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Incidence and risk factors for nonmelanoma skin cancer after heart transplantation

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Abstract

Introduction. The incidence of skin cancer in heart transplant (HT) patients is higher than in the general population, reversing the proportion of cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) with a predominance of the former. The etiologic role of new immunosuppressants is not well known. We sought to ascertain the incidence of SCC and BCC in HT patients and the risk factors for its occurrence.

Patients and Methods. We report the incidence of all types of post-HT skin cancer, SCC, and BCC among adult HT patients in Spain (4089 subjects) as well as the influence of gender, age at heart transplant, immunosuppression, and sunlight exposure.

Results. The incidence rates of SCC and BCC, per 1000 persons/year, were 8.5 and 5.2, respectively. Males had a higher risk of SCC but not BCC. Induction therapy increased the risk of SCC and BCC. The relative risk of mycophenolate mofetil (MMF) was 0.3 (0.2–0.6; $P < .0005$) and azathioprine (AZA) 1.8 (1.2–2.7; $P < .0032$) for SCC, whereas tacrolimus and cyclosporine showed no difference. The relative risk of BCC was not affected by any immunosuppressant.

Conclusion. Age at transplantation >45 years, induction therapy use, and high sunshine zone were risk factors for both SCC and BCC. Different immunosuppressive agents have different risks of nonmelanoma skin cancer, as AZA increases the risk of SCC and MMF is a protective factor. The relative risk of BCC was not affected by any immunosuppressor.

Skin cancers are the most common malignancies among solid organ transplant recipients.[1] Epidemiologic data have shown that skin cancer is more frequent in sun-exposed areas and in light-skinned individuals with blue eyes and blonde hair.[2] Age, immunosuppressive therapy, and viral warts could also be important risk factors.[3, 4 and 5] Most of the data about the incidence of skin cancer in transplant patients is from kidney recipients,[6, 7, 8 and 9] but there are not as many studies in heart transplant (HT) patients, who generally receive higher levels of immunosuppressive therapy than do other transplant recipients.

Regarding the type of skin cancer, it has been reported that cutaneous squamous cell carcinoma (SCC) is more frequent than basal cell carcinoma (BCC) in transplant patients, as opposed to the situation in the general population,[3, 5, 6, 10, 11 and 12] although not all studies obtain the same results,[7 and 13] suggesting that differences could be influenced by factors such as the length of immunosuppression,[7] the sunlight exposure, or the quality of the registry of skin tumors.[3]

Since publication of the first studies examining the influence of immunosuppression[14] on the onset of skin cancer in heart transplantation, new drugs have appeared with widespread use, such as mycophenolate mofetil (MMF), tacrolimus, and interleukin (IL) 2R-blockers. To date, no study has examined the influence of the most commonly used immunosuppressants on the incidence of skin cancer BCC and SCC in patients with heart transplantation.

The present study is based on the Spanish Post-Heart Transplant Tumor Registry (SPHTTR), composed of the data on tumors in all adult patients who have undergone HT in Spain from 1984 to December 2003. We report the incidence of all types of post-HT skin cancer, SCC, and BCC among adult HT patients in Spain, as well as the influence of gender, age at heart transplantation, immunosuppression, antiviral prophylaxis, and sunlight exposure.

Methods

Patients and Study Protocol

A total of 4089 patients aged >15 years who underwent HT in Spain between 1984 and December 31, 2003, were identified in the SPHTTR. We excluded patients who died in the first 3 months after HT (n = 695) and 1 patient for whom the date of diagnosis of a first post-HT tumor had not been recorded. The remaining 3393 patients were followed to December 2004.

Variables

The outcome data analyzed were the occurrence of post-HT skin cancers (SCC and BCC), together with date of diagnosis and location. The treatment variables considered were the use of induction therapy, the agents employed for this purpose, and the duration of treatment; the agents used for maintenance of immunosuppression in each of 4 post-HT periods (the first 3 months, months 4–12, months 13–24, and >2 years post-HT). Other possible risk factors considered were gender, pre-HT smoking, and age at HT (<45, 45–54, 55–64, and ≥65 years).

