JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2018 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 71, NO. 1, 2018
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.10.077

Temporal Trends of De Novo Malignancy Development After Heart Transplantation

Jong-Chan Youn, MD, PhD,[a] Josef Stehlik, MD, MPH,[b] Amber R. Wilk, PhD,[c,d] Wida Cherikh, PhD,[c,d] In-Cheol Kim, MD, PhD,[e] Gyeong-Hun Park, MD, PhD,[f] Lars H. Lund, MD, PhD,[g] Howard J. Eisen, MD,[h] Do Young Kim, MD,[a] Sun Ki Lee, MD, PhD,[a] Suk-Won Choi, MD, PhD,[a] Seongwoo Han, MD, PhD,[a] Kyu-Hyung Ryu, MD, PhD,[a] Seok-Min Kang, MD, PhD,[i] Jon A. Kobashigawa, MD[j]

ABSTRACT

BACKGROUND Malignancy is a concern in cardiac transplant recipients, but the temporal trends of de novo malignancy development are unknown.

OBJECTIVES The goal of this study was to describe the temporal trends of the incidence, types, and predictors of de novo malignancy in cardiac transplant recipients.

METHODS The authors analyzed the temporal trends of post-transplant incidence, types, and predictors of malignancy using 17,587 primary adult heart-only transplant recipients from the International Society for Heart and Lung Transplantation registry. The main study outcomes included the incidence of, types of, and time to de novo malignancy.

RESULTS The risk of any de novo solid malignancy between years 1 and 5 after transplantation was 10.7%. The cumulative incidence by malignancy type was: skin cancer (7.0%), non-skin solid cancer (4.0%), and lymphoproliferative disorders (0.9%). There was no temporal difference in the time to development according to malignancy type. However, the cumulative incidence of de novo solid malignancy increased from 2000 to 2005 vs. 2006 to 2011 (10.0% vs. 12.4%; $p < 0.0001$). Survival in patients after de novo malignancy was markedly lower than in patients without malignancy ($p < 0.0001$). Older recipients and patients who underwent transplantation in the recent era had a higher risk of de novo malignancy.

CONCLUSIONS More than 10% of adult heart transplant recipients developed de novo malignancy between years 1 and 5 after transplantation, and this outcome was associated with increased mortality. The incidence of post-transplant de novo solid malignancy increased temporally, with the largest increase in skin cancer. Individualized immunosuppression strategies and enhanced cancer screening should be studied to determine whether they can reduce the adverse outcomes of post-transplantation malignancy. (J Am Coll Cardiol 2018;71:40–9)

From the [a]Division of Cardiology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea; [b]Division of Cardiovascular Medicine, University of Utah School of Medicine, Salt Lake City, Utah; [c]United Network for Organ Sharing, Richmond, Virginia; [d]ISHLT Transplant Registry, Dallas, Texas; [e]Division of Cardiology, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [f]Department of Dermatology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea; [g]Department of Medicine, Unit of Cardiology, Karolinska Institutet, Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [h]Division of Cardiology, Drexel University College of Medicine, Hahnemann University Hospital, Philadelphia, Pennsylvania; [i]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; and the [j]Division of Cardiology, Cedars-Sinai Heart Institute, Los Angeles, California. This research was supported by the 2015 Transplant Registry Early Career Award Grant from the International Society for Heart and Lung Transplantation and by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning (NRF-2015R1C1A1A02036645). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. Dr. Stehlik has served as a consultant to Medtronic. Dr. Kobashigawa has received a research grant from Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 31, 2017; revised manuscript received October 23, 2017, accepted October 26, 2017.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

De novo malignancy is an important cause of long-term morbidity and mortality in solid organ transplant recipients (SOTRs) (1,2). The incidence of de novo malignancy has been reported to be approximately 20% after 10 years of chronic immunosuppression, and other studies have also shown an overall 2- to 4-fold elevated risk of malignancy (1-6). Cardiac transplant recipients are at particularly increased risk of developing de novo malignancies, with a risk 4-fold higher than that of renal transplant recipients (6-12). However, previous studies on malignancy after heart transplantation have had limitations, such as being single-center or single-country studies without temporal trends analysis (6,10-12).

SEE PAGE 50

The goal of the present study, therefore, was to characterize the incidence of, types of, and time to de novo malignancy after heart transplantation and to analyze the temporal trends of characteristics for patients with de novo malignancy according to different eras (2000 to 2005 vs. 2006 to 2011) using the data from the International Society for Heart and Lung Transplantation (ISHLT) Heart and Lung Transplant Registry. In addition, the survival rates of patients after de novo malignancy were compared with those of patients without malignancy; the objective was to determine whether patients with malignancy in the recent era had better survival compared with those in the remote era. Finally, we tried to identify risk factors associated with the development of de novo malignancy after heart transplantation. Because cancer screening is mainly performed by primary care physicians in many countries, a better understanding of cancer risk in cardiac transplant recipients would help to identify opportunities to improve post-transplant outcome in these patients.

METHODS

STUDY POPULATION. This retrospective cohort study was conducted by using data collected in the ISHLT Heart and Lung Transplant Registry. The ISHLT Registry collects data on thoracic organ transplants performed worldwide. The ISHLT Registry requires submission of core donor, recipient, and transplant procedure variables at baseline and at yearly follow-up. We did not ascertain vital status with civic registries independent of ISHLT; however, due to close regulatory monitoring of transplant programs, the vital status of patients is typically well documented. The present analysis includes only those patients in whom malignancy status after transplant was reported.

The registry provided de-identified patient-level data on all heart transplant recipients. Because no patient or center identifiers were included in the ISHLT dataset, our center did not require institutional review board approval, and patient consent was not required. The analysis cohort included all primary heart-only transplants in adult recipients (≥18 years of age) performed between January 2000 and December 2011. Follow-up data were available through June 2015. There were 42,343 transplants meeting these criteria. Of these, 24,756 were excluded from further analysis, resulting in 17,587 cases for analysis. Non-mutually exclusive reasons for exclusion were as follows: multi-organ and heterotopic transplants, pre-transplant history of malignancy, death or patient survival status unknown 1 year post-transplant, malignancy status not reported post-transplant, and maintenance or immunosuppression information not reported at either discharge or 1 year post-transplant. Recipient, donor, and transplant characteristics are tabulated in Online Table 1 for patients with known malignancy status at 3 or 5 years.

