The Epidemiology of Transplant-Associated Keratinocyte Cancers in Different Geographical Regions

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Introduction

There are believed to be more than 1 million individuals worldwide currently with an organ allograft [1], and a further steep increase in numbers is expected in the next decade. The life-enhancing benefits of organ transplantation are undisputed, but come at a cost. Complications from graft-preserving iatrogenic immunosuppression include a significantly increased risk of malignancy. More than 40 primary malignant neoplasms were reported in the first 4,000 patients to undergo renal transplantation [2], and this early observation has been consistently supported by subsequent studies [3–7].

The overall risk for any cancer is reported to be two- to sixfold greater than in the general population, although for many common cancers, including lung, colon, breast, and prostate, the risk is small or is not increased [6–9]. In contrast, there is a disproportionate increase in the incidence of four tumour types, namely, keratinocyte cancers (KC) (comprising basal cell carcinoma and squamous cell carcinoma), post-transplant lymphomas/lymphoproliferative disorders (PTLD), anogenital dysplasias, and Kaposi's sarcoma, with smaller but significant increases in hepatocellular and renal cancers and some sarcomas [3, 6, 8, 10–12].

In Caucasian adults, KC are overwhelmingly the most common post-transplant tumour [4]. KC are also the most frequent malignancy following paediatric renal transplantation and the second most common (after lymphoproliferative disease) after other transplantations in children [13, 14]. Different post-transplant cancer patterns are seen in other populations. For example, Kaposi's sarcoma is the most common post-transplant skin tumour among organ transplant recipients (OTR) from endemic areas, such as around the Mediterranean and sub-Saharan Africa, or in those of Caribbean origin [5]. Similarly, Kaposi's sarcoma is the most common post-transplant malignancy in Saudi Arabia [15, 16], whereas urogenital cancers

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and hepatoma are the most common malignancies in Taiwan [17, 18]. In a cohort of 542 renal transplant recipients (RTR) from South Africa, the incidence of overall cancer was comparable in white and non white patients, but although KC was the most common cancer in whites, Kaposi's sarcoma was the most common cancer in non whites, in whom it accounted for almost 80% of all cancers [19].

Accumulating evidence suggests that tumours that occur at high frequencies in the transplant population are those associated with a viral aetiology; anogenital cancer is unequivocally associated with human papillomavirus (HPV) infection (specifically, high-risk mucosal types such as HPV 16), non-Hodgkin's lymphoma with Epstein–Barr virus, and Kaposi's sarcoma with human herpesvirus 8 [9]. The viral aetiology of such tumours of the skin is described in later chapters.

Keratinocyte Cancers

Keratinocyte cancers (KC) are the most common cancers in fair-skinned individuals [20–22], and the two main types, basal cell carcinoma and squamous cell carcinoma, are clinically and histologically distinct. Basal cell carcinomas (BCC) are slow-growing tumours that arise de novo and rarely metastasize [23–26]. Squamous cell carcinomas (SCC) grow more rapidly, are associated with Bowen's disease (carcinoma in situ) and with precursor lesions, namely, actinic keratoses (AK), and have a potential for metastasis [27, 28]. BCC are considerably more common in the general population than SCC, with a BCC/SCC ratio in the UK of about 4:1 [29], and also in Australia of 4:1 in 1985, but lowering to 2.5:1 in 1995 [30].

Epidemiological data and laboratory studies strongly implicate ultraviolet radiation (UVR) as the major aetiological factor for KC (reviewed in [31]) and worldwide, the incidence has been increasing dramatically since the 1960s, with an annual increase of 3% to 8% in white populations [29, 30, 32–35], probably as a consequence of greater affluence, sun-seeking behaviour, and ageing populations [36]. More than 1 million cases per year are recorded in the United States [28, 37] and more than 44,000 cases per year in the UK, although precise estimation of incidence trends is very difficult, because KC are not recorded by the majority of cancer registries [38–40]. Based on rates in South Wales where accurate local skin cancer registration does exist, incidence is estimated at up to 265.4 per 100,000 [29]. This rate would equate to 100,000 cases per year in the UK at large, substantially more than the registered 44,000 cases. Although mortality is low [39], KC are a cause of significant morbidity and a major burden on health care resources [31, 39, 41, 42].

Region-Specific Factors in the Epidemiology of Post-Transplant Skin Cancer

Historically, the earliest report of increased cutaneous SCC in OTR came from Australia in the early 1970s when Walder and colleagues reported 7 patients with KC in a group of 51 RTR immunosuppressed for up to 6 years [43]. Many more

SCC than BCC were diagnosed, substantially reversing the ratio seen in the general population. Further reports of KC in transplant patients from the United States and Australia followed [44–51]. These reports confirmed the predominance of SCC over BCC, and many additionally demonstrated a progressive increase in KC incidence with duration of immunosuppression. In fact, many early studies had reported no increased risk for BCC [43, 47, 50], but later studies indicated an excess risk for BCC, of the order of 2- to 10 fold [51–53].

