HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2023 November 15.

Published in final edited form as:

Cancer. 2022 November 15; 128(22): 3985–3994. doi:10.1002/cncr.34462.

Cancer risk associated with cytomegalovirus infection among solid organ transplant recipients in the United States

Jennifer M. Geris, PhD, MPH[1,2], **Logan G. Spector, PhD**[1], **Ruth M. Pfeiffer, PhD**[3], **Ajit P. Limaye, MD**[4], **Kelly J. Yu, PhD, MPH**[3], **Eric A. Engels, MD, MPH**[3]

[1]Division of Epidemiology & Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis MN, USA

[2]Institute for Molecular Virology, University of Minnesota, Minneapolis MN, USA

[3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda MD, USA

[4]Division of Allergy & Infectious Diseases, Department of Medicine, University of Washington, Seattle WA, USA

Abstract

Background: Cytomegalovirus (CMV) is among the most common viral infections following solid organ transplantation (SOT). Associations of CMV with cancer risk among SOT recipients have been incompletely evaluated.

Methods: We used linked data from the United States SOT registry and 32 cancer registries. We used Poisson regression to compare cancer incidence across CMV risk groups based on donor (D) and recipient (R) IgG serostatus: high-risk (R−/D+), moderate-risk (R+), and low-risk (R−/D−).

Results: We evaluated 247,318 SOT recipients during 2000–2017 (20.3% CMV R−/D+, 62.9% R+, 16.8% R−/D−). CMV seropositive recipients were older, more racially/ethnically diverse, and had lower socioeconomic status than seronegative recipients. Compared to CMV R−/D− recipients, R−/D+ and R+ recipients had lower incidence of diffuse large B-cell lymphoma (DLBCL; (adjusted incidence rate ratio [aIRR]:0.74, 95% confidence interval [CI]: 0.59-0.91, and 0.83, 0.69-1.00, respectively). CMV serostatus modified the association between EBV status and DLBCL (p=0.0006): DLBCL incidence was increased for EBV R−/D+ recipients (aIRR: 3.46, 95%CI: 1.50-7.95) among CMV R−/D− recipients but not among other CMV risk groups.

Correspondence: Jennifer M. Geris, Division of Epidemiology & Clinical Research, Department of Pediatrics, University of Minnesota, 420 Delaware Street, Minneapolis, MN 55455. grimm074@umn.edu. Phone: 612-626-4595. Fax: 612-626-1667.

Author Contributions

Jennifer M. Geris: Study conception and design, data collection, analysis and interpretation of results, and writing and revision of the manuscript. **Logan G. Spector**: Study conception and design, data collection, analysis and interpretation of results, and critical review of the manuscript. **Ruth M. Pfeiffer:** Study conception and design, analysis and interpretation of results, and critical review of the manuscript. **Ajit P. Limaye:** Study conception and design, analysis and interpretation of results, and critical review of the manuscript. **Kelly J. Yu:** Data collection and critical review of the manuscript. **Eric A. Engels:** Study conception and design, data collection, analysis and interpretation of results, critical review of the manuscripts, and supervision.

Conflict of Interest Disclosures

Ajit P. Limaye holds grants or contracts with Merck, Amplyx, Moderna, and Takeda; Receives consulting fees from Merck, Novartis, GSK, J&J, and AlloVir; Receives royalties from UpToDa, andnd is a participatory member on a data safety and monitoring board or advisory board with Novartis and NobelPharma. The other authors made no disclosures.

Compared to CMV R−/D− recipients, R−/D+ recipients had lower incidence of small intestine cancer (aIRR: 0.23, 95%CI: 0.09-0.63), and R+ recipients had higher incidence of lung cancer (1.24, 1.05-1.46). CMV status was not associated with risk for other cancers.

Conclusions: CMV status was not associated with risk for most cancers among SOT recipients. The inverse association with DLBCL may reflect protective effects of CMV prophylaxis or treatment with off-target efficacy against EBV infection (the major cause of lymphoma in SOT recipients).

Precis

Cancer is a major adverse outcome of solid organ transplantation (SOT), and prior donor and recipient cytomegalovirus (CMV) infections are common; however, associations of CMV with cancer risk among SOT recipients have been incompletely evaluated. In this analysis of 247,318 SOT recipients, an inverse association between risk of CMV infection and diffuse large B-cell lymphoma was observed; however, CMV status was not associated with risk for most other cancers.