RATES OF MALIGNANCY DEVELOPMENT. A competing risks extension of the Kaplan-Meier method was used to estimate the rates of developing each type of malignancy between years 1 and 5 after transplantation (**Table 1**). The only other competing event considered in this analysis was death. The analysis was based on the first event that occurred; therefore, if patients developed malignancy before death, they had a malignancy event in the analysis rather than a death event. Rates were computed separately for each type of malignancy. Some patients may have experienced >1 type of malignancy; thus, the sum of the rates for individual malignancies may be larger than the overall rate. The results are stratified according to transplant era. Of note, because we planned to examine what effect the events in the first year post-transplant had on the risk of malignancy, and because death due to de novo malignancy is unlikely in the first year post-transplant, patients who died or were diagnosed with malignancy before 1 year after transplant were excluded.

SURVIVAL RATES. Patient survival rates were computed via the Kaplan-Meier method and compared by using the log-rank test statistic. For patients in whom malignancy was diagnosed between years 1 and 5 after transplantation, the diagnosis date was used for time zero. The median time to diagnosis for malignancies diagnosed within 5 years after transplantation was computed for each type of

ABBREVIATIONS AND ACRONYMS

ISHLT = International Society for Heart and Lung Transplantation

MMF = mycophenolate mofetil

SCC = squamous cell carcinoma

SOTR = solid organ transplant recipient

TABLE 1 Incidence of De Novo Malignancy Between Years 1 and 5 After Heart Transplantation

		Development of Malignancy Between Years 1 and 5 After Transplant		
		2000-2005 (n = 8,555)	2006-2011 (n = 9,032)	p Value*
De novo solid tumor	Total	10.0 (842)	12.4 (1,035)	<0.0001
Skin cancer	Total	6.4 (535)	8.4 (703)	<0.0001
	Skin: squamous	4.0 (339)	5.9 (494)	<0.0001
	Skin: basal cell	3.1 (264)	3.5 (298)	0.0068
	Skin: melanoma	0.5 (38)	0.6 (51)	0.0066
Non-skin solid cancer	Total	4.0 (335)	4.5 (367)	0.0040
	Kaposi's sarcoma	0.0 (1)	0.1 (10)	–
	Brain	0.0 (3)	0.0 (4)	–
	Renal	0.2 (16)	0.2 (18)	0.1121
	Vulva/perineum/ penis/scrotum	0.0 (2)	0.0 (3)	–
	Uterus	0.0 (1)	0.0 (3)	–
	Ovarian	0.0 (2)	0.0 (2)	–
	Testicular	0.0 (4)	0.0 (2)	–
	Esophagus	0.1 (9)	0.1 (11)	–
	Stomach	0.1 (8)	0.0 (3)	–
	Small intestine	0.0 (0)	0.0 (0)	–
	Pancreas	0.0 (4)	0.1 (11)	–
	Larynx	0.1 (5)	0.1 (6)	–
	Tongue/throat	0.1 (6)	0.1 (11)	–
	Thyroid	0.0 (2)	0.1 (5)	–
	Bladder	0.1 (12)	0.2 (14)	0.1047
	Breast	0.2 (20)	0.2 (16)	0.0692
	Prostate	1.3 (109)	1.4 (115)	0.0859
	Colorectal	0.3 (26)	0.2 (20)	0.0491
	Primary hepatic	0.0 (1)	0.1 (9)	–
	Metastatic liver	0.1 (8)	0.1 (5)	–
	Lung	1.1 (92)	1.0 (79)	0.0450
	Sarcoma	0.0 (2)	0.0 (4)	–
	Other cancer	0.2 (21)	0.3 (26)	0.0517
De novo lymphoproliferative disorders	Total	1.0 (83)	0.9 (75)	0.1118

Values are % (n). *A p value was computed via an independent sample Student's *t*-test and only computed if there were at least 10 events in each era. A competing risks extension of the Kaplan-Meier method was used to estimate the rates of developing each type of malignancy between year 1 and year 5 after transplant.

malignancy. For patients who were not reported to have a malignancy within the median time for that malignancy, time zero was designated as the median time to malignancy development in the corresponding group of patients who developed a malignancy. For example, for patients who developed skin malignancy within 5 years, the median time to development was 893 days; therefore, survival rates were computed starting at day 893 when assessing survival in this control group cohort.

MULTIVARIABLE ANALYSES. Cox proportional hazards regression models were used to assess the relationship of various potential recipient, donor, and transplant risk factors and the development of malignancy within 5 years, conditional on survival to 1 year (deaths before 1 year were excluded) for each malignancy type.

All continuous factors were included in the models considering the use of a restricted cubic spline to allow for the most flexible fit of the functional form. When appropriate, continuous variables were modeled only as linear terms and are specified as such. The detailed list of variables considered for inclusion in the multivariate models can be found in the Online Appendix. A backward selection method was used to determine which risk factors to retain in each model. A p value <0.05 was considered significant, and a p value ≥0.05 but <0.10 was considered borderline significant. Variables forced into the model regardless of statistical significance were recipient age, diagnosis group (categorical), and transplant era.

Statistical analyses were performed by using SAS Enterprise Guide 5.1 (SAS Institute, Inc., Cary, North Carolina) and R version 0.99.486 (RStudio Team [2015], RStudio: Integrated Development for R. RStudio, Inc., Boston, Massachusetts).

