Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2021 July ; 30(7): 1312–1319. doi:10.1158/1055-9965.EPI-21-0044.

Solid organ transplantation and survival among individuals with a history of cancer

Eric A. Engels[1], **Gregory Haber**[1], **Allyson Hart**[2], **Charles F. Lynch**[3], **Jie Li**[4], **Karen S. Pawlish**[4], **Baozhen Qiao**[5], **Kelly J. Yu**[1], **Ruth M. Pfeiffer**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

[2]Department of Medicine, Hennepin Healthcare, University of Minnesota, Minneapolis, MN

[3]Department of Epidemiology, The University of Iowa, Iowa City, IA

[4]Cancer Epidemiology Services, New Jersey Department of Health, Trenton, NJ

[5]Bureau of Cancer Epidemiology, New York State Department of Health, Albany, NY

Abstract

Background: The success of immunotherapy highlights a possible role for immunity in controlling cancer during remission for cancer patients in the general population. A prior cancer diagnosis is common among solid organ transplant candidates, and immunosuppressive medications administered to transplant recipients may increase recurrence risk.

Methods: Using linked data from the United States solid organ transplant registry and 13 cancer registries, we compared overall and cancer-specific survival among cancer patients who did vs. did not receive subsequent transplantation. We used Cox regression in cohort and matched analyses, controlling for demographic factors, cancer stage, and time since cancer diagnosis.

Results: The study included 10,524,326 cancer patients with 17 cancer types; 5425 (0.05%) subsequently underwent solid organ transplantation. The median time from cancer diagnosis to transplantation was 4.17 years. Transplantation was associated with reduced overall survival for most cancers, especially cervical, testicular, and thyroid cancers (adjusted hazard ratios [aHRs] for overall mortality: 3.43-4.88). In contrast, transplantation was not associated with decreased cancer-specific survival for any cancer site, and we observed inverse associations for patients with breast cancer (aHRs for cancer-specific mortality: 0.65-0.67), non-Hodgkin lymphoma (0.50-0.51), and myeloma (0.39-0.42).

Conclusions: Among US cancer patients, subsequent organ transplantation was associated with reduced overall survival, likely due to end-stage organ disease and transplant-related complications. However, we did not observe adverse associations with cancer-specific survival, partly reflecting careful candidate selection.

Address correspondence to: Eric A. Engels, MD MPH, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr, Room 6E226, Bethesda, MD 20892 USA, Telephone 240-276-7186.

Conflict of interest statement: The authors declare no potential conflicts of interest.

Impact: These results do not demonstrate a detrimental effect of immunosuppression on cancer-specific survival and support current management strategies for transplant candidates with previous cancer diagnoses.

Introduction

With improvements in cancer treatment, survival following a cancer diagnosis has greatly improved over recent decades in the United States (US) (1). A recent advance has been the introduction of checkpoint inhibitors, which are therapeutic monoclonal antibodies that inactivate immune checkpoint proteins expressed in tumors, thereby unleashing components of the cellular immune system (including CD4-positive T-cells and cytotoxic CD8-positive T-cells) to target cancer cells. These medications are effective for a range of advanced cancers, including cancers of the lung, kidney, and bladder, and melanoma (2).

Following initial therapy and resolution of clinically detectable sites of cancer, patients treated with checkpoint inhibitors can have remissions extending for years without evidence of residual disease (3). Such long-term remissions may be explained by cytotoxic killing and complete elimination by activated T-cells of even microscopic collections of cancer cells. An alternative explanation is that there remain small undetected foci of malignant cells held in control by the immune system (4). An analogous model has been proposed for "immunosurveillance" in preventing development of incident cancers (5), which likewise involves components of the cellular immune system. Under the immunosurveillance model, the immune system can eliminate some abnormal cells early in the carcinogenic process, but at a later stage the immune system engages in an ongoing dynamic equilibrium with premalignant or malignant cells to suppress their outgrowth (5).

The immune system may likewise help control cancer during remission for cancer patients in the general population, not only those treated with immunotherapy (4). If so, then immunosuppressive medical conditions or medications would be expected to increase the risk of relapse and decrease survival among cancer patients. Solid organ transplantation provides life-saving treatment for patients with end-stage organ disease, but transplant recipients must be administered immunosuppressive medications that target T-cell function to prevent organ rejection. Indeed, immunosuppression contributes substantially to an increased incidence of cancer among transplant recipients (6, 7). Furthermore, because of concern that immunosuppression may increase the risk of cancer relapse, the presence of a previous cancer diagnosis is an important consideration in evaluating patients with end-stage organ disease for possible transplantation (8).

Current evaluation and management of potential transplant candidates with a prior cancer is largely influenced by clinical experience. The largest patient series reported results from the Cincinnati Transplant Tumor Registry (CTTR) through 1997 regarding 1137 individuals with prior cancer who received an organ transplant (9). Risk of cancer relapse following transplantation varied widely among these recipients, but was highest for those with previous melanoma, breast or bladder cancer, or myeloma, and also when the interval between cancer treatment and transplantation was less than 2-5 years. Current guidelines for evaluation of transplant candidates therefore generally recommend a waiting period

depending on the type of cancer (i.e., site) and stage at diagnosis, and indicate that such individuals should be carefully evaluated to confirm that they manifest no evidence of residual cancer (10-12). Prognosis of similar cancer patients in the general population is also used as a clinical benchmark to help gauge the appropriateness of offering transplantation to a potential candidate with a previous cancer (13-15). However, no study has systematically compared cancer patients who received a solid organ transplant with others who did not, so the degree to which this benchmarking is appropriate, or whether transplant-associated immunosuppression leads to greater risk of relapse or death among individuals with a previous cancer, is unknown.

With the aging of the general population and improvements in cancer survival, the prevalence of cancer has increased among people evaluated as candidates for organ transplantation and those who eventually receive a transplant (16). In the present study, we used linked cancer and transplant registry data to assess survival among individuals with cancer who subsequently received an organ transplant. We evaluated 17 different types of cancer, comparing transplanted patients to other cancer patients in the general population who did not receive a transplant. We present analyses for overall survival but focus on cancer-specific survival (i.e., absence of death due to cancer), because the relationship between transplantation and cancer-specific survival captures, at least in part, any adverse impact of transplant-associated immunosuppression on risk of relapse.

