Epidemiogic aspects of skin cancer in organ-transplant recipients

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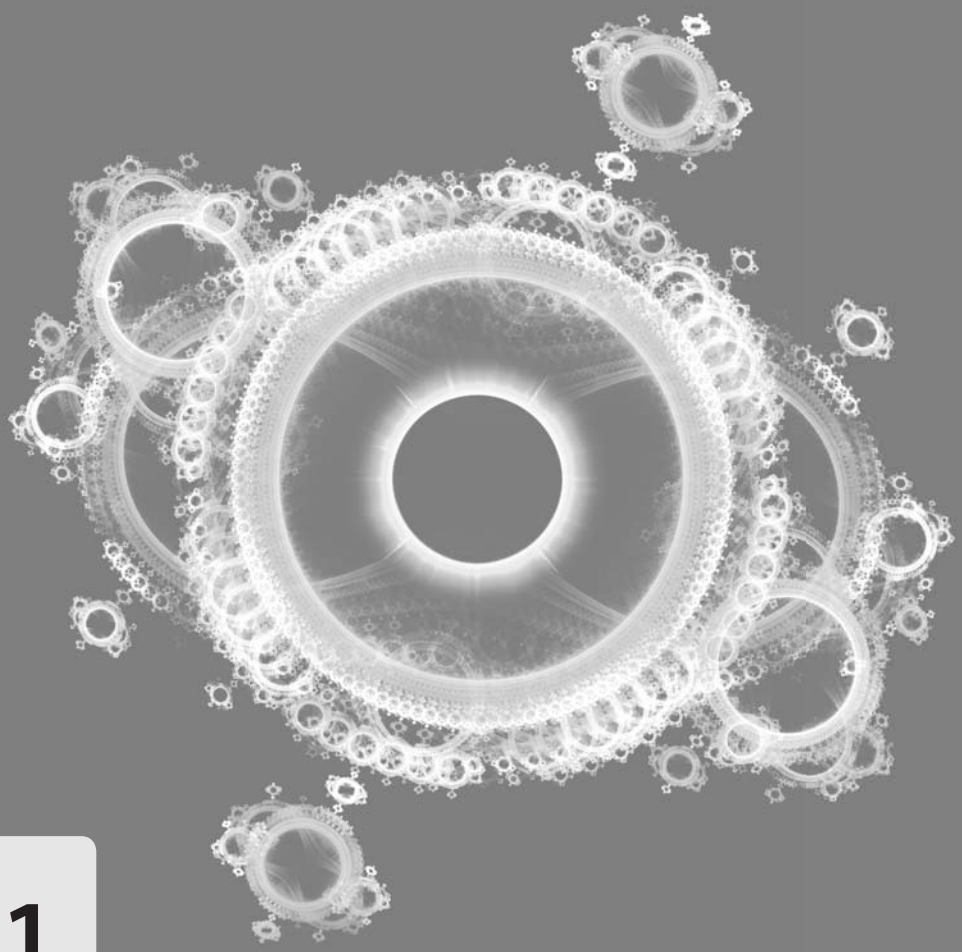

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General introduction

Parts of this introduction have been published before as:

The epidemiology of transplant-associated keratinocyte cancers in different geographical regions. *Cancer treatment and research. 2009; 146: 75-95*