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY POPULATION. Baseline characteristics, including recipient, donor, and transplant characteristics, of the study population according to malignancy status at 3 years (n = 14,426) and 5 years (n = 10,829) are summarized in Online Table 1. For patients with known malignancy status at 5 years, the mean recipient age was 52.2 ± 11.9 years, and 77.3% of recipients were male. The main underlying diagnoses of heart failure leading to heart transplantation were nonischemic cardiomyopathy (47.4%) and coronary artery disease (43.9%). Twenty-eight percent of patients underwent at least 1 pre-transplant mechanical circulatory support device procedure. The mean donor age was 31.1 ± 12.2 years, and 72.2% of donors were male. The mean ischemia time was 3.2 ± 1.0 h. The most common maintenance immunosuppression included calcineurin inhibitors, either tacrolimus (49.2%) or cyclosporine (46.2%), and cell cycle inhibitors, most commonly mycophenolate mofetil (MMF) (85.6%). Almost 43% of transplant recipients were hospitalized for any reason between discharge and 1 year post-transplant.

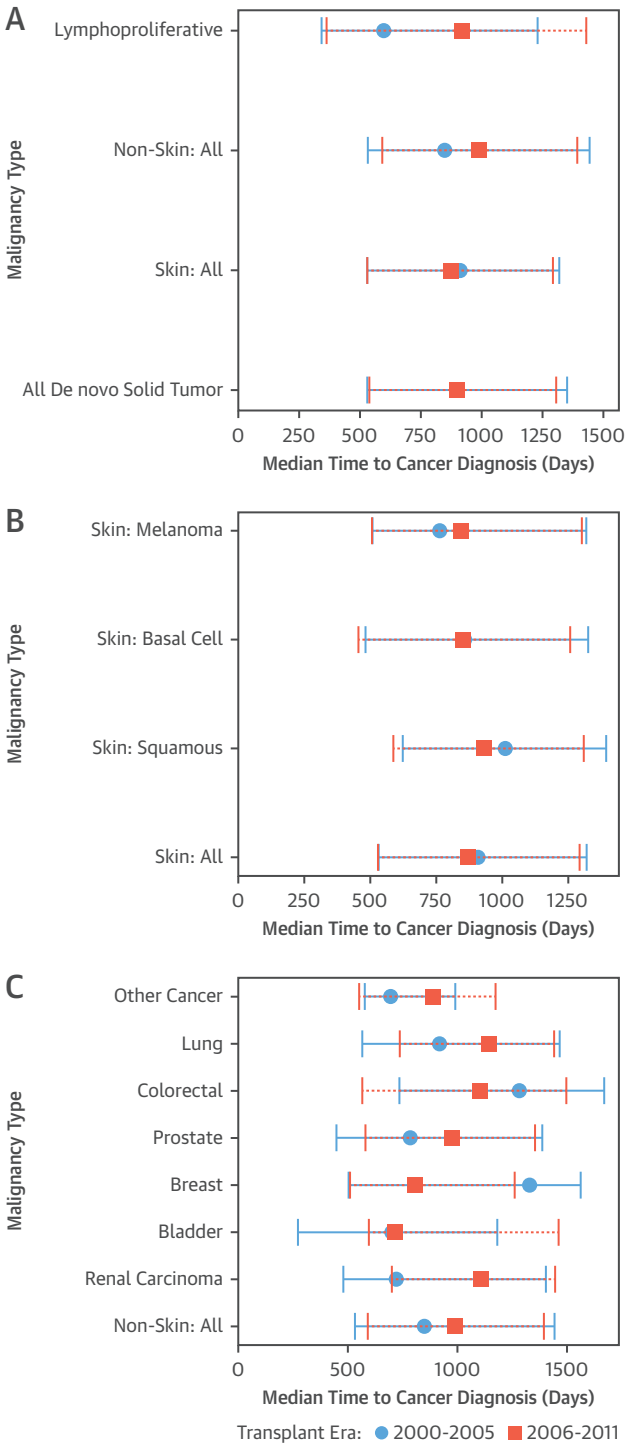
RISK OF DE NOVO MALIGNANCY WITHIN 5 YEARS AFTER HEART TRANSPLANTATION. Table 1 summarizes the rates of development of de novo malignancy after heart transplantation. The incidence

of any de novo solid malignancy between years 1 and 5 after transplantation throughout the entire period was 10.7%. The cumulative incidence of de novo solid malignancy was higher in the 2006 to 2011 cohort compared with the 2000 to 2005 cohort (12.4% vs. 10.0%; $p < 0.0001$). This increase was predominantly owing to the higher incidence of skin cancer in the more recent cohort (8.4% in 2006 to 2011 vs. 6.4% in 2000 to 2005; $p < 0.0001$). The cumulative incidence of non-skin solid cancer was also higher in the more recent era, but the degree of this increase was relatively small (4.5% in 2006 to 2011 vs. 4.0% in 2000 to 2005; $p = 0.004$). The incidence of lymphoproliferative disorders was not significantly different between the 2 cohorts (0.9% in 2006 to 2011 vs. 1.0% in 2000 to 2005; $p = 0.1118$). Within the de novo skin cancer group, the incidence of squamous cell carcinoma (SCC) increased from 4.0% to 5.9%, and the incidence of basal cell carcinoma from 3.1% to 3.5%, both of which were statistically significant ($p < 0.05$). Within the de novo non-skin solid cancer group, the most frequent malignancies were prostate cancer (1.4% in 2006 to 2011 and 1.3% in 2000 to 2005) and lung cancer (1.0% in 2006 to 2011 and 1.1% in 2000 to 2005).

TIME TO NEW DIAGNOSIS OF MALIGNANCY AFTER TRANSPLANT. Given the change in the cumulative incidence of malignancy, we were interested to know whether the time from transplant to diagnosis differed between transplant eras. For any malignancy, the median time to diagnosis was similar for the 2 eras: 899 days in 2001 to 2005 and 900 days in 2006 to 2011 ($p = 0.6605$). We also explored time to malignancy in the 2 eras between the different malignancy subgroups and found no significant differences according to malignancy type (Figure 1).

