Cancer rates after kidney transplantation

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ABSTRACT

INTRODUCTION: Previous studies demonstrated a 3-5-fold increased cancer risk in kidney allograft recipients compared with the general population. Our aim was to estimate cancer frequencies among kidney allograft recipients who were transplanted in 1997-2000 and who were immunosuppressed according to a more modern steroid-free standard protocol based on basixilimab, ciclosporine and mycophenolate mofetil.

MATERIAL AND METHODS: This was a retrospective cohort study of patients receiving their first kidney allograft in 1997-2000 at Odense University Hospital, Denmark (n = 90). Histologically verified cancers were identified from a detailed search of the individual patient's medical records.

RESULTS: During an average follow-up time of 8.4 years, a total of 14 cancers were observed. The cancer incidence rate was 18.5 (95% confidence interval (CI): 11.0-31.3) per 1,000 years, and the cancer prevalence was 13.4% (95% CI: 5.6-21.2%) among survivors in 2007. The relative risk of prevalent cancer was 3.6 (95% CI: 2.0-6.5) compared with the general population. Patients with cancer had a poorer survival than patients without cancer.

CONCLUSION: The observed cancer incidence rate and prevalence were similar to figures derived from studies performed in the earlier eras of kidney transplantation. Reducing cancer rates after kidney transplantation remains an important challenge for nephrologists.

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Previous studies demonstrated that kidney transplantation (Tx) is associated with a 3-5-fold increased risk of cancer compared with the general population [1-5]. However, these studies were primarily or exclusively based on cohorts of patients who were transplanted in the 1970s, 1980s and early 1990s. During the past two decades, transplantation practices and results have changed: new immunosuppressive regimens have been introduced and graft and patient survival have increased. These changes may have altered cancer risks.

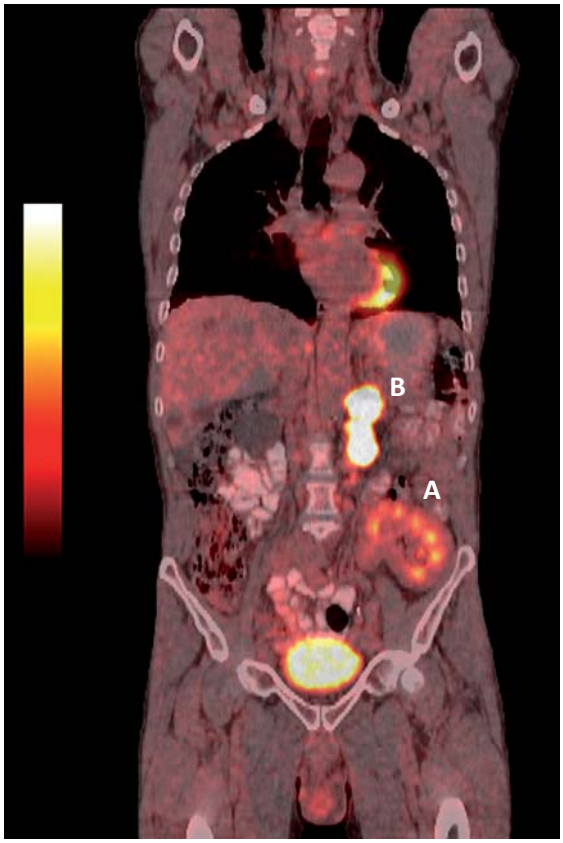
For more than a quarter of a century, we have been using a steroid-free standard protocol for immunosuppression after Tx. As from the mid-1990s, basiliximab became the preferred agent for induction and cyclosporine A (CyA) and mycophenolate mofetil (MMF) became the preferred agents for maintenance immunosuppression at our centre.

The aims of the present study were to estimate the overall cancer incidence rate and prevalence in patients transplanted at our center during the 1997-2000 period, and to compare these estimates with those derived from previous studies performed in an earlier era of immunosuppression and with those of the general local population.

MATERIAL AND METHODS

The present study is a retrospective cohort study of all patients who received their first kidney allograft at the Department of Nephrology, Odense University Hospital, Denmark, during the 1997-2000 period. The study was conducted in the spring of 2010.

For each patient, the following data were extracted from medical records: date of birth, sex, previous cancer diagnosis, date of Tx, human leukocyte antigen (HLA)-mismatch, panel reactive antibody, rejection characteristics, post-transplantation cancer diagnosis, date of cancer diagnosis as confirmed by histology, and type of



Positron emission tomography demonstrating kidney allograft (A) and malignant lymphoma (B) in the abdomen.