Materials and Methods

We used data from the Transplant Cancer Match (TCM) Study, a linkage of the US solid organ transplant registry (Scientific Registry of Transplant Recipients [SRTR]) with multiple state and metropolitan area cancer registries (https://transplantmatch.cancer.gov/) (6). For this study, we restricted analysis to 13 cancer registries that provided information on cause of death (COD) (Table 1 note). The study is considered non-human subjects research by the National Institutes of Health and was approved by participating cancer registries.

We included all individuals in the general population with an invasive cancer reported to these cancer registries, where the cancer was the individual's first cancer diagnosis. We restricted the patient diagnosis dates to fall between 1987 (the first year of SRTR data) or the first year of coverage in each cancer registry, whichever was later, and the last year of cancer registry coverage (the latest such year was 2017). We excluded patients who had a solid organ transplant before or in the same month of cancer diagnosis. The remaining potentially eligible patients (N=12,780,863) were categorized into cancer sites based on topography and morphology codes (https://seer.cancer.gov/siterecode/).

With the linked SRTR data, we identified the subset of cancer patients who received a transplant after their cancer diagnosis. We then excluded transplanted patients where the transplanted organ was consistent with possible treatment for the cancer, regardless of the specified indication for transplantation (N=10,962 [0.1% of cancer patients in the general population], of which 8967 were liver transplants in liver cancer patients; see Supplemental Table 1). Finally, we excluded cancer sites for which there were fewer than 40 transplanted patients (N=2,229,166 [17.4%]), male breast cancers (N=14,117 [0.1%]), and patients for

whom the COD was missing or unknown (N=2292 [0.02%]). Following these successive exclusions, the final study sample included 10,524,326 general population cancer patients, among whom 5425 (0.05%) received a subsequent transplant.

Cancer patients were followed from diagnosis until death or end of cancer registry coverage. Cancer-specific survival was the primary outcome of our analyses, but we also present results for overall survival for comparison. We identified cancer-specific deaths among patients using the underlying COD, based on a modified version of the COD recode proposed by Howlader *et al.* (17) Specifically, if the patient's cancer was their only cancer diagnosis, then death due to any cancer was considered a cancer-specific death. If their cancer was the first of multiple diagnosed cancers, then death due to cancer of that organ system or an ill-defined primary site was considered a cancer-specific death. We abstracted data from cancer registries on summary stage at diagnosis (localized, regional, distant, or unknown); this scheme does not apply to hematologic malignancies, so these were considered unstaged. Information on initial cancer treatment in broad categories (surgery, radiation, chemotherapy) was categorized as provided, absent, or unknown.

We used two complementary statistical approaches to compare overall or cancer-specific survival between transplanted and other (i.e., untransplanted) cancer patients in the general population. Both methods analyzed data for each cancer site separately and accounted for the interval from cancer diagnosis to transplantation in the transplanted patients. First, we constructed Cox regression models in which cancer patients were followed from diagnosis (i.e., cohort analysis), with transplantation treated as a time-dependent exposure. Thus, the hazards of death in transplanted and untransplanted patients were compared using risk sets defined at each timepoint after diagnosis at which a cancer patient was transplanted. To control for potential confounding, we stratified the baseline hazard of these Cox models by sex, calendar year of diagnosis (5-year intervals), and cancer stage, and adjusted for age at diagnosis using restricted cubic splines.

Second, we created a matched group to allow for finer adjustment for potential confounding and analysis of subsets of patients (i.e., matched analysis). For each cancer patient who received a transplant, we randomly selected up to 10 cancer patients from the general population as controls, who had not themselves received a transplant at the time that the patient was transplanted (i.e., selection timepoint, measured from cancer diagnosis). These untransplanted cancer patients were matched to each patient according to cancer site, stage, sex, age at diagnosis, calendar year of diagnosis, and end year of cancer registry coverage to allow for similar duration of follow-up (see Table 1 note for details). Only one patient was excluded because there was no matched patient, and 5406 (99.7%) of the remaining patients had 10 controls each. We then combined the transplanted and matched patients and utilized Cox regression to assess the association between patient status (i.e., transplantation) and subsequent survival. Follow-up started at selection, ensuring that transplanted and matched patients began with the same elapsed time since cancer diagnosis. Analyses were conducted separately for each cancer site, stratifying the baseline hazard of each Cox model on matched set and adjusting for age using restricted cubic splines (to more finely control for potential confounding by age than accounted for in the matching). In this way, all matching variables, including time from cancer diagnosis, were accounted for in the analysis.

Finally, we conducted several sensitivity analyses of our results for cancer-specific mortality. First, we performed additional adjustment for first course of cancer treatment recorded in the cancer registries (surgery, radiotherapy, chemotherapy). Second, we further adjusted models for race/ethnicity. Third, for non-Hodgkin lymphoma (NHL), we performed cohort analyses separately for the most common subtypes (diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL]).

We present results for overall or cancer-specific survival as adjusted hazard ratios (aHRs) for the development of their complementary outcomes (i.e., overall or cancer-specific mortality). The proportionality assumption of each Cox regression model was assessed using a score test based on weighted Schoenfeld residuals. None of the models exhibited evidence for non-proportionality. We present results using a two-sided p-value cutoff of 0.05 and 95% confidence intervals (95%CIs), but because we made multiple comparisons, we highlight associations with $p<0.0029$ based on a Bonferroni cutoff for 17 cancer sites.

Results

Characteristics of the included cancer patients are presented in Table 1. Compared to untransplanted patients, those who received a transplant were more frequently male (61.7% vs. 49.1%), non-White (32.1% vs. 21.8%), and younger (median age 55 vs. 65 years). Seventeen cancer types were assessed. The most common malignancies among the 5425 patients who received a transplant after their diagnosis were cancers of the prostate (30.1% of patients), breast (15.3%), colorectum (9.9%), and thyroid (7.3%), as well as NHL (8.0%), whereas among untransplanted patients, lung cancer was more common (14.7%) and thyroid cancer less common (2.8%). Among transplanted patients, the most frequently transplanted organs were kidney (63.8%), liver (16.6%), heart (11.6%), and lung (5.0%).