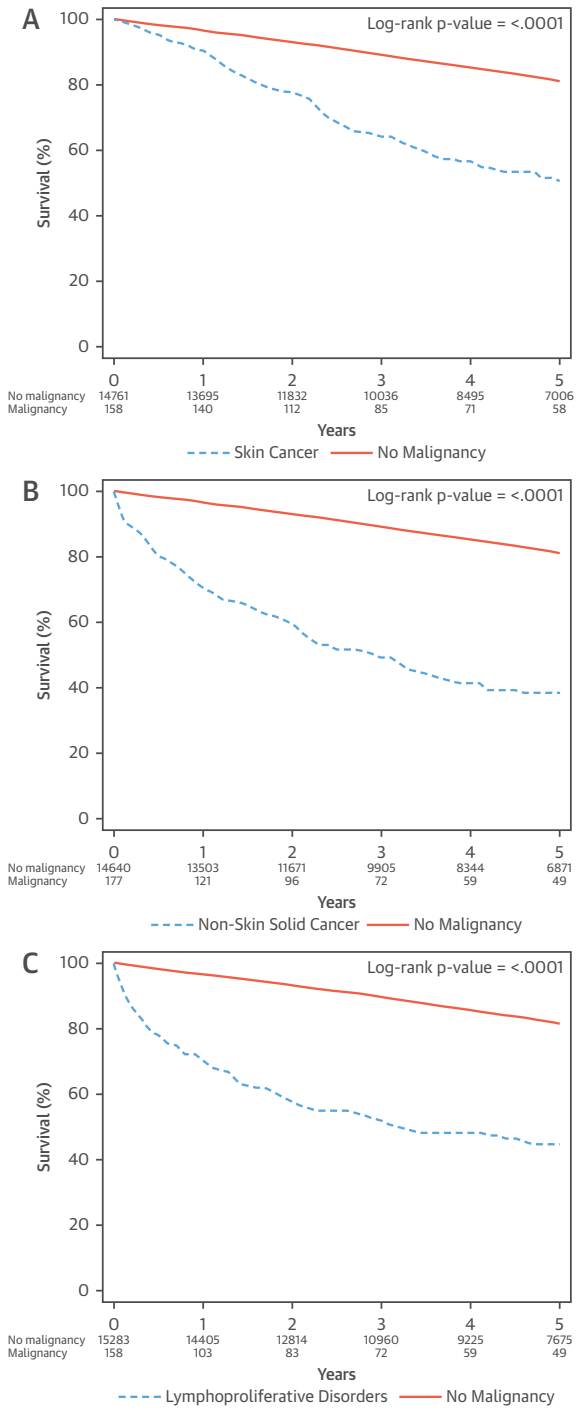
SURVIVAL ANALYSIS. For all types of cancer, survival rates of patients after de novo malignancy were markedly lower than those of patients without malignancy diagnosed within the median time of cancer diagnosis for the respective cancer types (Figure 2). All comparisons of patient survival rates between those who developed a malignancy between years 1 and 5 (using time at cancer diagnosis as time zero) and those who did not develop a malignancy (designating time zero as the median time to diagnosis in the former group) were statistically significant. When the patient survival rates after malignancy development were stratified according to transplant era, higher survival was seen in the more recent era, but

FIGURE 1 Median Time to Development of De Novo Malignancy Between Years 1 and 5 After Transplantation



Median time to development of **(A)** any de novo solid malignancy, **(B)** de novo skin cancer, and **(C)** de novo non-skin solid cancer. Calculations are limited to malignancies diagnosed in at least 10 patients between years 1 and 5 after transplantation. None of the comparisons was statistically significant. Bar graphs are shown for interquartile range.

FIGURE 2 Survival After the Diagnosis of De Novo Malignancy Compared With Survival in Patients Without Cancer



(A) Skin cancer, **(B)** non-skin solid cancer, and **(C)** lymphoproliferative disorders. Time 0 for patients with cancer is time of cancer diagnosis. The control group is composed of patients without a diagnosis of cancer by the median time of cancer diagnosis in the cancer group. Time 0 for the control group is the median time of cancer diagnosis in the corresponding group of patients with cancer (skin cancer, 893 days; non-skin solid cancer, 948 days; and lymphoproliferative disorders, 948 days).

this finding was not statistically significant for any malignancy type (Figure 3).

RISK FACTORS FOR POST-TRANSPLANT MALIGNANCY. Three multivariable proportional hazards models were used to assess the association between various potential recipient, donor, and transplant factors and the risk of developing de novo skin malignancy, non-skin solid malignancy, and lymphoproliferative disorder after heart transplantation.

For skin malignancy, recipient age and transplant era had large effects, with older recipients and those undergoing transplantation more recently having a higher risk of de novo skin malignancy within 5 years (Table 2). Additional risk factors for the development of skin malignancy within 5 years of transplant included larger height, use of interleukin-2 receptor antagonist or muromonab-CD3 induction, hospitalization between discharge and 1 year post-transplant, human leukocyte antigen DR mismatches (1 or 2 vs. 0), donor/recipient cytomegalovirus mismatch, use of azathioprine versus MMF 1 year post-transplant, and congenital heart disease or retransplant/graft failure diagnoses versus cardiomyopathy. Similar to skin cancer, the risk factors for development of non-skin solid cancer within 5 years included age, more recent transplantation, height, and hospitalization between discharge and 1 year post-transplant. Several additional risk factors were identified that were unique, including a recipient history of smoking and the presence of drug-treated systemic hypertension. Risk factors for the development of de novo lymphoproliferative disorders included no cell cycle inhibitor use versus MMF or azathioprine versus MMF use at 1 year follow-up, overweight, negative Epstein-Barr virus serostatus, hospitalization between discharge and 1 year post-transplant, and use of antithymocyte globulin induction.

