INVESTIGATIVE REPORT

Skin Cancer Risk Among Solid Organ Recipients: A Nationwide Cohort Study in Denmark

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This study assessed the risk of skin cancer following transplantation of 4 types of solid organs, and the risk of skin cancer in patients with chronic diseases that lead to organ transplantations. A population-based cohort of 5279 Danish patients who underwent heart, lung, renal and liver transplantation, and 77,782 patients with chronic heart, lung, renal and liver diseases during 1977–2006 were included in the study. Linkage to the Danish Cancer Registry allowed complete follow-up for basal cell carcinoma, squamous cell carcinoma and malignant melanoma. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated. The SIR for squamous cell carcinoma was highest among heart (SIR = 113; 95% CI: 74–166), then renal (SIR = 81; 95% CI: 68–96), lung (SIR = 65; 95% CI: 28–128) and liver (SIR = 60; 95% CI: 27–113) recipients. SIR for squamous cell carcinoma was 4.8 (95% CI: 2.2–9.0) among renal failure patients, but not greatly elevated among patients with the other chronic diseases studied. Organ transplantation is a risk factor for squamous cell carcinoma, with immunosuppressive treatments being the most likely explanation for the association. *Key words: skin cancer; organ transplantation; epidemiology; standardized incidence ratio.*

Solid organ transplantation is a treatment offered to an increasing number of patients with chronic organ diseases (1). Although life-saving, organ transplantation is associated with an overall 3–5-fold increased risk of malignancies (2–5), especially non-melanoma skin cancers (NMSC) (including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) (6–9), with a reported 65–250-fold increased risk of SCC of the skin (10). To our knowledge, only 3 population-based studies (8, 11, 12) with longer follow-up times (6.8, 4.8 and 5.6 years, respectively) have evaluated skin cancer risk among organ recipients other than renal recipients. However, none of these population-based studies compared risk across all 4 individual types of solid organ transplantation and the risk from the underlying chronic diseases. Thus, it is

unknown how skin cancer risk differs among recipients of heart, lung, renal and liver transplants, and to what extent this risk is affected by the risk from the chronic diseases that lead to organ transplantation.

Different mechanisms may underlie the high risk of skin cancers among organ recipients. The risk may arise from the underlying chronic disease leading to need for organ transplantation and/or to treatments used to treat a particular disease. Alternatively, the risk may be due to the organ transplantation procedure and/or the immunosuppressive treatments used to prevent organ rejection (13). If certain underlying chronic diseases or their treatments lead to high risk of skin cancer post-transplantation, we would expect this risk to be elevated among patients with chronic diseases before organ transplantation. If the transplant procedure itself is the main risk factor underlying the high risk, we would expect the risk to be the same among patients undergoing different types of organ transplantation. Finally, if the immunosuppressive regimen is the main risk factor for excess skin cancer risk among organ recipients, we would expect the risk to differ according to type of immunosuppressive regimen (1).

We therefore assessed the risk of BCC, SCC and malignant melanoma (MM) among Danish heart, lung, renal, and liver recipients in a population-based cohort study using data from 1977 through 2006. We compared this risk of BCC, SCC and MM among organ recipients before transplantation by examining risk among patients with chronic diseases of the heart, lung, renal and liver that may lead to transplantation.

MATERIALS AND METHODS

This population-based cohort study was conducted in Denmark, which has a population of approximately 5.3 million. The National Health Service provides tax-supported healthcare to the entire Danish population, including free access to hospital care. National data on hospital diagnoses and cancer incidence can be linked using the unique 10-digit civil registration number (CPR number) assigned to all Danish residents (14).