Sunlight exposure was evaluated according to data from the Spanish National Institute of Meteorology from 1997 to 2004. Hospitals that performed HT (n = 16) were divided into 2 groups: Zone 1 (4 hospitals) of low sunshine (<2500 hours of sunshine per year) and zone 2 (12 hospitals) of high sunshine (>2500 hours of sunshine per year).

Statistical Analysis

For each patient, the number of years at risk was defined as the time between the date of HT and December 2004 or death, whichever occurred first. The incidence, per 1000 person-years, of skin cancer, and of both SCC and BCC, was estimated for each gender and age group, and for follow-up to 3 months, 6 months, and 1, 2, 3, 4, 5, and 10 years. Univariate risk analyses were performed to estimate the influence of age group, gender, pre-HT smoking, MMF in the first 3 months, tacrolimus in the first 3 months, induction therapy, induction with OKT3, induction with either equine or rabbit anti-thymocyte globulin (ATG), induction with basiliximab, induction with daclizumab, and hours of sunshine per year.

Multivariate Poisson regression models were fitted in which the association of tumors with induction in general and with induction by OKT3 and by ATG was evaluated while adjusting for age group, gender, pre-HT smoking, and immunosuppression in the first 3 months with MMF and/or tacrolimus. The criterion for statistical significance was $P < .05$.

Results

As described,[14] in the SPHTTR 3393 patients were followed to December 2004. Most (84.7%) of the patients were men, and the age at the time of transplantation was 51.4 ± 11.0 years, with a median follow-up of 5.2 years (mean, 5.8; maximum, 20.2). By age group, 762 patients (22.5%) were aged <45 years, 1044 (30.8%) 45–54 years, 1365 (40.2%) 55–64 years, and 222 (6.5%) >65 years. Of the patients, 48.9% had been smokers before HT. Data on the use of individual immunosuppressive agents are listed in Table 1. Steroids were used by virtually all patients in the first 3 months post-HT, and by 62.2% after 2 years. The use of cyclosporine and azathioprine declined gradually with increasing time post-HT, whereas tacrolimus, MMF, and sirolimus exhibited the reverse trend. OKT3, ATG, basiliximab, and daclizumab were used almost exclusively in the first 3 months post-HT, presumably for induction therapy. On this basis, induction therapy was used in 60.5% of the patients.

Table 1. Patients Receiving Each Kind of Immunosuppresor (Percentages) by Period Post-HT

	<3 Months	3–12 Months*	1–2 Years†	>2 Years†	At Any Time
n	3393	3127	2763	2763	—
Cyclosporine	79.1	73.6	73.0	64.4	84.4
Azathioprine	60.5	53.7	54.1	42.7	68.8
Prednisone	98.5	83.2	73.7	62.2	99.2
Tacrolimus	8.3	12.2	12.6	17.2	21.9
MMF	25.6	28.4	27.5	40.2	48.0
Sirolimus	0.4	0.5	0.5	6.3	6.6
Everolimus	0.2	0.2	0.2	0.6	0.8
OKT3	37.4	0.2	0.0	0.2	44.3
ATG	14.3	1.7	0.4	0.3	17.1
Basiliximab	5.6	0.0	0.0	0.0	6.7
Daclizumab	3.4	0.0	0.0	0.0	4.1

* Percentages of the 3127 patients who survived 1 year.
† Percentages of the 2763 patients who survived 2 years.

A total of 324 skin cancers developed in 204 patients with the following distribution: 169 (54.2%) were SCC, 104 BCC (33.3%), 9 melanoma, 39 miscellaneous (4 Kaposi sarcoma, 23 undifferentiated malignant tumors, 5 adenocarcinoma, 6 metastatic, 1 neuroectodermal), and 3 unknown.