Transplanted patients were more likely than untransplanted patients to have localized stage cancer at diagnosis (68.5% vs. 47.9%) and less likely to have regional stage (13.4% vs. 21.9%) or distant stage cancer (1.4% vs. 15.1%) (Table 1). Most cancers among transplanted patients were diagnosed at localized stage regardless of site (Figure 1A). The median time from cancer diagnosis to transplantation was 4.17 years overall (interquartile range 1.75-7.58 years) and ranged between 3.5 to 5.5 years for most sites. Exceptions included short median times for lung cancer and myeloma (medians 3.42 and 3.50 years, respectively) and a long median time for testicular cancer (6.17 years). The distribution of times between cancer diagnosis and transplantation are shown for each cancer site in Figure 1B. For the combined group of transplanted patients, the interval from diagnosis to transplant increased with more advanced stage (median 4.17, 4.25, and 4.62 years for localized, regional, and distant stage patients). Additional details are included in Supplemental Table 2. As expected, matched patients closely resembled the transplanted patients (Table 1).

Transplantation was associated with significantly reduced overall survival (i.e., increased aHRs for overall mortality) for most cancer sites (Table 2). These elevations mostly appeared stronger in the matched analysis, although the results were qualitatively similar to the cohort analysis (Table 2). The strongest elevations in overall mortality were seen for

cervical, testicular, and thyroid cancers (adjusted hazard ratios [aHRs] 3.43-4.88 in the cohort analysis, 3.52-4.38 in the matched analysis). The only cancer for which overall mortality following transplantation was not at least borderline increased in either analysis was myeloma (aHR 0.89 in both analyses).

In contrast, transplantation was not associated with reduced cancer-specific survival (i.e., increased aHRs for cancer-specific mortality) for any cancer (Table 3). Results were similar in the cohort and matched analyses. While most associations were null, we observed decreased cancer-specific mortality following transplantation in both analyses for patients with breast cancer (aHRs 0.65-0.67), NHL (0.50-0.51), and myeloma (0.39-0.42); the results for myeloma met the Bonferroni cutoff for significance in both analyses. There was also decreased cancer-specific mortality associated with transplantation in the cohort analysis for colorectal and kidney cancers (aHRs 0.66 and 0.28, respectively), with comparable but non-significant associations in the matched analysis.

In a sensitivity analysis, additional adjustment for cancer treatment produced generally similar results, although with wide confidence intervals, and the association with cancer-specific mortality was no longer significant for NHL (Table 3). Similarly, results were unchanged with further adjustment for race/ethnicity (Supplemental Table 3). Finally, among NHL subtypes, suggestive but nonsignificant inverse associations with cancer-specific mortality were observed for DLBCL (aHR 0.57, 95%CI 0.24-1.36; based on N=5 deaths in transplant recipients), follicular lymphoma (0.53, 0.13-2.13; N=2), and CLL/SLL (0.59, 0.26-1.30; N=6).

Discussion

We evaluated 5425 patients with 17 different types of cancer who received a solid organ transplant following their diagnosis. In line with recent guidelines designed to select patients with a good prognosis (10-12), most transplanted cancer patients had localized stage cancer, and there was a median of 4.17 years between cancer diagnosis and transplantation. Compared with other untransplanted patients from the general population, those who received a transplant had higher overall mortality. Somewhat reassuringly, however, we did not detect any increase for cancer-specific mortality in transplanted patients compared to non-transplanted patients, and indeed, cancer-specific survival appeared better in transplanted patients with breast cancer, NHL, and myeloma.

It is important to interpret our findings in the context of how patients are selected for organ transplantation. For instance, several characteristics of the transplanted cancer patients reflect this selection (Table 1, Figure 1). First, transplanted patients were younger on average than non-transplanted cancer patients, likely a manifestation of selection by transplantation programs for relatively healthy individuals with few comorbidities other than their prior cancer and end-stage organ disease. Second, there was an over-representation in the transplanted group of certain cancers with good prognosis (e.g., thyroid and prostate cancers) and under-representation of those with poor prognosis (e.g., lung and pancreatic cancers, the latter being too rare to analyze). Third, wait times were longer for patients with more advanced stage cancers. These patterns reflect both the relatively few patients with

lethal cancers who live long enough to be considered for transplant and selection criteria applied by programs to offer transplantation to patients with a high likelihood of being cured and good prognosis (10-12). Other factors also may have contributed. For example, the typically young age at diagnosis for testicular cancer and onset of end-stage organ disease later in life may explain the long interval between diagnosis and transplantation for this malignancy.

Our analyses adjusted for these characteristics, but remaining differences between the patient groups limited our ability to assess the effect of transplantation *per se* on mortality. For example, the higher overall mortality in the transplanted patients, compared with untransplanted patients, partly reflects medical complications of transplantation, but the effects of end-stage organ disease also contributed. Furthermore, our observation of better cancer-specific survival among transplant recipients for several cancers was unexpected. We believe that this pattern reflects some degree of residual confounding due to strong selection of candidates for transplantation who have an excellent prognosis with regards to their cancer, rather than a protective effect of transplantation itself in preventing cancer recurrence. To be considered for transplantation, individuals with a prior cancer must have completed cancer treatment, and typically they have undergone a thorough evaluation to ensure there is no evidence of residual or recurrent disease. In contrast, our comparison group of cancer patients from the general population were a mixture of individuals with good and poor prognosis. We had limited information on stage and treatment, and we lacked data on other important predictors of outcomes, including performance status and tumor characteristics (e.g., molecular markers). Furthermore, while the transplant recipients underwent a detailed evaluation to rule out persistent cancer at the time they were considered for transplantation (a “healthy screening” effect), we were unable to select similar comparison patients from the general population.

Myeloma is a notable example, where cancer-specific survival was substantially better in transplanted compared with untransplanted patients and where the results met a stringent test of statistical significance (Table 3). The early series from the CTTR reported a very high recurrence rate (67%) in myeloma patients who received a solid organ transplant (9). This malignancy is still thought to be incurable, but prognosis has improved dramatically with the introduction of new treatments, and many patients can have long-term remission (18, 19). Recent guidelines recommend that patients with prior myeloma who are listed for transplantation should have evidence for a deep remission as manifested by an absence of circulating monoclonal immunoglobulin protein and a negative bone marrow biopsy (15). In contrast, many myeloma patients in our comparison group of untransplanted patients from the general population would not have been in deep remission. We adjusted our analyses for baseline characteristics of the myeloma patients and time since cancer diagnosis, but we lacked data on clinical stage, other prognostic markers (e.g., cytogenetic abnormalities), and secondary treatments (e.g., autologous stem cell transplantation) (19). Moreover, renal disease is a common complication of myeloma and is associated with elevated mortality (20). We excluded cancer patients whose transplant might have been part of the treatment for their cancer, including myeloma patients who received a kidney transplant. Therefore, the remaining transplanted group probably had little kidney involvement, which may have contributed to favorable overall mortality (Table 2).