DISCUSSION

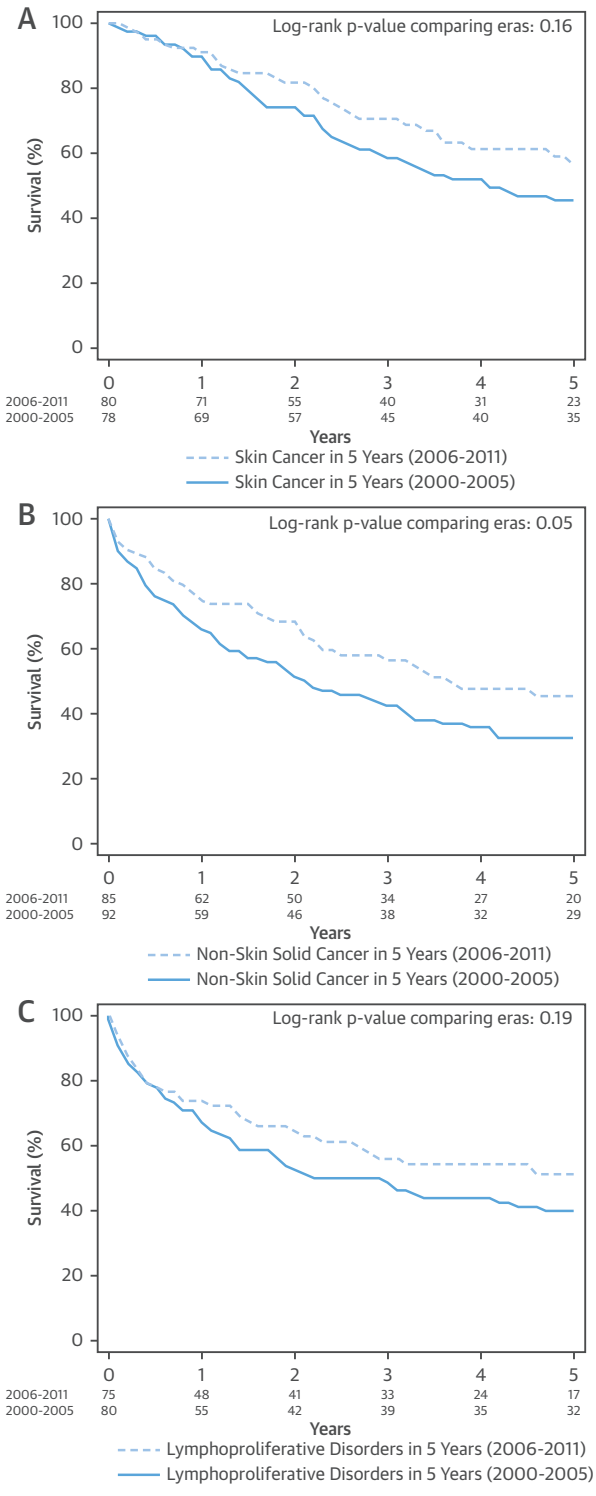
In this cohort of 17,587 adult cardiac transplant recipients from the ISHLT Registry, >10% developed de novo malignancy between years 1 and 5 after transplantation, which was in turn associated with a significantly increased risk of mortality (Central Illustration). The incidence of de novo malignancy increased in the recent era (2006 to 2011 vs. 2000 to 2005), with the largest increase seen in skin cancer. Survival rates of patients after de novo malignancy were markedly lower than those of patients without malignancy for all types of cancer. Importantly, the increased risk of mortality was sizeable even for patients diagnosed with skin cancer; this finding is in contrast to the general population, in whom

survival after skin cancer is typically favorable. When the patient survival rates after de novo malignancy were stratified according to transplant era, survival rates were higher in the more recent era, but this finding was not statistically significant for any malignancy type. Multivariate analysis revealed that primarily older recipients and patients who underwent transplantation more recently had a higher risk of de novo skin cancer and non-skin solid cancer.

Skin cancers account for >40% of malignancies in organ transplant recipients, and they include SCC, basal cell carcinoma, and melanoma (13). The risk for the development of non-melanoma skin cancer is known to increase >10-fold in chronically immunosuppressed patients who undergo solid organ transplantation (14). Reduced immune surveillance, the direct carcinogenic effect of immunosuppressive agents, and proliferation of oncogenic viruses may contribute to the development of skin cancer in these patients. It is well known that the incidence of cutaneous SCC increases with the duration and degree of immunosuppression (15-18). Chronic immunosuppression may increase the incidence of cutaneous SCC and, to a lesser extent, basal cell carcinoma. In the United States, approximately 20% of heart transplant recipients will develop skin cancer within 10 years after transplantation. It is therefore plausible that more vulnerable older recipients and the more intensified immunosuppression in recent years may have precipitated the increase in the incidence of de novo skin cancer, including SCC. The risk of malignancy is of increasing concern because early survival continues to improve in heart transplant recipients, and malignancy becomes relatively more important than other causes of morbidity and mortality with increasing time post-transplant (19). In addition, as an increasing number of older patients receive heart transplants (20,21), including after mechanical circulatory support, this population may be particularly vulnerable (22).

Another possible explanation for the increased incidence of de novo solid malignancies in the recent era, especially for skin cancer, can be found in the increasing incidence of skin cancer in the general population. Because cutaneous SCC and basal cell carcinoma are not typically reported to cancer registries, the exact incidences of these malignancies are unknown. However, recent studies revealed that the incidence of non-melanoma skin cancer, including SCC and basal cell carcinoma, is increasing worldwide (23-27). Although skin cancer in the general population exhibited a high and stable survival rate in 2006 to 2011 (27), the survival rate of

FIGURE 3 Survival After Report of Malignancy According to Era



(A) Skin cancer, **(B)** non-skin solid cancer, and **(C)** lymphoproliferative disorders. Time 0 is time of cancer diagnosis.

