Transpl Int (2000) 13 [Suppl 1]: S394–S398

L. Kyllönen
K. Salmela
E. Pukkala

Cancer incidence in a kidney-transplanted population

L. Kyllönen (✉) · K. Salmela
Division of Transplantation,
Department of Surgery,
Helsinki University Central Hospital,
Kasarmikatu 11, FIN-00130 Helsinki 13,
Finland

E. Pukkala
Finnish Cancer Registry, Liisankatu,
FIN-00100 Helsinki 10, Finland

Abstract A study on cancer incidence after kidney transplantation was performed using data of national transplant and cancer registries. Since 1964 up to 30 June 1997, 3440 kidney transplantations were performed on 2890 patients. From 1967 to 1997, 230 posttransplantation malignancies were found in 20 817 patient-years of follow up. The standardised incidence ratio (SIR) was 3.33 compared to the general population. The SIR was highest in skin cancer (39.2). The SIRs were high in cancers of the lip (23.0), thyroid (8.08), kidney (8.0), lower urinary tract (3.2), non-Hodgkin lymphoma (4.8), ovary (3.9) and colon (3.9). Skin cancer and lymphomas had much higher SIRs in men than in women whereas lower urinary tract cancer had a higher SIR in women. During the first 10 follow up years, life-table analysis indicates a higher cancer risk in cyclosporine-treated patients, but this may be biased by their shorter follow up as the overall SIR was equal in both groups. This population study shows the increased incidence of cancer in the transplant population and points out the importance of cancer surveillance in the years following kidney transplantation.

Key words Malignant neoplasms · Kidney transplantation · Population study

Introduction

A successful renal transplantation grants the recipient a better quality of life and the society great savings in the total cost of treatment. The life-long immunosuppressive regimen required has, however, been associated with a high incidence of cancer in these patients. There is much discussion in medical literature on malignancies after organ transplantation. Few of the studies published give reliable data on relative risks of cancers, through lack of control populations.

In Finland all kidney transplantations have been performed by a single centre and a thorough follow up of the patients has been possible through the co-operation of the network of regional and local hospitals. The nationwide Finnish Cancer Registry has been functioning for over four decades, and its coverage is essentially complete as evidenced by clinical studies on national cancer incidence and treatment results [10, 16]. We studied the incidence of cancer in this comprehensive country-wide kidney-transplanted population.

Patients and methods

Since 1964 up to 30 June 1997, 3440 kidney transplantations were performed at our centre on 2890 patients, 1719 men and 1171 women, with a mean age of 41.5 years. At transplantation, 124 patients were under 16 years of age. Up to late 1981 the immunosuppression consisted of methylprednisolone and azathioprine (conventional). Since then cyclosporine A has been included in the regimen and triple therapy has, since 1985, been used systematically in cadaveric kidney transplantations which at present comprise over 95% of all kidney transplantations. Mono- and polyclonal T-cell antibodies have been used mainly in induction therapy in highly immunised patients and in treatment of steroid resistant rejections in 124 patients since 1982. The mean age at transplantation was

40.3 years in the conventional group and 42.6 years in the cyclosporine group.

Personal data of these patients were linked with data in the files of the Finnish Cancer Registry where cancer data are recorded according to primary tumour site and histology. For the follow-up period for cancer incidence, 1967–1997, 2884 patients produced 20 817 patient-years of follow up. The observed numbers were compared to the expected numbers of site-specific malignancies in the national population stratified by age, sex and calendar time. Standardised incidence ratios (SIRs) were calculated according to patient sex, age, length of follow up and type of immunosuppression. The 95% confidence intervals (CI) were calculated under the assumption that the observed number of cases followed a Poisson distribution.

The follow-up time was divided into three periods, the first from zero to 2 years posttransplant to identify cancers appearing soon after transplantation, the second from 2 to 10 years and the third over 10 years post transplant. Cancer incidence figures for time of follow up after first kidney transplantation were calculated using the Kaplan-Meier product-limit method.

Results

A total of 230 malignancies (Table 1) were found compared to the expected number of 69 which gave an overall SIR of 3.33 with a 95% CI of 2.91–3.77. There were 90 cancers in women with an expected number of 30.9, a SIR of 2.91 with CI 2.34–3.58, and 140 cancers in men with an expected number of 38.15, a SIR of 3.67 with CI 3.09–4.30. The average age at transplantation for patients who later developed cancer was 47.2 years and the average time posttransplant at cancer diagnosis was 8.2 years.