For the analysis of the incidence, per 1000 person-years, we excluded 12 tumors (9 melanoma and 3 unknown) and we achieved a follow-up of 19,883.4 person-years. Skin cancer (nonmelanoma) had an incidence of 15.7 cases per 1000 person-years (95% confidence interval [CI], 14–17.5), SCC had an incidence of 8.5 cases per 1000 person-years (95% CI, 7.3–9.9), and BCC 5.2 cases per 1000 person-years (95% CI, 4.3–6.3). The incidence of skin cancer (nonmelanoma), SCC, and BCC at 3 and 6 months, and 1, 2, 3, 4, 5, and 10 years is shown in Table 2. The incidence of nonmelanoma skin cancer was 16.6 (95% CI, 14.8–18.7) in men and 10.5 (95% CI, 7.4–15) in women. Both SCC and BCC were more common in men than women. In men, the incidence of SCC was higher than BCC, 9.3 (95% CI, 7.9–10.8) versus 5.4 (95% CI, 4.4–6.6); in women, the incidence of SCC and BCC was similar, 4.1 (95% CI, 2.3–7.2) versus 4.4 (95% CI, 2.6–7.6). The relative risk for men was 1.6 (1.1–2.3; P = .0155) for nonmelanoma skin cancer, 2.3 (1.3–4.1; P = .0048) for SCC, and 1.2 (0.7–2.2; P = .5083) for BCC.

Table 2. Incidence of Nonmelanoma Skin Cancer, SCC, and BCC

		Skin cancer (Nonmelanoma)		Skin Cancer (SCC)		Skin Cancer (BCC)
	Person-years	Tumors	IR* (95% CI†)	Tumors	IR* (95% CI†)	Tumors
Overall	19,883.4	312	15.7 (14–17.5)	169	8.5 (7.3–9.9)	104
Cumulative at						
3 months	846.3	2	2.4 (0.6–9.5)	0	—	1
6 months	1.674.4	6	3.6 (1.6–8)	1	0.6 (0.1–4.2)	4
1 year	3.260.8	16	4.9 (3–8)	3	0.9 (0.3–2.9)	10
2 years	6.159.9	38	6.2 (4.5–8.5)	17	2.8 (1.7–4.4)	15
3 years	8.678.1	56	6.5 (5–8.4)	25	2.9 (2–4.3)	21
4 years	10.886.6	78	7.2 (5.7–9)	39	3.6 (2.6–4.9)	26
5 years	12.787.3	109	8.5 (7.1–10.3)	53	4.1 (3.2–5.4)	38
10 years	18.306.4	260	14.2 (12.6–16)	142	7.8 (6.6–9.1)	85
Gender						
Male	16.940.0	281	16.6 (14.8–18.7)	157	9.3 (7.9–10.8)	91
Female	2.943.4	31	10.5 (7.4–15)	12	4.1 (2.3–7.2)	13
Age group (y)						
<45	5.259.0	23	4.4 (2.9–6.6)	11	2.1 (1.2–3.8)	10
45–54	6.135.1	86	14 (11.4–17.3)	51	8.3 (6.3–10.9)	23
55–64	7.547.1	179	23.7 (20.5–27.5)	98	13 (10.7–15.8)	64
≥65	942.2	24	25.5 (17.1–38)	9	9.6 (5–18.4)	7

* Incidence per 1000 person-years.
† Confidence interval.

For nonmelanoma skin cancer, the incidence per 1000 person-years increased from 4.4 among patients aged <45 years at HT to 25.5 among patients aged ≥65 years (Table 2), with relative risks of 3.2 (95% CI, 2–5.1; $P < .0001$) for 45–54 year-olds, 5.4 (3.5–8.4; $P < .0001$) for 55–64 year-olds, and 5.8 (3.3–10.3; $P < .0001$) among patients aged ≥65 years, relative to those under 45 (Table 3). Similarly, for SCC, the incidence increased from 2.1 in the youngest age group to 9.6 in the oldest, with relative risks of 4 (95% CI, 2.1–7.6; $P < .0001$), 6.2 (3.3–11.6; $P < .0001$), and 4.6 (1.9–11; $P < .0002$) relative to those under 45. Likewise, for BCC, the incidence increased from 1.9 in the youngest age group to 7.4 in the oldest (relative risk [RR], 3.9; 95% CI, 1.5–10.3; $P < .002$) relative to those under 45.