TABLE 2 Multivariable Analysis of Factors Associated With Development of Malignancy Between Years 1 and 5 After Transplant

	Factor	AHR (95% CI)	p Value
Skin cancer (no. of events = 1,235)	Recipient age: linear + quadratic terms	–	<0.0001
	Transplant era: 2006–2011 vs. 2000–2005	1.70 (1.51–1.91)	<0.0001
	Induction: OKT3, yes vs. no	1.43 (1.10–1.87)	0.0077
	Recipient sex: female vs. male	0.61 (0.48–0.78)	<0.0001
	Recipient height: linear + quadratic terms	–	0.0001
	Recipient diagnosis group		
	CHD vs. cardiomyopathy	1.72 (1.00–2.95)	0.0497
	Other vs. cardiomyopathy	1.34 (0.92–1.98)	0.1313
	Retransplant/graft failure vs. cardiomyopathy	1.56 (1.03–2.35)	0.0359
	Valvular heart disease vs. cardiomyopathy	0.81 (0.53–1.23)	0.3148
	CAD vs. cardiomyopathy	1.06 (0.93–1.20)	0.3719
	Cell cycle inhibitor at 1-yr follow-up		
	None vs. MMF	0.88 (0.72–1.08)	0.2096
	AZA vs. MMF	1.37 (1.07–1.75)	0.0124
	Donor/recipient CMV mismatch: yes vs. no	1.33 (1.17–1.51)	<0.0001
	HLA-DR mismatches		
	0 vs. 2	1.36 (1.10–1.67)	0.0048
	1 vs. 2	1.20 (1.06–1.35)	0.0034
	Recipient HBV core antibody: positive vs. negative	0.63 (0.44–0.89)	0.0098
	Center volume within prior 365 days: linear + quadratic terms	–	0.0069
	Recipient maximum most recent PRA: linear + quadratic terms	–	0.0828
	Recipient diabetes: yes vs. no	0.84 (0.73–0.96)	0.0084
	Hospitalization between discharge and 1-yr post-transplant: yes vs. no	1.15 (1.03–1.29)	0.0132
	Induction: IL2RA, yes vs. no	1.15 (1.01–1.31)	0.0289
	Recipient EBV serostatus: negative vs. positive	0.85 (0.74–0.98)	0.0224
Non-skin solid cancer (no. of events = 702)	Recipient age: linear + quadratic terms	–	<0.0001
	Recipient smoking history >10 pack-yrs: yes vs. no	1.75 (1.49–2.07)	<0.0001
	Transplant era: 2006–2011 vs. 2000–2005	1.49 (1.28–1.73)	<0.0001
	Hospitalization between discharge and 1 yr post-transplant: yes vs. no	1.30 (1.12–1.51)	0.0005
	Recipient drug-treated systemic hypertension: yes vs. no	1.19 (1.02–1.39)	0.0237
	Recipient height: linear term; per 10-cm increase	1.11 (1.02–1.20)	0.0166
	Recipient diagnosis group		
	CHD vs. cardiomyopathy	1.40 (0.66–3.00)	0.3799
	Other vs. cardiomyopathy	0.70 (0.36–1.37)	0.2977
	Retransplant/graft failure vs. cardiomyopathy	1.58 (0.92–2.71)	0.0983
	Valvular heart disease vs. cardiomyopathy	1.04 (0.64–1.70)	0.8728
	CAD vs. cardiomyopathy	0.94 (0.79–1.10)	0.4241
	Cell cycle inhibitor at 1-yr follow-up		
	None vs. MMF	1.06 (0.82–1.36)	0.6810
	AZA vs. MMF	1.31 (0.97–1.77)	0.0820

Continued on the next page

patients who underwent cardiac transplants and were diagnosed with de novo skin cancer was markedly lower, however, than that of cardiac transplant patients without skin cancer in our study.

Recently, Acuna et al. reported that SOTRs are at increased risk of cancer-specific death, regardless of age, sex, organ transplanted, or transplant period, which could serve to justify pursuing targeted cancer screening in these patients (28,29). However, controversy still exists about such targeted cancer screening programs, owing to the reduced life expectancy and competing causes of death in these patients (30). Although there are some established recommendations for cancer screening in SOTRs, recommendations vary among organizations and are generally limited to kidney recipients. Although there is consensus on the recommendations for skin cancer screening in the general population, and these recommendations extend to SOTRs, recommendations for screening in other malignancies are highly variable.

ISHLT guidelines recommend that cardiac transplant recipients have close skin cancer surveillance, including education on preventive measures and yearly dermatologic examinations. Recommendations regarding screening for breast, colon, and prostate cancer in the general population should also be

TABLE 2 Continued

	Factor	AHR (95% CI)	p Value
Lymphoproliferative disorders (no. of events = 158)	Cell cycle inhibitor at 1-yr follow-up		
	None vs. MMF	3.11 (2.08–4.65)	<.0001
	AZA vs. MMF	1.72 (0.93–3.18)	0.0816
	Induction: ATG, yes vs. no	1.76 (1.02–3.03)	0.0423
	Hospitalization between discharge and 1 yr post-transplant: yes vs. no	1.72 (1.24–2.38)	0.0011
	Recipient EBV serostatus: negative vs. positive	1.61 (1.13–2.28)	0.0083
	Working at 1-yr post-transplant	0.49 (0.32–0.73)	0.0005
	Recipient weight: linear + quadratic terms	–	0.0043
	Recipient BMI: linear + quadratic terms	–	0.0609
	Center volume within prior 365 days: linear + quadratic terms	–	0.0619
	Recipient age: linear + quadratic terms	–	0.1560
	Transplant era: 2006–2011 vs. 2000–2005	0.96 (0.67–1.35)	0.7970
	Recipient diagnosis group		
	CHD vs. cardiomyopathy	1.50 (0.53–4.24)	0.4475
	Other vs. cardiomyopathy	1.16 (0.42–3.21)	0.7713
	Retransplant/graft failure vs. cardiomyopathy	2.00 (0.80–5.01)	0.1391
	Valvular heart disease vs. cardiomyopathy	1.00 (0.31–3.20)	0.9996
	CAD vs. cardiomyopathy	1.21 (0.85–1.73)	0.2958

ATG = antithymocyte globulin; AHR = adjusted hazard ratio; AZA = azathioprine; BMI = body mass index; CAD = coronary artery disease; CHD = congenital heart disease; CI = confidence interval; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; IL2RA = interleukin-2 receptor antagonist; MMF = mycophenolate mofetil; OKT3 = muromonab-CD3; PRA = panel reactive antibody.

followed in cardiac transplant recipients (31). In addition, it is recommended that chronic immunosuppression be minimized where possible, particularly in patients at high risk for malignancy. Some data suggest that higher recipient age is strongly associated with increased risk of death from infection and malignancy, whereas it is associated with reduced risk of death from acute rejection, cardiac allograft vasculopathy, and graft failure (32). In addition to reduction of chronic immunosuppression, it would seem that avoidance of immunosuppression induction in patients at high risk of de novo malignancy after transplant would be advisable. However, there have been few efforts to systematically tailor immunosuppression according to age or cause-specific morbidity and mortality risk.

