Epidemiogic aspects of skin cancer in organ-transplant recipients

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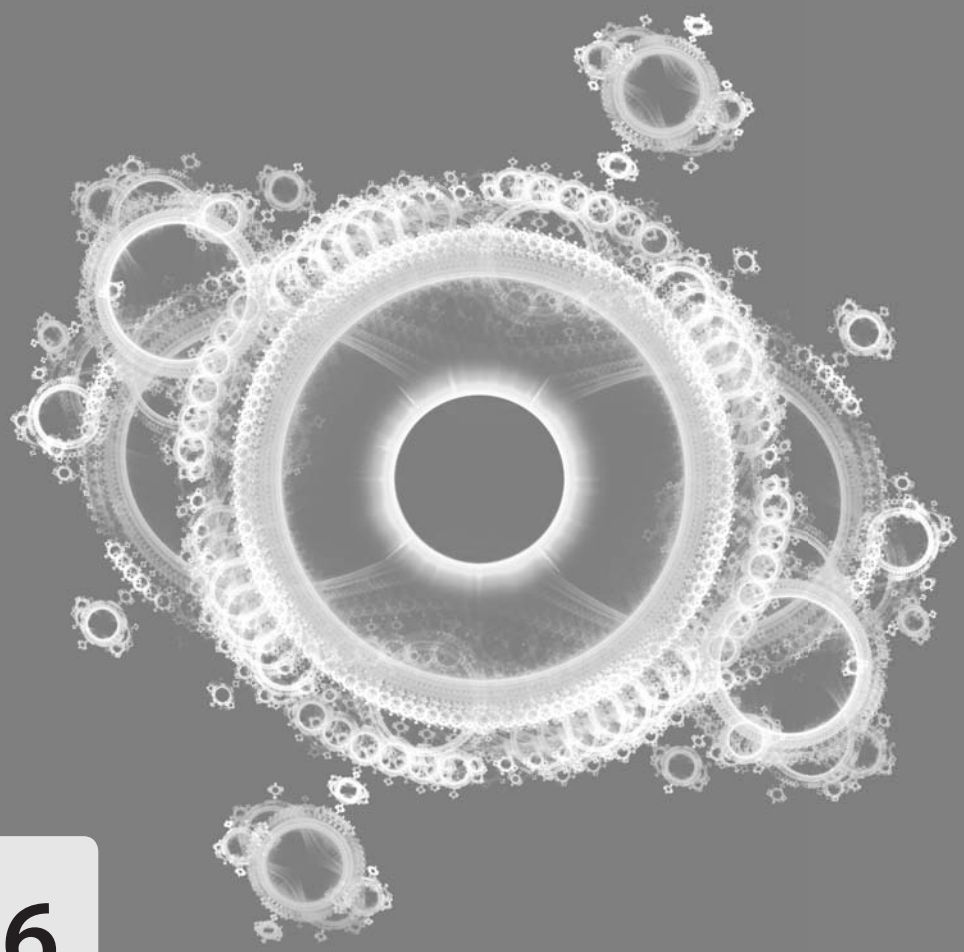

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Cutaneous squamous- and basal-cell carcinomas are associated with an increased risk of internal malignancies in kidney transplant recipients

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Submitted

Abstract

The aim of this study was to investigate whether the development of cutaneous squamous- and basal-cell carcinomas is associated with an increased risk of internal malignancies in kidney transplant recipients.

In a cohort study, all 1869 patients receiving a kidney transplantation between 1966 and 2006 at the Leiden University Medical Center were followed. All malignancies which had developed between 1966 and 2007 were recorded. Time-dependent Cox regression analyses were used to study the association between the development of skin cancer and internal malignancies.

Among 1869 kidney transplant recipients, 176 (9.4%) developed cutaneous squamous- and 142 (7.6%) basal-cell carcinomas. A total of 142 (7.6%) patients developed internal malignancies after transplantation. In patients with squamous-cell carcinoma the adjusted risk to develop internal malignancies was 3.5 (2.2-5.6) and for basal-cell carcinoma patients, this risk was 2.1 (1.2-3.5). Particularly, the risk to develop carcinomas of the digestive organs, lungs and male genital organs was increased.