Keywords

Cytomegalovirus (CMV); solid organ transplantation; leukemia; lymphoma; solid tumors

Introduction

The field of solid organ transplantation (SOT) has made significant strides since the 1980s as a treatment for end-stage organ disease. However, long-term use of immunosuppressive medications to prevent rejection remains a source of morbidity among transplant recipients. In particular, opportunistic viral infections are a cause of post-transplant complications, including malignancy and reduced long-term graft survival.[1-3]

Cytomegalovirus (CMV) is among the most common viral infections to cause illness following SOT. CMV is a member of the herpesvirus family which establishes lifelong latency and can undergo periodic reactivation. In immunocompetent individuals, CMV infection is typically asymptomatic.[4,5] However, in transplant recipients, CMV infection can cause severe organ disease and allograft rejection. The occurrence of active CMV infection varies according to pre-transplant donor/recipient serostatus, intensity of immunosuppression, and the organ transplanted.[6] In the context of transplantation, CMV infection can result from primary infection (donor-transmitted or community-acquired) or super-infection with a new variant in someone previously infected.[7,8] Alternatively, immunosuppressive therapy required for transplantation may cause reactivation of previous CMV infection due to depressed immune surveillance.[9,10]

CMV may also contribute to cancer in SOT recipients. It has been reported that CMV seronegative transplant recipients who receive a CMV positive organ have elevated risk of post-transplant lymphoproliferative disorder (PTLD, a spectrum of conditions that includes lymphoma).[11,12] In a study of liver recipients who seroconverted to Epstein-Barr virus (EBV), CMV disease was reported in 54% of patients who developed PTLD but in only 18% of patients who did not develop PTLD.[13] In addition, hospitalization for CMV

disease during the first year post-transplant has been associated with subsequent risk of non-Hodgkin lymphoma (NHL).[14]

The relationship between CMV infection and other cancers arising after transplantation is not well-defined. A study in the United Kingdom that included nearly 12,300 SOT recipients found no association between CMV recipient and donor status and the incidence of post-transplant cancer.[15] However, the sample size was small for some outcomes. Among patients in the general population, CMV nucleic acids and proteins have been detected in tumor samples of breast, colon, and prostate cancers as well as glioblastoma.[16-18] However, one study has suggested that CMV may indirectly have a protective effect against the development of cancer in transplant recipients by stimulating T-cells after acute infection.[19]

Recently, CMV infection has emerged as a potential risk factor for acute lymphoblastic leukemia (ALL), a common pediatric malignancy. In a population-based case-control study, CMV DNA was detected in newborn dried blood spots among 9.7% of ALL cases but in only 3.0% of healthy controls (odds ratio: 3.71).[20] A second study using data from Swedish registries found that medically documented CMV infection acquired in early childhood was associated with an 11-fold increased risk of hematological malignancies, including ALL.[21]

Cancer is a major adverse outcome of SOT, and prior donor and recipient CMV infections are common. We therefore examined associations of pretransplant CMV donor and recipient serostatus (as indicators of risk of active CMV infection after transplantation) with risk of malignancy among SOT recipients.

Materials and Methods

The Transplant Cancer Match Study (http://transplantmatch.cancer.gov) has been previously described in detail.[3] Briefly, the study links data from the Scientific Registry of Transplant Recipients (SRTR), which includes all US transplants since 1987, with 32 US state and regional cancer registries. The study is considered non-human subjects research by the National Cancer Institute and was approved, as required, by participating cancer registries.

For the present study, we included recipients of a first organ transplant who resided in a region covered by a participating cancer registry at the time of transplantation. Data on CMV IgG serostatus at the time of transplant were unavailable for most recipients before 2000; therefore, we restricted analysis to transplants in 2000 and onward. Of the 672,603 individuals in the US who received a first transplant during 1987-2017, we excluded 211,973 because they were transplanted outside of participating cancer registry regions, 117,404 because they were transplanted before the year 2000 or lacked follow-up, 29,875 because they had a cancer diagnosis before transplantation, and 1127 because they had human immunodeficiency virus infection or more than one donor. Finally, we excluded an additional 19,139 transplant recipients who were missing CMV IgG serostatus or, if they were seronegative, their donor was missing CMV serostatus. After these exclusions, 247,318 transplants were included in the final analysis.

Incident cancers after transplantation were identified from the linked cancer registries and classified using a modified version of the Surveillance, Epidemiology, and End Results

(SEER) program site recode, updated for hematopoietic malignancies based on the World Health Organization (WHO) 2008 classification.[22,23] Lymphoma subtypes were classified according to current International Lymphoma Epidemiology Consortium guidelines.[24] We analyzed cancer sites with at least 60 cases among transplant recipients. When there were fewer than 60 cases, we grouped similar sites or collapsed them into a miscellaneous group.