Reports of skin cancer in RTR resident in temperate climates appeared later in the literature. Review to the end of the 20th century shows an excess risk for KC reported from Scandinavia [54, 55], the Netherlands [53], Britain [3, 50, 56–58], and Ireland [59]. Again, a predominance of SCC was found, but many also reported an increased incidence of BCC, especially in populations from southern Europe in Italy and Spain [60, 61]. The overall risk of KC in transplant recipients was reported as 4 times that expected in the Irish population [59], 7 to 17.6 times that expected in Scandinavia [54, 55], and up to 250 times that expected in the Netherlands [53].

Variability of estimates between these studies is likely to reflect many factors, including the case mix of the populations and differences in race, skin type, age, UV exposure, and mean duration of immunosuppression, as well as differences in the methods employed to estimate the occurrence rates of KC. Some studies have reported incidence, others cumulative incidence, others relative risk or the factor by which KC incidence is increased in OTR compared to a specified reference population. Other studies did not report the statistical methods used. One of the main difficulties is the lack of high-quality population-based studies based on national cancer registries and calendar period-specific incidence rates in the general population. Here the Scandinavian countries and Ireland have a great advantage with the reliable reporting of cutaneous SCC (reporting of BCC is more problematic) to a comprehensive national cancer registry [8, 10, 62–64]. In many (most) other countries there are no accurate comparison rates for skin cancer risk in the general population because of their lack of registration. Reporting only the first of multiple tumours in any one individual leads to further underestimation of the true incidence.

We have undertaken a systematic review of all available reports in the literature of skin cancers in solid organ transplant recipients, and reviewed those in which the baseline characteristics have been clearly stated and the authors have reported either a cumulative rate of skin cancer or an incidence rate or a relative risk. Despite the lack of comparative regional data, it has been possible to draw some conclusions about the epidemiology of skin cancers in transplant recipients in different regions of the world.

Search Strategy

An extensive literature search was performed in PubMed using synonyms for relevant words of the clinical question: “What is the incidence of skin cancer post-organ transplantation?” First, a combination of “skin cancer” and “transplantation” (both

as subheadings) was made in which "transplantation" was matched to the subheading "adverse effects and/or complication." Only English articles were included, and case reports and editorials were excluded, resulting in 448 articles. To include articles reporting malignancies in general without skin cancer as a subheading, "transplantation" (matched to "incidence") and "malignancies" were combined, which resulted in 501 articles. Finally, a broad selection was performed (7,786 references) using various terms for "skin cancers" combined with terms for "transplantation" matched to "incidence," resulting in an additional 428 articles. Full details of search synonyms are given in Box 1 (see Appendix).

After exclusion of duplicates, a total of 1,377 articles remained. A selection was made using title and/or abstract, resulting in 329 articles that appeared to match the clinical question of the incidence of skin cancer post-solid organ transplantation. For these 329 articles, full texts were evaluated and scored (A, B, C, D, or no score) where A was a "good article" with cumulative rate of skin cancer given and B was a "sufficient article" without cumulative rate of skin cancer, but with incidence rate or relative risk given. The full scoring system is given in Box 1 (Appendix). Only data from "A" and "B" articles have been used for the tables and graphs shown in this chapter. Complete details on "A" and "B" articles are available at the SCOPE website: http://www.scopenetwork.org/.

Summary of the Evidence

Data from 58 "good" or "sufficient" articles (scoring "A" or "B") were used to compare the incidence of skin cancer after organ transplantation in Australia, USA/Canada, southern Europe, and northern Europe. Comparative rates for SCC, KC, or BCC are shown in Table 1a–c, respectively. Table 2 documents the relative risk of SCC and BCC where this has been directly compared in the same population using the same epidemiological methods. Table 3 shows reported SCC/BCC ratios according to organ transplant type (heart, kidney, liver). Cumulative incidences from different regions of the world are shown graphically (Fig. 1), with population-based standardized incidence ratios (SIR) for SCC and BCC in Fig. 2.

Discussion

The influence of organ and pretransplant diseases on post-transplant malignancy has already been addressed (see preceding chapter by Euvrard and Claudy). Here we focus on the epidemiology of post-transplant skin cancers with reference to region-specific factors. Most of the population-based studies examining the incidence of post-transplant skin cancer pertain to populations of northern Europe, Australia, and the United States, whereas most of the studies from developing countries have not been population based and the number of patients and years of follow-up are limited. Consequently, there is an absence of good comparative data. It is apparent that the highest incidence rates have been reported in Australia [65–67], whereas

Table 1 (a) Risk of SCC in organ transplant recipients[a]; (b) risk of KC in organ transplant recipients[b]; (c) risk of BCC in organ transplant recipients[c]