ORIGINAL ARTICLE

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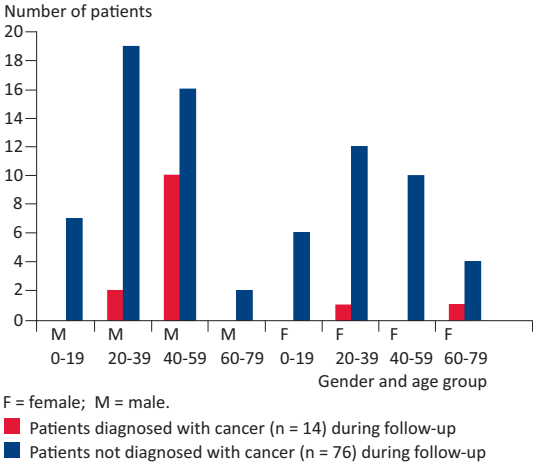
donor (living or deceased). Each patient was followed up until either the date of first cancer diagnosis, emigration, loss to follow-up, death or end of study (10 March 2010).

In our clinical practice, cancer screening is based on regular monitoring of body weight, performance status and Epstein Barr virus polymerase chain reaction analysis of plasma. The crude total cancer prevalence of the general Danish population in 2007 was obtained from Nordcan (Danish Cancer Society) [6] and The Cancer Register (Danish National Board of Health) [7].

FIGURE 1

Gender and age at kidney transplantation of 90 patients who received their first kidney transplant in 1997-2000, and who were or were not diagnosed with a cancer during follow-up.



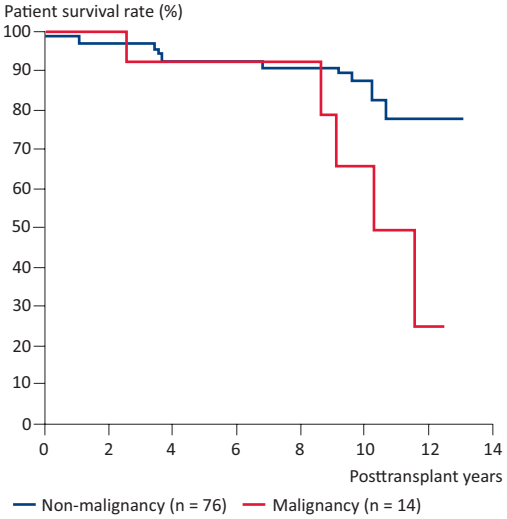
F = female; M = male.

Patients diagnosed with cancer (n = 14) during follow-up

Patients not diagnosed with cancer (n = 76) during follow-up

FIGURE 2

Kaplan-Meier survival plot of 90 patients who received their first kidney transplant in 1997-2000 according to presence or absence of malignant disease during follow-up.



Statistical analysis

The cancer incidence rate of the Tx cohort was calculated as new cases divided by observational time divided by the number of persons in the cohort. The total cancer prevalence of our study cohort was calculated in 2007 as the number of prevalent cancers divided by the number of living recipients. The relative risk of total cancers was calculated as the observed prevalence in the Tx cohort divided by the most recent data on total cancer prevalence of the general population (2007).

MedCalc version 11.2.1.0 (Mariakerke, Belgium) was used for the Kaplan-Meier analysis and for Fisher's exact test. The level of statistical significance was $p < 0.05$.

Trial registration: not relevant.

RESULTS

A total of 126 patients were kidney transplanted at our centre during the 1997-2000 period. The present cohort consists of the subgroup of 90 patients who had their first allograft in this period. Among these 90 patients, there were 34 females (38%) and 56 males (62%). Eight of the 90 patients were children (age below 15 years). Women had a mean age at transplantation of 39.4 years, standard deviation (SD) 18.6 years (range 2.9-75.6 years) and the mean age among men was 38.3 years, SD 14.5 years (range 10.0-66.8 years). Thirty-one patients (34%) received their kidney from a living donor, 59 (66%) from a deceased donor.

The average follow-up time was 8.4 years (95% CI: 7.5-9.3 years) and the overall follow-up time was 756.2 patient years. Fourteen patients (16%) were followed up until their first cancer diagnosis, 18 patients (20%) were lost to follow-up before March 2010, accounting for 43.2 patient-years, and 17 (18%) patients were followed up until their death. The remaining 41 patients (46%) were followed up until the end of the study. The patients who were lost to follow up were assumed not to have developed cancer after the date of their end of follow-up.

A total of 14 (95% CI: 8.1-23.0) new malignancies were found during follow-up (12 males, two females) as shown in **Figure 1**. The cancer incidence rate was 18.5 (95% CI: 11.0-31.3) per 1,000 patient-years.

The prevalence of any cancer in 2007 was 0.13 (0.06-0.21). The prevalence of any cancer in the general population in 2007 was 0.037 (0.0372-0.0376) [7], which yields a relative risk of any cancer of 3.6 (2.0-6.5).

