Surveillance of Nonmelanoma Skin Cancer Incidence Rates in Kidney Transplant Recipients in Ireland

Finian J. Bannon,[1,6] Jennifer A. McCaughan,[2] Carol Traynor,[3] Katie O'Brien,[5] Anna T. Gavin,[1] Alexander P. Maxwell,[2] Harry Comber,[5] and Peter J. Conlon[3,4]

Background. The incidence of nonmelanomatous skin cancer (NMSC) is substantially higher among renal transplant recipients (RTRs) than in the general population. With a growing RTR population, a robust method for monitoring skin cancer rates in this population is required.

Methods. A modeling approach was used to estimate the trends in NMSC rates that adjusted for changes in the RTR population (sex and age), calendar time, the duration of posttransplant follow-up, and background population NMSC incidence rates. RTR databases in both Northern Ireland (NI) and the Republic of Ireland (ROI) were linked to their respective cancer registries for diagnosis of NMSC, mainly squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).

Results. RTRs in the ROI had three times the incidence ($P<0.001$) of NMSC compared with NI. There was a decline ($P<0.001$) in NMSC 10-year cumulative incidence rate in RTRs over the period 1994–2009, which was driven by reductions in both SCC and BCC incidence rates. Nevertheless, there was an increase in the incidence of NMSC with time since transplantation. The observed graft survival was higher in ROI than NI ($P<0.05$) from 1994–2004. The overall patient survival of RTRs was similar in NI and ROI.

Conclusion. Appropriate modeling of incidence trends in NMSC among RTRs is a valuable surveillance exercise for assessing the impact of change in clinical practices over time on the incidence rates of skin cancer in RTRs. It can form the basis of further research into unexplained regional variations in NMSC incidence.

Keywords: Kidney, Transplantation, Nonmelanoma skin cancer, Incidence, Surveillance.

(*Transplantation* 2014;00: 00–00)

Improved immunosuppressive regimens have succeeded in overcoming the early immunological barriers to kidney transplantation for many patients with end-stage renal disease. RTRs now experience improved long-term outcomes (*1*) because of higher rates of graft function (*2*) and longer graft survival (*3*). However, observational studies have shown that RTRs experience a 3-fold or greater relative risk for different cancers (*4–6*), confirming concerns about possible side effects of immunosuppression on cancer risk (*7*). For NMSC, even greater relative risks of 10- to 250-fold have been reported (*8*). In addition, NMSC, in particular SCC, frequently has a more aggressive course in RTRs (*9*).

In observational studies, increased NMSC incidence rates in RTRs are associated with both azathioprine and cyclosporin usage (*10, 11*). In vitro and in vivo experiments have proposed direct carcinogenic mechanisms for these observed associations (*12, 13*) with one randomized study directly quantifying a carcinogenic effect reporting that higher cyclosporin doses result in greater NMSC rates (*14*). Observational studies (*15–17*) in RTRs that compare effects of different

The Northern Ireland Cancer Registry is funded by the Public Health Agency of Northern Ireland. J.A.M. is the recipient of a Kidney Research UK Clinical Research Fellowship and is supported by the Northern Ireland Kidney Research Fund.

The authors declare no conflicts of interest.

[1] Northern Ireland Cancer Registry, Centre for Public Health, Queen's University Belfast, UK.
[2] Nephrology Research, Centre for Public Health, Queen's University Belfast, UK.
[3] Department of Nephrology, Beaumont Hospital, Dublin, Ireland.
[4] Royal College of Surgeons in Ireland, Dublin, Ireland.
[5] National Cancer Registry of Ireland, Cork, Ireland.
[6] Address correspondence to: Finian J. Bannon, M.A., Ph.D., Northern Ireland Cancer Registry, Centre for Public Health, Queen's University Belfast, Mulhouse Building, Grosvenor Road, Belfast, BT12 6BJ, Northern Ireland.E-mail: f.j.bannon@qub.ac.uk

F.J.B. linked datasets, performed the statistical analysis, and wrote the primary draft of the paper. J.A.M. and C.T. updated and prepared the Northern Ireland renal recipients dataset and participated in the writing of the paper. K.O. coordinated the Republic of Ireland cancer incidence dataset and performed preliminary statistical analysis. A.T.G. oversees the Northern Ireland cancer incidence register. A.P.M. oversees the Northern Ireland renal recipients' database and participated in the writing of the paper. H.C. oversees the Republic of Ireland cancer incidence database and coordinated and hosted the teleconferences, and is the coinitiator of the study. P.J.C. manages the Republic of Ireland renal recipients' database and participated in the writing of the paper and is the coinitiator of the study.