Study cohorts

The nationwide Danish National Patient Registry (DNPR) was used to identify all patients, who underwent solid organ transplantation, or who were diagnosed with a chronic disease that may lead to organ transplantation during the period 1 January 1977 to 31 December 2006. The DNPR contains information on

all patient contacts with non-psychiatric hospital departments in Denmark, including CPR number, dates of hospital admission, admitting department, surgical procedures, discharge diagnoses, and since 1995, outpatient visits. Diagnoses were coded using the International Classification of Diseases (ICD), 8th edition (ICD-8) system through 1993, and the ICD-10 system, thereafter (15). In the DNPR, surgical procedures are coded according to the Danish version of the Nordic Classification of Surgical Procedures (NCSP).

Using the codes presented in Table I, we identified 5279 organ transplant recipients; of these, 459 received a heart, 384 received a lung, 4010 received a renal transplant, and 426 received a liver. Table I also shows the mean dose of immunosuppressive therapy by type of organ transplantation. Using the codes also provided in Table I, and then searching records for both inpatient and outpatient visits, we identified 77,782 patients with a relevant chronic organ disease: 44,827 with heart failure, 12,925 with emphysema, 5899 with renal failure, and 14,131 with liver failure.

Data on cancer incidence

We determined the incidence rate of skin cancers among patients in the study cohorts through linkage with the Danish Cancer Registry (DCR). The DCR has collected information on cases of primary cancer on a nationwide basis since 1943. It has been found to be 95% complete, with a validity of 98% (16). DCR files include information on cancer type, site, morphology, and cancer history. Since 1978, the DCR has coded tumours according to the 10th revision of the International Classification of Diseases (ICD-10), and the third version of the International Classification of Diseases for Oncology (ICD-O-3) (17), which includes a 4-digit code for tumour morphology. Throughout the study period, the ICD-10 codes were generated by uniform conversion of the two ICD-O-3 codes (topography and morphology) for each case.

For MM, we used ICD-10 codes C43 and for NMSC we used ICD-10 codes C44. For BCC we included only cancers with the following ICD-O-3 morphology codes: 80903, 80913, 80923, 80933, 80943 and 80953. For SCC we included only cancers with ICD-O-3 codes 80513, 80523, 80703, 80713, 80743, 80753 and 80763.

Statistical analyses

Organ transplant recipients and patients with selected chronic organ diseases were followed from the date of transplantation, or first admission date for the chronic organ disease, to the date of first primary skin cancer, death, emigration, or the end of the study (31 December 2006). We censored chronic organ disease patients on the date of organ transplantation, or at age 65 years for patients with heart failure and emphysema, and at age 70 years for patients with renal and liver failure. Age 65 years is the formal age limit for heart and lung transplantation and age 70 years is the formal age limit for renal and liver transplantation (18). The number of skin cancers observed among organ recipients and chronic organ disease patients was compared with the number of skin cancers expected in the general Danish population. To

Table I. *Organ transplantation type, chronic organ diseases, and associated Nordic Classification of Surgical Procedure (NCSP) codes, and/or International Classification of Diseases, 8th edition (ICD-8) and ICD-10 codes, and immunosuppressive regimen*

Transplantation type	ICD-8 and/or NCSP code	ICD-10 and/or NCSP code	Immunosuppressive regimen[a]
Condition with heart transplantation	Procedure code: 32209, 32219, 32240	DZ941, or procedure code: KFQA00, KFQA10, KFQA20, KFQA30, KFQA40	High-dose induction therapy up to one year after transplantation Maintenance therapy: azathioprine 1–2 mg/kg, ciclosporin A serum levels 150/200 ng/ml, and prednisolone 0.07 mg/kg (1).
Condition with lung transplantation	Procedure code: 35609	DZ942, or procedure code: KGDG03, KGDG10, KGDG13, KGDG30, KGDG96	High-dose induction therapy up to one year after transplantation Maintenance therapy: azathioprine 0.5–1 mg/kg, ciclosporin A serum levels 125/150 ng/ml, and prednisolone 0.05 mg/kg[1].
Condition with renal transplantation	Y9509, or procedure code: 57480-57490	DZ940, or procedure code: KKAS00, KKAS10; KKAS20	High-dose induction therapy up to one year after transplantation Maintenance therapy: azathioprine 1 mg/kg, ciclosporin A serum levels 100 ng/ml, and prednisolone 0.05 mg/kg[2].
Condition with liver transplantation	Procedure code: 47270-47279	DZ944, or procedure code: KJJC10, KJJC20, KJJC30, KJJC40	High-dose induction therapy up to 3 months after transplantation Maintenance therapy: two-drug therapy, typically azathioprine[b] 0.8 mg/kg, or ciclosporin A serum levels 24–48 ng/ml[3].
Heart failure	427.09	DI509, DI500	
Emphysema	492.09	DJ439	
Renal failure	584	DN189	
Liver failure	571.99	DK703	