Because of the cost and complexity of organ transplantation, most transplant recipients have health insurance and access to advanced medical care, which is not the case for all US cancer patients. Socioeconomic and health insurance status have strong associations with cancer survival (21, 22). Such differences between transplanted and untransplanted cancer patients may partly explain the inverse associations that we observed for some cancers, e.g., breast cancer (22, 23).

We observed better cancer-specific survival among NHL patients who received a transplant, but this is a heterogeneous group of disease subtypes with different clinical behaviors (24). Unfortunately, the number of patients in our study was too small to allow evaluation of NHL subtypes separately. In a prior study using data from the TCM Study, Arron et al. found a suggestive association of increased cancer-specific mortality among melanoma patients who subsequently underwent transplantation (aHR 1.7, 95%CI 0.6-4.5) (25). However, that analysis was based on only 68 transplanted melanoma patients, and our current analysis with an increased number of patients (N=277) failed to confirm that finding (Table 3).

Our study has several strengths. It is the largest published series of cancer patients who received a subsequent organ transplant, and our population-based design ensured that our sample was representative of both transplanted and untransplanted cancer patients in the US. We used two complementary statistical approaches to systematically compare mortality in these two groups (cohort and matched analyses), and both approaches produced similar results. Nonetheless, two methodologic points related to analyses of cancer-specific survival should be considered. First, we relied on CODs obtained by cancer registries from death certificate records to identify cancer-specific deaths, and we may have missed positive associations between transplantation and cancer-specific mortality if some deaths were miscoded. Second, we may have missed associations if the hazards for death from cancer and other causes were not statistically independent, e.g., if transplanted individuals who would have died from their cancer were especially likely to die from transplant-related complications. Our primary analysis used standard Cox models rather than competing risk models to assess associations between transplantation and mortality outcomes, because we were interested in the potential biologic effects of immunosuppression rather than the absolute risk of death from cancer and other diseases (26). As expected, the associations between transplantation and cancer-specific mortality tended to be more strongly inverse in competing risk models, reflecting the much greater mortality from non-cancer causes among patients with end-stage organ disease (Supplemental Table 4). Finally, we made multiple statistical comparisons, which could have led to some chance findings. In particular, one might therefore discount the associations between transplantation and cancer-specific mortality for some cancers (e.g., breast cancer) that did not meet our Bonferroni threshold for statistical significance.

Our results provide limited evidence against an ongoing protective benefit of immunity in preventing relapse among cancer patients in the general population, i.e., in containing cancer cells in a dynamic equilibrium during remission (4), because if that biologic model were true we might have observed reduced cancer-specific survival among cancer patients who subsequently underwent solid organ transplantation. However, the issues noted above prevent a definitive conclusion on this question. Moreover, a possible adverse effect of

transplantation on containment of cancer is supported by studies that demonstrate reduced cancer-specific survival among patients who develop cancer after they are already immunosuppressed due to human immunodeficiency virus infection or transplantation (27-29). It also would have been informative in the present study to perform analyses separately for each cancer site according to stage and time from cancer diagnosis to transplantation. Unfortunately, the number of transplanted patients in each stratum was limited and the results appeared unstable. For these reasons, we cannot rule out a modest-sized adverse effect of transplantation on survival for specific cancer sites or subgroups.

For most types of malignancy, candidate evaluation guidelines recommend that patients with a previous cancer diagnosis should be considered for solid organ transplantation only after they complete their cancer treatment, wait a variable period of several years, and manifest no evidence for active disease (10-12); consultation with an oncologist is recommended. We observed that individuals who received a transplant under US practice patterns experienced a similar survival from their cancer relative to other cancer patients in the general population. These results are reassuring and suggest that one may use data from cancer registries as a benchmark to gauge prognosis for potential transplant recipients with a previous cancer diagnosis. However, it is important to remain somewhat cautious. As noted above, these transplant recipients are a selected group, and we lacked information on some important prognostic factors that would have been useful for adjusted or stratified analyses.

In 2020, an American Society of Transplantation working group published an expert consensus statement (14, 15) recommending continued careful evaluation of candidates with a prior cancer diagnosis but, in general, fewer restrictions than prior guidelines on referral to transplantation. Our study does not provide data to recommend for or against reducing barriers to transplantation, although it may be reasonable to cautiously expand such opportunities. Cancer needs to be considered with other medical comorbidities when assessing transplant eligibility (8). Importantly, several studies have demonstrated elevated overall mortality among recipients with a pre-transplant cancer diagnosis compared to other transplant recipients without a prior cancer (30), but we did not include transplant recipients without cancer in the present study.

In conclusion, we did not find lower cancer-specific survival associated with solid organ transplantation in the US. Nonetheless, cancer patients who receive a transplant are selected because of their good prognosis, which limits the ability to make strong biological and clinical inferences from comparisons with the heterogeneous group of other cancer patients in the general population. Our study provides reassurance to clinicians that the prognosis of carefully selected patients for transplantation can be benchmarked using estimates of cancer-specific mortality of cancer patients in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported in part by the Intramural Research Program of the National Cancer Institute (E.A. Engels, G. Haber, K.J. Yu, R.M. Pfeiffer).

The authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration, the SRTR (Ajay Israni, Bertram Kasiske, Paul Newkirk, Jon Snyder), and the following cancer registries: the states of California (Cyllene Morris), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Florida (Brad Wohler), Georgia (Rana Bayakly), Hawaii (Brenda Hernandez), Iowa, Illinois (Lori Koch), Kentucky (Jaclyn Nee), Michigan (Georgetta Alverson), New Jersey (Xiaoling Niu), New York (Amy Kahn), North Carolina (Chandrika Rao), Ohio (Roberta Slocumb), Pennsylvania (Jim Rubertone), Texas (Leticia Nogueria), and Utah (Janna Harrell), and the Seattle-Puget Sound area of Washington (Margaret Madeleine). We also thank analysts at Information Management Services for programming support (David Castenson, Matthew Chaloux, Michael Curry, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

The SRTR is currently operated under contract number HHSH250201500009C by the Hennepin Healthcare Research Institute, Minneapolis, MN. Previously the SRTR was managed under contracts HHSH250201000018C and HHSH234200537009C. The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201800002I), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Iowa (HSN261201000032C and N01-PC-35143), New Jersey (HHSN261201300021I, N01-PC-2013-00021), New York (75N91018D00005 [Task Order 75N91018F00001]), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN2612013000171). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (5U58DP003875-01), Illinois (5U58DP003883-03), Maryland (U58DP12-1205 3919-03), Michigan (5U58DP003921-03), New Jersey (5NU58DP006279-02-00), New York (6NU58DP006309), North Carolina (U58DP003933) and Texas (5U58DP000824-04). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, Massachusetts (Massachusetts Cancer Prevention and Control Cooperative Agreement 5458DP003920), New Jersey, New York (including the Cancer Surveillance Improvement Initiative), Texas, Utah, and Washington, as well as the University of Utah and Fred Hutchinson Cancer Research Center in Seattle, WA.

References

1. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, Mariotto A, Lake AJ, Wilson R, Sherman RL, Anderson RN, Henley SJ, Kohler BA, Penberthy L, Feuer EJ, Weir HK. Annual Report to the Nation on the Status of Cancer, 1975–2014, Featuring Survival. J Natl Cancer Inst. 2017;109(9). Epub 2017/04/05. doi: 10.1093/jnci/djx030. PubMed PMID: 28376154; PMCID: PMC5409140.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–64. Epub 2012/03/23. doi: 10.1038/nrc3239. PubMed PMID: 22437870; PMCID: Pmc4856023. [PubMed: 22437870]
3. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hogg D, Hill A, Márquez-Rodas I, Haanen J, Guidoboni M, Maio M, Schöffski P, Carlino MS, Lebbé C, McArthur G, Ascierto PA, Daniels GA, Long GV, Bastholt L, Rizzo JI, Balogh A, Moshyk A, Hodi FS, Wolchok JD. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019;381(16):1535–46. Epub 2019/09/29. doi: 10.1056/NEJMoa1910836. PubMed PMID: 31562797. [PubMed: 31562797]
4. Engels EA. Epidemiologic perspectives on immunosuppressed populations and the immunosurveillance and immunocontainment of cancer. Am J Transplant. 2019;19(12):3223–32. Epub 2019/06/18. doi: 10.1111/ajt.15495. PubMed PMID: 31206226; PMCID: PMC6883125. [PubMed: 31206226]
5. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3(11):991–8. [PubMed: 12407406]

6. Engels EA, Pfeiffer RM, Fraumeni JF Jr., Kasiske BL, Israni AK, Snyder JJ, Wolfe RA, Goodrich NP, Bayakly AR, Clarke CA, Copeland G, Finch JL, Fleissner ML, Goodman MT, Kahn A, Koch L, Lynch CF, Madeleine MM, Pawlish K, Rao C, Williams MA, Castenson D, Curry M, Parsons R, Fant G, Lin M. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891–901. [PubMed: 22045767]
7. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370(9581):59–67. [PubMed: 17617273]
8. Hart A, Engels EA. Balancing uncertain risks in candidates for solid organ transplantation with a history of malignancy: Who is safe to transplant? Am J Transplant. 2020. Epub 2020/10/22. doi: 10.1111/ajt.16366. PubMed PMID: 33084186.
9. Penn I Evaluation of transplant candidates with pre-existing malignancies. Ann Transplant. 1997;2(4):14–7. Epub 1997/01/01. PubMed PMID: 9869873.
10. Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, Kumar D, Oberbauer R, Pascual J, Pilmore HL, Rodrigue JR, Segev DL, Sheerin NS, Tinckam KJ, Wong G, Knoll GA. KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation. 2020;104(4S1 Suppl 1):S11–S103. Epub 2020/04/18. doi: 10.1097/TP.0000000000003136. PubMed PMID: 32301874. [PubMed: 32301874]
11. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG, Snell GI, Verleden GM, Zamora MR, Glanville AR. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2015;34(1):1–15. Epub 2014/08/03. doi: 10.1016/j.healun.2014.06.014. PubMed PMID: 25085497.
12. Martin P, DiMartini A, Feng S, Brown R Jr., Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology. 2014;59(3):1144–65. Epub 2014/04/10. doi: 10.1002/hep.26972. PubMed PMID: 24716201. [PubMed: 24716201]
13. Zwald F, Leitenberger J, Zeitouni N, Soon S, Brewer J, Arron S, Bordeaux J, Chung C, Abdelmalek M, Billingsley E, Vidimos A, Stasko T. Recommendations for Solid Organ Transplantation for Transplant Candidates With a Pretransplant Diagnosis of Cutaneous Squamous Cell Carcinoma, Merkel Cell Carcinoma and Melanoma: A Consensus Opinion From the International Transplant Skin Cancer Collaborative (ITSCC). Am J Transplant. 2016;16(2):407–13. Epub 2016/01/29. doi: 10.1111/ajt.13593. PubMed PMID: 26820755. [PubMed: 26820755]
14. Al-Adra DP, Hammel L, Roberts J, Woodle ES, Levine D, Mandelbrot D, Verna E, Locke J, D'Cunha J, Farr M, Sawinski D, Agarwal PK, Plichta J, Pruthi S, Farr D, Carvajal R, Walker J, Zwald F, Habermann T, Gertz M, Bierman P, Dizon DS, Langstraat C, Al-Qauod T, Eggener S, Richgels JP, Chang GJ, Geltzeiler C, Sapisochin G, Ricciardi R, Krupnick AS, Kennedy C, Mohindra N, Foley DP, Watt KD. Pre-Transplant Solid Organ Malignancy and Organ Transplant Candidacy: A Consensus Expert Opinion Statement. Am J Transplant. 2020. Epub 2020/09/25. doi: 10.1111/ajt.16318. PubMed PMID: 32969590.
15. Al-Adra DP, Hammel L, Roberts J, Woodle ES, Levine D, Mandelbrot D, Verna E, Locke J, D'Cunha J, Farr M, Sawinski D, Agarwal PK, Plichta J, Pruthi S, Farr D, Carvajal R, Walker J, Zwald F, Habermann T, Gertz M, Bierman P, Dizon DS, Langstraat C, Al-Qaoud T, Eggener S, Richgels JP, Chang GJ, Geltzeiler C, Sapisochin G, Ricciardi R, Krupnick AS, Kennedy C, Mohindra N, Foley DP, Watt KD. Preexisting melanoma and hematological malignancies, prognosis, and timing to solid organ transplantation: A consensus expert opinion statement. Am J Transplant. 2020. Epub 2020/09/26. doi: 10.1111/ajt.16324. PubMed PMID: 32976703.
16. Livingston-Rosanoff D, Foley DP, Leverson G, Wilke LG. Impact of Pre-Transplant Malignancy on Outcomes After Kidney Transplantation: United Network for Organ Sharing Database Analysis. Journal of the American College of Surgeons. 2019;229(6):568–79. Epub 2019/11/02. doi: 10.1016/j.jamcollsurg.2019.06.001. PubMed PMID: 31666186; PMCID: PMC6879822. [PubMed: 31666186]

17. Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. J Natl Cancer Inst. 2010;102(20):1584–98. [PubMed: 20937991]

18. D'Agostino M, Bertamini L, Oliva S, Boccadoro M, Gay F. Pursuing a Curative Approach in Multiple Myeloma: A Review of New Therapeutic Strategies. Cancers. 2019;11(12). Epub 2019/12/19. doi: 10.3390/cancers11122015. PubMed PMID: 31847174; PMCID: PMC6966449.

19. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548–67. Epub 2020/03/27. doi: 10.1002/ajh.25791. PubMed PMID: 32212178. [PubMed: 32212178]

20. Fotiou D, Dimopoulos MA, Kastritis E. Managing renal complications in multiple myeloma. Expert review of hematology. 2016;9(9):839–50. Epub 2016/07/19. doi: 10.1080/17474086.2016.1210003. PubMed PMID: 27426872. [PubMed: 27426872]

21. Grant SR, Walker GV, Guadagnolo BA, Koshy M, Mahmood U. A brighter future? The impact of insurance and socioeconomic status on cancer outcomes in the USA: a review. Future oncology (London, England). 2016;12(12):1507–15. Epub 2016/02/26. doi: 10.2217/fon-2015-0028. PubMed PMID: 26911861.

22. Coughlin SS. Social determinants of breast cancer risk, stage, and survival. Breast cancer research and treatment. 2019;177(3):537–48. Epub 2019/07/05. doi: 10.1007/s10549-019-05340-7. PubMed PMID: 31270761. [PubMed: 31270761]

23. Abdel-Rahman O Impact of NCI Socioeconomic Index on the Outcomes of Nonmetastatic Breast Cancer Patients: Analysis of SEER Census Tract-Level Socioeconomic Database. Clinical breast cancer. 2019;19(6):e717–e22. Epub 2019/09/15. PubMed PMID: 31519450. [PubMed: 31519450]

24. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Varidman JW. WHO classification of tumours of hematopoietic and lymphoid tissues. Lyon: IARC Press; 2008.

25. Arron ST, Raymond AK, Yanik EL, Castenson D, McCulloch CE, Clarke CA, Paddock LE, Niu X, Engels EA. Melanoma Outcomes in Transplant Recipients With Pretransplant Melanoma. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2016;42(2):157–66. Epub 2016/01/29. doi: 10.1097/dss.0000000000000602. PubMed PMID: 26818209.

26. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009;170(2):244–56. Epub 2009/06/06. doi: 10.1093/aje/kwp107. PubMed PMID: 19494242; PMCID: PMC2732996. [PubMed: 19494242]

27. D'Arcy ME, Coghill AE, Lynch CF, Koch LA, Li J, Pawlish KS, Morris CR, Rao C, Engels EA. Survival after a cancer diagnosis among solid organ transplant recipients in the United States. Cancer. 2019;125(6):933–42. Epub 2019/01/10. doi: 10.1002/cncr.31782. PubMed PMID: 30624768; PMCID: PMC6403005. [PubMed: 30624768]

28. Miao Y, Everly JJ, Gross TG, Tevar AD, First MR, Alloway RR, Woodle ES. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation. 2009;87(9):1347–59. Epub 2009/05/09. doi: 10.1097/TP.0b013e3181a238f6. PubMed PMID: 19424035. [PubMed: 19424035]

29. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States. J Clin Oncol. 2015;33(21):2376–83. Epub 2015/06/17. doi: 10.1200/jco.2014.59.5967. PubMed PMID: 26077242; PMCID: Pmc4500831. [PubMed: 26077242]

30. Acuna SA, Huang JW, Daly C, Shah PS, Kim SJ, Baxter NN. Outcomes of Solid Organ Transplant Recipients With Preexisting Malignancies in Remission: A Systematic Review and Meta-Analysis. Transplantation. 2017;101(3):471–81. Epub 2016/04/22. doi: 10.1097/tp.0000000000001192. PubMed PMID: 27101077. [PubMed: 27101077]