Received 16 October 2013. Revision requested 8 November 2013.
Accepted 4 February 2014.
Copyright © 2014 by Lippincott Williams & Wilkins
ISSN: 0041-1337/14/0000-00
DOI: 10.1097/TP.0000000000000115

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

immunosuppressants (e.g., cyclosporin vs. tacrolimus) on NMSC risk are susceptible to hidden confounding because their usage occurred in different historical periods that probably varied in other aspects of clinical management. Caution is required, therefore, when using observational data such as RTR databases to estimate differences in immunosuppressant effects where the impact of other significant cancer risk determinants cannot be adjusted for in the analysis.

This study, which linked national cancer registry data to comprehensive RTR databases, proposes that observational data be used both as a surveillance tool and as a platform for exploring aspects of clinical management. The study focuses on establishing an unbiased estimate of the trend in age-specific excess incidence rates of NMSC among RTRs over a 16-year period using a modelling framework. The approach accounts for 1) the age-sex population structure, 2) time since transplantation, 3) background NMSC rates, and 4) two adjacent national renal transplant programs in NI and in the ROI. These two countries have separate health-care systems and independent transplant programs.

RESULTS

Description of the Recipient Population

In the period 1984 to 2009, approximately 3507 first kidney transplants took place in Ireland whose recipients were alive at sometime in 1994–2009 with less than 10 years since transplantation; 906 were performed in NI and 2,601

TABLE 1. Description of the renal transplant recipient population, cancer statistics, and performance indicators

Measure	Northern Ireland	Republic of Ireland	Island of Ireland
Numbers of recipients 1984–2009 alive on January 1, 1994	906	2601	3507
Person-years in study[1]	5,127	13,590	18717
Mean age at transplant	41.0[a]	41.8[a]	41.6
% male recipients	61.3[a]	62.9[a]	62.5
% White recipients	99.0	96.0	96.7
Mean donor age	38.2[a]	34.2[b]	35.3
Type of transplant (% living donor)	0.08[a]	0.03[b]	0.05
Mean HLA mismatch	2.13[a]	2.87[b]	2.68
Recipient incidence (one per recipient[2])			
NMSC	51	343	394
SCC	27	239	266
BCC	31	195	226
Recipient incidence rate[3] 1994–2009 (95% CI)			
NMSC	1022[a]	2759[b]	2182
SCC	675[a]	1576[b]	1263
BCC	403[a]	1477[b]	1096
Population incidence rate[3] 1994–2009 (95% CI)			
NMSC	116.4[a]	143.7[b]	134.7
SCC	31.5[a]	44.7[b]	40.3
BCC	86.5[a]	106.5[b]	100.0
Standardised incidence ratio (95% CI)			
NMSC	8.2[a]	18.0[b]	15.6
SCC	19.1[a]	46.3[b]	40.9
BCC	6.0[a]	11.7[b]	10.4
Non-Hodgkin lymphoma (C82–C85)	13.2[a]	6.8[a]	8.5
All cancers (excl C44)	2.0[a]	1.6[a]	1.7
5-year observed graft survival[4]			
1994–2004	74.2[a]	82.2[b]	80.2
1994–1999	69.0[a]	78.8[b]	76.4
2000–2004	79.9[a]	86.2[a]	84.5
5-year observed patient survival[4]			
1994–2004	88.7[a]	89.0[a]	88.9
1994–1999	85.7[a]	85.6[a]	85.6
2000–2004	91.2[a]	90.4[a]	90.6

[1] Recipients were censored at the earliest of 1) first diagnosis, 2) death, or 3) after 10 years of follow-up, or 4) December 31, 2009.
[2] Owing to different policies between NICR and NCRI, only the first NMSC, or SCC or BCC is considered for the study.
[3] Rate here is a European age-standardized rate per 100,000, only one tumor type per recipient.
[4] Observed survival was calculated using the Kaplan-Meier method. In calculating the graft survival, recipients were censored at death.
[a, b] Statistics within a row comparing ROI and NI with different letter superscripts are significantly ($P<0.05$) different from each other.