The primary site with the highest SIR (39.2) was skin (Table 2) followed by lip, small bowel, thyroid, kidney, lymphomas, colon and lower urinary tract. In women, the SIR of vulvar cancer and urinary tract cancers was high (17.0 and 10.3) whereas the SIR for breast cancer was 1.2. In men, the SIR for skin cancer was much higher than in women (51.3 vs 15.6). The SIR for lip cancer in men was 22.1, that for small bowel cancers was 18.5 and nodal lymphoma in men had a SIR of 6.7. The otherwise common cancers in men, lung and prostate cancers had low SIRs of 1.4 and 0.6, respectively.

When the treatment groups were compared, the overall SIRs were very similar: 3.27 in the conventional immunosuppression patients and 3.42 in patients with cyclosporine immunosuppression. There was no difference in the SIRs of skin and lip cancers between patients with these two types of immunosuppression. However, in patients with conventional immunosuppression, the SIRs for colon and thyroid cancer were high (5.2 and 11.3), whereas in patients with cyclosporine, lymphomas and small bowel cancers had significantly increased SIRs (5.6 and 19.6).

The ratio of observed to expected numbers of cancers was highest in patients aged 30–44 years (SIR 5.5, CI 3.9–7.3) and slightly lower in age groups 45–59 and 60–74 years (SIR 3.4, CI 2.7–4.2 and SIR 2.7, CI 2.1–3.3, respectively). In the age groups over and under these limits the numbers of cancers were too small for significant differences from the expected to appear.

The relative cancer risk varied little with length of follow up after transplantation. The overall SIR for cancers in the first 2 years after transplantation was 3.0, for the follow-up period 2–10 years posttransplant it was 3.1 and for the follow up over 10 years it was 3.9. In patients with conventional immunosuppression the SIRs in the follow-up periods of 0–2 years and 2–9 years

Table 1 Number of cancers in 2890 kidney-transplanted patients in 20817 patient-years follow up

Site	Male	Female
All cancers	140	90
Lip	12	2
Other oropharyngeal	2	4
Gastric	2	3
Small bowel	4	–
Colon	6	7
Pancreas	5	–
Other G-I cancer	3	4
Respiratory	16	3
Breast	–	13
Cervix uteri	–	2
Corpus uteri	–	4
Ovaries	–	8
Other female genital	–	4
Male genital	6	–
Kidney	15	7
Ureter, bladder, urethra	4	4
Melanoma	2	1
Skin	45	7
Neurological	3	1
Thyroid	4	7
Other endocrine	–	1
Other	2	4
Lymph nodes	8	1
Hodgkin's disease	–	2
Myeloma	1	1

Table 2 Primary sites of malignancies with significantly increased standardised incidence ratios *(SIRs)* in 2890 kidney-transplanted patients. (*Obs* observed, *Exp* expected, *CI* confidence interval)

Site	Obs	Exp	SIR	95% CI
All sites	230	69	3.33	2.91–3.77
Skin	52	1.33	39.22	29.29–51.43
Lip	14	0.61	22.98	12.56–38.55
Small bowel	4	0.34	11.78	3.21–30.14
Pleura	2	0.24	8.35	1.01–30.17
Thyroid gland	11	1.36	8.08	4.04–14.46
Kidney	22	2.76	7.98	5.00–12.08
Lymph nodes	9	1.90	4.75	2.17–9.01
Colon	13	3.30	3.94	2.10–6.73
Ureter, bladder, urethra	8	2.47	3.24	1.40–6.38