[a]In recent years, the newer immunosuppressive drugs, i.e. mycophenolate mofetil, tacrolimus, and sirolimus, have been introduced, and may replace or reduce dose of the conventional immunosuppressive medications.

[b]Azathioprine may be replaced by prednisolone 0.07 mg/kg.

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obtain this expected number, gender-specific skin cancer rates (computed according to 5-year age groups and 5-year calendar periods) were multiplied with the corresponding person-years of the organ recipients and patients with chronic organ disease. The standardized incidence ratio (SIR), the ratio of the observed to the expected number of cancers, and 95% confidence intervals (CI) were computed using Byars approximation (19). In our analyses, we compared risk of skin cancers by type of organ transplantation and by type of chronic disease. The cancer endpoints were BCC, SCC and MM. Follow-up for skin cancers was divided into 3 time-segments, <1 year, 1–4 years and 5–10 years.

We analysed data using SAS® software (SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Data Protection Agency.

RESULTS

Descriptive data

A total of 5279 patients undergoing organ transplantation (3265 males (62%) and 2014 females (38%)) were followed for 35,615 person-years (P-Y), yielding a median length of follow-up of 5 years. The median age at transplantation was 46 years (range 0–95 years) (Table II). A total of 77,810 patients had a hospital admission related to one of the chronic organ diseases potentially leading to transplantation (66% males and 34% females). They were followed for 280,926 P-Y, yielding a median length of follow-up of 2 years. The median age at hospital admission was 58 years (range: 0–70 years) (Table III). During follow-up 437 heart failure patients, 223 emphysema patients, 757 renal failure patients and 138 liver failure patients were censored due to organ transplantation (data not shown).

Non-melanoma skin cancer risk following organ transplantation

Generally, the BCC:SCC ratio was 1:1 among all organ recipients. The incidence rate of BCC and SCC among heart recipients was highest 5–10 years after transplantation (BCCs: 4.4 per 1000 P-Y; SCCs: 20.4 per 1000 P-Y). Based on a total of 14 BCCs and 26 SCCs, this yielded a SIR of 5.6 (95% CI: 3.1–9.5) for BCC, and 113 (95% CI: 74–166) for SCC. Among lung recipients, the incidence rate of BCC and SCC was highest 5–10 years after transplantation (BCCs: 9.7 per 1000 P-Y; SCCs: 9.7 per 1000 P-Y). Based on a total of 7 BCC cases and 8 SCC cases, lung recipients had a SIR of 4.1 (95% CI: 1.7–8.5) for BCC and 65 (95% CI: 28–128) for SCC.

Among renal recipients, the incidence rate of BCC and SCC was highest 5–10 years after transplantation (BCCs: 3.0 per 1000 P-Y; SCCs: 2.4 per 1000 P-Y). Based on a total of 141 BCCs and 127 SCCs, this yielded a SIR of 6.9 (95% CI: 5.8–8.1) for BCC and 81 (95% CI: 68–96) for SCC. Among liver recipients, the incidence rate of BCC and SCC was also highest 5–10 years after transplantation (BCCs: 4.7 per 1000 P-Y; SCCs: 7.8 per 1000 P-Y). Based on a total of 9 BCCs and 9 SCCs, liver recipients had a SIR of 4.6 (95% CI: 2.1–8.7) for BCCs and 60 (95% CI: 35–48) for SCCs (Table IV).