Country	Authors	Year	Type of Transplant	No of patients	Length of follow up (years)	Incidence/ 1000/year	Ratio[d,e,f] of observed to expected incidence (95% CI)
(a)							
Australia	Ong	1999	Heart	400	5.5 (0.5–13) Median	379	
USA	Hoxtell	1977	kidney	495			36.4 (9.9–93)
Canada	Gupta	1986	kidney	523			18 (17–20)
Spain	Espana	1995	Heart	92	3.6 (0.1–9.5) Mean	29	
Italy	Montagnino	1996	kidney	854			6.2 ($p = 0.002$)
Norway	Gjersvik	2000	kidney	1020			49 (33–70)
The Netherlands	Hartevelt	1990	kidney	764	8.7 (1–21) Mean	7.6	253 (172–334)
United Kingdom	Bordea	2004	kidney	979	7.5 (2–23) Mean	71	
Ireland	Moloney	2006	kidney	1558	5.72 (0–16) Median		82 (73–91)
(b)							
USA	Otley	2005	heart	8594	3.0 Median	52	
USA	Otley	2005	liver	8075	2.9 Median	11	
Spain	Espana	1995	heart	92	3.6 (0.1–9.5) Mean	45	
Spain	Herrero	2005	liver	170	5.2 (0.5–14) Median	43	20.3 (14.7–27.3)
Italy	Naldi	2000	heart	267	2.5 (0.2–10) Median	15	
Italy	Naldi	2000	kidney	1062	4.0 (0.3–26) Median	9.1	
Sweden	Blohme	1984	kidney	129	(3–16) Only range		7.6 (4.1–13.11)[g]
Sweden	Lindelof	2000	kidney	5356	5.6 (0–24) Mean		109 (95–123) men 93 (73–116) women
Sweden	Adami	2003	kidney	5931	6.8 (0–27) Mean		56 (50–63)
The Netherlands	Hartevelt	1990	kidney	764	8.7 (1–21) Mean	9.0	
The Netherlands	Haagsma	2001	liver	174	5.1 (1.5–19) Median		70 (28–144)
UK	Bordea	2004	kidney	979	7.6 (2–23) Mean	141	
Ireland	Moloney	2006	kidney	1558	5.7 (0–16) Median		33.3 (30.3–36.2) Excluding carcinoma-in-situ

Table 1 (continued)

Country	Authors	Year	Type of Transplant	No of patients	Length of follow up (years)	Incidence/ 1000/year	Ratio[d,e,f] of observed to expected incidence (95% CI)
(c)							
Australia	Ong	1999	Heart	400	5.5 (0.5–13) Median	127	
USA	Hoxtell	1977	kidney	495			3.4 (0.7–9.9)
Canada	Gupta	1986	kidney	523			1.4 (0.7–2.2)
Spain	Espana	1995	Heart	92	3.6 (0.1–9.5) Mean	26	
Italy	Montagnino	1996	kidney	854			5.7 ($p = 0.02$)
The Netherlands	Hartevelt	1990	kidney	764	8.7 (1–21) Mean	3.3	10 (6–15)
United Kingdom	Bordea	2004	kidney	979	7.6 (2–23) Mean	22	
Ireland	Moloney	2006	kidney	1558	5.7 (0–16) Median		16 (14–18)

[a] SCC: Squamous cell carcinoma; CI: Confidence interval; No: number;
[b] KC: Keratinocyte Skin Cancers; CI: Confidence interval; No: number;
[c] BCC: Basal cell carcinoma; CI: Confidence interval; No: number;
[d] SCC: Observed incidence in transplant patients divided by the expected incidence in the general population.
[e] KC: Observed incidence in transplant patients divided by the expected incidence in the general population. Blohme used psoriasis patients as "general population."
[f] BCC: Observed (age specific) incidence in transplanted patients divided by the expected incidence in the (age specific) general population.
[g] Estimated.

Table 2 Relative risk of SCC compared with relative risk of BCC

Country	Authors	Year	No of pt	Length follow up (years)	Ratio* of observed to expected incidence (95% CI) SCC	Ratio* of observed to expected incidence (95% CI) BCC
Renal transplant recipients						
USA	Hoxtell	1977	495		36 (9.9–93)	3.4 (0.7–9.9)
Canada	Gupta	1986	523		18(17–20)	1.4 (07–2.0)
Italy	Montagnino	1996	854		6.2 (p = 0.002)	5.7 (p = 0.02)
The Netherlands	Hartevelt	1990	764	8.7 (1–21) Mean	253 (172–334)	10 (6–15)
Ireland	Moloney	2006	1558	5.7 (0–16) Median	82 (73–91)	16 (14–18)

SCC: Squamous cell carcinoma; BCC: Basal cell carcinoma; CI: Confidence interval; No: number; pt: patients;
*Observed (age specific) incidence in transplanted patients divided by the expected incidence in the (age specific) general population.