Kidney transplant recipients with squamous- and basal-cell carcinomas have an increased risk to develop internal malignancies. [167 words]

Introduction

Kidney transplant recipients (KTR) have a significantly increased risk of malignancy [1-5]. The incidence of malignancies is 2- to 6-fold higher than in the general population [4-7]. Especially the incidences of non-melanocytic skin cancer (NMSC), comprising squamous-cell carcinoma (SCC) and basal-cell carcinoma (BCC), post-transplant lymphoma, anogenital dysplasia, thyroid cancer and Kaposi's sarcoma are increased [1;4;6;8-12]. NMSC are the most common post-transplant malignancies [9] and many KTR develop multiple malignancies [13;14].

In the general population, patients with a cutaneous SCC have a 2-fold increased risk of internal malignancies [15-17], but some studies showed no increased risk of internal malignancies, or even a slightly decreased risk, after the development of cutaneous SCC [18-20]. In the general population, the development of BCC was also associated with an increased risk of internal malignancies [15;21;22]. The other way round, internal malignancies were also associated with an increased risk of cutaneous SCC {Hemminki, 2003 2422 /id; Brennan, 2005 2420 /id}.

No previous studies have investigated the association between NMSC and internal malignancies in KTR. In this study we investigated the risk of internal malignancies after the development of cutaneous SCC or BCC in KTR.

Material and methods

Patients

We performed a cohort study of all 1869 patients who received a first kidney transplantation at the LUMC between March 1966 and January 2006. The follow-up of the patients ended arbitrarily on 1 June, 2007. The study adhered to the Declaration of Helsinki Principles and the medical ethical committee of the LUMC had approved the study design.

Collection of data

Data recorded for all KTR included the date of the first transplantation, age at transplantation, sex, and the dates of cancer, death or last follow-up. The main outcomes of cancer were the diagnoses of internal malignancies, cutaneous SCC and/or BCC and were collected from the computerized oncological registry of the LUMC, the database from the department of Pathology and the national histological database (PALGA) [25]. The medical charts were also hand searched for the diagnosis of cancer.

Premalignant lesions and in situ carcinomas were excluded.

The diagnoses of internal malignancies were based on the International Classification of Diseases 10th Modification Diagnoses Codes (ICD-10). Different from the ICD-10 classification we classified lip carcinomas as cutaneous SCC or BCC and not as internal malignancies.

Immunosuppressive regimens

Between 1966 and 1986, the immunosuppressive treatment of KTR in our clinic consisted of duo therapy with prednisolone and azathioprine (Aza), but shortly after 1986 all new KTR were immunosuppressed with prednisolone and cyclosporine A (CsA). From the mid 90th occasionally KTR were treated with prednisolone, mycofenolatemofetil (MMF) and CsA.

KTR, in whom acute graft rejections were observed, were generally initially treated with methylprednisolone. When this therapy was not sufficient to prevent further rejection a second rejection treatment with ATG and a third rejection treatment with once more methylprednisolone were given. In exceptional cases OKT3 was given when a fourth rejection treatment was needed. With the exception of some rare patients, induction treatments with ATG and/or OKT3 were not given to KTR who were transplanted in the LUMC between 1966 and 1995.

Statistical analyses

We calculated the time on immunosuppression by adding the times between the different transplantations and subsequent rejections or until the patient was censored. If there was no rejection, we used the time between the transplantation and the end of the study or until the patient was censored (development of malignancy, last follow-up visit, or death of the patient).

For statistical analyses we used Chi-square tests for categorical variables and Student's T-tests for continuous variables. Cox proportional hazard analyses were used to calculate hazard ratios for the development of internal malignancies, SCC or BCC and to adjust for potentially confounding factors. Time-dependent Cox regression analyses were used to measure the effect of time-dependent risk factors. As opening dates for the analyses we used the date of the first transplantation; as closing dates we used the date of diagnosis of cancer, the date of the patient's death or the date of last follow up. Patients were not censored from the analyses at graft failure.

KTR who had already cancer before the first kidney transplantation or patients who were lost to follow up at the first transplantation were excluded from all analyses. P-values below 0.05 were considered significant. All statistical calculations were performed using SPSS for Windows version 16 (SPSS Inc, Chicago, IL).