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Organ transplantation

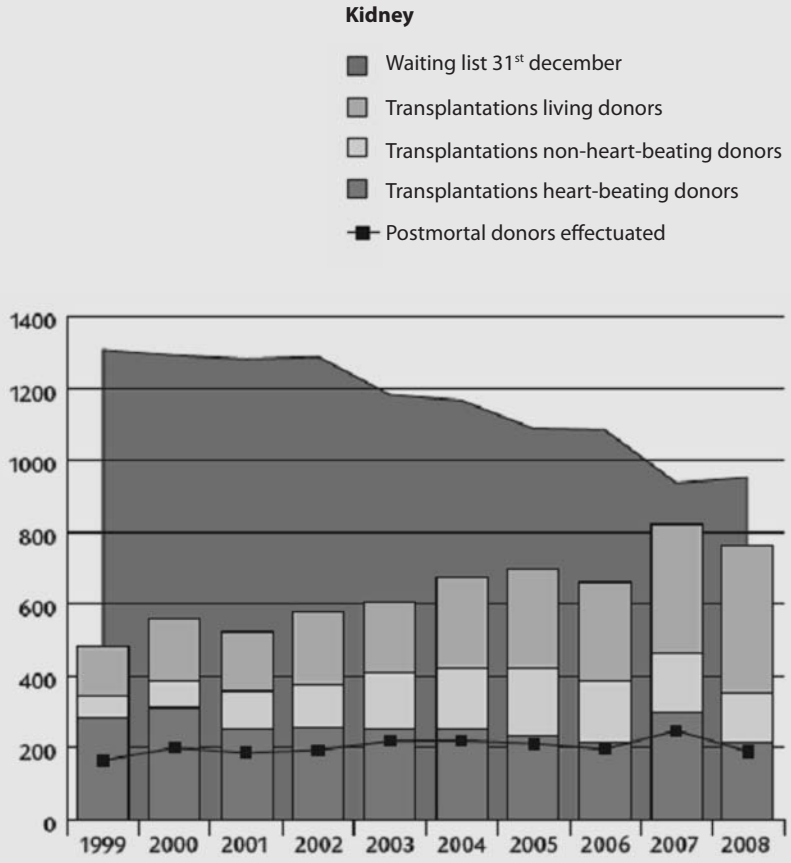
The first successful organ transplantation was a kidney transplantation between identical twins in Boston in 1954 [1-3]. Several years later, chemical immunosuppression with corticosteroids and azathioprine enabled transplantation between nonidentical individuals. Since 1966, kidney transplantations have also been performed in the Leiden University Medical Center (LUMC), the Netherlands. The introduction of new immunosuppressive agents and improvements in surgical techniques and post-transplant care made organ transplantation a routine and preferred therapy for treatment of end-stage renal, cardiac, hepatic and pulmonary failure [3] and pancreatic transplantation provides similar benefits for diabetic patients [4].

Currently, there are believed to be more than one million individuals worldwide with an organ allograft [5], and this number will further increase. However, the success is complicated by several problems, including the discrepancy between the demand for and the supply of organs and the need for continuous immunosuppressive medication. In the Netherlands, roughly 1200 patients are on the waiting list for organ transplantation and the mean time to kidney transplantation is approximately 4 years (figure 1). Complications from graft-preserving immunosuppression include an increased risk of malignancies [6], and of fungal, viral and parasitic infections [7, 8]. This chapter will provide a background of current knowledge of post-transplant cancer, with a focus on skin cancer. Furthermore, the increased incidence of other skin diseases in organ transplant recipients (OTR) will be discussed.

Incidence of cancer in organ transplant recipients

In the first 4000 patients undergoing kidney transplantation, over 40 primary malignant neoplasms were reported [6]. The increased risk of malignancies in OTR has been consistently supported by subsequent studies [9-13]. The overall risk for any cancer can be estimated to be 2- to 5-fold greater in OTR than in the general population [13-17]. This increased incidence has been shown to predominantly result from the occurrence of 4 distinct tumor types, namely non-melanocytic skin cancer (NMSC), lymphoproliferative disorders, anogenital dysplasias and Kaposi's sarcoma [9, 14, 16-19]. Recent data have indicated that thyroid cancers can be added to the group of more frequent cancers following organ transplantation [20]. Smaller, but significant, increases in hepatocellular and kidney cancers and some sarcomas have been observed [9, 14-17, 19]. For many common cancers including lung, colon, breast and prostate, the risk has been reported