Melanoma skin cancer risk following organ transplantation

The incidence rate of MM was low among all organ recipients. Based on only eight observations, the SIR was 1.2 (95% CI: 0.5–2.3) for MM among all organ recipients (see Table IV).

Non-melanoma skin cancer risk among patients with chronic organ diseases

The incidence rates of BCC and SCC were lower among patients with selected chronic organ diseases, compared with those calculated for organ recipients. The BCC:SCC ratio was 7:1 among patients with heart failure, emphysema, and liver failure. It was lower among renal failure patients, but remained constant during follow-up. A total of 156 BCCs and 21 SCCs were observed among heart failure patients, yielding a SIR of 0.9 (95% CI: 0.7–1.0) for BCCs and 1.4 (95% CI: 0.9–2.1) for SCCs. A total of 81 BCCs and 11 SCCs were observed among emphysema patients, yielding a SIR of 1.2 (95% CI: 1.0–1.5) for BCCs and 2.1 (95% CI: 1.1–3.8) for SCCs.

Among renal failure patients, 23 BCCs and 9 SCCs were observed, yielding a SIR of 1.1 (95% CI: 0.7–1.6)

Table II. *Characteristics of 5279 organ recipients by type of transplant, Denmark, 1977–2006*

	Heart (*n*=459)	Lung (*n*=384)	Renal (*n*=4010)	Liver (*n*=426)	Total (*n*=5279)
Proportion (%)	9	7	76	8	100
Gender, *n* (%)					
Male	368 (80)	184 (48)	2478 (62)	235 (55)	3265 (62)
Female	91 (20)	200 (52)	1532 (38)	191 (45)	2014 (38)
Median age at transplantation, years (range)	50 (2–89)	53 (11–82)	44 (1–95)	47 (1–85)	46 (0–95)
Age-distribution at entry, *n* (%)					
<40 years	129 (28)	77 (20)	1621 (41)	150 (35)	1977 (37)
40–49 years	103 (22)	80 (21)	977 (24)	91 (21)	1251 (24)
50–59 years	163 (36)	152 (40)	981 (24)	136 (32)	1432 (27)
>60 years	64 (14)	75 (19)	431 (11)	49 (12)	619 (12)

Table III. *Characteristics of 77,810 patients with selected chronic organ diseases by type of disease, Denmark, 1977–2006*

	Heart failure (*n*=44,846)	Emphysema (*n*=12,927)	Renal failure (*n*=5901)	Liver failure (*n*=14,136)	Total (*n*=77,810)
Proportion (%)	58	17	8	17	100
Gender, *n* (%)					
Male	30,579 (68)	7260 (56)	3532 (60)	9627 (68)	50,978 (66)
Female	14,267 (32)	5667 (44)	2369 (40)	4509 (32)	26,812 (34)
Median age at first discharge date, years (range)	59 (0–65)	57 (0–65)	57 (0–70)	54 (0–70)	58 (0–70)
Age-distribution at entry, *n* (%)					
<40 years	2706 (6)	1054 (8)	1086 (18)	1205 (9)	6051 (8)
40–49 years	5171 (12)	1838 (14)	854 (15)	3773 (27)	11,636 (15)
50–59 years	18,211 (41)	5493 (43)	1543 (26)	5484 (39)	30,731 (39)
>60 years	18,758 (42)	4542 (35)	2418 (41)	3674 (26)	29,392 (38)

for BCCs and 4.8 (95% CI: 2.2–9.0) for SCCs. A total of 56 BCCs and 4 SCCs were observed among liver failure patients, yielding a SIR of 1.0 (95% CI: 0.8–1.3) for BCCs and 0.9 (95% CI: 0.3–2.4) for SCCs (Table V).

Melanoma skin cancer risk among patients with chronic organ diseases

The incidence rate of MM among patients with chronic organ diseases was the same as that observed in the general Danish population. Based on 54 observations, the overall SIR for MM was 0.8 (95% CI: 0.6–1.1) among all patients with chronic organ diseases. Further details are shown in Table V.