Table 3 SCC/BCC ratios

Country	Authors	Year	No of pt	% pt KC	SCC/BCC ratio	Mean no of cancers	Length of follow up (years)	Mean time to presentation (years)
Heart transplant recipients								
Australia	Ong	1999	400	38	3.0		5.5 (0.5–13) Median	
USA	Lampros	1998	248	17	8.6	4.7	5.1 Mean	3.3 Mean
Spain	Espana	1995	92	16	1.5		3.6 (0.08–9.5) Mean	2.6 Mean
Italy	Caforio	2000	300	16	1.4		4.6 (0.1–12) Mean	
Italy	Naldi	2000	267	8.6	1.1		2.5 (0.2–10) Median	
Italy	Fortina	2004	230	21	2.2	2.5	9.1 (3.0–15.6) Mean	5.2 Mean
Renal transplant recipients								
Australia	Bouwes Bavinck	1996	1098	25	2.9	10	5.0 (0–24.3) Median	4.6 (0.3–8.9) Mean
Australia	Ramsay	2002	361	52	2.0	21	7.1 (2.3–13.1) Median	4.2 Median
Australia	Carroll	2003	310	42	3.1		(0->20) only range given	
South Africa	Moosa	2005	185	5.4	1.7	5.9	6.3 Mean	5.3 Mean
Spain	Fuente	2003	174	22	0.7	3.6	6.0 (1–11.7) Median	3.3 Mean
Spain	Marcen	2003	793		1.0		6.3 (0.5–12) Mean+/−SD	9.4 (3.4–16) Mean+/−SD
Italy	Naldi	2000	1062	6.7	2.6		4.0 (0.25–26) Median	
France	Euvrard	1995	580		2.4		Unclear	
Netherlands	Hartevelt	1990	764	6.2	3.6		8.7 (1–21) Mean	9.1 (4.6–14) Mean
UK	Liddington	1989	598	4.8	3.6	3.2	(0–12) Only range	7.1 (3.6–11) Mean
UK	Bordea	2004	979		3.2		7.6 (2–23) Mean	7.8 Mean
Ireland	Moloney	2006	1558		2.6		5.7 (0–16) Median	
Liver transplant recipients								
Spain	Xiol	2001	137	10	4.0	1.5	5.8 (3.6–8.7) Median	
The Netherlands	Haagsma	2001	174	6.9	1.6	1.8	5.1 (1.5–19) Median	
UK	Kelly	1998	888	1.7	4.0		4.4 (2.6–6.2) Mean	

SCC: Squamous cell carcinoma; BCC: Basal cell carcinoma; No: number; pt: patients;
KC: Keratinocyte skin cancers; % pt KC: Percentage of patients with a keratinocyte skin cancer;
SD: Standard deviation; SCC/BCC ratio:

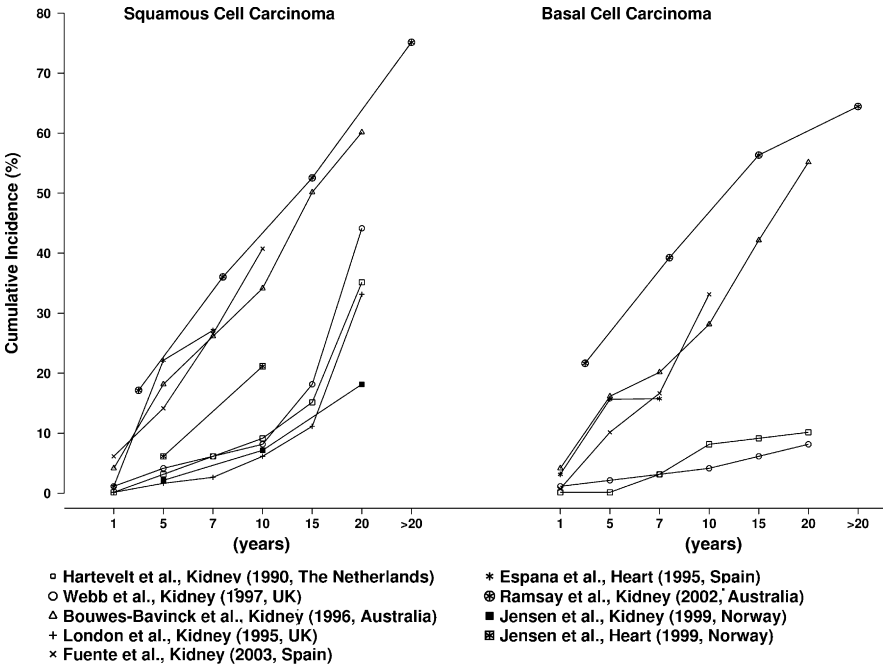


Fig. 1 Cumulative incidence

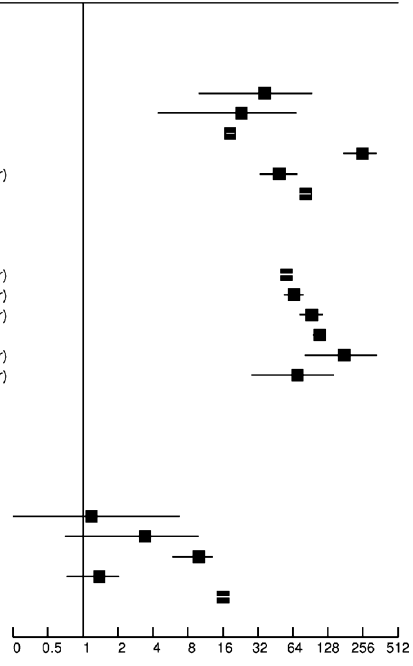
KC is reported infrequently in darker-skinned communities from developing countries. In developing countries, the overall incidence of any post-transplant cancer is generally much lower, with one review finding that only around 5% of 15,825 OTR developed malignancy compared with around 14% of 36,628 OTR from developed countries [19]. Japan and Taiwan seem to differ from both Western countries and the developing world. Two recent studies report little or no KC and no Kaposi's sarcoma [18, 68]. There was one study from South Africa examining skin cancer in 542 RTR [69], but no others from developing countries with data on KC, perhaps reflecting its rarity in these populations post transplantation. This finding accords with the data from South Africa, where skin cancers excluding Kaposi's sarcoma were seen only in patients of European origin [69].

An Increased Incidence of Post-Transplant SCC Occurs in All Areas of the Developed Western World and Is Highest at Low Latitudes

Studies throughout the Western world confirm a greatly increased incidence in cutaneous SCC after organ transplantation and consistently show that this risk increases with duration after transplantation (see Table 1a, Fig. 1). The highest risk is seen for heart transplant recipients in Australia, where an incidence of 379 per 1,000

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 (83-92)	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/94-2001
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 (83-92)	NK	NK	177 (81-336)	148	Norway / CR	Y/1yr/calendar(1yr)
Haagsma et al, 2001 (79-96)	First	7/0.1	70 (26-144)	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
Hartevelt et al, 1990 (66-88)	All	18/1.81	10 (6-15)	764	Leiden / Eindhoven CR	Y/5yrs/83-85
Gupta et al, 1986 (66-84)	NK	NK	1.4 (0.7-2)	523	Toronto / Detroit	Y/1yr/77-78
Moloney et al, 2006 (94-01)	All	143/8.9	16 (14-18)	1558	Ireland / CR	Y/1yr/94-2001

SIR & 95% CI



* CR= Cancer Registry; ** Mixture= Eindhoven before 1989 and National Cancer Registry after 1989
Y= yes; NK: not known; O= observed; E= expected; yr= year; No= number; CI= confidence interval

Fig. 2 Standardised incidence ratio (SIR)

person years at risk has been recorded [66]. Similarly, Bouwes Bavinck [65] and Ramsay [70] found equivalent high risks for SCC in the subtropical/tropical Australian state of Queensland, with a cumulative incidence at 20 years of 60% and 75% for those transplanted over 20 years (Fig. 1). Another study from Australia reported lower than expected rates, namely, a cumulative incidence of 38% for SCC at 20 years or more post transplant [71], but this was not a true incidence, rather a predicted incidence based on the number of skin cancers recorded between two different time points using data acquired from the ANZDATA cancer registry. Furthermore, the ANZDATA cancer registry lacks completeness for skin cancer: A previous study found ANZDATA failed to report 28% of post-transplant skin cancers [70] and recorded only the first episode of SCC (or BCC) post transplant.

A study from Spain [72] gave only cumulative incidence up to 10 years post transplant but showed high rates of increase similar to those observed in Australia (see Fig. 1). Studies from the UK [73] and The Netherlands [53] found lower 20-year cumulative incidence rates for SCC, 30% and 35%, respectively. Indeed, Australian rates were consistently higher than rates reported in diverse European centres for which incidence or relative risk estimates were available (see Table 1a). Studies from Spain, UK, and The Netherlands found an incidence for SCC of 29 per 1,000, 71 per 1,000, and 7.6 per 1,000 person-years, respectively [53, 61, 74]. The high incidence in this UK study can be explained by the inclusion of cumulative (multiple) SCC for given individuals, with an average of six tumours per patient [74]. The incidence of the first SCC would be lower by a factor of six, at least.

Cutaneous SCC Is the Dominant Skin Cancer Following Organ Transplantation, and There Is a High Incidence of Multiple Tumours

The most frequently encountered post-transplant skin cancers are SCC, and in some transplant cohorts SCC account for 90% of all skin cancers [75]. Unfortunately, valuable information on SCC incidence in other studies from the United States, Southern Europe, and Northern Europe is missing because they reported only all KC combined (as shown in Table 1b), rather than SCC and BCC separately. The post-transplant KC incidence rate in cardiac transplant recipients (CTR) from the United States and Spain is very similar [61, 76], with 52 and 45 per 1,000 person-years, respectively. Two studies from The Netherlands and Italy [53, 77] found an incidence for post-transplant KC of 9 per 1,000 person-years based their incidence data on the first SCC or first BCC, so their estimates were considerably lower than that reported from Oxford, UK [74], of 141 per 1,000 (also in a cohort of RTR) in which precancerous lesions and multiple tumours were recorded. A high increase in risk (for SCC or KC generally) has been seen in studies from Sweden, Norway, The Netherlands, and Ireland, where there are relatively low rates of SCC in the general population, particularly in younger adults (see Table 1a,b). For example, one study that examined more than 5,000 OTR from Sweden reported a relative risk of 109 for men, 93 for women, and, compared with the general Swedish population,