The majority of transplant centers that use a strategy of antiviral prophylaxis do not routinely monitor for CMV infection during or after the period of prophylaxis. Clinically, CMV infection is only assessed in recipients with signs or symptoms suggestive of CMV disease. Neither active CMV infection nor CMV disease is captured in the SRTR. Moreover, US transplant centers do not reliably report follow-up data to the SRTR on CMV antibody status after transplantation. In a preliminary analysis, we assessed early follow-up data on CMV IgG and IgM to look for seroconversion among CMV seronegative recipients, but these data were available for a very small fraction of SOT recipients (2.5% and 1.7%, respectively).

For these reasons, we used pretransplant CMV IgG serostatus of recipients and their donors to group recipients into well-accepted clinical categories that vary in their risk for posttransplant CMV infection and disease.[9,25] Specifically, CMV serostatus was categorized into three risk groups according to SRTR data on pretransplant IgG serostatus of recipients and donors: high risk (recipient seronegative and donor seropositive [R−/D+]), intermediate risk (recipient seropositive regardless of donor serostatus [R+]), and low risk (recipient and donor seronegative [R−/D−]).[9]

Other data obtained from the SRTR included recipient characteristics (sex, age at transplantation, race/ethnicity), transplant characteristics (transplanted organ, calendar year), and immunosuppression medications (induction and baseline immunosuppression maintenance therapies). EBV serostatus in donors was reported according to measured IgG antibodies (viral capsid or EBV nuclear antigen) or IgM (viral capsid); we considered an individual positive if they were positive for any of these serologic markers. We then categorized recipients into three EBV risk groups according to recipient and donor status, as described for CMV. The tumor status with respect to EBV (EBV+ and EBV−) was identified for cases of diffuse large B-cell lymphoma (DLBCL), the most common NHL subtype, through linked SRTR data on PTLD. Socioeconomic status (SES) was assessed utilizing seven area-based measures according to recipients' ZIP code at the time of transplantation, using an index developed by Yost et al.[26]

Follow-up for cancer started at the time of transplantation and ended at the earliest of death, graft failure, retransplantation, loss to follow-up by the SRTR, or end of cancer registry coverage. We calculated incidence rates for each cancer for recipients in each CMV risk group. To compare cancer risk by CMV risk group, we estimated incidence rate ratios (IRRs) using multivariable Poisson regression models adjusted for sex, age at transplantation, race/ethnicity, SES quintile, transplanted organ (kidney, liver, or other/multiple), and EBV risk group. For DLBCL, we assessed risk by time post-transplantation and separately for EBV+ and EBV− DLBCL in a secondary analysis. In addition, the

interaction of CMV and EBV risk groups on DLBCL risk was assessed by including an interaction term in the multivariable models.

Reported *P* values are two-sided. Because our study is exploratory, we did not correct the analysis for multiple testing and considered a p-value less than 0.05 statistically significant. We also assessed whether any associations are significant using a Bonferroni threshold (p-value less than 0.05/94 = 0.0005 to account for analysis of 47 cancer types and 2 CMV risk groups). Stata/MP version 16.1 (StataCorp, College Station, Texas) was used for all statistical analyses.

Results

We evaluated 247,318 solid organ transplant recipients with 1,245,369 total person-years of follow-up. Overall, 62.9% of recipients in the cohort were CMV seropositive pretransplant (R+), while 20.3% were CMV seronegative with a seropositive donor (R−/D+) and 16.8% seronegative with a seronegative donor (R−/D−). Table 1 describes demographic and transplant characteristics of these individuals by CMV risk group. The R+ group was more likely to be female than the R−/D+ and R−/D− groups (42.2% vs. 33.2 and 32.7%, respectively; p<0.001) and was also older (median age: 53 vs. 48 and 47 years; p<0.001). The greatest racial/ethnic diversity was among the R+ group, among which 51.5% identified themselves as other than non-Hispanic White. R+ recipients tended to also be EBV seropositive (67.4%), and this proportion was slightly higher than among the R−/D+ and R−/D− groups (61.7% and 62.2%, respectively; p<0.001). Kidneys were the most commonly transplanted organ across all three groups (61.4% of transplants overall).