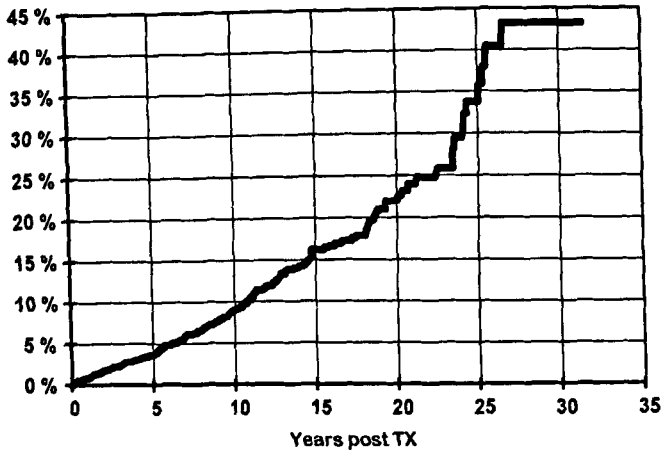

Fig. 1 Overall cancer incidence in 2990 kidney-transplanted patients in Finland, 1967–1997

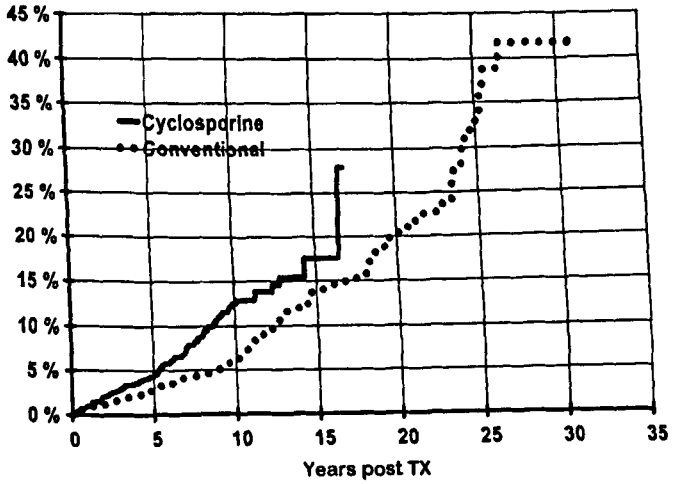

Fig. 2 Cancer incidence in 2990 kidney-transplanted patients in Finland, 1967–1997, according to type of immunosuppression. Conventional = azathioprine and methylprednisolone; cyclosporine = cyclosporine, azathioprine and methylprednisolone

were lower (2.3 and 2.5) than in the cyclosporine group (3.3 and 3.7). However, when the follow-up period was over 10 years posttransplantation, the SIR in the conventional immunosuppression patients was 4.3 compared to 1.4 in the cyclosporine group. A certain bias is inevitable as in the conventional group, 3996 patient-years had accumulated in the over 10-year follow up and in the cyclosporine group only 536 patient-years. In the small group of 124 patients with T-cell antibody therapy, five cancers have been diagnosed.

Kidney cancers and small bowel lymphomas were over-represented in the first follow-up period (0–2 years), vulvar and lymph node cancer in the second period (2–10 years) and kidney cancer in women and colon cancer in the third period (over 10 years).

In the life-table analysis of cancer incidence (Fig. 1), it appears that 16.2% of patients had developed cancer by 15 years and 22% at 20 years post-transplantation in this patient population. When patients with cyclosporine and conventional immunosuppression were compared (Fig. 2), the cancer risk seemed to be higher in the cyclosporine group ($P < 0.01$). The short follow up in the cyclosporine group does not allow comparison of the risk at longer follow-up times.

In addition to the nine lymphomas in lymph nodes, one gastric tumour, two small bowel tumours and one each of lung, liver, brain, testicle and skin tumours were histologically classified as lymphomas. Three cases of posttransplant lymphoproliferative disease (PTLD) have been recognised. The one gastric and one of the nodal lymphomas were considered to have been PTLD as was one other that was not classified as a cancer nor registered in the Cancer Registry during this time period. All except one of the patients with lymphoma or PTLD were men.

Among the skin cancers there were three cases of Kaposi's, all situated in the lower extremities. One case of malignant disease (Hodgkin's disease) has been diagnosed in the 124 patients transplanted under the age of 16 years.