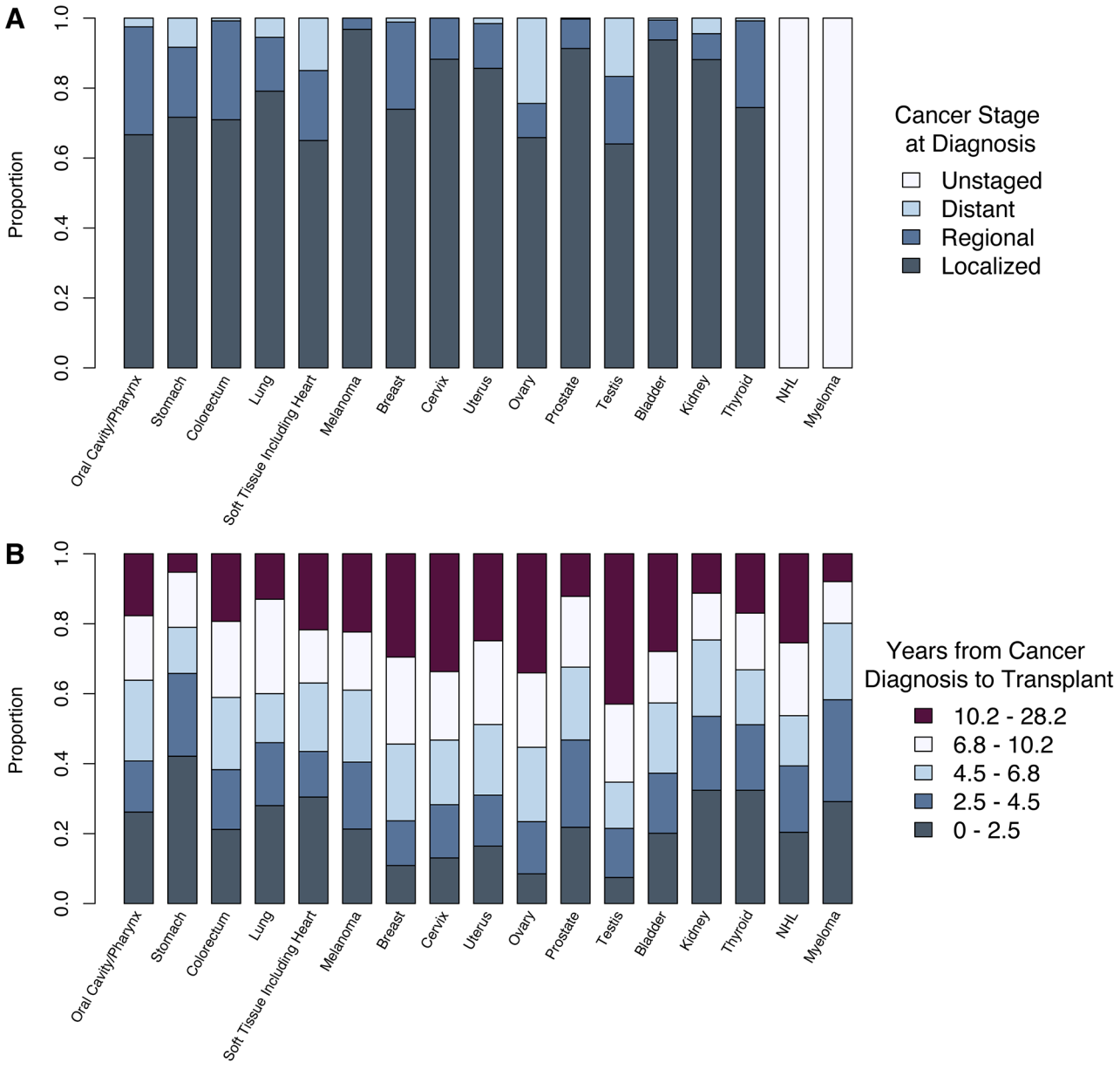

Figure 1.

Characteristics of transplanted cancer patients according to cancer site. A. Stage at cancer diagnosis. B. Time from cancer diagnosis to transplantation. Stage at diagnosis is based on summary stage classification and was unavailable for non-Hodgkin lymphoma and myeloma patients. For other cancer sites, patients with unknown stage are not depicted; the proportion of such patients ranged from 3% to 14% across sites (see Supplemental Table 2 for details).

Table 1.

Characteristics of transplanted and untransplanted cancer patients

Characteristic	Transplanted patients	Untransplanted patients	Matched patients[a]
Total number	5425	10,518,901	54,363
Age at diagnosis in years, median (IQR)	55 (47-61)	65 (55-74)	55 (47-61)
Sex			
Male	3346 (61.7%)	5,160,815 (49.1%)	33,531 (61.7%)
Female	2079 (38.3%)	5,358,086 (50.9%)	20,832 (38.3%)
Race/ethnicity			
Non-Hispanic White	3682 (67.9%)	8,224,861 (78.2%)	41,721 (76.7%)
Non-Hispanic Black	869 (16.0%)	999,414 (9.5%)	5282 (9.7%)
Hispanic	560 (10.3%)	812,637 (7.7%)	4651 (8.6%)
Asian/Pacific Islander	257 (4.7%)	342,484 (3.3%)	1767 (3.3%)
Other/unknown	57 (1.1%)	139,505 (1.3%)	942 (1.7%)
Cancer site			
Oral cavity/pharynx	130 (2.4%)	291,716 (2.8%)	1300 (2.4%)
Stomach	76 (1.4%)	209,231 (2.0%)	735 (1.4%)
Colorectum	538 (9.9%)	1,349,943 (12.8%)	5367 (9.9%)
Lung	100 (1.8%)	1,545,340 (14.7%)	988 (1.8%)
Soft tissue including heart	46 (0.8%)	84,549 (0.8%)	675 (1.2%)
Melanoma	277 (5.1%)	450,759 (4.3%)	2770 (5.1%)
Breast	829 (15.3%)	1,983,088 (18.9%)	8284 (15.2%)
Cervix	92 (1.7%)	152,439 (1.4%)	920 (1.7%)
Uterus	213 (3.9%)	405,751 (3.9%)	2130 (3.9%)
Ovary	47 (0.9%)	203,514 (1.9%)	470 (0.9%)
Prostate	1632 (30.1%)	1,984,788 (18.9%)	16,309 (30.0%)
Testis	121 (2.2%)	88,320 (0.8%)	1200 (2.2%)
Bladder	204 (3.8%)	323,797 (3.1%)	2023 (3.7%)
Kidney	142 (2.6%)	336,220 (3.2%)	1412 (2.6%)
Thyroid	395 (7.3%)	299,389 (2.8%)	3950 (7.3%)
Non-Hodgkin lymphoma	432 (8.0%)	647,368 (6.2%)	4320 (7.9%)
Myeloma	151 (2.8%)	162,689 (1.5%)	1510 (2.8%)
Stage at diagnosis			
Localized	3718 (68.5%)	5,040,332 (47.9%)	37,270 (68.6%)
Regional	725 (13.4%)	2,303,073 (21.9%)	7292 (13.4%)
Distant	78 (1.4%)	1,590,719 (15.1%)	744 (1.4%)
Unstaged[b]	583 (10.7%)	810,057 (7.7%)	5830 (10.7%)
Unknown	321 (5.9%)	774,720 (7.4%)	3227 (5.9%)

Abbreviations: IQR interquartile range

Cancer patients were contributed by the following cancer registries (calendar years of diagnosis): California (1988-2012), Colorado (1988-2014), Connecticut (1987-2009), Georgia (1995-2010), Illinois (1987-2013), Iowa (1987-2009), Kentucky (1995-2011), New Jersey (1987-2016), New York (1995-2017), Ohio (1996-2015), Pennsylvania (1987-2013), Seattle/Puget Sound (1987-2014), and Texas (1995-2014).