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

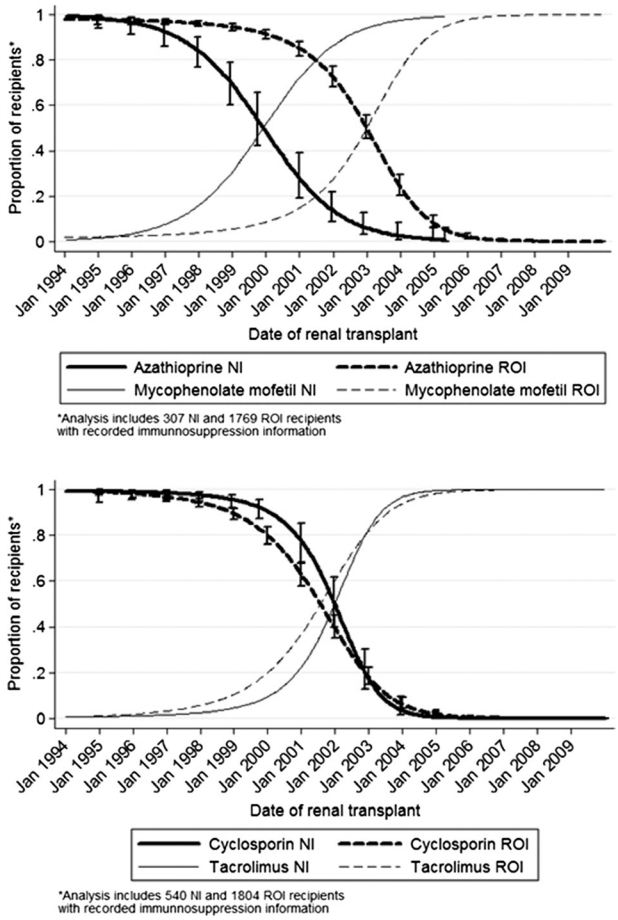

FIGURE 1. Trends in the proportion of renal transplant recipients prescribed different immunosuppressants (intention-to-treat: azathioprine, mycophenolate, cyclosporin, and tacrolimus) from 1994 to 2009, with 95% confidence intervals for azathioprine and cyclosporin.

in the ROI. Mean age at transplant was 41.6 years, and 62.5% of recipients were male (Table 1). From 1994 to 2009, 51 and 343 cases of NMSC occurring in 5127 and 13,590 person-years of follow-up were diagnosed in NI and ROI, respectively (Table 1).

From 1994 to 2009, NMSC standardized incidence rate (SIR) for the NI renal transplant population was 8.2 ($P<0.05$) and for the ROI cohort was 18.0 ($P<0.05$); likewise for SCC, the SIRs were 19.1 and 46.3 ($P<0.05$), respectively. The all-Ireland SIRs in RTRs for non-Hodgkin lymphoma and all cancers excluding NMSC were elevated ($P<0.05$) at 8.5 and 1.7, respectively (Table 1).

Table 1 compares graft and recipient survival between the transplant centers. Five-year graft survival was higher ($P<0.05$) in ROI (82.2%) than in NI (74.2%) from 1994 to 2004. However, the observed 5-year patient survival was not significantly different between NI and ROI.

The proportion of first-transplant RTRs receiving cyclosporin/tacrolimus or azathioprine/mycophenolate mofetil (on an intention-to-treat basis) over calendar time is presented in Figure 1. By 2003, most RTRs were commenced on tacrolimus, while mycophenolate mofetil was adopted in NI (2002) 3 years before ROI (2005).

Excess Incidence Modeling Results

There was a significant difference between countries with ROI having 3.2 times the incidence rate of NMSC than NI ($P<0.001$; Table 2). Male subjects were 2.4 times more likely ($P<0.001$; Table 2) to develop NMSC than female subjects.

The number of knots required for the splines to describe nonlinearity was surprisingly small ($n\leq2$). Figure 2A shows that the 10-year cumulative excess incidence of NMSC decreased ($P<0.05$) from 1994 to 2009 (calendar timescale) and was higher in the ROI than in NI; a reduction in the 10-year cumulative excess incidence for both SCC and BCC contributed to this decline. Both for NMSC and BCC, interaction terms for the calendar by follow-up time were required in the model.

Figure 2B shows that the excess incidence of NMSC and SCC increased ($P<0.05$) soon after transplantation (follow-up timescale) and was higher in the ROI than in NI. For both NMSC and BCC, the calendar and follow-up time interacted— in the early calendar years, the excess incidence increased soon after transplant, but in later calendar years, the excess incidence increased more gradually (not shown).

