Thyroid cancer and renal transplantation: a meta-analysis

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Abstract

Kidney transplantation and the associated immune suppression are associated with a significantly increased risk of developing cancer during long-term follow-up. Thyroid cancer has been recognised as a potential post-transplant risk but has not yet been subject of a focused review. We therefore performed a meta-analysis on data of 50 861 patients with a total follow-up of 198 595 patient-years and identified a 6.9-fold higher standardised incidence ratio (95% confidence interval 5.6–8.7, $P < 0.001$) of thyroid cancer post renal transplantation as compared with a non-transplant group. All such cancers were of papillary type as far as histopathology was known. The mean time to discovery was 6.0 years post transplantation. This puts thyroid cancer into the group of high cancer risk following solid organ transplantation which already includes cervical cancer, non-melanoma skin cancer, oral and lip cancer and haematological malignancies. It is unclear what causes the increased cancer incidence. Inclusion of thyroid ultrasound in long-term post-transplant evaluation may help to ensure timely recognition of this condition.

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Introduction

Organ transplantation is currently considered the best option available in most types of end-stage organ failure. Success rates of organ transplantation have significantly improved over recent decades. This success mostly relates to improvements in immuno-suppressive therapy and long-term care. However conversely, patients are now exposed to the long-term consequences of impaired immune function.

One meta-analysis of population-based studies indicates a significant increase in thyroid cancer in renal transplant patients among many other cancers (Grulich *et al.* 2007). These include cancers of the cervix, lip, skin and lymphomas (Grulich *et al.* 2007).

At present, it is not clear if addition of further data would corroborate the outcome of this former meta-analysis as far as thyroid cancer is concerned, which kind of thyroid cancer is observed, or at which time interval such transplant-related thyroid cancer appears.

In view of this, we focused on thyroid cancer in renal transplant recipients and carried out a meta-analysis with review of thyroid-specific information.

Materials and methods

In designing our meta-analysis, we reviewed published work available of conducting meta-analyses of observational studies (Stroup *et al.* 2000, Wright *et al.* 2007). Accordingly, we defined the below criteria for studies to be entered into the meta-analysis:

Inclusion criteria

- 1) All studies had to be published in English
- 2) All studies were cohort studies of organ transplant recipients
- 3) Studies matched transplant population to standardised population to calculate a standardised incidence ratio (SIR)
- 4) Studies stated incidence of thyroid cancer and SIR of thyroid cancer

Exclusion criteria

- 1) Bone marrow transplantation studies were excluded
- 2) Some studies collected data on incident cancer through cancer registries in developed countries. Those studies that merely accepted thyroid or other cancer diagnoses without confirming that these were notified to a cancer registry were excluded

The author (D K) searched for articles reported up to January 2009 in PubMed, with the combination of search terms ‘cancer’, ‘transplantation’, ‘thyroid’, ‘organ’, ‘transplant’, ‘renal’ and ‘immunosuppression’. The search was restricted to studies published in English. The search results were restricted to the presence of these words in the title or abstract of the articles.

A preliminary search of these terms yielded 13 477 search items. The author (D K) went through all these items and identified 288 relevant publications based on the title of these of publications. Study of the abstracts of these 288 publications identified 120 publications which seemed to contain relevant data. These 120 publications were read in full-text and scrutinised for the presence of data allowing safe calculation of the SIR. This process revealed nine studies appropriate for analysis based on the criteria set out above. In addition to this, the references of the nine relevant articles were also scrutinised to identify any further articles not revealed by the above search. All the studies included in this publication were reviewed in full by all authors.

In addition, any further data required for conducting the analysis were obtained by contacting the relevant

authors of the studies included to obtain any data not provided in the former publication.