an overall 100-fold increased risk for SCC [63]. Thus, the increase in risk of skin cancer observed in OTR in North Europe may be higher than that demonstrated in sunny countries such as Australia because the baseline incidence in North Europe is so much lower. Moloney et al., in a population-based study in Ireland over a 7-year period [64], noted age-specific patterns of increase in KC incidence. There was a steady increase from the second year on after transplantation in older RTR (age 50 years or older), but a later and much greater increase in younger RTR (age less than 50 years), reaching incidence rates 200 times those in an age-matched nontransplanted population and peaking 10 to 12 years after transplantation.

The cumulative incidence of KC in renal transplant recipients follows a similar pattern to that seen for SCC, with the highest reported risk in Australia [65, 70] and lower cumulative incidence in Europe [3,53,64,73] and America [78]. A study from South Africa [69] found a cumulative incidence of KC at 10 years post transplant of 7%, but KC was limited to white patients of European origin, who comprised only one-third (34%) of the RTR cohort.

Tumour burden is compounded by the multiplicity of KC in OTR, which can be very high [55, 65, 74, 79]. Bouwes Bavinck et al. [65] found 2,751 KC in 271 OTR in Australia, Bordea et al. [74] reported an average of 6 tumours per patient in the UK, and Blohme and Larko [55] reported 2 patients in Scandinavia with more than 100 skin lesions each.

Apart from geographical influences, the prevalence of patients with multiple skin lesions varies from study to study also because of differences in length of follow-up and age of patients, with a range of 26% to 73% [51, 53, 55, 80, 81]. Careful cataloguing of all KC over a 16-year period in a cohort of RTR from London, UK, found that although two-thirds of skin cancer patients had multiple tumours, it was a minority of these who carried the majority of the tumour burden, with 22 RTR (3.4% of the whole cohort) having 10 or more SCC and accounting for 59% of the total SCC burden. Similarly, 56 RTR (8.5% of cohort) with 4 or more SCC account for 83% of the total number of SCC (Proby and Harwood, unpublished data).

Post-Transplant BCC Show Smaller Increases Than SCC with a Reversal in the BCC to SCC Ratio, Although Regional Differences Exist

BCC are the second most common cancers in fair-skinned OTR, and approximately 30% to 50% of OTR with SCC also have BCC [75]. Although BCC is the most common skin cancer in the general population, all studies of post-transplant skin cancers have shown smaller increases in BCC compared with SCC (see Table 1c). Consequently, when compared with skin cancers in the general population, the ratio of BCC to SCC is usually reversed, although the extent of this reversal differs in various regions of the world (see Tables 2, 3). In The Netherlands [53], a 10-fold increase in BCC was found, compared with a 250-fold increase in risk of SCC,

and a complete reversal in the SCC/BCC ratio from 1:4 to 3.6:1. A reversal of similar magnitude is seen in Australian transplant recipients of European origin, with four studies reporting an SCC/BCC ratio between 2.0 and 3.8 [65, 66, 70, 71]. An early study from the United States [49] reported a 10-fold difference in the relative risk of SCC compared with BCC, and a study from Canada [80] examining relative increase showed a SCC/BCC difference of the same order of magnitude (Table 2).

The magnitude of the SCC/BCC ratio is not always so high, however. Lower SCC/BCC ratios have been reported in studies from Spain and Italy [60, 61, 72, 82–84] (see Table 3). In the UK [73], the risk of SCC post transplant appeared to increase exponentially, whereas the risk of developing BCC seemed to increase linearly with increasing years of immunosuppression. Fuente et al. [72] similarly noted a linear increase in BCC compared to a more exponential increase in SCC, with increasing duration post transplant. Consequently, a gradual increase in the SCC/BCC ratio was observed over time. Studies of skin cancer rates in the immunocompetent general population in Australia have reportedly shown a secular change in the SCC/BCC ratio from 1:4.5 in 1985 [85] to 1:2.5 in 1995 [30]. This finding was speculated to reflect a reduction in incidence of BCC occurring in young people, perhaps the result of improved sun protection from childhood. This dynamic situation, together with latitude differences in the SCC/BCC ratio also seen in Australia [30], suggests that level of sun exposure influences the proportion of BCC and SCC seen post transplant. An alternative explanation for the apparent excess of BCC in transplant populations from Southern Europe is that their darker 'Mediterranean' skin type is relatively protective against SCC in the early post-transplant years but is perhaps less protective against BCC development.