DISCUSSION

Advancements in renal transplantation over the past 3 decades have widened access to transplantation for individuals with end-stage renal disease and improved both graft and recipient survival (*1, 2*). The growing population of RTRs on the Island of Ireland, therefore, requires surveillance to detect when any new aspect of clinical management poses a risk factor for cancer. This study, combining population-based RTR and cancer registry databases, has shown that it is possible to obtain unbiased trend estimates in excess NMSC incidence in the RTR population.

RTRs in ROI had 3.2 times the excess incidence risk of developing NMSC than in NI. However, it is possible that

TABLE 2. Excess incidence relative risk of a) nonmelanoma skin cancer (NMSC) b) squamous cell carcinoma (SCC), and c) basal cell carcinoma (BCC) in renal transplant recipients on the Island of Ireland during the years 1984–2009, comparing country and sex

	Relative risk (95% CI)		
	NMSC	SCC	BCC
Country: ROI vs. NI	3.21 (2.29–4.50)	4.12 (2.69–6.31)	2.72 (1.74–4.26)
Sex: male vs. female	2.36 (1.82–3.06)	2.78 (2.03–3.80)	2.23 (1.56–3.18)

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

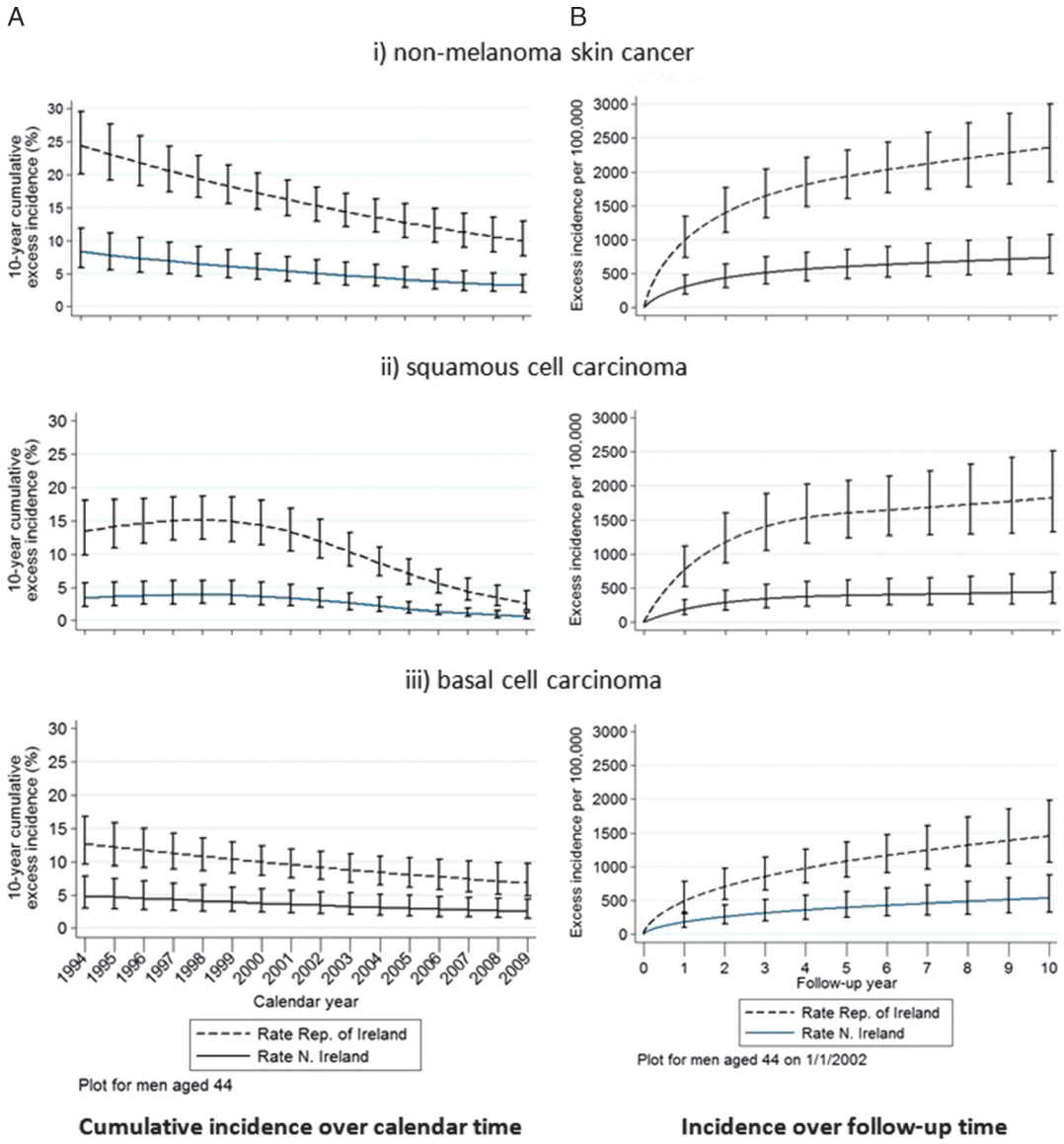

FIGURE 2. A, The 10-year cumulative excess incidence (with 95% confidence intervals) by country in male renal transplant recipients aged 44 on the Island of Ireland over the calendar years 1994–2009, and (B) the excess incidence rate over the 10-year follow-up as at January 1, 2002, for i) nonmelanoma skin cancer, ii) squamous cell carcinoma, and ii) basal cell carcinoma.

this difference is due to population bias, referral and management bias, or NMSC registration biases.

The RTR populations in both countries are from comparable ethnic backgrounds (96%–99% White) (Table 1), and each country shares similar environmental risks for NMSC such as latitude, annual hours of sunshine (*18, 19*), and proportion of each population employed in outdoor occupations (*20, 21*). The rate of NMSC in the general population in the ROI (143/100,000) is comparable to NI (116/100,000) giving a ratio of 1.2. This is likely to be a surrogate for the population bias, if present, in the RTR population. The analysis in this study adjusted for this small difference in background incidence rates. Population bias is therefore unlikely to explain the discrepancy in NMSC incidence between the RTR populations in NI and ROI.

The second source of possible confounding is the potential difference between referral and management of RTRs with suspected skin malignancies. In both jurisdictions, RTRs are reviewed regularly by nephrologists with expertise in transplantation. It has been standard practice in both countries for the past 20 years to refer RTRs with skin lesions suggestive of NMSC to a dermatology clinic for biopsy (*22, 23*). Even if such skin lesions are excised in primary care, guidelines recommend histologic confirmation of the nature of the lesion (*24*). In both NI and ROI, the cancer registries are populated by histologic data so skin biopsies performed on RTRs in primary care will be included. There is therefore no appreciable difference in the referral and management practice for RTRs with suspicious skin lesions between NI and ROI.