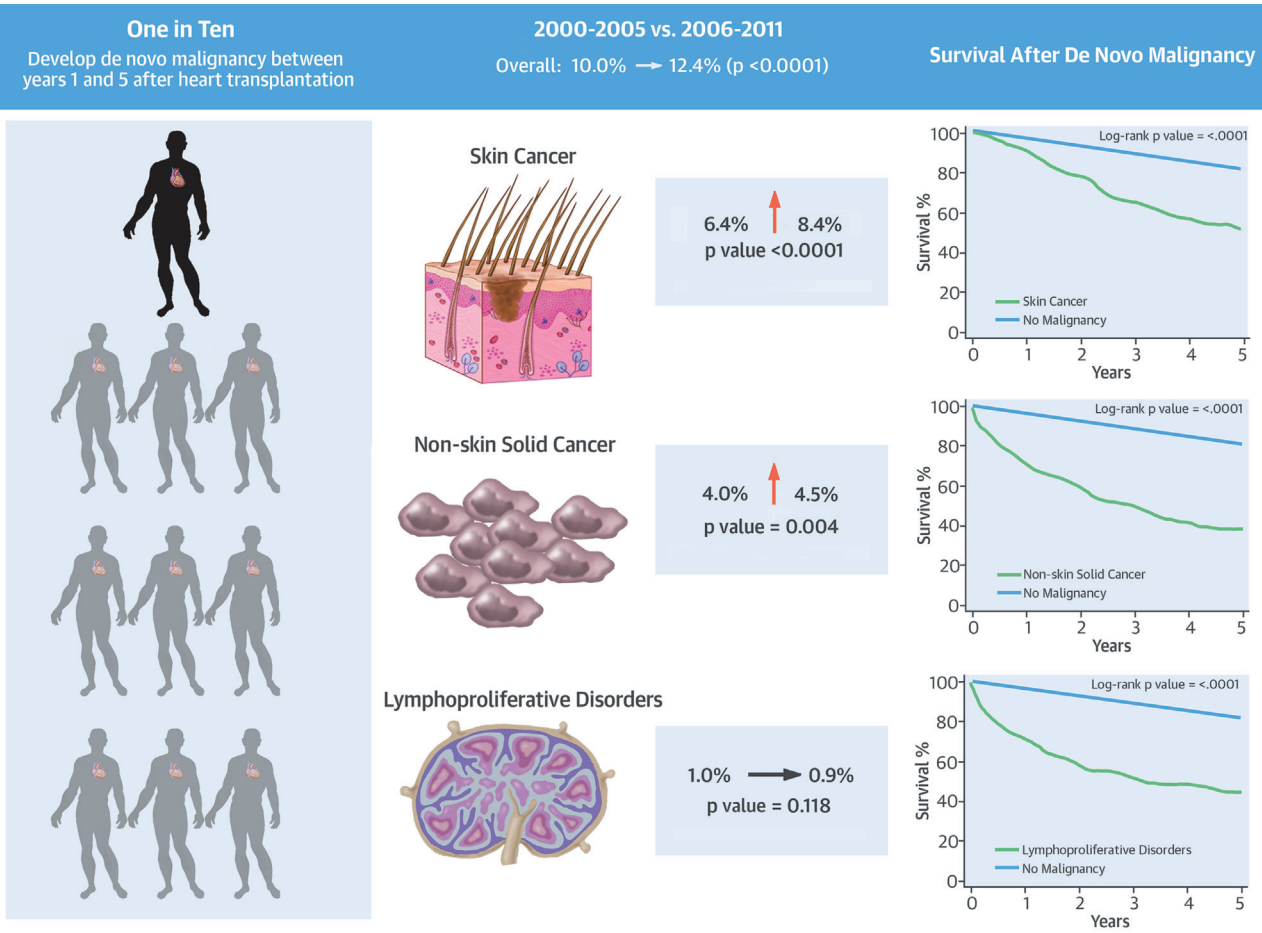
Considering the increased burden of de novo malignancy in cardiac transplant recipients, additional effort needs to be directed toward formulating evidence-based cancer screening recommendations and optimized immunosuppression protocols for these patients. Relevant stakeholders, including oncologists, primary care physicians, and public health experts, as well as transplant cardiologists and immunologists, might be involved in the formulation of screening recommendations. In addition, it may be reasonable to consider the risk of de novo posttransplant malignancy in older patients when making decisions regarding candidacy for heart transplant versus left ventricular assist device as destination therapy.

STUDY LIMITATIONS. There is no guideline or consensus statement available to direct cancer surveillance methods after heart transplantation. Therefore, cancer surveillance methods might have varied according to each institution's strategies. Second, we could not verify the detailed information regarding the stage, subtypes, and treatment of individual malignancies, as well as the ethnicity of the recipients, due to limitations of the ISHLT Registry data. Finally, we also could not confirm the detailed underlying mechanisms of the increased incidence of de novo malignancy in this study. We cannot rule out that the increased incidence of cancer in the most recent cohort of heart transplant recipients resulted from better cancer screening in these patients. However, even if this scenario is the case, the implications of our study do not change, as the survival of patients with malignancy, including skin cancer alone, still remains far below the survival of those without cancer, even in the more recent patient cohort.

CONCLUSIONS

This large international registry study documents the risk of a wide spectrum of de novo malignancies and temporal trends in malignancy incidence after heart transplantation. More than 10% of recipients

CENTRAL ILLUSTRATION **De Novo Malignancy After Heart Transplantation**



Youn, J.-C. et al. J Am Coll Cardiol. 2018;71(1):40–9.