The most frequent cancer in our cohort was non-melanoma skin cancer (NMSC) (n = 6). The second most frequent cancer was malignant melanoma (n = 3). The remaining cancers were non-Hodgkin lymphoma (n = 2) and single cases of synovial sarcoma, Hodgkin's disease and neuroendocrine carcinoma.

The patient survival rates one, five, and ten years after Tx were 99.8%, 92.7% and 65.9% for patients with a cancer diagnosis. Their median survival time was 10.3 years (**Figure 2**). In the non-malignancy group, patient survival rates one, five, and ten years after Tx were 98.6, 93.4 and 87.6%, respectively. The survival rates differed significantly (log-rank test, $\chi^2 = 5.39$; degree of freedom = 1; p = 0.02).

Twelve of 56 males and two of 34 females developed cancer during follow-up (non-significant). Among living donor recipients, two of 31 patients developed cancer *versus* 12 of 59 deceased donor recipients (non-significant).

Among the 14 patients who developed cancer, four (29%; 95% CI: 12-55%) had experienced at least one previous rejection episode (one patient had two episodes). Among the 76 malignancy-free patients, 18 (24%; 95% CI: 16-34%) had experienced a rejection episode. The frequency of rejection did not differ significantly between groups.

Among patients who developed cancer, the average number of HLA mismatches at locus A, B and DR were 1.21 (95% CI: 0.91-1.52), 1.14 (95% CI: 0.80-1.49) and 1.14 (95% CI: 0.80-1.49). The corresponding numbers among malignancy-free patients were 0.70 (95% CI: 0.56-0.84), 1.01 (95% CI: 0.86-1.16) and 1.00 (95% CI: 0.86-1.14). Only HLA A mismatches differed significantly. Only one patient had panel-reactive antibodies before Tx. This patient did not develop cancer during follow-up.

In two patients, the immunosuppressive treatment was changed from ciclosporin (calcineurin inhibitor) to sirolimus (mammalian target of rapamycin (mTOR) inhibitor) because of cancer. No other patients in the cohort were treated with mTOR inhibitor.

DISCUSSION

We found a cancer incidence rate of 18.5 per 1,000 person-years in our cohort of patients receiving their first kidney allograft during 1997-2000. In 2007, the prevalence of any cancer was 0.13 (0.06-0.21). **Table 1** presents the findings of previously published studies for comparison.

Overall, our findings correspond to figures reported from earlier retrospective cohort studies that all included patients who were kidney transplanted in the earlier eras of kidney transplantation and immunosuppression (before 1995) (Table 1). As an exception, Ju et al [4] observed a much lower cancer incidence in a Korean population despite the fact that their average follow-up time was longer than in most other studies (which would tend to increase cancer frequencies [5]). Possibly, their findings may be explained by racial differences in cancer incidences or by less effective cancer detection. As another extreme, Dantal et al [10] reported cancer incidence rates and prevalences more than twice as high as those observed in most other studies. Their findings are most likely explained by the unique prospective design of their study – all other studies in the field were retrospective.

The most frequently observed cancer in our study was NMSC with a total of six cases, accounting for 43% of all cancers. Identical figures were published for Sweden [3] (40%). In an Australian study, the contribution of NMSC to all cancers was much higher (76%) [13]. This may be explained by differences in sun exposure and skin types between Australia and the Scandinavian countries.

We observed no cases of lung, breast, prostate, or colon cancer in our cohort. These types of cancers are the most frequent in the general Danish population. Our finding thus indicates that the risk of common cancers is not elevated in kidney recipients. Similar conclusions were reached in several other and larger studies in kidney recipients whose relative risk of common cancers

TABLE 1

Key figures of the present and previously published cohort studies investigating the total cancer incidence rate after kidney transplantation.

Study	Country	Study period	Cohort, n	Mean follow-up, years	Patients with new-onset malignancies, n	Total cancer incidence rate per 1,000 patient-years (95% confidence interval)
Birkeland et al [1]	The Nordic countries	1964-1986	5,692	5.7	471	14.5 (13.3-15.9)
Adami et al [3]	Sweden	1970-1997	5,004	7.4	639	17.3 (16.0-18.7)
Kyllonen et al [8]	Finland	1964-1997	2,890	7.2	230	11.0 (9.7-12.6)
Ju et al [4]	South Korea	1979-2007	2,630	9.4	177	7.2 (6.2-8.3)
Wimmer et al [5]	Germany	1978-2005	2,419	9.5	421	18,3 (16.7-20.2)
Behrend et al [11]	Germany	1968-1995	1,497	8.4	147	11.7 (9.9-13.7)
Webb et al [9]	United Kingdom	1967-1995	1,069	4.9	93	17.8 (14.5-21.8)
Ducloux et al [12]	France	1993-2004	363	4.9	32	18.0 (12.7-25.5)
Dantal et al [10]	France	1989-1995	231	5.5	60	47.2 (36.7-60.8)
Our study	Denmark	1997-2010	90	8.4	14	18.5 (11.0-31.3)