Occurrence of Keratinocyte Cancer Increases After All Types of Solid Organ Transplantation, Although Level of Increase May Vary

When data on post-transplant skin cancer rates are available in both cardiac transplant recipients (CTR) and renal transplant recipients (RTR) from the same centre, the risk appears to be greater after cardiac transplantation [62, 77, 81, 86]. This risk may be partly (or wholly) the result of the generally older age, male predominance, and higher level of immunosuppression of cardiac transplant recipients however and thus it is therefore difficult to directly compare these two groups.

A cancer registry-based study from Italy compared KC risk in 1,062 RTR and 267 CTR [77] and concluded that there was no definite increased risk amongst CTR after adjustment for age at transplantation and sex. Another Italian study [81] and two studies from Norway based on the same data ([62] [see Fig. 1]; [86]) reported an approximately threefold higher risk of skin cancer in CTR compared with RTR, but differed in their interpretation of its significance. Fortina et al. [81] found that organ type was not independently associated with risk after a multivariate analysis;

Gjersvik et al. [86] attributed the increased risk to higher levels of immunosuppression in CTR, whereas Jensen et al. [62] reported a threefold increased risk for CTR even after adjustment for age and immunosuppressive regimen.

The risk for development of KC is also increased in liver transplant recipients (LTR). In similarly large cohorts of OTR from the United States, both followed for approximately 3 years, Otley and coworkers [76] reported an incidence for KC of 52 per 1,000 patient-years for CTR compared with 11 per 1,000 patient-years for LTR. However, a study from Spain with 170 LTR followed for an average of 5 years found an incidence for KC of 43 per 1,000 patient years [87], and an earlier study from The Netherlands reported a relative risk for KC of 70 in LTR [88], similar to increased risks seen in CTR and RTR (see Table 1b). Cumulative incidence for KC up to 15 years post liver transplantation was available in these two studies from Spain and The Netherlands. The pattern of increase with duration of transplant was similar in the two studies and closely resembles patterns seen after CTR and RTR. There may be regional differences, with higher tumour numbers reported from Spain [87], but there are too few studies to confirm this.

Risk Factors for Post-Transplant Keratinocyte Cancer

Many of the studies reviewed examined risk factors for KC development using univariate and/or multivariate analyses (Cox proportional hazard risk models). The most important factors that appeared to favour development of skin cancer were age at transplantation, sex (male), fair skin type, high sunlight exposure (including the presence of actinic keratoses), and length and level of immunosuppression. Few investigators found all these to be independent risk factors, but many of the same factors were reported across a wide range of studies [56,62,64,65,67,72,74,77,82,83]. Ferrándiz et al. [82], in a prospective study examining the first 3 years of immunosuppression in RTR from Spain, found a cumulative risk for KC of 18%, with age at transplantation and occupational sun exposure being significant risk factors. From Italy, Naldi et al. [77] found age at transplantation and male sex to be the most important risk factors. Also from Italy, Caforio et al. [83] found older age at transplantation, fair skin, high sunlight exposure, actinic keratosis, and a high rejection score to be independently associated with an increased SCC risk in CTR. They proposed that a high rejection score in the first year post transplantation might be a useful predictor for patients at risk because cumulative immunosuppressive load is so difficult to calculate. However, other studies have not found an association between the number of rejections and development of KC in transplant recipients [74, 77, 89, 90].

A study based in Queensland, Australia, involving 361 Caucasian RTR found SCC risk was strongly associated with blue eyes, duration of residence in a hot climate, and pretransplantation SCC, whereas high tumour numbers were associated with being born in a place with a hot climate, childhood sunburn, pretransplantation actinic keratoses, and smoking [67]. Meanwhile, in Europe, Bouwes Bavinck et al.

[91] found a strong and significant association with number of keratoses and presence of SCC after controlling for sex, age, and skin type and, in a recent multicentre study, again found that a high number of warty keratoses was a significant and independent risk factor for SCC, OTR with more than 50 keratotic skin lesions having an adjusted odds ratio of 12.1 [92]. All these risk factors are discussed in more detail elsewhere in this book.

Standardized Incidence Ratio (Fig. 2)

Population-based standardized incidence ratios (SIR) were only available from a limited number of studies, with an overrepresentation of Scandinavian countries because of their long history of national cancer registration [8, 10, 12, 62] (see Fig. 2). Cancer registration in Finland, for instance, started in 1952. Studies from The Netherlands used a combination of national and city cancer registries [53, 88]. Kinlen et al. [49] used the Birmingham Cancer Registry as "representative" of the UK population, while a study from Canada [80] used a cancer registry with the same latitude. Hoxtell et al. [49] used the USA Third National Survey to derive their ratios. Those population-based SIR that were available for post-transplant SCC and post-transplant BCC are illustrated in Fig. 2.