More than 10% of heart transplant recipients developed de novo malignancy between years 1 and 5 after transplantation, which was associated with increased mortality, with a temporal increase in de novo solid malignancy in the recent period.

developed de novo malignancy between years 1 and 5 after transplantation, which resulted in a significantly increased risk of mortality. Based on our findings, further research is necessary to investigate the best approaches for prevention and early detection of de novo malignancy. Individualized immunosuppression and intensified cancer screening, especially for skin cancer, should be studied to determine whether these approaches can reduce the adverse outcomes of post-transplantation malignancy.

ACKNOWLEDGMENT The authors acknowledge the contributions of Leah B. Edwards, PhD, to the manuscript.

ADDRESS FOR CORRESPONDENCE: Dr. Jong-Chan Youn, Division of Cardiology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Keunjaebong-gil 7, Hwaseong, Gyeonggi-do 18450, Republic of Korea. E-mail: jong.chan.youn@gmail.com. OR Dr. Seok-Min Kang, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. E-mail: smkang@yuhs.ac. OR Dr. Jon A. Kobashigawa, Division of Cardiology, Cedars-Sinai Heart Institute, 127 S. San Vicente Boulevard, Third Floor Cardiology, A3107, Los Angeles, California 90048. E-mail: kobashigawaj@cshs.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Heart transplant recipients are at increased risk of developing de novo malignancies, and those who develop malignancy face significantly shortened survival.

TRANSLATIONAL OUTLOOK: Further studies are needed to develop individualized immunosuppression strategies for heart transplant recipients to reduce the frequency of de novo malignancies and improve survival.

REFERENCES

1. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. Transplantation 2005;80: S254–64.

2. Engels EA, Pfeiffer RM, Fraumeni JF Jr., et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891–901.

3. Penn I. Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant 1993;12:S328–36.

4. Hunt SA. Malignancy in organ transplantation: heart. Transplant Proc 2002;34:1874–6.

5. Kapoor A. Malignancy in kidney transplant recipients. Drugs 2008;68 Suppl 1:11–9.

6. Frohlich GM, Rufibach K, Enseleit F, et al. Statins and the risk of cancer after heart transplantation. Circulation 2012;126:440–7.

7. Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. Lancet 1993;342:1514–6.

8. Fortina AB, Caforio AL, Piaserico S, et al. Skin cancer in heart transplant recipients: frequency and risk factor analysis. J Heart Lung Transplant 2000;19:249–55.

9. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant 2004;4: 905–13.

10. Crespo-Leiro MG, Alonso-Pulpon L, Vazquez de Prada JA, et al. Malignancy after heart transplantation: incidence, prognosis and risk factors. Am J Transplant 2008;8:1031–9.

11. Yagdi T, Sharples L, Tsui S, Large S, Parameshwar J. Malignancy after heart transplantation: analysis of 24-year experience at a single center. J Card Surg 2009;24:572–9.

12. Doesch AO, Muller S, Konstandin M, et al. Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. Transplant Proc 2010;42:3694–9.

13. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003; 348:1681–91.

14. Athar M, Walsh SB, Kopelovich L, Elmets CA. Pathogenesis of nonmelanoma skin cancers in organ transplant recipients. Arch Biochem Biophys 2011;508:159–63.

15. Ramsay HM, Reece SM, Fryer AA, Smith AG, Harden PN. Seven-year prospective study of nonmelanoma skin cancer incidence in U.K. renal transplant recipients. Transplantation 2007;84: 437–9.

16. Fortina AB, Piaserico S, Caforio AL, et al. Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. Arch Dermatol 2004;140:1079–85.

17. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med 2001;344:975–83.

18. Lampros TD, Cobanoglu A, Parker F, Ratkovec R, Norman DJ, Hershberger R. Squamous and basal cell carcinoma in heart transplant recipients. J Heart Lung Transplant 1998; 17:586–91.

19. Rossano JW, Dipchand AI, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35:1185–95.

20. Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report—2013; focus theme: age. J Heart Lung Transplant 2013; 32:951–64.

21. Youn JC, Han S, Ryu KH. Temporal trends of hospitalized patients with heart failure in Korea. Korean Circ J 2017;47:16–24.

22. Ciarka A, Edwards L, Nilsson J, Stehlik J, Lund LH. Trends in the use of mechanical circulatory support as a bridge to heart transplantation across different age groups. Int J Cardiol 2017;231: 225–7.

23. Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: rapid incidence increase among young Danish women. Int J Cancer 2010;127: 2190–8.

24. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012; 166:1069–80.

25. Xiang F, Lucas R, Hales S, Neale R. Incidence of nonmelanoma skin cancer in relation to ambient UV radiation in white populations, 1978-2012: empirical relationships. JAMA Dermatol 2014;150: 1063–71.

26. Callens J, Van Eycken L, Henau K, Garmyn M. Epidemiology of basal and squamous cell carcinoma in Belgium: the need for a uniform and compulsory registration. J Eur Acad Dermatol Venereol 2016;30:1912–8.

27. Hollestein LM, de Vries E, Nijsten T. Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008. Eur J Cancer 2012;48:2046–53.

28. Acuna SA, Fernandes KA, Daly C, et al. Cancer mortality among recipients of solid-organ transplantation in Ontario, Canada. JAMA Oncology 2016;2:463–9.

29. Schmid M, Chun FK, Trinh QD. Targeted cancer screening after solid-organ transplantation. JAMA Oncology 2016;2:470.

30. Acuna SA, Huang JW, Scott AL, et al. Cancer screening recommendations for solid organ transplant recipients: a systematic review of clinical practice guidelines. Am J Transplant 2017;17:103–14.

31. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29: 914–56.

32. Wever-Pinzon O, Edwards LB, Taylor DO, et al. Association of recipient age and causes of heart transplant mortality: implications for personalization of post-transplant management—an analysis of the International Society for Heart and Lung Transplantation registry. J Heart Lung Transplant 2017;36:407–17.

KEY WORDS heart transplantation, immunosuppression, malignancy, temporal trends, prognosis

APPENDIX For an expanded Methods section and supplemental table, please see the online version of this paper.