Table 3. RR of Nonmelanoma Skin Cancer, SCC, and BCC Associated With Various Factors

	Skin Cancer (Nonmelanoma)		Skin Cancer (SCC)		Skin Cancer (BCC)
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)
Gender					
Male	1.6 (1.1–2.3)	.0155	2.3 (1.3–4.1)	.0048	1.2 (0.7–2.2)
Female	1.00	—	1.00	—	1.00
Age group (y)					
<45	1.00	—	1.00	—	1.00
45–54	3.2 (2–5.1)	<.0001	4 (2.1–7.6)	<.0001	2 (0.9–4.1)
55–64	5.4 (3.5–8.4)	<.0001	6.2 (3.3–11.6)	<.0001	4.5 (2.3–8.7)
≥65	5.8 (3.3–10.3)	<.0001	4.6 (1.9–11)	.0002	3.9 (1.5–10.3)
Pre-HT smoking	1.1 (0.9–1.3)	.5155	1.3 (1–1.7)	.0941	0.9 (0.6–1.3)

CI, confidence interval; RR, relative risk.

When we analyzed the influence of the use of different immunosuppressive drugs in the first 3 months after HT and regardless of any later use, MMF and tacrolimus were both associated with a lower risk of nonmelanoma skin cancer, at the expense of a reduction in the risk of SCC (RR, 0.3; 95% CI, 0.2–0.6; $P = .0005$ for MMF and RR, 0.00; $P = .007$ for tacrolimus) but not in the BCC incidence (RR, 0.7; 95% CI, 0.4–1.3; $P = .21$ for MMF and RR, 0.7; 95% CI, 0.2–2.2; $P = .55$ for tacrolimus). Azathioprine was associated with an increased SCC risk (RR, 1.8; 95% CI, 1.2–2.7; $P = .003$) and cyclosporine was neutral.

Induction therapy was a risk factor for nonmelanoma skin cancer (RR, 2.1; 95% CI, 1.6–2.7; $P < .0001$), SCC (RR, 2.3; 95% CI, 1.6–3.4; $P < .0001$) and BCC (RR, 2.6; 95% CI, 1.6–4.2; $P < .0001$), but only OKT3 was associated with both SCC and BCC (Table 4). In the univariate analyses, the influence of ATG differed from that of OKT3 in that ATG was associated only with an increased risk of BCC (RR, 2.2; 95% CI, 1.2–4; $P = .0102$).

Table 4. RR of Nonmelanoma Skin Cancer, SCC, and BCC Associated With Various Factors

	Skin cancer (Nonmelanoma)		Skin Cancer (SCC)		Skin Cancer (BCC)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MMF (yes/no)	0.5 (0.3–0.7)	.0002	0.3 (0.2–0.6)	.0005	0.7 (0.4–1.3)	.2123
Tacrolimus (yes/no)	0.2 (0.1–0.7)	.0058	0.00	.0077	0.7 (0.2–2.2)	.5524
Azathioprine (yes/no)	1.5 (1.1–1.9)	.0074	1.8 (1.2–2.7)	.0032	1.5 (0.9–2.4)	.1052
Cyclosporine (yes/no)	1.1 (0.8–1.5)	.6810	1.4 (0.9–2.3)	.1456	1.1 (0.6–1.9)	.7415
Induction therapy	2.1 (1.6–2.7)	<.0001	2.3 (1.6–3.4)	<.0001	2.6 (1.6–4.2)	.0001
OKT3	2.5 (1.9–3.3)	<.0001	3 (2.1–4.3)	<.0001	2.9 (1.8–4.8)	<.0001
ATG/thymoglobulin	1.6 (1.1–2.2)	.0156	1.2 (0.7–2.1)	.4354	2.2 (1.2–4)	.0102
Basiliximab	0.5 (0.1–2.1)	.3401	0.00	.1619	0.9 (0.1–6.7)	.9186
Daclizumab	0.00	.1496	0.00	.3083	0.00	.4428
		Sunlight exposure (h/y)				
<2500	1.00	—	1.00	—	1.00	—
>2500	5.7 (3.7–8.8)	<.0001	8.7 (4.3–17.8)	<.0001	3 (1.7–5.4)	.0001

ATG, antithymocyteglobulin; CI, confidence interval; RR, relative risk.

The relative risk of developing SCC in patients who were transplanted in a high sunshine zone (>2500 hours/year) was 8.7 (95% CI, 4.3–17.8; $P < .0001$) in relation to patients who were transplanted in a low sunshine zone, and in BCC the RR was 3 (95% CI, 1.7–5.4; $P = .0001$).