Results

Baseline characteristics of the KTR

Between March 1966 and January 2006, 1906 patients received their first kidney transplant in Leiden. Thirty-seven patients had already a malignancy before the transplantation and they were excluded from further analyses. Of the remaining 1869 KTR the median age at transplantation was 43.9 years (range 3.8 – 77.5) with a median follow up of 9.2 (range 0 -39.9) years. Altogether, 176 (9.4%) had developed cutaneous SCC; 142 (7.6%) BCC and 142 (7.6%) internal malignancies, whereas 1529 (81.8%) KTR did not develop any type of cancer. A total of 88 patients developed both SCC and BCC. Cutaneous SCC and BCC were, by far, the most frequently diagnosed cancers after transplantation [13]. In a single patient, the maximum number of SCC was 68 and the maximum number of BCC was 28. In total, there were more than 1800 SCC and BCC in these patients [13]. For this study, however, only the first SCC and BCC were considered. One hundred forty-two patients developed together 151 internal malignancies, of which 112 were carcinomas, 8 leukemias, 22 lymphomas and 2 sarcomas and in 7 cases the cellular type was undefined.

In total, 29 SCC and 8 BCC of the lip had been diagnosed in 31 KTR. In 8 of these patients, SCC of the lip was the first presentation of SCC and in 7 patients BCC of the lip was the first presentation of BCC.

Risk factors of cancer

To identify possible risk factors for the development of cutaneous SCC, BCC or internal malignancies, we analyzed the influence of sex, age at the first transplantation, the years of the first transplantation, the maintenance immunosuppressive therapy and time on immunosuppression on the risk of SCC, BCC and internal malignancies (Table 1).

Patients with SCC were significantly more often male and were significantly younger at their first transplantation compared with patients without cancer (Table 1). Performing Cox proportional hazard analyses, however, older age at transplantation appeared to be a risk factor for the development of SCC, because young patients at transplantation were much longer in the follow-up than older patients, as we have

Table 1 Baseline characteristics of 1869 kidney-transplant recipients without and with different types of malignancy.

	No Malignancy	Basal-cell carcinoma	Squamous-cell carcinoma	Internal malignancy	P-value compared with no malignancy
Number of patients: N*	1529	142	176	142	
Sex: N (%)					
Female	587 (38.4)	48 (33.8)	57 (32.4)	63 (44.4)	SCC: 0.05
Male	942 (61.6)	94 (66.2)	119 (67.6)	79 (55.6)	BCC: 0.15
					IM: 0.07
Age at first transplantation (yrs)					
Median (25% - 75%)	43.8 (32.3 – 54.8)	41.7 (31.7 – 49.9)	39.1 (28.5 – 47.3)	46.1 (35.1 – 53.3)	SCC: 0.001
					BCC: 0.17
					IM: 0.04
Age at first cancer (yrs)					
Median (25% -75%)		56.0 (41.8 – 65.9)	58.5 (46.1 – 64.2)	62.3 (51.3 – 69.6)	
Years of first transplantation: N (%)					
1966-1975	169 (11.1)	32 (22.5)	54 (30.7)	22 (15.5)	SCC: <0.001
1976-1985	320 (20.9)	65 (45.8)	84 (47.7)	51 (35.9)	BCC: <0.001 IM: <0.001
1986-1995	430 (28.1)	32 (22.5)	34 (19.3)	54 (38.0)	
1996-2006	610 (39.9)	13 (9.2)	4 (2.3)	15 (10.6)	
Immunosuppressive therapy: N (%)					
Aza combination	497 (34.3)	98 (69.0)	146 (83.0)	77 (54.2)	SCC: <0.001
MMF combination	487 (33.6)	13 (9.2)	5 (2.8)	14 (9.9)	BCC: <0.001 IM: <0.001
CyA or Tac	464 (32.0)	31 (21.8)	25 (14.2)	51 (35.9)	

Time on immunosuppression (yrs)					
0 – 9	988 (64.6)	27 (19.0)	21 (11.9)	53 (37.3)	SCC: <0.001
10 – 19	367 (24.0)	48 (33.8)	64 (36.4)	62 (43.7)	BCC: <0.001 IM: <0.001
20 or more	174 (11.4)	67 (47.2)	91 (51.7)	27 (19.0)	

SCC; squamous-cell carcinoma; BCC: basal-cell carcinoma; IM: internal malignancy.
*Some patients had internal malignancy, squamous-cell carcinoma and/or basal-cell carcinoma together. This fact is reflected here by overlapping of the numbers of patients in these categories.

reported before [13]. By contrast, patients with internal malignancies were significantly older at their first transplantation than patients who did not develop cancer and they were older at the time that they developed internal malignancies compared with the time that patients developed SCC or BCC (Table 1).