was found to be close to one [1, 3, 8, 14]. This phenomenon indicates that immunosuppression plays an insignificant role in the development of common cancers. It also indicates that the risk of acquiring these cancers is primarily influenced by environmental factors such as smoking, nutrition, physical activity, the chemical environment and by genetic factors.

We find cancer frequencies of patients who were kidney-transplanted in the newer era of immunosuppression (1997-2000) that were similar to estimates derived from earlier cohorts, irrespective of lower levels of immunosuppression.

This demonstrates that kidney transplanted patients are still facing a considerably increased risk of developing cancers compared with the general population. The fact that NMSC was the most frequent cancer and that malignant melanoma was the second most frequent cancer highlights that an increased focus on sun protection must be considered the most obvious and promising tool for reducing post-transplantation cancer rates. Also, regular dermatological surveillance of kidney-transplanted patients could probably prevent some skin cancers and at least guarantee detection and efficient treatment of skin malignancies at an early stage. It is clear that more effective sun protection increase the risk of vitamin D deficiency in transplanted patients, and vitamin D deficiency may have several unfavorable consequences for the patients. It may even increase their cancer risk [12, 15]. It is therefore probably wise to recommend vitamin D supplementation along with sun protection after kidney transplantation [16]. Kidney transplanted patients face an increased risk of virus-related cancers (lymphomas, hepatocellular carcinoma, cervical cancer of the uterus) [2]. We observed no such cancers in our cohort, however, which was probably due to the small size of our cohort. The risk of virus-related cancer can be reduced with low dosing of immunosuppressives, but this benefit should always be balanced against the increased risk of allograft rejections and losses. Vaccination is another way of reducing virus-related cancers, but it is not known how efficient this strategy is because of the poor antibody response of patients with end-stage renal disease and of patients in immunosuppressive treatment [17]. Screening for common cancers such as prostate and breast cancer carries the risk of achieving falsely positive results [17].

Patients with end-stage kidney disease face one of two alternatives: regular dialysis treatment or transplantation. Although kidney transplantation is associated with a considerably increased risk of cancer, it is important to recognize that dialysis treatment is also associated with an increased risk of cancer compared with the general population, although the risk is much more modest. We found a 260% increased cancer risk (relative risk of 3.6) in our Tx cohort. An approximately 40% increased cancer risk has been reported in dialysis patients [18]. It is essential to mention that the overall survival of Tx patients is clearly higher than that of patients on regular dialysis therapy despite their higher risk of cancer [19].

At our centre, steroids are totally avoided for induction and maintenance therapy except for high-risk patients (e.g. ABO mismatch) and rejection episodes. Accordingly, the patients of the present study were routinely maintained on CyA and MMF. Our finding that the total cancer prevalence and the incidence rate of our cohort correspond to those reported from most other centres where patients were typically maintained on steroids, CyA and MMF, indicates that the exclusion of steroids from routine immunosuppression does not modify the risk of cancer after Tx.

In our study, two immunosuppressed patients were changed from ciclosporin to mTOR inhibitor. Previously, a shift to mTOR inhibitor has been suggested to reduce the general post-Tx cancer risk, especially the risk of NMSC [20]. However, a longer follow-up period is required to establish the result [20].

Our report is based on a single-centre study. This may be considered an advantage because it means that our study population was homogenous with respect to immunosuppressive protocol and clinical follow-up practices. Also, the single-centre study design gave us easy access to full-length medical records of our patients, including all pathology reports, which increased the validity of our findings and ensured that all cancers identified in our cohort were included in the analyses. An important weakness of our study was the small sample size (n = 90) and the retrospective design. The small sample size gave rise to large confidence intervals of our estimates and the retrospective design means that some patients may have developed cancers that were never detected. The true cancer rates after kidney transplantation is probably somewhat higher that our estimate as suggested by the findings of the only prospective study in the field [10].

In conclusion, we found a significant 3.6-fold increased risk of cancer in kidney-transplanted patients compared with the general population. The cancer incidence rates observed in the present study were similar to rates reported from studies performed in earlier eras of kidney transplantation. Not surprisingly, we found a significantly reduced ten-year survival rate among kidney transplantation patients who developed cancer. Reducing cancer rates after kidney transplantation remains an important challenge that should be given high priority.

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