[a] Matched patients were individually matched to transplanted patients. They had not received an organ transplant at the time of selection and were matched to transplanted patients according to cancer site, stage, sex, age at diagnosis (0-20, 21-40, 41-60, 61-80, 80-100 years), calendar year of diagnosis (1986-1992, 1993-1997, 1998-2002, 2003-2007, 2008-2012, 2013-2017), and end year of cancer registry coverage (2007-2009,2010-2012, 2013-2015, 2016-2017).

[b] Cancer stage at diagnosis was not available for hematologic malignancies (non-Hodgkin lymphoma and myeloma).

Table 2:

Association of transplantation with overall mortality among cancer patients

Cancer site	Deaths in transplanted patients, N	Cohort analysis Adjusted HR (95% CI)[a]	Matched analysis Adjusted HR (95% CI)[b]
Oral cavity/pharynx	48	1.69 * (1.27, 2.25)	2.12 * (1.53, 2.93)
Stomach	29	1.25 (0.87, 1.79)	1.79 * (1.17, 2.73)
Colorectum	218	1.80 * (1.58, 2.06)	2.56 * (2.19, 2.99)
Lung	55	1.14 (0.87, 1.48)	1.50 (1.10, 2.04)
Soft tissue including heart	16	1.40 (0.86, 2.29)	2.63 * (1.74, 3.98)
Melanoma	84	2.58 * (2.08, 3.20)	3.03 * (2.34, 3.93)
Breast	264	2.30 * (2.04, 2.60)	3.01 * (2.61, 3.48)
Cervix	32	3.46 * (2.44, 4.89)	3.52 * (2.30, 5.38)
Uterus	77	2.87 * (2.30, 3.59)	3.03 * (2.31, 3.99)
Ovary	18	2.58 * (1.62, 4.09)	3.71 * (2.09, 6.56)
Prostate	576	2.66 * (2.45, 2.88)	3.00 * (2.71, 3.31)
Testis	20	3.43 * (2.21, 5.33)	4.38 * (2.48, 7.74)
Bladder	115	2.45 * (2.04, 2.95)	3.15 * (2.51, 3.95)
Kidney	45	1.60 * (1.19, 2.14)	2.03 * (1.45, 2.84)
Thyroid	88	4.88 * (3.96, 6.02)	4.23 * (3.24, 5.52)
Non-Hodgkin lymphoma	135	1.51 * (1.27, 1.79)	1.94 * (1.59, 2.36)
Myeloma	51	0.89 (0.68, 1.18)	0.89 (0.66, 1.21)

Abbreviations: CI confidence interval, HR hazard ratio

[a] Hazard ratios in the cohort analysis are based on Cox models in which the baseline hazard is stratified by sex, calendar year of diagnosis (5-year intervals), and cancer stage, and are adjusted for age at cancer diagnosis using a cubic spline.

[b] Hazard ratios in the matched analysis are based on Cox models stratified on matched set and further adjusted for age using a cubic spline.

* Association is statistically significant at Bonferroni p-value cutoff of 0.0029.

Table 3:

Association of transplantation with cancer-specific mortality among cancer patients

Cancer site	Cancer-specific deaths in transplanted patients, N	Cohort analysis Adjusted HR (95% CI)[a]	Matched analysis Adjusted HR (95% CI)[b]	Matched analysis Adjusted HR (95% CI)[c]
Oral cavity/pharynx	13	1.16 (0.67, 2.00)	1.14 (0.63, 2.04)	1.26 (0.63, 2.54)
Stomach	5	0.42 (0.18, 1.01)	0.45 (0.18, 1.13)	0.50 (0.14, 1.74)
Colorectum	23	0.66 (0.44, 0.99)	0.68 (0.44, 1.04)	0.50 (0.28, 0.90)
Lung	17	0.63 (0.39, 1.02)	0.85 (0.50, 1.42)	1.20 (0.65, 2.21)
Soft tissue including heart	8	1.12 (0.56, 2.25)	1.75 (0.94, 3.25)	1.73 (0.68, 4.40)
Melanoma	15	1.31 (0.79, 2.18)	0.87 (0.44, 1.75)	0.76 (0.34, 1.69)
Breast	31	0.67 (0.47, 0.96)	0.65 (0.45, 0.94)	0.53 (0.33, 0.86)
Cervix	3	1.00 (0.32, 3.10)	0.91 (0.27, 3.10)	1.29 (0.30, 5.63)
Uterus	4	0.69 (0.26, 1.83)	0.62 (0.22, 1.71)	0.63 (0.19, 2.14)
Ovary	1	0.29 (0.04, 2.05)	0.37 (0.05, 2.74)	0.51 (0.05, 5.40)
Prostate	48	0.79 (0.60, 1.05)	0.91 (0.67, 1.23)	1.01 (0.69, 1.46)
Testis	2	2.01 (0.50, 8.05)	2.71 (0.47, 15.4)	1.31 (0.12, 14.3)
Bladder	12	0.90 (0.51, 1.59)	1.18 (0.66, 2.14)	1.60 (0.82, 3.12)
Kidney	3	0.28 (0.09, 0.88)	0.32 (0.10, 1.03)	0.37 (0.11, 1.24)
Thyroid	4	1.01 (0.38, 2.71)	0.70 (0.25, 1.95)	1.15 (0.36, 3.73)
Non-Hodgkin lymphoma	21	0.50 * (0.33, 0.77)	0.51 (0.32, 0.80)	0.73 (0.40, 1.31)
Myeloma	17	0.42 * (0.26, 0.68)	0.39 * (0.23, 0.65)	0.33 * (0.17, 0.64)

Abbreviations: CI confidence interval, HR hazard ratio

[a] Hazard ratios in the cohort analysis are based on Cox models in which the baseline hazard is stratified by sex, calendar year of diagnosis (5-year intervals), and cancer stage, and are adjusted for age at cancer diagnosis using a cubic spline.

[b] Hazard ratios in the matched analysis are based on Cox models stratified on matched set and further adjusted for age using a cubic spline.

[c] Hazard ratios are from a sensitivity analysis in which the matched analysis was additionally adjusted for initial cancer treatment.

* Association is statistically significant at Bonferroni p-value cutoff of 0.0029.