Discussion

The increase in cancer incidence after organ transplantation has been demonstrated in several studies. Registry data on cancers complicating kidney transplantation is already available with a follow up of almost 30 years, but there are also data on increased incidence of malignancies after hepatic and cardiac transplantation [4, 6, 7, 14]. Although there are some differences between the findings of the reports due to geographical, ethnic and local factors, and some variation depending on the organ transplanted, the predominance of certain malignancies has been well confirmed. The number of studies with a defined control population is, however, small [1, 11, 15]. These population-based epidemiological studies have been criticised, mainly due to their small number of cases compared to global data [14]. It is true that regional registries cannot have high numbers of rare malignancies even in immunosuppressed transplant recipients with increased cancer risk. The importance of acquiring cancer data on a transplant population is, however, for counselling individual patients and the community concerning the risks of long-term immunosuppression, and there the data of epidemiological studies with a well-defined background reference population are of the utmost importance. As the population of long-time survivors will expand during the next 10 years, our knowledge on cancer incidence in an ageing transplanted population will increase. Many of them, even when

based on global registries, however, though lack of control populations, are of little value in counselling patients and planning rational surveillance policies, as the relative risks for cancers are impossible to glean from that kind of study. Although the numbers of cancers in population studies tend to be small, leading to a certain uncertainty in the results, these are the only studies where true relative risks can be evaluated.

The population of Finland, which is the population background of this study, is just over 5 million. The stability of the population and the fact that one transplant centre gives transplant service to the whole country with as yet no patient lost to follow up, as well as the national Cancer Registry, gives a reliable and ideal basis for evaluation of cancer risks after kidney transplantation. An earlier study from our centre [11] showed a SIR of 2.7 within a follow up of 12 055 patient years. In the present study the number of patients has increased by one half and the follow up has almost doubled. The increase in cancer risk after transplantation appears to be at the same level as in many other studies [9, 12]. Interestingly, in the combined Nordic study of patients transplanted between 1964 and 1982, where Finland also was included [1], the SIR was 4.5, clearly higher than in the present material. The SIR of all cancers combined was somewhat higher in men than in women, which is mainly accounted for by the high SIR in skin cancer in men.

The increase in skin cancers was highest and has almost doubled compared to our earlier figures, but still did not quite reach the high levels that have been reported in studies from Australia and New Zealand [2, 15]. It was also three times as high in men than in women. The incidence of cancer of the lip was also high but it was similarly increased in both sexes. As the incidence of skin cancers has been connected to sun exposure the slightly lower risk in these northern latitudes is to be expected.

Cancer of the thyroid also had a high SIR in both sexes as had kidney cancer. In the EDTA-ERA study, thyroid cancers were more frequent in both dialysis and transplantation patients than in normal populations [3]. In patients being evaluated for transplantation, an over 3% prevalence of renal cell carcinoma has been shown [5, 8]. Seven of the observed 22 renal cancers in our study were diagnosed less than 2 years after transplantation. This confirms the importance of including ultrasound screening of native kidneys in the pretransplant work up as well as in the posttransplant follow up schedule. This concerns all patients but, in particular, patients with polycystic degeneration who are known to have a much higher incidence of renal adenocarcinoma than the normal population [13].

In our previous study, the cancer risk in cyclosporine-treated patients was slightly lower than in patients with conventional immunosuppression but, as the follow up has lengthened their cancer incidence seems to have increased over that of the earlier, conventionally treated patient group. There is, however, a clear bias caused by the differences in follow-up times, as very little follow up has accumulated after 10 years of transplantation in the cyclosporine group. Some of the differences in the cancer incidence curves can be accounted for by the small difference in mean ages between the groups, but in the SIR calculations this was eliminated. In the most representative group of cancers, skin cancer, no significant difference in SIRs could be discerned between the immunosuppressive regimens. This agrees with the findings of others showing no relationship of skin cancer to any particular immunosuppressive agent [2].

Lymphomas in the lymph nodes, which in many studies are very conspicuous, were rather few in number and occurred almost exclusively in men. A high SIR was found only in the cyclosporine group of patients, but the small number of these cancers can of course cause spurious differences. As the tumours in the Cancer Registry are primarily classified according to site, the SIR values only showed nodal lymphomas. Almost as many tumours classified histologically as lymphomas were found in different sites. The rather low increase in lymphoma incidence could be attributed to our restricted use of immunosuppressants, especially anti-lymphocyte globulins.

The patterns of cancers in male and female patients observed in our study differed somewhat. The male patients had more skin and lip cancers and all but one case with lymphoma or PTLD were in male recipients. The small absolute number of lymphomas and PTLDs in the present study may be explained by our relatively restrictive policy with the use of anti-lymphocyte antibody preparations. An interesting finding is that cancers typical for men, such as cancers of lung, stomach and prostate, and cancers typical for women, such as breast cancer, were not represented more than in the general population.