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

The third possibility is that the difference in NMSC incidence is an artifact of cancer registration. The completeness indicators (percentage of cases microscopically verified, mortality: incidence ratio, and percentage of cases diagnosed by death certificate only) of the NI and ROI cancer registries are similar (*25*), and suggest high levels of completeness. It is implausible that a difference exists between the countries in NMSC registration among RTRs but is absent in the general population where incidence rates are comparable. The potential for registration bias is further reduced by including only the RTR's first case of NMSC in the analysis. Finally, analyses restricted to the first case of SCC and BCC showed similar excess incidence differences between countries. These potential confounders do not adequately explain the difference in NMSC incidence between NI and ROI.

We have shown a significantly increased 5-year graft survival in the ROI compared with NI (82.2% vs. 74.2%). It is plausible that RTRs in the ROI have been exposed to higher levels of immunosuppression than in NI (*26*), resulting in reduced immunologic injury and better graft survival but an increased incidence of NMSC. Unfortunately, it is not possible to directly compare levels of immunosuppression across both jurisdictions as robust data on prescribed immunosuppressant doses or drug levels over time is not available.

The 10-year cumulative excess incidence rate of NMSC among Irish RTRs has decreased from 1994 to 2009 (Fig. 2A). The reduction in NMSC in recent years may reflect reduced propensity to malignancy with modern immunosuppression, or it may be a response to a reduction in the amount of immunosuppression as clinicians target lower calcineurin inhibitor levels in an effort to reduce the associated nephrotoxicity. Between 1999 and 2009, the routine immunosuppression prescribed to RTRs on the island of Ireland changed from azathioprine/cyclosporin to mycophenolate mofetil/tacrolimus (Fig. 1). Cyclosporin and azathioprine have direct carcinogenic properties; cyclosporin inhibits apoptosis by interfering with mitochondrial function (*12*), and azathioprine induces chronic oxidative stress (*13*). Immunosuppressants may also exert an indirect carcinogenic effect by reducing the effectiveness of immune surveillance (*27*). As alluded to previously, a measure of immune function, plus other aspects of transplant treatment that could determine NMSC risk, such as HLA (human leukocyte antigen) matching policy and the use of induction therapy, would be necessary variables to include in a multivariate analysis of excess NSMC risk in RTRs. Only in this way can observational data furnish unbiased effect estimates of clinical management on NMSC risk in the absence randomized controlled trials.