DISCUSSION

We found the highest risk of SCC among heart recipients, who are maintained on the highest dose regimen of immunosuppressive medication. This confirms that the general level of immune suppression is probably the

primary risk factor for SCC. Renal failure patients also had a high risk of SCC, which similarly may be related to the immunosuppressive treatments for renal failure, or the immune cell dysfunction associated with renal failure prior to transplantation (20). This pre-existing increased risk of SCC among patients with renal failure may explain the relatively high risk for SCC among renal recipients, observed in our study.

Increased risk for squamous cell carcinoma

SCC risk has been associated specifically with ciclosporin use among patients who have not undergone transplantation (21), as well as organ recipients. Two previous studies indicated that organ recipients receiving ciclosporin-based regimens were more likely to experience SCC than those receiving azathioprine and corticosteroids (8, 22). This agrees with our findings of the highest risk of SCC among heart recipients, who are maintained on the highest dose ciclosporin (1) because of the fatal consequences of allograft loss. The greater

Table IV. *Skin cancer risk following solid organ transplantation by type of transplant, Denmark, 1977–2006*

	Heart	Lung	Renal	Liver	Total
Incidence rate of skin cancer; <1 year of follow-up (per 1000 P-Y)					
BCC	5.2	3.2	2.0	0	2.8
SCC	5.2	0	1.1	0	1.7
MM	0	0	0.2	0	0.2
Incidence rate of skin cancer after 1–4 years of follow-up (per 1000 P-Y)					
BCC	5.1	4.0	1.9	5.2	3.4
SCC	7.7	6.6	1.7	2.1	3.4
MM	0.9	0	0.3	0	0.3
Incidence rate of skin cancer after 5–10 years of follow-up (per 1000 P-Y)					
BCC	4.4	9.7	3.0	4.7	5.5
SCC	20.4	9.7	2.4	7.8	6.3
MM	0	3.2	0.2	0	0.2
Observed/expected cases, *n*					
BCC	14/3	7/2	141/20	9/2	171/27
SCC	26/0.2	8/0.1	127/1.6	9/0.2	170/2
MM	1/0.6	1/0.4	6/5	0/0.5	8/7
Standardized incidence ratio (95% CI)					
BCC	5.6 (3.1–9.5)	4.1 (1.7–8.5)	6.9 (5.8–8.1)	4.6 (2.1–8.7)	6.4 (5.5–7.5)
SCC	113 (74–166)	65 (28–128)	81 (68–96)	60 (27–113)	82 (70–95)
MM	1.8 (0.1–10)	2.6 (0.1–15)	1.1 (0.4–2.4)	0	1.2 (0.5–2.3)

BCC: basal cell carcinoma; SCC: squamous cell carcinoma; MM: malignant melanoma; 95% CI: 95% confidence interval; P-Y: person-years.

Table V. *Skin cancer risk following selected chronic organ diseases in Denmark, 1977–2006*

	Heart failure	Emphysema	Renal failure	Liver failure	Total
Incidence rate of skin cancer <1 year of follow-up (per 1000 P-Y)					
BCC	1.2	1.2	1.5	1.4	1.2
SCC	0.2	0.1	0.6	0.0	0.2
MM	0.3	0.1	0.2	0.1	0.2
Incidence rate of skin cancer after 1–4 years of follow-up (per 1000 P-Y)					
BCC	1.0	1.0	1.5	0.9	1.0
SCC	0.1	0.2	0.5	0.0	0.2
MM	0.2	0.1	0.8	0.1	0.2
Incidence rate of skin cancer after 5–10 years of follow-up (per 1000 P-Y)					
BCC	1.1	1.8	1.0	1.1	1.3
SCC	0.1	0.1	0.6	0.1	0.1
MM	0.2	0.2	0.3	0.1	0.2
Observed/expected cases, *n*					
BCC	156/178	81/66	23/22	56/55	316/321
SCC	21/15	11/5	9/2	4/4	45/26
MM	30/37	11/14	9/5	4/12	54/67
Standardized incidence ratio (95% CI)					
BCC	0.9 (0.7–1.0)	1.2 (1.0–1.5)	1.1 (0.7–1.6)	1.0 (0.8–1.3)	1.0 (0.9–1.1)
SCC	1.4 (0.9–2.1)	2.1 (1.1–3.8)	4.8 (2.2–9.0)	0.9 (0.3–2.4)	1.7 (1.2–2.3)
MM	0.8 (0.6–1.2)	0.8 (0.4–1.4)	2.0 (0.9–3.7)	0.3 (0.1–0.9)	0.8 (0.6–1.1)