The data were then extracted and analysed. We identified observed and expected numbers of cancer cases by selected cancer sites or grouping of sites. The authors (N D & R A-A) carried out the statistical analysis. The SIRs of commonly known cancers and cancers well established to have increased risk in the organ transplant population were compared with that of thyroid cancer. In addition, features such as mean age of patients at transplantation, the mean time to development of cancer, the number of thyroid cancers and histology were tabulated, where available. We also attempted to obtain data on how these thyroid cancers were originally identified. We identified whether detection occurred in the setting of a structured screening programme or was an incidental discovery by contacting the authors of the studies. The majority of studies available for evaluating thyroid cancer in the transplant population is retrospective and predominantly review the cancer risk in the renal transplant population. All but one study were found to report on renal transplant patients. In order to reduce any form of bias, only data related to renal transplantation were reviewed in our analysis. The SIRs were specifically calculated and requested from authors for the relevant cancers used in our comparison.

The number of cancer cases observed and expected was tabulated by cancer site and in cases, where the expected cases were not presented, this was calculated by using the reported SIRs. The overall SIRs for the studies were calculated by author (R A-A and N D) by weighting the studies based on their sample size.

Table 1 Distribution of organ transplants in included studies

Study authors	Renal transplants (n)	Liver transplants (n)	Heart transplants (n)	Lung transplants (n)	Pancreas transplants (n)	Combination transplantation (n)	Recipients of renal transplants (n)
Hoshida et al. 1997	1744	0	0	0	0	0	1744
Adami et al. 2003	5004	394	236	117	26	154	5931
Birkeland et al. 2000	1821	0	0	0	0	0	1821
Kyllonen et al. 2000	3440	0	0	0	0	0	2890
Pond et al. 2005	10 989	0	0	0	0	0	10 989
Vajdic et al. 2006	10 180	0	0	0	0	0	10 180
Makitie et al. 2008	3440	0	0	0	0	0	2890
Végso et al. 2007	2852	0	0	0	0	0	2535
Villeneuve et al. 2007	11 391	0	0	0	0	0	11 391
Total (n)	50 861	394	236	117	26	154	51 788
Percentage of total	98.2	0.8	0.5	0.2	0.1	0.3	100.1

The number of renal transplants indicates the number of organ transplant procedures performed. The column ‘recipients of renal transplants’ indicates the number of patients receiving these transplants. Data relating to non-renal transplant were excluded from meta-analysis in order to avoid a bias.

Table 2 Summary of studies included in the analysis

	Study title	Type of study	Multicentre	Type of transplant	Number of patients in study (n)
1	Cancer risk after renal transplantation in Japan (Hoshida <i>et al.</i> 1997)	Retrospective	Yes	Renal	1744
2	Cancer risk following organ transplantation: a nationwide cohort study in Sweden (Adami <i>et al.</i> 2003)	Retrospective	Yes	Multiorgan	5931
3	Cancer risk in patients on dialysis and after renal transplantation (Birkeland <i>et al.</i> 2000)	Retrospective	Yes	Renal	1821
4	Cancer incidence in a kidney-transplanted population (Kyllonen <i>et al.</i> 2000)	Retrospective	Yes	Renal	2890
5	Thyroid cancer in the renal transplant population: epidemiological study (Pond <i>et al.</i> 2005)	Retrospective	Yes	Renal	10 989
6	Cancer incidence before and after kidney transplantation (Vajdic <i>et al.</i> 2006)	Retrospective	Yes	Renal	10 180
7	Head and neck cancer in renal transplant patients in Finland (Makitie <i>et al.</i> 2008)	Retrospective	Yes	Renal	2890
8	Malignancies after renal transplantation during 33 years at a single centre. (Végso <i>et al.</i> 2007)	Retrospective	No	Renal	2535
9	Cancer incidence among Canadian kidney transplant recipients (Villeneuve <i>et al.</i> 2007)	Retrospective	Yes	Renal	11 391

Statistical analysis

In our meta-analysis, we obtained an estimate from each study of the unadjusted relative risk (RR) with 95% confidence intervals (CIs). We used a random effect model and calculated pooled effects (95% CIs) for RR using the inverse variance method. We performed the Breslow-Day test for homogeneity of RRs, Cochran–Mantel–Haenszel test for the null hypothesis of no effect ($RR = 1$), and the Mantel–Haenszel common RR estimate and depicted results using a forest plot. We assessed publication bias by using a funnel plot and Begg’s test to find out whether there was a bias towards publication of studies with positive results among the smaller studies. We also examined the influence of individual studies, in which the meta-analysis estimates are derived omitting one study at a time to see the extent to which inferences depend on a particular study or group of studies. The statistical package STATA v9.1 (www.stata.com) was used.