The statistical analyses that are conventionally used to investigate excess cancer incidence in solid organ transplant populations are standard incidence ratios and semiparametric regression approaches to time-to-event data, that is, Cox regression. These approaches have limited ability to adjust for two concurrent but independent timescales; "calendar time" reflects the changes in the management of transplant recipients from 1994 to 2009, and "follow-up time" reflects the impact of cumulative years of immunosuppression on cancer risk. Intuitively, these effects are independent, and each has been adjusted for in the analysis to observe their true and unbiased impact on NMSC incidence. Figure 2A shows how the incidences of NMSC, BCC, and SCC have reduced with calendar time when the follow-up time and recipient demographics (in this case, age and sex) are controlled. This is likely to reflect advances in renal transplantation with more judicious choice of immunosuppressive therapies and improved patient education. On the contrary, Figure 2B demonstrates the cumulative risk of NMSC, BCC, and SCC, which increases with follow-up time, when calendar time and recipient demographics are controlled. This is likely to reflect prolonged exposure to immunosuppression, and this pattern is consistent with inflammation-driven carcinogenesis (*28*) or an infectious component to NMSC (*6*), as opposed to the long-term carcinogenesis acting through a genetic mode (*29*). The modeling approach, which has been employed in this study, has highlighted what occurred in the two different timescales through their mutual adjustment. It is probable that other studies investigating NMSC incidence in solid organ transplantation over a prolonged period fail to demonstrate the impact of novel immunosuppressive therapies and a prolonged immunosuppressive burden on NMSC risk because of the attenuating effect of calendar time on NMSC incidence.

Transforming the timescale variables into restricted cubic splines allows them to be modeled as continuous variables and makes their nonlinearity (Fig. 2) and interaction easier to handle; this is important when disentangling the independent effects of the two timescales on excess incidence. The adjustment for background population NMSC incidence in the analysis was not critical because the excess incidence rate among RTRs was large relative to the background population rate. Nevertheless, this adjustment establishes the excess incidence rate, which is appropriate when comparing NMSC risk between periods and territories with differing background population incidence rates. Improved smoothing of the background population incidence rates could be better achieved by using a modeling technique (*30*), which would be important when estimating excess incidence in less common cancer types in RTRs.

In conclusion, linking national RTR databases to cancer registry information can be used to estimate and monitor cancer rates in RTRs in an ever-changing clinical environment. The identification of interjurisdiction variability in cancer rates suggests that modifiable etiologic factors are present, for example, differences in immunosuppressive protocols. Finding differences in cancer rates will generate hypotheses for further research that can hopefully be translated into reductions in cancer incidence in RTRs.

MATERIALS AND METHODS

Recipient Cohort

Recipients of kidney transplants on the island of Ireland who were alive in years 1994–2006, and less than 10 years posttransplant, were included in the analysis. Kidney transplantation in the ROI takes place at Beaumont Hospital and in NI at Belfast City Hospital, and each unit has performed 3478 and 1770 transplants since inception, respectively. Figure 3 summarizes the number of transplants taking place in both countries from 1984 to 2009, the years relevant to this study. The European age-standardized transplant rate in the population (per 1,000,000) increased in both countries from 1984 to 1991 but then remained constant in the ROI until 2009,