Discussion

Our study includes the largest number of heart transplant patients with skin tumors. As described, SCC is the most common skin tumor in HT recipients followed by BCC. However, the ratio between them varies in different studies and it has been suggested that this variability could be due to the quality of the registry. We found that the SCC/BCC ratio was 1.62:1, which is very similar to the ratio described by Caforio et al[3] in a prospective study with close follow-up of HT recipients by a dermatologist.

The incidence, per 1000 person-years, of SCC and BCC increased with time of follow-up. One important finding is the relationship of the gender and the type of tumor. Although both types of skin tumors were more common in men, in the univariate analysis this difference was significant only in SCC.

In the univariate analysis of nonmelanoma skin cancer, the use of both MMF and FK in the first 3 months emerged as protective factors, whereas AZA was a risk factor and cyclosporine had no effect. This was due to the influence of these drugs on the incidence of SCC; in BCC there was no modification, in agreement with the results of the study by Caforio et al, which showed that a high rejection score was a risk factor for skin tumor of the SCC type but not BCC.[3] It is noteworthy that the group of patients exposed to FK showed no SCC, which suggests it is a strong protective factor, but it must be remembered that this was a small group of patients. The beneficial role of MMF at the onset of cancer has been described previously in vitro[15 and 16] and in vivo,[17 and 18] as has the deleterious effect of AZA,[19] but there is little information about the effect of calcineurin inhibitors on the appearance of skin tumors in cardiac transplantation.

Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes after ultraviolet B radiation. This suggests that the increased risk of skin cancer observed in organ transplant patients may be a result not only of systemic immune suppression but also the local inhibition of DNA repair and apoptosis in skin by calcineurin inhibitors.[20]

The possible beneficial effect of FK in SCC tumors in cardiac transplantation has not been described previously. Referring to all types of tumors, in The International Society for Heart and Lung Transplantation (ISHLT) Registry the use of tacrolimus seemed to be protective in the univariate analysis, but it was not significant on multivariate analysis.[21] Whether different immunosuppressive modalities are associated with an increased occurrence of nonmelanoma skin cancer in cardiac transplant recipients remains controversial.[22 and 23] In renal transplantation, FK seems to be a risk factor for developing nonmelanoma skin cancer,[24 and 25] but in the liver transplant population it could be protective.[26]

Another surprising observation was that induction therapy resulted in an increased incidence of both SCC and BCC, especially among those patients who received OKT3, although ATG therapy only increased the incidence of BCC. According to data from the ISHLT Registry, induction

immunosuppression does not seem to increase the risk of subsequent malignancy and neither OKT3 nor ATG use was associated with a significantly increased risk of malignancy.[21]

Leiter et al[27] reported that intensive ultraviolet light exposure in childhood and adolescence was causative for the development of BCC, whereas for the etiology of SCC a chronic ultraviolet light exposure in the earlier decades was noted. In our study, high sunlight exposure was a risk factor for the emergence of both types of tumors, but specially SCC, which seems to be associated with cumulative exposure to sunlight.

In conclusion, the present study confirms a higher incidence of SCC versus BCC in patients with a heart transplant. Age >45 years, induction therapy, and high sunlight exposure are risk factors for both SCC and BCC. Our results suggest that the occurrence of SCC in heart transplant patients depends on the immunosuppressive therapy used and not just the duration and level of inmunosuppression. MMF was a protective factor for SCC, whereas azathioprine was a risk factor and tacrolimus and cyclosporine had no effect. No immunosuppressive drug was associated with BCC.