Results

Our analysis included nine studies comprising a total of 50 371 pure renal transplants (98.2%) and 927 mixed and other solid organ transplants (1.8%; [Table 1](#)). These studies were based in a number of countries, which included Australia and New Zealand, Canada, Denmark, Finland, Hungary and Sweden. We considered the sample size of the mixed and non-renal transplant group as too small for meta-analysis. As a consequence, only patients who underwent renal transplantation were included here.

[Table 2](#) shows a summary of the studies included in our analysis with details of the studies. As can be noted, all the studies were retrospective and the largest study had over 11 000 patients.

The overall mean age at transplantation was 44.4 years (range: 40.3–53.1 years) with a mean follow-up time of 8.2 years ([Table 3](#)). In total, all the studies

Table 3 Demographic details of included studies

Study	Data source	Geographic origin	Length of follow-up time	Number of patients (n)	Number of all cancers (n)	Mean follow-up time (years)	Patient-years (years)	Mean age at transplantation (years)
Adami et al. 2003	Swedish inpatient register	Sweden	1970–1997	5931	692	6.8	40 360	42
Kyllonen et al. 2000	Finland transplant registry	Finland	1967–1997	2844	230	7.2	20 817	41.5
Birkeland et al. 2000	Danish registry	Denmark	NR–1995	1821	209	7.9	13 734	45
Hoshida et al. 1997	Multicentre Japan	Japan	1970–1995	2744	45	7.4	12 982	??
Végso et al. 2007	Budapest transplantation centre	Hungary	1973–2007	2535	193	9.8	??	53.1
Pond et al. 2005	ANZDATA registry	Australia and NZ	1963–2002	10 689	23	??	??	48.2
Vajdic et al. 2006	ANZDATA	Australia and NZ	1982–2003	10 180	1236	8.5	NR	41
Makitie et al. 2008	Helinski hospital	Finland	1964–1997	3440	113	10.2	29 465	40.3
Villeneuve et al. 2007	Canadian cancer registry	Canada	1981–1998	11 155	778	7.4	81 237	??
Total	—	—	—	51 339	3519	8.2 ^a	198 595 ^a	44.4 ^a

^aNB the figures displayed in italic we are awaiting further data from authors to adjust these.

accumulated a surveillance of 198 595 patient-years. A total number of 3519 cancers and haematological malignancies were observed (Table 3).

Meta-analysis for the SIR for thyroid cancer showed it to be significantly elevated at 6.94 (95% CI 5.55–8.69; $P<0.001$). Figure 1 shows the forest plot for individual and overall RR measures. The pooled estimate of RRs using the random effect model (RR) was 6.94 (95% CI 5.55–8.69; $P<0.001$). Heterogeneity test was not significant ($Q=12.47$, $P=0.131$). There was no evidence of publication bias using Begg’s test ($P=0.118$; Fig. 2).

A sensitivity analysis (Table 4) indicates that the omission of any of the studies led to changes in estimates between 6.13 (4.92–7.64) and 8.01 (6.83–9.40). The changes were not significant.

The more common epithelial cancers such as breast, prostate, colorectal and ovarian were not significantly increased in the transplant population (Table 5). In addition, cancers related to viral infection such as non-melanoma skin, cervix uteri and lip cancers were found at increased rates in the transplant population (Table 5). Kidney and bladder cancers were also found to be increased in the transplant population (Table 5).

None of the studies had routine neck US scanning as part of their screening post renal transplantation. In total, there were 115 thyroid cancers and almost all were noted to be papillary carcinomas (Table 6). The overall mean time to thyroid cancer development with the day of transplantation defined as day 0 was 72.0 months as compared to the 92.7 months for all other cancers.

Discussion

Our data show that the risk of thyroid cancer is significantly increased following allogenic kidney transplantation (SIR 6.94 95% CI 5.55–8.69 $P<0.001$). The majority of cancer appears about 6 years following transplant. With the exception of those cancers with unspecific histology, they all are of papillary type.