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

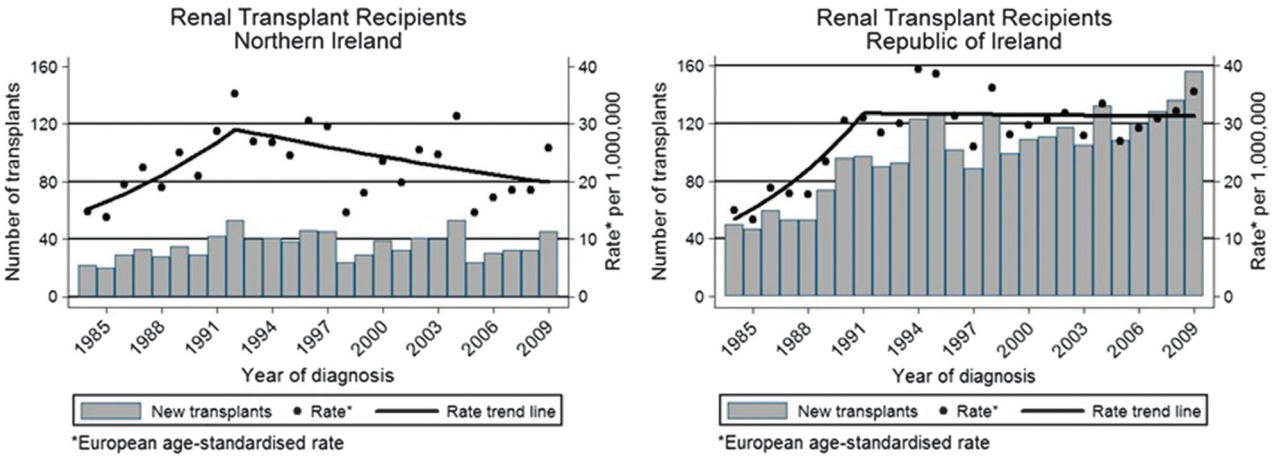

FIGURE 3. Distribution of renal transplant recipients from 1984 to 2009, with observed and fitted rates.

while showing a 2.2% per annum decline in NI. Recipients are discharged from the transplant center at 3 months and followed in regional units across the island by nephrologists. Clinical data, including recipient age, sex, date of transplant, acute rejection episodes, prescribed immunosuppressive therapy, and date of death, are recorded prospectively in both transplant units.

Cancer Incidence

Recipients were linked to cancer registries for diagnosis of NMSC between 1994 and 2009. The National Cancer Registry of Ireland (NCRI) matched on names, dates of birth, sex, and address using a probabilistic algorithm, whereas the Northern Ireland Cancer Registry (NICR) matched on national Health and Care Number or hospital numbers. As the NICR's registration policy for NMSC is to register no more than one SCC and one BCC diagnosis per patient, only the first tumor per RTR was considered in the analyses. Both NCRI and NICR register all types of malignant cancer in their populations according to internationally validated standards; their quality indicators are sufficient for acceptance in top internationally recognized publications of cancer statistics (*25, 31*).

Statistical Analysis

The incidence data were analyzed as time-to-event in fully parametric models estimated by a user-led Stata program called *stpm2* (*32*). RTRs were followed from their date of transplant, and their time-to-event data were right censored (if transplant had already occurred) from January 1, 1994, when NMSC registration was available in both countries, and left censored at the earliest occurrence of the following: first diagnosis of NMSC, 10 years of follow-up, death, or 31st December 2009. An RTR's follow-up time, or person-time, in the study, was split into periods defined by calendar year, with the midpoint of each period used to represent the calendar time and age of RTR for that period. The models included effects for country, sex, age, calendar time (1994–2009), and follow-up time (0–10 years) after kidney transplant, and a calendar time by follow-up time interaction. The program *stpm2* uses restricted cubic splines to model time-to-event data. In addition, restricted cubic splines were used to model the nonlinear effects of calendar time and age on excess incidence. Sensitivity analysis was performed restricting NMSC cases to SCC, or BCC, which are diagnosed on the basis of histology.

A table of background NMSC incidence rates (by sex, country, single year of age, and calendar year) was generated to adjust for background incidence rates; the rates were smoothed by using 3 years of incidence and population data centered on the given calendar year. These rates are incorporated into the analysis by *stpm2* to estimate the excess incidence rates in RTRs over the background population incidence rates and were previously matched to the split time-to-event data by the (attained) calendar year and age of RTR at the end point of these periods. To confirm the excess incidence approach above, standardized incidence ratios (SIRs) were also estimated to compare excess incidence among RTRs between countries.

It is necessary to graph predicted output from the model to observe how the required spline variables model the nonlinear relationship of the time-variables and excess incidence, while keeping the sex and age at a fixed level. The predicted 10-year cumulative excess incidence rate was plotted over calendar time at mean age during follow-up (44 years) and mode sex (male). The predicted excess incidence rate was plotted against follow-up time at fixed mid-calendar period date, January 1, 2002, mean age during follow-up (44 years), and mode sex (male). We report excess incidence rate over follow-up time, rather than 10-year cumulative excess incidence rate, as it shows better the development of NMSC risk in the RTR during follow-up. Excess incidence relative risk estimates for sex and country were estimated directly from their effect coefficients produced by the model.