As could be expected, most patients with cancer were transplanted before 1996 and, as a consequence, were more often immunosuppressed with Aza and had a longer time on immunosuppression than patients without cancer (Table 1).

Patients with cutaneous SCC or BCC are at risk for subsequent internal malignancies

Table 2 shows the distribution of patients without and with SCC or BCC prior to the development of internal malignancies. Of the KTR with internal malignancies 22.0% had developed a prior SCC, whereas in patients without internal malignancies only 7.9% had developed SCC. Adjustment for age and sex reduced the hazard ratio, suggesting that there was partially confounding by these factors for the association between SCC and internal malignancies (Table 2). Inclusion of the patients who developed SCC after internal malignancies or additional adjustment for immunosuppressive therapy did not influence the hazard ratios, importantly (data not shown).

To analyze whether patients with SCC were at increased risk for a specific type of internal malignancy, time-dependent hazard ratios were calculated for the different types of internal malignancy, separately. The hazard ratio, adjusted for age and sex, for the 32 carcinomas of the digestive organs was 4.2 (1.8-9.7), for the 21 carcinomas of the lower respiratory system 4.6 (1.5-14.5) and for the 11 carcinomas of the male genital organs 7.3 (1.7-32.5). The risks of other types

Table 2 Risk of internal malignancy in patients with prior squamous-cell carcinoma or basal-cell carcinoma.

	No internal malignancy	Internal malignancy	Non-adjusted Hazard ratio (95% CI)	Hazard ratio adjusted for age and sex (95% CI)
Squamous-cell carcinoma: N (%)				
No	1590 (92.1)	103 (78.0)	1	1
Yes	137 (7.9)	29 (22.0)	5.0 (3.1-8.0)	3.5 (2.2-5.6)
Basal-cell carcinoma: N (%)				
No	1610 (93.3)	117 (86.7)	1	1
Yes	117 (6.7)	18 (13.3)	2.8 (1.7-4.8)	2.1 (1.2-3.5)

of internal malignancy, for example of the 22 lymphomas or of the 12 carcinomas of the female genital organs were not significantly increased after the development of SCC (data not shown). The risk of internal malignancy in BCC patients was only significantly increased for the 32 carcinomas of the digestive organs, with a hazard ratio of 2.8 (1.1-6.9).

Patients with internal malignancies are not at risk for subsequent SCC or BCC

Table 3 shows the distribution of patients without and with internal malignancies prior to the development of SCC or BCC. Of the KTR with SCC, 6.8% had developed a prior internal malignancy and in KTR with BCC 5.6% had developed a prior internal malignancy, whereas in patients without SCC 6.1% had developed an internal malignancy and in patients without BCC 6.7% had developed an internal malignancy. After adjustment for sex and age the hazard ratios of developing SCC or BCC after the development of internal malignancies were not statistically significant (Table 3).

Patients with BCC are at risk for subsequent SCC, and patients with SCC are at risk for subsequent BCC

Table 4 shows the distribution of patients without and with BCC prior to the development of SCC and the other way round. Of the KTR with SCC 32.8% had developed a prior BCC and of the KTR with BCC 42.6% had developed a prior SCC. BCC patients were at a highly increased risk to develop SCC and SCC patients were at a

Table 3 Risk of squamous-cell carcinoma or basal-cell carcinoma in patients with prior internal malignancy.

	No squamous-cell carcinoma	Squamous-cell carcinoma	Non-adjusted Hazard ratio (95% CI)	Hazard ratio adjusted for age and sex (95% CI)
Internal malignancy: N (%)				
No	1590 (93.9)	137 (93.2)	1	1
Yes	103 (6.1)	10 (6.8)	2.0 (1.0-3.9)	1.6 (0.82-3.2)
	No basal-cell carcinoma	**Basal-cell carcinoma**		
Internal malignancy: N (%)				
No	1610 (93.3)	117 (94.4)	1	1
Yes	117 (6.7)	7 (5.6)	1.6 (0.69-3.6)	1.1 (0.50-2.6)

Table 4 Risk of squamous-cell carcinoma in patients with prior basal -cell carcinoma and vise versa.