With time, our experience of cancer risk in the organ-transplanted population will be increased. During the last decade several new immunosuppressive agents have been introduced. The focus of interest has been the prevention of acute allograft rejection and graft survival. With better early immunosuppression, the number of long-time survivors will increase. In the future, more concern should be addressed, not only to the early survival of the graft, but also to the optimal monitoring of immunosuppression in the long term in order to diminish the risk of acquired malignancy. This is extremely important as transplantation has also been extended to patients in their young and very early years of life.

Acknowledgements This study was supported by a grant from Einar and Karin Stroem Foundation.

References

1. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohme I, Forsberg B, Eklund B, Fjeldborg O, Friedberg M, Frödin L, Glattre E, Halvorsen S, Holm NV, Jakobsen A, Jørgensen HE, Ladefoged J, Lindholm T, Lundgren G, Pukkala E (1995) Cancer risk after renal transplantation in the Nordic countries 1964–1986. Int J Cancer 60: 183–189
2. Bouves Bavinck JN, Hardie DR, Green A, Cutmore S, MacNaught A, O'Sullivan B, Siskind V, Woude FJ van der, Hardie IR (1996) The risk of skin cancer in renal transplant recipients in Queensland, Australia. Transplantation 61: 715–721
3. Brunner FP, Landais P, Selwood NH (1995) Malignancies after renal transplantation: the EDTA-ERA registry experience. European Dialysis and Transplantation Association-European Renal Association. Nephrol Dial Transplant 10 (Suppl 1):74–80
4. Curtil A, Robin J, Tronc F, Ninet J, Biossont P, Champsaur G (1997) Malignant neoplasms following cardiac transplantation. Eur J Cardiothorac Surg 12: 101–106
5. Doublet JD, Peraldi MN, Gattegno B, Thibault P, Sraer JD (1997) Renal cell carcinoma of native kidneys: prospective study of 129 renal transplant patients. J Urol 158: 42–44
6. Frei U, Bode U, Repp H, Schindler R, Brunkhorst R, Vogt P, Hauss J, Pichlmayr R (1993) Malignancies under cyclosporine after kidney transplantation: analysis of a 10-year period. Transplant Proc 25: 1394–1396
7. Galve ML, Cuervas-Mons V, Figueras J, Herrero I, Mata M, Clemente G, Prieto M, Margarit C, Berbardos A, Casafont F (1999) Incidence and outcome of de novo malignancies after liver transplantation. Transplant Proc 31: 1275–1277
8. Gulanikar AC, Daily PP, Kilambi NK, Hamrick-Turner JE, Butkus DE (1998) Prospective pretransplant ultrasound screening in 206 patients for acquired renal cysts and renal cell carcinoma. Transplantation 66: 1669–1672
9. Hoshida Y, Tsukuma H, Yasunaga Y, Xu N, Fujita MQ, Satoh T, Ichikawa Y, Kurihara K, Imanishi M, Matsuno T, Aozasa K (1997) Cancer risk after renal transplantation in Japan. Int J Cancer 71: 517–520
10. Kyllönen LE, Teppo L, Lehtonen M (1987) Completeness and accuracy of registration of colorectal cancer in Finland. Ann Chir Gynaecol 76: 185–190
11. Kyllönen L, Eklund B, Pukkala E (1994) Cancer incidence in a kidney transplanted population. Transpl Int 7 (Suppl 1):350–352
12. London NJ, Farmery SM, Will EJ, Davison AM, Lodge JP (1995) Risk of neoplasia in renal transplant patients. Lancet 346: 403–406
13. Penn I (1995) Primary kidney tumours before and after renal transplantation. Transplantation 59: 480–485
14. Penn I (1999) Posttransplant malignancies. Transplant Proc 31: 1260–1262
15. Sheil AG, Mahoney JF, Horvath JS, Johnson JR, Tiller DJ, Kelly GE, Stewart JH (1979) Cancer following renal transplantation. Aust NZ J Surg 49: 617–620
16. Teppo L, Pukkala E, Lehtonen M (1994) Data quality control of a population-based cancer registry. Experience in Finland. Acta Oncol 33: 365–369