Figure 1 Kidney transplantations in the Netherlands



The number of patients on the waiting list for a kidney transplantation on the 31st December per year is presented in blue. The number of patients receiving a living,
non-heart beating or heart-beating kidney transplantation per year in the Netherlands are presented by bars. Source of information: www.transplantatiestichting.nl
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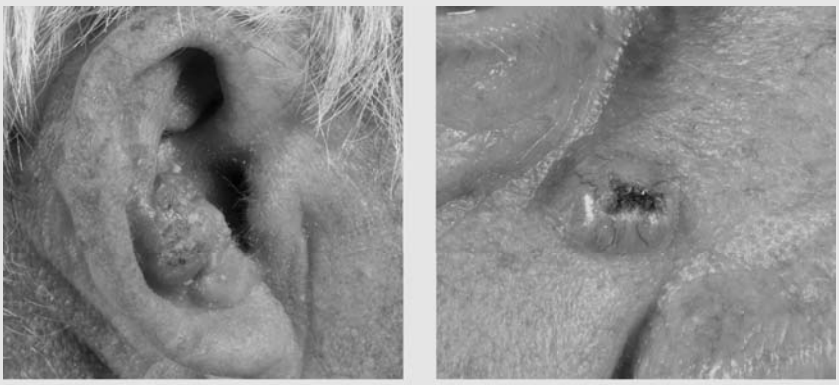
to be marginally or not significantly increased [12-14, 21]. Other studies have even shown a slightly reduced incidence of breast [22, 23] and prostate carcinoma [22].

Skin cancer

The incidence of malignant melanoma has been shown to be 3-fold elevated in OTR compared with the general population [22, 24]. Although low in absolute terms, the incidence of Kaposi's sarcoma represented a 200-fold higher risk [17]. The incidence of NMSC, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), has reported to be roughly 55 times elevated [14, 25-28]. As this increased NMSC risk results in excessive number of patients with NMSC, we will focus on the development of NMSC in OTR.

NMSC is a collective term for SCC and BCC. SCC arise from malignant proliferation of the keratinocytes of the epidermis. The common clinical presentation of SCC is an erythematous keratotic papule or nodule that arises within a background of sun-damaged skin (Figure 2a). Lesions may ulcerate and have metastatic potential in around 5% [29]. BCC arise from the basal layer of epidermis. No universally accepted classification exists for BCC, but the most common variant, accounting for approximately 60% of all primary BCC presents as a raised, translucent papule or nodule with telangiectasias (Figure 2b). As the lesions enlarge ulceration may occur, but usually BCC do not metastasize [29].

Figure 2 Representative images of skin cancer **A**) Patient with a squamous cell carcinoma of the ear. **B**) Patient with a basal cell carcinoma on the cheek.