References

1. S. Euvrard, J. Kanitakis, A. Claudy. Skin cancers after organ Transplantation. N Engl J Med, 348 (2003), p. 1681.
2. D. Berg, C.C. Otley. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol, 47 (2002), p. 1.
3. A.L. Caforio, A.B. Fortina, S. Piaserico, *et al*. Skin cancer in heart transplant recipients: risk factor analysis and relevance of immunosuppressive therapy. Circulation, 102 (2000), p. III222.
4. Boyle J, Mackie RM, Briggs JD, et al: Cancer, warts, and sunshine in renal transplant patients: a case-control study. Lancet 1:702, 21984.
5. B.B.B. Barr, E.C. Benton, K. Mclaren, *et al*. Human papilloma virus infection and skin cancer in renal allograft recipients. Lancet, 1 (1989), p. 124.
6. M.M. Hartevelt, J.N. Bouwes Bavinck, A.M. Kootte, *et al*. Incidence of skin cancer after renal transplantation in the Netherlands. Transplantation, 49 (1990), p. 506.
7. C. Ferrándiz, M.J. Fuente, M. Ribera, *et al*. Epidermal dysplasia and Neoplasia in kidney transplant recipients. J Am Acad Dermatol, 33 (1995), p. 590.
8. P. Jensen, S. Hansen, B. Moller, *et al*. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol, 40 (1999), p. 177.
9. P. Jensen, B. Moller, S. Hansen. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol, 42 (2000), p. 307.
10. S. Euvrard, J. Kanitakis, C. Pouteil-Noble, *et al.* Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol, 33 (1995), p. 222.
11. C.S. Ong, A.M. Keogh, S. Kossard, *et al*. Skin cancer in Australian heart transplant recipients. J Am Acad Dermatol, 40 (1999), p. 27
12. T.D. Lampros, A. Cobanoglu, F. Parker, *et al*. Squamous and basal cell carcinoma in heart transplant recipients. J Heart Lung Transplant, 6 (1998), p. 586.
13. L. Naldi, A.B. Fortina, S. Lovati, *et al*. Risk of nonmelanoma skin cancer in Italian organ transplant recipients: A registry-based study. Transplantation, 70 (2000), p. 1479.
14. M.G. Crespo-Leiro, L. Alonso-Pulpón, J.A. Vázquez De Prada, *et al*. Malignancy after heart transplantation: incidence, prognosis and risk factors. Am J Transplant, 8 (2008), p. 1031.
15. G.E. Koehl, F. Wagner, O. Stoeltzing, *et al*. Mycophenolate mofetil inhibits tumor growth and angiogenesis in vitro but has variable antitumor effects in vivo, possibly related to bioavailability. Transplantation, 83 (2007), p. 607.
16. S. Stracke, L. Ramudo, F. Keller, *et al.* Antiproliferative and overadditive effects of everolimus and mycophenolate mofetil in pancreas and lung cancer cells in vitro. Transplant Proc, 38 (2006), p. 766.
17. C. Buell, J. Koo. Long-term safety of mycophenolate mofetil and cyclosporine: a review. J Drugs Dermatol, 7 (2008), p. 741.
18. P.R. Mydlarski. Mycophenolate mofetil: a dermatologic perspective. Skin Therapy Lett, 10 (2005), p. 1.
19. G. Wong, J.R. Chapman. Cancers after renal transplantation. Transplant Rev (Orlando), 22 (2008), p. 141.
20. D.B. Yarosh, A.V. Pena, S.L. Nay, *et al*. Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B Irradiation. J Invest Dermatol, 125 (2005), p. 1020.
21. J.O. O'Neill, J.B. Edwards, D.O. Taylor. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: Analysis of the transplant registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant, 25 (2006), p. 1186.
22. A. Geusau, D. Dunkler, E. Messeritsch, *et al*. Non-melanoma skin cancer and its risk factors in an Austrian population of heart transplant recipients receiving induction therapy. Int J Dermatol, 47 (2008), p. 918.
23. C. Ulrich, E. Stockfleth. Azathioprine, UV light, and skin cancer in organ transplant patients—do we have an answer?. Nephrol Dial Transplant, 22 (2007), p. 1027.
24. M. Navarro, M. López-andreu, A. Rodríguez-benot, *et al*. Cancer incidence and survival in kidney transplant patients. Transplant Proc, 40 (2008), p. 2936.

25. T. Imao, N. Ichimaru, S. Takahara, *et al*. Risk factors for malignancy in Japanese renal transplant recipients. Cancer, 109 (2007), p. 2109.
26. S.K. Perera, F.J. Child, N. Heaton, *et al*. Skin lesions in adult liver transplant recipients: a study of 100 consecutive patients. Br J Dermatol, 154 (2006), p. 868.
27. U. Leiter, C. Garbe. Epidemiology of melanoma and nonmelanoma skin cancer—the role of sunlight. Adv Exp Med Biol, 624 (2008), p. 89.