Conversely, malignancies commonly encountered in the general population, such as carcinoma of the breast, prostate, lung and colon, are not seen more frequently in transplant recipients.

It is uncertain as to whether the increased risk of thyroid cancer post transplantation is related to chronic immune suppression alone or eventually also related to pre-existing cancer risk factors. End-stage kidney

Figure 1 The Forest plot depicts the scattering of the odds ratio (OR) with 95% confidence intervals (CI) for the studies entering meta-analysis. The squares indicate sample size as inverse variance weights. The rhombus indicates the OR of the combined studies with 95% CI.

disease (ESKD) or dialysis is associated with an increased risk of cancer in general as demonstrated in a study of long-term cancer incidence of 831 804 patients on dialysis (Maisonneuve *et al.* 1999). Importantly, the overall cancer risk associated with ESKD was lower than the risk post transplantation. Studies that fail to record the increased cancer risk in patients with ESKD still show an increased risk for thyroid cancer in dialysis patients (RR=2.0; Kantor *et al.* 1987). As far as thyroid cancer is concerned, a study by Brunner *et al.* (1995) which mapped cancer incidences using European Dialysis and Transplant Association-European Renal Association cancer registry found an increased incidence of thyroid cancer both in transplanted patients as well as in patients with chronic renal failure treated by maintenance haemodialysis. The vast majority of cancer occurrence in post-transplant recipients is that of *de novo* cancer

Figure 2 The funnel plot shows the scatter plot of the natural logarithm of the odds ratio (lnOR) of SIR of thyroid cancer on the vertical axis as an expression of the effects of transplantation on disease-specific mortality plotted against the standard error of the natural logarithm of the odds ratio of SIR (S.E.M. of lnOR) of thyroid cancer on the horizontal axis as an expression of the study size. Begg's test has not identified a significant funnel plot asymmetry ($P=NS$).

rather than the result of an ascertainment bias (Vajdic *et al.* 2006). In addition, we noted that neck US scanning was not part of routine screening in any of the studies, thus it is likely that all thyroid cancers detected were incidental findings. The lack of excess risk of prostate and breast cancers (commonly diagnosed by opportunistic screening) also argues against this bias playing an important role. However, these inferences need to be treated with the *caveat* that specifically papillary thyroid cancer can have a very long latency. Our data show that the average time of discovery of the thyroid cancer is 6 years following transplant. It is impossible to know how many of these cancers would have been initiated in the pre-transplant episode. The most important question in this matter is whether the rate of *de novo* initiation or growth of cancers or both factors are altered by the post-transplantation state. Indeed, it is not unlikely that post-transplant immunosuppression could have modified the clinical course of latent disease which thereby became clinically detectable and relevant. We can only speculate as to the drivers behind thyroid carcinogenesis in the setting of chronic immune depression. There is considerable evidence that viral infection may contribute to thyroid carcinogenesis, including enteroviruses, Epstein-Barr virus (Shimakage *et al.* 2003), and human papilloma virus B19 (Wang *et al.* 2008), and human hepatitis C virus (Antonelli *et al.* 2009). Immune surveillance by dendritic cells may be among the mechanism of thyroid cancer control (Schott 2006). The pattern of solid organ cancers found to be increased following renal transplantation seems to be associated with a viral oncogenic pathway of induction, such as cervical cancer, non-melanoma skin cancer and lip cancer. Thyroid and renal cancers seem to be an exception to this pattern as noted from our analysis.

It would be of interest to determine whether an increased risk of cancer (specifically thyroid cancer) is present in other immunodeficient populations.

Table 4 Sensitivity analysis

Study omitted	RR	95% Confidence Intervals	
Birkeland <i>et al.</i> 2000	6.87	5.42	8.70
Hoshida <i>et al.</i> 1997	6.78	5.35	8.59
Végso <i>et al.</i> 2007	6.13	4.92	7.64
Adami <i>et al.</i> 2003	7.31	5.95	8.99
Kyllonen <i>et al.</i> 2000	6.72	5.20	8.70
Makitie <i>et al.</i> 2008	7.05	5.53	8.99
Pond <i>et al.</i> 2005	6.99	5.52	8.86
Villeneuve <i>et al.</i> 2007	8.01	6.83	9.40
Vajdic <i>et al.</i> 2006	6.80	5.14	90.00
Combined	6.94	5.55	8.69