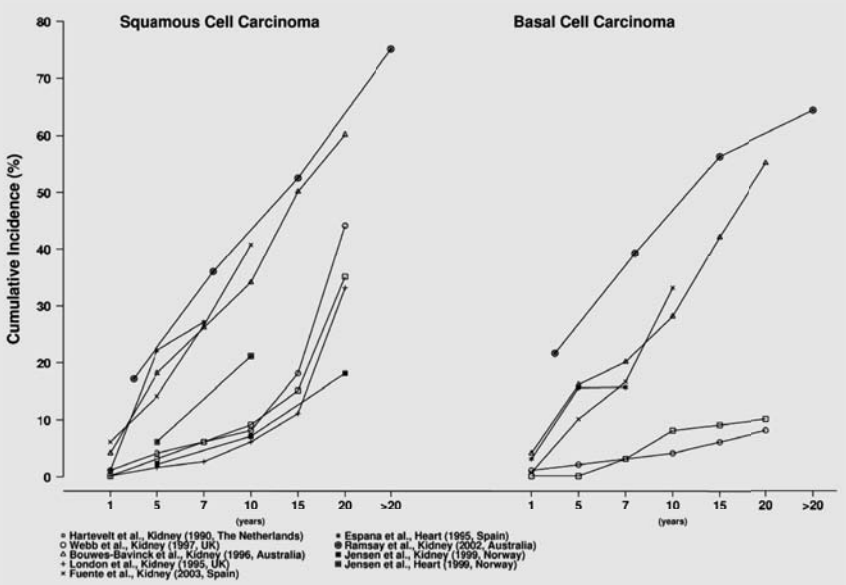
A B

The first report of increased NMSC in OTR came from Australia in the early 1970s, reporting seven patients with NMSC in a group of 51 kidney transplant recipients (KTR), which were immunosuppressed for up to 6 years [30]. Other studies from highly sun exposed areas in the USA and Australia followed [31-36], suggesting that sun exposure is an important risk factor for the development of NMSC. In OTR a predominance of SCC over BCC was shown [31-36], while in the general population BCC are more common than SCC. When reports of skin cancer in OTR in more temperate climates, such as Scandinavia, the Netherlands, Britain and Ireland, showed increased incidences of NMSC as well [9, 35, 37-43], it became more evident that limited sun exposure combined with immunosuppression can also result in the development of NMSC. A progressive increase in NMSC incidence with duration of immunosuppression was observed, indicating that immunosuppression is the key factor facilitating the development of NMSC in OTR [9, 39, 44-48]. Incidences of NMSC in OTR vary to a large extent from a 4- to 250-fold increased risk compared with the general population [39, 43]. Variability in the incidences between these studies may reflect that many factors play a role in NMSC development, including population differences in race, skin type, age, UV exposure and mean duration and type of immunosuppression. Furthermore, the variability in outcome may result from differences in the methods employed to determine the occurrence of NMSC. Some studies have reported incidence, others cumulative incidence, others relative risk, or the factor by which NMSC incidence is increased in OTR compared to a specified reference population. Yet others did not report the statistical methods used. We selected the population-based studies with high quality statistical analyses and summarized the data in Figure 3 and Table 1.

Several studies measured cumulative incidence of cutaneous SCC and BCC after organ transplantation (Figure 3). Bouwes Bavinck et al [44] and Ramsay et al [48] found equivalently high risks for SCC in the tropical Australian state of Queensland, with a cumulative incidence at 20 years of approximately 60% for both SCC and BCC (Figure 3). A study from Spain [46] only demonstrated cumulative incidence up to 10 years post-transplant, but showed a similar cumulative incidence compared with Australia (Figure 3). Meanwhile studies from the UK [49] and the Netherlands [39] found lower 20-year cumulative incidence rates for SCC of 34% and 40% respectively and 20-year cumulative incidence rates for BCC of 7% and 10%.

Another measure to express the incidence is the incidence rate per person years. The highest incidence rate that has been observed was 379 per 1,000 person years at risk for SCC and 127 per 1,000 person years for BCC in heart transplant recipients (HTR) in Australia [50] (Table 1). Studies from Spain, UK and The Netherlands found an incidence for SCC of 29/1,000, 71/1,000 and 7.6/1,000 person years respectively and for BCC of

Figure 3 Cumulative incidence of skin cancer in organ transplant recipients.



26/1,000, 22/1,000 and 3.3/1,000 person years [39, 45, 51]. To allow a proper comparison the incidence in the UK study (71/1,000) should be decreased by a factor 6, since this was the average number of cumulative SCC scored for given individuals [51].

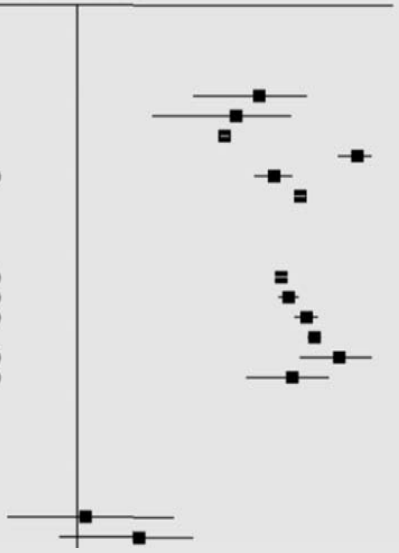
Other studies have provided incidence rates compared with the general population, presenting population-based standardized incidence ratios (SIR) [14-16, 27, 47]. To measure the SIR accurately, it is of importance that all cutaneous SCC and BCC are accurately reported to a comprehensive national cancer registry. The population-based SIR that were available for post-transplant SCC and post-transplant BCC are illustrated in Table 1. Based on these studies the risk for SCC is approximately 70 times increased and the risk for BCC 7 times increased compared with the general population.