BCC: basal cell carcinoma; SCC: squamous cell carcinoma; MM: malignant melanoma; 95% CI: 95% confidence interval; P-Y: person-years.

carcinogenic effect of ciclosporin compared with other immunosuppressive medications arises from direct cellular effects promoting cancer progression in most cell types, contemporaneously with its immunosuppressive action (23). On the other hand, a higher risk for SCC associated specifically with azathioprine has also been reported among organ recipients (24–26). Azathioprine may increase risk of SCC through a photosensitizing mechanism, as azathioprine is known to induce selective UVA photosensitivity (27). Thus, it is yet to be explored which particular immunosuppressive drug is the most important risk factor for SCC among organ recipients. Alternatively, others and our findings may reflect that the general level and potency of immune suppression is the main risk factor.

The renal failure patients in our study also had a high risk of SCC. Renal failure patients (e.g. glomerulonephritis patients) may have had many years of exposure to immunosuppressive drugs, such as glucocorticoids, cyclophosphamide and ciclosporin (28). Alternatively, the immune cell dysfunction, including impaired granulocyte activity, suppressed T-lymphocyte function, and impaired macrophage Fc receptor function, which has been described in patients with renal failure, may explain the excess risk of SCC among these patients (20). This pre-existing increased risk of SCC among patients with renal failure may explain the relatively high risk for SCC among renal recipients, although renal recipients receive a comparable level of immunosuppressive medication to lung recipients.

Increased risk for basal cell carcinoma

Risk for BCCs among all organ recipients was also elevated, although lower than the risk for SCCs. The mechanism underlying the increased BCC risk among organ recipients is unlikely to be the same as that underlying the increased risk of SCC. Since we found similar risks for BCC associated with all 4 types of organ transplantation, the risk association is unlikely to be explained by the level of immune suppression.

Melanoma risk is not significantly increased

We found a slightly increased risk of MM among heart, lung and renal recipients. Our risk association was lower than that reported in a Norwegian study, in which transplant recipients had a SIR of 3.4 (95% CI: 1.7–5.9) for MM (8). Nevertheless, estimates for MM in our study were based on few observations, lacking statistical precision, and therefore definite conclusions cannot be drawn.

Strengths and limitations of this study

Our large population-based study population allowed us to quantify risk estimates with relatively high statistical precision, and to disaggregate patients by type of organ transplantation and chronic organ disease. Furthermore, the uniformly organized Danish healthcare system allows a true population-based design, avoiding selection bias due to loss to follow-up. The median length of follow-up among organ recipients was 5 years, which is an important strength, as BCC and SCC occurrence was highest 5–10 years after transplantation. Diagnostic bias (i.e. surveillance bias (29)) is unlikely to explain our findings. This bias results when patients with a more severe disease receive more medical attention, and hence are diagnosed with additional conditions that might otherwise remain undetected. Had this bias been

present, we would have expected the incidence of skin cancers to be highest the first year after hospital admission for organ transplantation or chronic organ disease. This was not the case. A study weakness is our choice of study design, including only the first occurrence of skin cancers, in particular SCC. By not including multiple SCCs in these organ recipients, we failed to demonstrate the true burden of SCC among these organ recipients. Furthermore, we may have included some patients with a chronic organ disease, who never would have undergone organ transplantation because of contraindications, such as smoking in the case of lung transplantation, and severe lung disease in the case of heart transplantation. Inclusion of these patients, as well as unmeasured confounding from other lifestyle factors, may have overestimated our risk estimates for skin cancer among patients with chronic organ diseases.