	No squamous-cell carcinoma	Squamous-cell carcinoma	Non-adjusted Hazard ratio (95% CI)	Hazard ratio adjusted for age and sex (95% CI)
Basal-cell carcinoma: N (%)				
No	1635 (96.6)	92 (67.2)	1	1
Yes	58 (3.4)	45 (32.8)	10.0 (6.8-14.7)	7.9 (5.3-11.7)
	No basal-cell carcinoma	**Basal-cell carcinoma**		
Squamous-cell carcinoma: N (%)				
No	1635 (94.7)	58 (57.4)	1	1
Yes	92 (5.3)	43 (42.6)	12.1 (7.6-19.1)	9.3 (5.8-14.9)

highly increased risk to develop BCC (Table 4). Inclusion of the patients who developed BCC after SCC and patients who developed SCC after BCC or additional adjustment for immunosuppressive therapy did not influence the hazard ratios, importantly (data not shown).

Discussion

This study showed a statistically significantly increased risk of internal malignancies in KTR with a prior SCC or BCC compared with KTR without skin cancer, which could be largely attributed to an increased risk of carcinomas of the digestive organs, lungs and male genital organs. The other way round, KTR with a prior internal malignancy did not show an increased risk to develop cutaneous SCC or BCC. KTR with a prior SCC had an increased risk of BCC and those with a prior BCC an increased risk of SCC.

The 3.5 and 2.1-fold increased risks of internal malignancies after a prior SCC or BCC, respectively, are compatible with the general population, in which a 1.2-2.0-fold increased risk of internal malignancies was reported in patients with a history of SCC or BCC [15;19;26]. In our study in KTR we did not find an increased risk of SCC or BCC after the development of internal malignancies, which is in contrast with the general population [23].

An inherited predisposition of cancer, a suboptimal immune response, or lifestyle factors (smoking, sun exposure) are all possible explanations for the increased risk of internal malignancies in patients with a prior SCC or BCC. For example, the elevated rate of lung carcinoma in patients with a prior SCC, with a hazard ratio of almost 5 in our study, is suggestive for a role of smoking, which is a well-known risk factor for both lung carcinoma and cutaneous SCC [27]. However, in the general population, an association between SCC and lung cancer was also apparent after adjustment for smoking, so that other factors may play a role, as well [15].

Our finding that KTR with a prior SCC have a 3 to 4-fold increased risk of carcinoma of the digestive organs is in disagreement with the study of Grant and Tuohimaa [18;20] who showed, in the general population, no increased risk or even a slightly decreased risk of colon carcinoma in patients with a prior diagnosis of skin cancer [18;20]. They hypothesized that the increased solar ultraviolet B radiation, to which patients with NMSC are usually exposed prior to the development of skin cancer, results in higher vitamin D levels, which are though to protect, among others, against colon carcinoma [20;28]. On the other hand, Chen et al reported a 78% higher risk for colorectal carcinoma in patients with NMSC [15]. A possible explanation of this apparent different association

may be that Chen's [15] and our study were performed in countries with relatively low amounts of summertime sun exposure (north-eastern part of the United States and the Netherlands), compared to Tuohimaa et al [20] showing a reduced risk of cancer in countries with high level of sun exposure (Australia, Singapore and Spain).

A possible limitation of our study is that we did not systematically collect data of potentially confounding factors, like smoking, sun exposure, skin type, education years and body mass index, so that we cannot adjust for these factors. In another study, however, it was shown that, adjustment for these factors did not decrease the increased risk of internal malignancies in patients with prior SCC or BCC [15].

This is the first study in KTR showing an increased risk of internal malignancies, in particular carcinomas of the digestive organs, lungs and male genital organs after the development of cutaneous SCC or BCC. Both nephrologists and dermatologists should be aware of the increased risk of internal malignancies in KTR with prior skin cancers and should be extra alert when skin cancers start to develop in their patients.

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