Besides the incidence of NMSC it is of importance to determine the number of NMSC tumors per individual to measure disease burden and to design a more rational follow-up of these patients. Bouwes Bavinck et al [44] found an average of 10 NMSC tumors per OTR in Australia, Bordea et al [51] an average of 6 tumors per OTR in the UK, and Blohme et al [38] reported two OTR in Scandinavia with over 100 skin lesions each.

Table 1 Standardized incidence ratio.

HISTOLOGY/ORGAN STUDY (YEARS)	COUNT O/E	SIR (95%CI)	No. patients	Country or city / Comparison group	Standardised by sex/age/reference years
SQUAMOUS CELL CARCINOMA					
KIDNEY TRANSPLANTATIONS					
Hoxtell et al, 1977 (68-74)	First	4/0.11	36 (10-93)	495	Minnesota /Mineapolis-St Paul (survey)	Y/10yrs/71-72
Kinlen et al, 1979 (70-78)	First	3/0.13	23 (4-68)	3823	UK/Birmingham CR*	Y/5yrs/74
Gupta et al, 1986 (66-84)	NK	NK	18 (17-20)	523	Toronto / Detroit	Y/1yr/77-78
Hartevelt et al, 1990 (66-88)	All	38/0.15	253 (172-334)	764	Leiden / Eindhoven CR	Y/5yrs/83-85
Gjersvik et al, 2000 (83-32)	NK	NK	49 (33-70)	1020	Norway / CR	Y/1yr/calendar(1yr)
Moloney et al, 2006 (94-01)	All	282/3.4	82 (73-91)	1558	Ireland / CR	Y/1yr/94-200†
OTHER ORGANS +/- KIDNEY TRANSPLANTATIONS					
Adami et al, 2003 (70-97)	First	278/4.95	56 (50-63)	5931	Sweden / National CR	Y/1yr/calendar(1yr)
Jensen et al, 1999 (63-92)	First	97/1.49	65 (53-79)	2561	Oslo / National CR	Y/1yr/calendar(1yr)
Lindelof et al, 2000 (W) (70-94)	All	77/0.8	93 (73-116)	5356	Sweden / National CR	Y/1yr/calendar(1yr)
(M)		248/2.3	109 (95-123)			
Gjersvik et al, 2000 (83-32)	NK	NK	177 (81-336)	148	Norway / CR	Y/1yr/calendar(1yr)
Haagsma et al, 2001 (79-96)	First	7/0.1	70 (28-144)	174	The Netherlands / Mixture**	Y/1yr/calendar(1yr)
BASAL CELL CARCINOMA					
KIDNEY TRANSPLANTATIONS					
Kinlen et al, 1979 (70-78)	First	1/0.85	1.2 (0-7)	3823	UK / Birmingham	Y/5yrs/74
Hoxtell et al, 1977 (68-74)	First	3/0.88	3 (0.7-10)	495	Minnesota /Mineapolis-St Paul (survey)	Y/10yrs/71-72