Table 5 Cancer-specific standardised incidence ratios (SIRs)

	Hoshida <i>et al.</i> 1997	Adami <i>et al.</i> 2003	Vajdic <i>et al.</i> 2006	Villeneuve <i>et al.</i> 2007	Kyllonen <i>et al.</i> 2000	Birkeland <i>et al.</i> 2000	Végso <i>et al.</i> 2007	Pond <i>et al.</i> 2005	Makitie <i>et al.</i> 2008	Overall
Thyroid	12.43 (2.38–33.70)	3.8 (1.4–8.2)	6.9 (4.69–9.8)	5.0 (3.17–7.50)	8.09 (4.04–14.47)	10.47 (0.14–58.26)	8.95	5.2 (2.0–16.6)	5.8 (3.0–10.2)	6.94 (5.55–8.69)
Prostate	–	1.1 (0.7–1.7)	0.95 (0.68–1.29)	0.91 (0.64–1.26)	–	–	0.65	–	–	0.965 (0.785–1.186)
Breast	1.53 (0.18–5.27)	1.0 (0.6–1.5)	1.03 (0.78–1.34)	1.31 (0.98–1.72)	1.20 (0.64–2.05)	1.45 (0.72–2.60)	0.86	–	–	1.158 (0.982–1.366)
Colorectal	–	–	1.71 (1.38–2.09)	1.4 (1.0–1.8)	–	–	0.34	–	–	1.65 (1.318–2.065)
Liver	1.36 (0.24–3.36)	1.1 (0.3–2.8)	3.19 (1.53–5.8)	1.8 (0.6–4.3)	–	–	3.25	–	–	2.069 (1.265–3.386)
Non-mela- noma skin	–	56.2 (49.8–63.2)	–	–	39.1 (29.2–51.27)	10.68 (8.84–12.79)	2.58	–	59.1 (44.1–77.5) M	32.649 (13.85–79.966)
Cervix uteri	–	57.7 (51.0–65.1)	–	–	–	–	–	–	23.3 (11.2–42.8) F	–
Oral: lip	–	2.0 (0.7–4.7)	2.5 (1.33–4.27)	1.6 (0.6–3.4)	–	–	–	–	–	2.124 (1.375–3.28)
Kidney	–	53.3 (38–72.5)	47 (41.76–52.91)	31.3 (23.5–40.8)	22.95 (12.55–38.51)	13.02 (10.75–15.63)	–	–	26.7 (16.1–41.7) M	30.422 (17.827–51.913)
Hodgkin's lymphoma	–	54.8 (39.0–74.9)	7.3 (5.69–9.22)	7.3 (5.69–9.22)	7.97 (5.00–12.07)	4.08 (1.50–8.88)	6.77	–	66.5 (26.75–137) F	9.563 (5.19–17.619)
Non-Hodg- kin's lymphoma	–	4.9 (3.3–7.1)	3.74 (1.51–7.71)	3.6 (1.7–6.9)	–	8.0 (1.65–23.38)	–	–	–	3.883 (2.413–6.248)
Bladder	6.61 (0.69–20.60)	6 (4.4–8.0)	9.86 (8.37–11.54)	8.87 (7.38–10.56)	–	5.48 (2.37–10.80)	1.32	–	–	7.285 (5.105–10.397)
Ovary	–	–	3.33 (2.4–4.5)	2.0 (1.3–3.0)	–	1.63 (0.53–3.81)	0.79	–	–	2.534 (1.869–3.437)
Testicular	–	2.3 (1.4–3.6)	1.15 (0.46–2.38)	1.5 (0.6–2.0)	–	–	–	–	–	1.547 (0.985–2.429)
All cancers	2.78 (1.8–3.28)	2.3 (0.9–3.8)	1.25 (0.34–3.19)	–	–	–	–	–	–	1.624 (0.697–3.783)
	–	2.3 (0.5–6.6)	3.4 (3.22–3.59)	2.5 (2.3–2.7)	3.33 (2.92–3.79)	3.59 (3.12–4.11)	1.33	–	–	3.211 (2.748–3.752)
	–	4.0 (3.7–4.4)	–	–	–	–	–	–	–	–
	–	3.9 (3.6–4.2)	–	–	–	–	–	–	–	–

The SIRs in the Adami *et al.* 2003 study are adjusted to include only renal transplant recipients. These adjusted figures are displayed in bold where available.

