency of HLA-DR1, when compared with matched RTR−C, or with healthy controls. It seems likely that the immunosuppression has an influence on oncogenesis sufficient to obscure any effect of DR1. The increased frequency of DQw2 in patients with NMSC has not been reported before. The increase is most pronounced for patients with SCC. DQw2 is associated with insulin-dependent diabetes mellitus (IDDM) but none of our patients with cancer had IDDM, whilst one of the matched RTR did have IDDM. How DQw2 might be exerting an effect on susceptibility to NMSC is unclear. One possible mechanism might be through a relationship between the impaired clearance of HPV antigens and DQw2. However, if this were the case it would seem probable that DQw2 would correlate with susceptibility to large numbers of warts, but we were unable to find such an association in our patients.

Our study fails to confirm the finding of Bouwes-Bavinck *et al.* [24] of the negative association between HLA-A11 and skin cancer in renal transplant recipients. When we initially looked for the association, in a group of 30 RTR+C, we found none positive for A11 [29]. It is only since we have been screening all patients, and have found unsuspected tumours, that we have lost the negative association with A11. This could possibly reflect some protective influence of A11, with patients positive for HLA-A11 having less numerous or less aggressive tumours. The Dutch group found an increase in A3 and B27 in patients with skin cancer [24]. We found no increase in B27, and although we did find an increase in A3, this was only when patients with SCC were compared with healthy controls. There was no significant difference in frequency of A3 when compared with matched RTR−C. Because RTR are an unusual group of patients, some having had renal disease with an immunological basis, we feel it is safest not to give too much weight to differences from healthy control panels. Overall we found 11 antigens showing significant differences in frequency between RTR+C against healthy controls, but none of these differences persisted with a control group of age- and duration-matched RTR−C.

Whilst these results suggest that there may be an effect of DR1 in the development of NMSC in non-immunosuppressed patients, and of DQw2 in RTR, these positive findings have to be treated with considerable caution in view of the small numbers of patients involved. However, this study does emphasise the very high rates of NMSC, particularly of SCC, in RTR in the U.K. The patients at particular risk are those who have been transplanted for 5 years or more, and who have skin types I or II. The finding of NMSC in 40% of patients in this group susggests that they should have regular dermatological surveillance as part of their care programme.

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Psychiatric Disorder in Patients with Advanced Breast Cancer: Prevalence and Associated Factors

Karen L. Pinder, Amanda J. Ramirez, M. Elizabeth Black, Michael A. Richards, Walter M. Gregory and Robert D. Rubens

The prevalence of psychiatric disorder and associated factors has been examined in 139 women with advanced breast cancer. Patients completed a self-report assessment of mood, the Hospital Anxiety and Depression Scale (HAD). They were also interviewed to obtain sociodemographic details, UICC performance status and past psychiatric history. Overall, 35 (25%) scored 11 or above (out of a maximum of 21) on either the anxiety or the depression subscales, or both, of the HAD and were therefore probable cases of anxiety and/or depression. These patients are likely to benefit from psychosocial intervention. Clinical anxiety was unrelated to any sociodemographic or disease related factors. Clinical depression was significantly more prevalent amongst patients in the lower socioeconomic classes ($P = 0.01$) and those with poor performance status ($P = 0.007$). Depression can be difficult to detect in patients with advanced breast cancer and these factors may be useful indicators to clinicians of patients at high risk of this disorder.
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INTRODUCTION

THERE IS an increasing clinical concern to improve the quality of life of patients with advanced breast cancer. However, little is known about the prevalence of clinically significant psychological disorder in this population, or its relationship to patient and illness related factors. A better understanding of these issues would provide an indication of the level of need for psychosocial intervention and support, and also help to identify those most likely to benefit from it.

This study aimed to estimate the prevalence of clinically significant anxiety and depression in a sample of women with advanced breast cancer using the Hospital Anxiety and Depression scale (HAD) [1]. This is a self-report mood questionnaire developed specifically for use in patients with physical disease and excludes symptoms that could be due either to physical illness or its treatment. Its use in assessing mood in patients with cancer has been recommended by the MRC Cancer Therapy Committee's working party on quality of life in cancer patients [2]. It has been validated against a psychiatric interview in a population of patients with advanced breast cancer and shown to provide a reasonable estimate of psychiatric disorder [3].

A further aim of the study was to examine the relationship between the psychiatric status of the patients and sociodemographic, personal, and disease and treatment parameters.

PATIENTS AND METHODS

The study sample consisted of 139 women with advanced breast cancer attending a clinical oncology unit. 86 of these formed a consecutive series of inpatient admissions. Patients admitted overnight for chemotherapy were excluded for reasons of convenience. 53 of the women were a series of outpatient clinic attenders who were either receiving endocrine therapy or were being observed without a specific systemic therapy. All patients had a histologically confirmed diagnosis of breast cancer with either inoperable locoregional recurrence or metastatic disease. 34 (24%) of the patients originally presented with locally advanced disease. For the remaining patients, the median time since first recurrence of the disease was 2.3 years (range 0–14 years). It was ensured that the patients had a level of alertness permitting participation in a 20-min interview.

All patients completed the HAD. This questionnaire enquires about symptoms of mood disturbance over the preceding week. It is made up of a seven-item anxiety subscale and a seven-item depression subscale. Each item is rated on a scale of 0–3, ranging from "not at all" to "very much". This gives a maximum subscale score of 21 for both depression and anxiety. The

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