SIR & 95% CI



The prevalence of OTR with multiple skin lesions was shown to vary between studies from 26 to 80%, which may be due to geographic differences, but also due to differences in length of follow-up and patient age [27, 33, 38, 39, 52-55]. According to a Scandinavian study, 25% of patients with a first NMSC have a second lesion within 13 months, and 50% have a second lesion within 3.5 years [27]. Liddington et al reported a mean interval of 15 months between detection of the first and second NMSC, and 11 months between the second and the third NMSC [42]. A French study showed that 34% of HTR and 52% of KTR with a first SCC developed a subsequent SCC within 3 years after the first SCC. After 5 years these percentages had risen to 64 and 67% in HTR and KTR, respectively [52]. A study from New Zealand showed that virtually all KTR with skin cancer developed multiple NMSC, with incidences of 30%, 50%, 60% and 80% at 1, 2, 3 and 5 years, respectively, after the first skin cancer [53]. These percentages are high compared with the general population, since the 3-year cumulative risk of a subsequent SCC after a first SCC in the general population has been described to be 18% [56]. While the risk for secondary SCC has been investigated in OTR, the risk of a subsequent BCC after the first BCC has not been reported in OTR. In the general population, approximately 50% of patients routinely treated for BCC developed multiple primary BCC during 10 years of observation [57, 58]. A meta-analysis of 7 independent studies showed a mean 3 year risk of 44% after an initial diagnosis of BCC [56].

Non-cutaneous malignancies

Large population-based cohort studies have reported that a range of non-cutaneous malignancies (NCM) occurs at increased rates in OTR, with an overall 2- to 5-fold increased cancer risk compared with the general population [13, 14, 16-18]. Among NCM we also count cancers of the mucous tissues. Anogenital dysplasias, comprising carcinoma of the vulva and anus, were 23- and 7-fold increased, respectively. The rate of lymphoproliferative disorders has been reported to be increased with a SIR of 7 for non-Hodgkin lymphoma [13, 14, 17, 18] and 4, 3 and 2 for Hodgkin's lymphoma [13, 14, 17, 18], multiple myeloma [13, 14, 17] and leukemia [13, 14, 17], respectively. Rates of liver and stomach cancer as well as epithelial lung cancer were approximately 2-fold increased. Most other common epithelial cancers, such as breast, prostate, ovarian and colorectal cancers, occurred at the same rate as in the general population [13, 14, 16-18]. Follow-up times of these studies were approximately 20 years.

Association between skin cancer and non-cutaneous malignancies in organ transplant recipients

In immunocompetent patients with cutaneous SCC, a 2-fold increased risk of NCM has been observed [59-61]. However, other studies did not show an overall increased risk of NCM in SCC patients [62]. In BCC patients, the overall cancer incidence has also been reported to be significantly elevated [61, 63, 64]. Vice versa, the occurrence of SCC as second primary malignancy after any NCM has been described to be increased in the general population [65]. Furthermore, Brennan et al showed an increased risk of NMSC after non-Hodgkin lymphoma [66]. The fact that cancer patients were at an increased risk for new primary cancers, may be explained by a common pathogenic pathway involved in the different types of cancer, and lifestyle factors of the patient, such as UV exposure, smoking and diet [67]. It is unknown whether the development of cutaneous SCC and/or BCC is associated with an increased risk of NCM in OTR as well, like in immunocompetent patients.

Risk factors for skin cancer in organ transplant recipients

The best-studied factors that appear to favor development of skin cancer are age at transplantation, male sex, fair skin type, high UV exposure, the presence of actinic keratoses, and the length and level of immunosuppression. Few investigators found all of these to be independent risk factors, but they were consistently reported across a wide range of studies [27, 28, 40, 44, 46, 47, 51, 68-71]. In a prospective study examining the first 3 years of immunosuppression in KTR from Spain, Ferrándiz [69] found a cumulative risk for NMSC of 18% with age at transplantation and occupational UV exposure being significant risk factors. Naldi from Italy [70] found age at transplantation and male sex to be the most important risk factors. Also from Italy, Caforio [68] found age at transplantation, fair skin type, high UV exposure, actinic keratoses and a high rejection score to be independently associated with an increased SCC risk in HTR. Since cumulative immunosuppressive load is difficult to calculate, a high rejection score in the first year post-transplantation was proposed to be a useful predictor for patients at risk. However, other studies did not confirm the association between number of rejections and development of NMSC in OTR [51, 70, 72, 73].