Conclusions

Organ transplant recipients are at greatly increased risk of keratinocyte cancers, particularly SCC, compared with their counterparts in the general population; this is true in all regions of the world and has been shown in multiple studies, even though many of these studies are limited by underreporting of KC incidence in the general population. The increased incidence in OTR is particularly notable in younger transplant recipients because post-transplant KC develop on average 20 years earlier than in the general population [20, 66]. SCC show a much greater increase post transplant than BCC, leading to a reversal in the normal SCC/BCC ratio, although region-specific differences in the frequency of post-transplant BCC alter the extent of this reversal. The SCC/BCC ratio is also influenced by time from transplantation because BCC show a steady linear increase compared with an exponential rise in post-transplant SCC. Post-transplant SCC are frequently multiple, leading to a very high burden of disease in some individuals and placing a heavy cost on the affected patients and health care resources alike.

It is difficult to compare studies from different regions of the world because of the diversity of characteristics of study populations (different ages, skin type, immunosuppressive regimens, length of follow-up, epidemiological methods, etc.) as well as the different environmental factors (notably latitude and level of sun exposure). It is clear, however, that post-transplant skin cancer is a major problem in temperate climates and an even greater problem in tropical and subtropical regions. Caucasians living in Australia have the highest incidence of post-transplant KC, and

southern Europe experiences higher rates than northern Europe. The SIR, however, may be at least as high in more temperate countries because of a relatively low frequency of these skin cancers in the general population, particularly in younger age groups. The type of transplantation may influence the extent of the problem, but any organ-specific risk is probably small when age and level of immunosuppression have been taken into account. Cardiac transplantation typically has the highest levels of immunosuppression, and therefore the highest rates of skin cancer, because of the catastrophic consequence of rejecting the donor organ. There is no firm epidemiological evidence for an oncogenic effect of a specific immunosuppressive regimen, and the level of immunosuppression rather than a specific agent may be the more important factor for skin cancer risk. Finally, solar ultraviolet radiation is the principal agent responsible for the development of KC, and it is therefore essential that all future investigations are able to account for its independent influence, even if only at the level of ambient sun exposure.

Appendix

Box 1 Search strategy

In PubMed, an extensive literature search was made using synonyms for relevant words of the clinical question. First, a combination of "skin cancer" and "transplantation" (both as subheadings) was made in which "transplantation" was matched to the subheading "adverse effects and/or complication". Only English or Dutch articles were included, and case reports and editorials were excluded; this resulted in 448 articles.

("Neoplasms, Basal Cell"[Majr] OR "Skin Neoplasms"[Majr] OR "Melanoma"[Majr] OR (("Carcinoma, Squamous Cell"[Majr] OR "squamous cell carcinoma"[ti] OR malignancy[ti] OR malignant[ti]) AND (skin[ti] OR dermis[ti] OR epidermis[ti])) OR melanoma[ti] OR melanoma∗[ti] OR "skin cancer"[ti] OR "skin cancers"[ti] OR "skin tumor"[ti] OR "skin tumors"[ti] OR "skin tumour"[ti] OR "skin tumours"[ti] OR "basal cell carcinoma"[ti]) AND (transplant[ti] OR transplants[ti] OR transplantation[ti] OR transplanted[ti] OR post-transplant[ti] OR "Transplantation/adverse effects"[MAJR] OR "Transplantation/complications"[MAJR])

To include articles that focus on malignancies in general without skin cancer as a subheading, "transplantation" (matched to "incidence") and "malignancies" were combined. Only English or Dutch articles were included, and case reports and editorials were excluded; this resulted in 501 articles.

("Neoplasms"[Majr:noexp] OR malignancy[ti] OR malignant[ti]) AND (transplant[ti] OR transplants[ti] OR transplantation[ti] OR transplanted[ti] OR post-transplant[ti] OR "Transplantation/adverse effects"[MAJR] OR "Transplantation/complications"[MAJR]) AND incidence.

Finally, a broad selection (7786 references) was performed using various terms for "skin cancers" combined with terms for "transplantation" matched to "incidence":

("Neoplasms, Basal Cell"[MeSH] OR "Skin Neoplasms"[MeSH] OR "Melanoma"[MeSH] OR (("Carcinoma, Squamous Cell"[MeSH] OR "squamous cell carcinoma") AND (skin OR dermis OR epidermis)) OR melanoma OR melanoma∗ OR "skin cancer" OR "skin cancers" OR "skin tumor" OR "skin tumors" OR "skin tumour" OR "skin tumours" OR "basal cell carcinoma") AND (transplant OR transplants OR transplantation OR transplanted OR post-transplant OR "Transplantation"[MeSH]) AND (incidence OR incidences OR incidenc∗).

Selection

After exclusion of duplicates, a total of 1,377 articles were found. A selection was made using title and/or abstract; this resulted in 329 articles that matched our clinical question. Full texts were evaluated and scored (A, B, C, D, or no score). The remaining A and B articles were used for tables and graphics in this book.

A (good article) when

- Baseline characteristics are clear
- Cumulative rate of skin cancer is present

B (sufficient article) when

- Baseline characteristics are clear
- Cumulative rate is unclear, but incidence rate or relative risk is given

C (doubtful article) when

- Only the number of patients with skin cancer is given
- No statistical analysis are used

D (insufficient article) when

- It does not match our clinical question

No score

- Paper not relevant at all

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