In conclusion, we found an excess risk of NMSC, especially SCC, among organ recipients. Risk of SCC was highest among heart recipients, who are maintained on the most potent immunosuppressive regimens. Risk of BCC was more modest and similar among all organ recipients. We found no increased risk for MM among organ recipients. Our study suggests that treatments associated with organ transplantation are risk factors for SCC.

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REFERENCES

1. Harringer W, Haverich A. Heart and heart-lung transplantation: standards and improvements. World J Surg 2002; 26: 218–225.
2. Hoover R, Fraumeni JF Jr. Risk of cancer in renal-transplant recipients. Lancet 1973; 2: 55–57.
3. Kinlen LJ, Sheil AG, Peto J, Doll R. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. Br Med J 1979; 2: 1461–1466.
4. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohme I, Forsberg B, et al. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. Int J Cancer 1995; 60: 183–189.
5. Birkeland SA, Lokkegaard H, Storm, HH. Cancer risk in patients on dialysis and after renal transplantation. Lancet 2000; 355: 1886–1887.
6. Bouwes Bavinck JN, Hardie DR, Green A, Cutmore S, MacNaught A, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. Transplantation 1996; 61: 715–721.
7. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 1990; 49: 506–509.
8. Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 1999; 40: 177–186.
9. Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. J Am Acad Dermatol 1999; 40: 27–34.
10. Veness MJ, Quinn DI, Ong CS, Keogh AM, Macdonald PS, Cooper SG, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. Cancer 1999; 85: 1758–1764.
11. Adami J, Gabel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer 2003; 89: 1221–1227.
12. Lindelöf B, Sigurgeirsson B, Gabel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol 2000; 143: 513–519.
13. Kuijken I, Bouwes Bavinck JN. Skin cancer risk associated with immunosuppressive therapy in organ transplant recipients: epidemiology and proposed mechanisms. BioDrugs 2000; 14: 319–329.
14. Frank L. Epidemiology. When an entire country is a cohort. Science 2000; 287: 2398–2399.
15. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen, JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999; 46: 263–268.
16. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry – history, content, quality and use. Dan Med Bull 1997; 44: 535–539.
17. World Health Organization, International Association of Cancer Registries, Lyon, France at website: http://www.who.int/classifications/icd/adaptations/oncology/en/.
18. Pallesen L, Kofod T, Kirkegaard P, Mortensen SA. Odontogen fokussanering forud for organ transplantation. Tandlægebladet 2008; 112: 518–527.
19. Breslow, NE, Day NE. Statistical methods in cancer research. Volume II – the design and analysis of cohort studies. IARC Sci Publ 1987; 1–406.
20. Meier P, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. J Am Soc Nephrol 2002; 13: 204–212.
21. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet 2001; 358: 1042–1045.
22. Glover MT, Deeks JJ, Raftery MJ, Cunningham J, Leigh IM. Immunosuppression and risk of non-melanoma skin cancer in renal transplant recipients. Lancet 1997; 349: 398.
23. Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 1999; 397: 530–534.
24. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant 2004; 4: 905–913.
25. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. Transpl Int 2006; 19: 607–620.
26. Terhorst D, Drecoll U, Stockfleth E, Ulrich C. Organ transplant recipients and skin cancer: assessment of risk factors with focus on sun exposure. Br J Dermatol 2009; 161 Suppl 3: 85–89.
27. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science 2005; 309: 1871–1874.
28. Klinger M, Mazanowska O. Primary idiopathic glomerulonephritis: modern algorithm for diagnosis and treatment. Pol Arch Med Wewn 2008; 118: 567–571.
29. Rothman KJ. Epidemiology: an introduction. New York: Oxford University Press, 2002.