REFERENCES

1. Traynor C, Jenkinson A, Williams Y, et al. Twenty-year survivors of kidney transplantation. *Am J Transplant* 2012; 12: 3289.
2. Pascual M, Theruvath T, Kawai T, et al. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med* 2002; 346: 580.
3. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; 342: 605.
4. Adami J, Gäbel H, Lindelöf B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Brit J Cancer* 2003; 89: 1221.
5. Villeneuve PJ, Schaubel DE, Fenton SS, et al. Cancer incidence among Canadian kidney transplant recipients. *Am J Transplant* 2007; 7: 941.
6. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; 348: 1681.
7. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. *Int J Cancer* 1995; 60: 183.
8. Rangwala S, Tsai KY. Roles of the immune system in skin cancer. *Brit J Dermatol* 2011; 165: 953.
9. Martinez JC, Clark CO, Stasko T, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients. *Arch Dermatol* 2003; 139: 301.
10. Glover MT, Deeks JJ, Raftery MK, et al. Immunosuppression and risk of non-melanoma skin cancer in renal transplant patients. *Lancet* 1997; 349: 398.
11. Ulrich C, Stockfleth E. Azathioprine, UV light, and skin cancer in organ transplant patients- do we have the answer? *Nephrol Dial Transplant* 2007; 22: 1027.

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

12. Athar M, Walsh SB, Kopelovich L, et al. Pathogenesis of nonmelanoma skin cancers in organ transplant recipients. *Arch Biochem Biophysics* 2011; 508: 159.
13. O'Donovan P, Perrett CM, Zhang X, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science* 2005; 309: 1871.
14. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two ciclosporin regimens. *Lancet* 1998; 351: 623.
15. Marcén R, Galeano C, Fernández-Rodriguez A, et al. Effects of the new immunosuppressive agents on the occurrence of malignancies after renal transplantation. *Transplant Proc* 2010; 42: 3055.
16. Bichari W, Bartiromo M, Mohey H, et al. Significant risk factors for occurrence of cancer after renal transplantation: a single center cohort study of 1265 cases. *Transplantation Proc* 2009; 41: 672.
17. Wisgehof HC, van der Boog PJM, de Fijter JW, et al. Increased risk of squamous-cell carcinoma in simultaneous pancreas kidney transplant recipients compared with kidney transplant recipients. *J Invest Dermatol* 2009: 129: 2886.
18. Met Office. Northern Ireland: climate. Available at: *http://www.metoffice.gov.uk/climate/uk/ni/print.html*. Accessed December 2013.
19. Met Éireann. Sunshine and solar radiation. Available at: *http://www.met.ie/climate-ireland/sunshine.asp*. Accessed December 2013.
20. Northern Ireland Statistics and Research Agency. Census 2011: Key Statistics for Northern Ireland. Belfast, Ireland: Northern Ireland Statistics and Research Agency; 2012: 27.
21. Central Statistics Office, Ireland. "Employment and Unemployment (ILO) ′000s". Available at: *http://www.cso.ie/en/statistics/labourmarket/principalstatistics/*. Accessed December 2013.
22. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; 159: 35.
23. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol* 2002; 146: 18.
24. *National Institute for Health and Care Excellence. Referral for suspected cancer*. London, UK: National Institute for Health and Care Excellence; 2005. (Publication number CG27).
25. International Agency for Research on Cancer. Cancer incidence on five continents, volume IX. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, et al, eds. Lyon, France: International Agency for Research on Cancer; 2007. (IARC Scientific Publications No. 160).
26. Morris PJ. Molly McGeown and renal transplantation. *Nephrol Dial Transplant* 1998; 13: 1388.
27. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002; 3: 991.
28. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. *Nature* 2008; 454: 436.
29. Aufman J, Khalil F. Carcinogenesis of Lung Cancer. In: Coppola D, ed. *Mechanisms of Oncogenesis*. Netherlands: Springer 2010: 203.
30. Baili P, Micheli A, Montanari A, et al. Comparison of four methods for estimating complete life tables from abridged life tables using mortality data supplied to EUROCARE-3. *Math Population Stud* 2005; 12: 183.
31. Berrino F, De Angelis A, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* 2007; 8: 773.
32. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J* 2009; 9: 265.

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.