The presence of human papillomavirus (HPV) has been suggested to be a risk factor for SCC, although a causative role for HPV in skin cancers in OTR has not been proven. HPV DNA was found in 65% to 90% of skin cancers that developed in OTR [74-76], while in immunocompetent individuals approximately in 40% of the skin cancers HPV

DNA was found [75, 77, 78]. The rate of HPV detection in normal sun-exposed skin has been described to be higher in OTR with skin cancer compared with those without skin cancer. This supports the hypothesis that OTR have persistent HPV infection that predisposes to oncogenesis [79]. However, HPV is also frequently present in the hair follicles and normal skin from OTR [80]. Furthermore, comparing OTR with and without skin cancer, others have shown an equally high prevalence of HPV DNA in keratotic skin lesions in both groups of patients, and a similar detection rate and spectrum of HPV infection in hyperkeratotic papillomas and actinic keratoses [81]. Recent epidemiological [77, 82] as well as experimental studies [83] have suggested a possible synergetic effect between HPV infection and UV radiation in carcinogenesis of the skin. Two major risk factors for skin cancer in OTR, UV exposure and prolonged immunosuppressive therapy, will be discussed in more detail below.

Ultraviolet radiation

UV exposure is the primary risk factor for NMSC both in the general population [84] and in OTR [68, 85]. This is illustrated by an increased risk of skin cancer in patients with high sun exposure before organ transplantation [46, 68, 86]. Furthermore, the cumulative risk for SCCs was reported to be greater in countries with a high level of UV radiation, such as Australia (34% at 10 years) [44] or Spain (33% at 10 years) [46], compared with countries with limited sun exposure, such as the Netherlands and Norway (7% at 10 years) [39, 47]. The preferential location of SCC on sun-exposed areas further supports the pathogenic role of sunlight [39]. It is assumed that the oncogenic properties of UV radiation are due to a direct mutagenic effect and an immunosuppressive effect. It has been shown that UV light is a keratinocyte mutagen, which can cause mutations, such as cytosine to thymine transitions at cytosine-containing dipyrimidine sites [87]. When these mutations affect the function of sufficient oncogenes, tumor-suppressive genes, and important housekeeping genes, outgrowh of neoplastic keratinocytes can occur. UV-induced immunosuppression is a highly complex process and several different pathways are involved [84, 88-90]. In particular, low doses of UV light radiation reduce the number and function of epidermal Langerhans' cells, impairing their role in the immune response against virus-infected cells and transformed cells. UV light radiation can also induce systemic immunosuppression by inducing the generation of soluble mediators, notably cis-urogenic acid and interleukin-10 [84, 88-90].

Immunosuppressive therapy

The maintenance immunosuppressive therapy in OTR usually consists of prednisone in combination with immunosuppressants such as azathioprine (purine-antagonist),

mycophenolate mofetil (inosinemonophosphatehydrogenase-inhibitor), cyclosporine or tacrolimus (calcineurine-inhibitors), and sirolimus or everolimus (mTOR-inhibitors). Acute rejection in OTR will usually be treated with high doses of polyclonal antibodies against thymocytes (ATG) and monoclonal antibodies against CD3 (muromonab). In hairless mousemodels it has been shown that classical immunosuppressants, azathioprine and cyclosporine, speeds up UV carcinogenesis and adversely affects repair of UV-induced DNA-damage in skin cells [91]. Moreover, Azathioprine has been reported to induce selective UVA photosensitivity, thus increasing the DNA damage caused by UV exposure [92]. Cyclosporine can impair UV-induced apoptosis, which also increases the risk of skin cancer [93]. In contrast to the traditional immunosuppressants, mycophenolate mofetil and sirolimus, did not enhance UV carcinogenesis [94]. Although mycophenolate mofetil, like azathioprine, interferes with purine synthesis, it does not give rise to incorporation of (6-thio-guanine) pseudobases that photosensitize DNA. Furthermore, sirolimus operates through an entirely different mechanism by blocking mTOR (mammalian target of rapamycin), which has been shown to have an antiangiogenic effect, resulting in impaired tumor outgrowth [94, 95]. However, so far, there is no convincing clinical evidence for differences in oncogenic potential between the specific immunosuppressive agents. Comparison of incidence rate by type of immunosuppressive drug is difficult, because the regimen of immunosuppressive agents is strongly associated with the time period in which the patient is transplanted. A recent study showed that treatment with azathioprine was associated with a significant increased risk for SCC [96]. Evidence also suggests that sirolimus, a mTOR inhibitor, compared with other immunosuppressive medications may confer a decreased risk of skin cancer [97, 98].