Table 6 Characteristics of thyroid cancer

Study	Number of renal transplant cases	Number of expected cases of thyroid cancer	Number of identified cases of thyroid cancers	Type of cancer	Screening method and diagnosis	Median time in months to development of thyroid cancer	Median time in months to development of any type of cancer
Hoshida <i>et al.</i> 1997	1744	0.2	3	All papillary cancers	US screening and incidental pick up – during annual check-up (1 case clinical)	33	58
Adami <i>et al.</i> 2003	5004	1.6	6	All papillary cancers	Incidental pick – picked up during annual check-up		
Birkeland <i>et al.</i> 2000	1821			??			
Kyllonen <i>et al.</i> 2000	3440	1.3	11	9 Papillary 2 Unknown	Screening involved annual check-up – no routine screening by US unless suspected.		98
Pond <i>et al.</i> 2005	10 989	4.4	23	14 Papillary 3 Mixed papillary 6 Unknown ??		68 (3–253)	102 (3–363)
Vajdic <i>et al.</i> 2006	10 180	6.2	31		Screening involved annual check-up	128.4	112.8
Makitie <i>et al.</i> 2008	3440	2.1	12	All papillary cancers	Screening involved annual check-up. No neck US screening	NR	
Végso <i>et al.</i> 2007	2852	0.7	6	All papillary	Screening involved annual check-up – no routine screening by US unless suspected.	58.5	
Villeneuve <i>et al.</i> 2007	11 391	4.6	23	??		NR	
Total	50 861	21.1	115	–	–	72.0	92.7

Awaiting further data from authors to adjust total calculations.

Grulich *et al.* (2007) have recently conducted a meta-analysis which compared the incidence of malignancy in people with HIV/AIDS and transplant recipients. They evaluated seven studies of people with HIV/AIDS ($n=44\,172$) and five studies of transplant recipients ($n=31\,977$). Interestingly, a similar pattern of increased risk of malignancy was identified in both populations (20 out of the 28 malignancies investigated). A large proportion of these 20 malignancies were associated with a known or suspected viral aetiology. The common epithelial cancers such as cancers of the colon, breast, rectum, ovary and prostate were not found to be increased in either population. The trends noted in this study were very similar to the pattern noted in our analysis. However, whereas there was an increased risk of thyroid cancer in the transplant population (5.91 95% CI 4.41–7.90), there was no increased risk of thyroid cancer in the HIV/AIDS population. This suggests that different immune mechanisms may be responsible for the development of thyroid cancer in immunosuppressed transplant patients. However, the differential immune modulation that results from treating these two patient groups provides a significant confounding factor. The majority of patients in the HIV/AIDS group was likely to be treated with combination anti-retroviral agents. It is possible that anti-retroviral agents interact directly with the mechanisms involved in the development of thyroid cancer. By evaluating the immune profiles of the HIV/AIDS population and comparing it to the transplant population, we may be able to determine what factors account for this observed difference in thyroid cancer risk.

The debate on the presumed cause of thyroid cancer should not overshadow the important conclusion which needs to be drawn from these results. Our analysis shows that all thyroid cancers occurring in the post-transplant setting are of papillary type, as far as specific histopathology information was available. Papillary thyroid cancer has an excellent prognosis with timely detection and appropriate treatment (Mazzaferri 2009). We therefore feel that ultrasound screening for thyroid lesions prior to transplantation and yearly thereafter during routine post-transplant surveillance should help to control a recognised risk factor in the long-term course.

Conclusion

Our meta-analysis has clearly demonstrated that the standardised incidence rate of thyroid cancer is elevated in renal transplant recipients. While the origin of this phenomenon is not clear, it supports the use of thyroid

ultrasound in the pre- and post-transplant setting in order to ensure timely detection of a curable disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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