Rather then the type of immunosuppressive agent, the total level of immunosuppression may determine the risk of skin cancer [44, 70, 99, 100]. In a prospective trial in which patients were randomly assigned, KTR receiving low dose cyclosporine regimen had a significantly lower incidence of secondary skin cancers compared with the patients using normal dose cyclosporine [68]. Furthermore, the greater degree of immunosuppression after heart transplantation, to prevent the catastrophic rejection of the donor organ, has been shown to result in a higher incidence of skin cancer in HTR compared with KTR [47, 54, 101, 102].

Other skin diseases in organ transplant recipients

Besides skin cancers, also benign skin tumors [28, 39, 44, 47] and fungal, viral, and bacterial skin infections [103-105] are frequently observed in OTRs. The prevalence of skin infections is very high and several studies have described that 55% to 97% of OTR do have some type of infection [104-108]. The spectrum of skin infections differs according to the post-transplant time period [105]. During the first month post-transplant, infections mainly result from surgical interventions [103]. After the first month post-transplant, infectious skin diseases are more frequently a result of severe immunosuppression, manifesting in infections with herpes viruses (herpes simplex virus, varicella-zoster virus, cyto-megalovirus, Epstein-Barr virus), yeasts (Candida), and bacteria [105]. Six months and more after transplantation, the chronic and progressive infections start to exert clinically significant effects [103, 105], of which infections with HPV have been most frequently described [79, 103, 109]. Compared with the large number of studies focusing on the development of malignant and benign skin tumors in OTR, infectious and inflammatory skin diseases were only studied scarcely [79, 103-109].

Aim and structure of the thesis

The aim of the studies presented in this thesis is broadly twofold. Firstly, we aimed to determine the pattern and frequency of SCC, BCC, NCM and skin diseases in OTR transplanted in the Leiden University Medical Center *(descriptive epidemiology)*. Increasing the recognition of these clinical complications can help to provide a rationale for more extensive follow-up of OTR and allow more rapid clinical interventions. Secondly, we aimed to identify causes for the increased incidence of malignancies in OTR *(analytic epidemiology)*. Identification of the risk factors involved in the development of SCC, BCC, and NCM may increase the efficiency of OTR follow-up.

Chapter 2 describes the standardized morbidity ratio of NCM, SCC and BCC in KTR who had received a transplantation at the Leiden University Medical Center between 1966 and 2006.
Chapter 3 determines the risk to develop a second SCC or BCC following the occurrence of the first SCC or BCC in a cohort of KTR and studies risk factors for the development of subsequent SCC or BCC.
Chapter 4 investigates the frequency and number of registered skin diseases in OTR

transplanted between 1966 and 2006 in a single centre, which were diagnosed between 1994 and 2006. Furthermore, the relative contributions of the different skin diseases in relation to the number of years after transplantation were studied.

Chapter 5 compares the cumulative incidence of skin cancer in SPKTR with the cumulative incidence of skin cancer in KTR in relation to potential risk factors of skin cancer.

Chapter 6 studies the risk of NCM after the development of cutaneous SCC and/or BCC in KTR.

Chapter 7 studies whether the number of transplantations, as a marker for the rejection status of the patient, is associated with the risk of the development of malignancies. The risk for cutaneous SCC and other malignancies are analyzed separately.

Chapter 8 summarizes and discusses the results described in the preceding chapters.

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