Education status different by CMV group, with a lower proportion of R+ recipients having an associate's/bachelor's degree or postgraduate education than among R−/D+ and R−/D− recipients (p<0.0001). R+ recipients also had a lower proportion of individuals in the two highest SES quintiles than the R−/D+ and R−/D− recipients (35.8% vs. 41.9% and 44.0%, respectively; p<0.001). Overall, 81.2% of recipients received some form of induction immunosuppressive therapy. For maintenance immunosuppression, 82.8% of recipients received tacrolimus and/or mycophenolate mofetil, 3.6% received cyclosporine and/or azathioprine, and 13.7% were given another combination of these medications.

We identified 2,339 incident hematologic malignancies during follow-up, including 61 Hodgkin lymphoma, 1,786 NHL, 276 leukemia, and 216 myeloma diagnoses. Among NHL subtypes, DLBCL was most common (66.8%). Sixty-two percent of leukemia cases were of myeloid lineage, with acute myeloid leukemia (AML) being the most common.

Table 2 describes hematologic malignancy incidence by CMV status. For Hodgkin lymphoma, risk was lower among the R+ group and R−/D+ groups compared to the R−/D− group, but these differences were not significant (adjusted IRR [aIRR]: 0.47, 95%CI: 0.19-1.18, and 0.75, 0.29-1.96, respectively). DLBCL risk was significantly lower in the R−/D+ group compared to the R−/D− group (aIRR: 0.74, 0.59-0.91), and showed a similar but non-significant association in the R+ group (aIRR: 0.83, 95%CI: 0.69-1.00). EBV status was available for a subset of 389 DLBCL tumors, of which 70% (n=274) were EBV+

and 30% (n=115) were EBV−. The risk of EBV+ DLBCL appeared lower among R+ (aIRR: 0.74, 95% CI: 0.52-1.08) and R−/D+ (0.66, 0.44-1.01) groups compared to the R−/D− group, although these differences were not significant. In contrast, the risk of EBV− DLBCL among the R+ (aIRR: 0.94, 95% CI: 0.51-1.74) and R−/D+ (0.90, 0.45-1.81) groups appeared more similar to the R−/D− group. There were no significant associations with other NHL subtypes.

For lymphoid leukemias overall, there was a non-significant inverse association for the R−/D+ group compared with the R−/D− group (aIRR: 0.65, 95%CI: 0.23-1.89). However, ALL risk did not differ for the R+ group (aIRR: 0.95, 95%CI: 0.23-3.85) and there were no cases among the R−/D+ group. The risk of myeloid leukemias did not differ across the CMV groups (Table 2).

We identified 11,831 incident solid cancer diagnoses. The most common were cancers of the lung (16.3%), prostate (13.3%), kidney (11.1%), colorectum (5.7%), and breast (5.6%). Incidence was not significantly elevated in the R+ and R−/D+ groups compared to the R−/D− group for most cancers (Table 3). Lung cancer incidence was higher among the R+ group than the R−/D− group (aIRR: 1.24, 95%CI: 1.05-1.46), but there was no statistical difference for the R−/D+ group (0.94, 0.77-1.14). In contrast, the R−/D+ group had lower incidence of small intestine cancer (aIRR: 0.23, 95%CI: 0.09-0.63) compared to the R−/D− group. The R+ group shared this inverse association, but the association was not significant (aIRR: 0.65, 95%CI: 0.37-1.16). None of the associations in Tables 2 or 3 met the Bonferroni p-value cutoff for significance.

Associations of CMV serostatus with DLBCL differed by time post-transplant (Figure 1). The greatest reduction in risk was seen immediately following transplantation (0-1.99 years) and 10+ post-transplant in both the R+ and R−/D+ groups compared to the R−/D− group. For the R+ group, this corresponded to a 37% reduction in risk 0-1.99 years following transplant (aIRR: 0.63, 95%CI: 0.42-0.94) and 34% reduction at 10+ years (0.66, 0.45-0.96). For the R−/D+ group, there was a nonsignificant reduction in risk 0-1.99 years post-transplant (aIRR: 0.73, 95%CI: 0.48-1.12) and a significant 51% reduction 10+ years post-transplant (0.49, 0.29-0.81).

CMV serostatus modified the association between EBV serostatus and DLBCL (p-interaction=0.0006, Figure 2 and Supplemental Table 1). In the absence of prior CMV infection (CMV R−/D− group), there was a significantly increased risk of DLBCL among EBV R−/D+ recipients compared to EBV R−/D− recipients (aIRR: 3.46, 95%CI: 1.50-7.95). In contrast, DLBCL risk was not significantly different among the EBV R−/D+ recipients in the CMV R+ or R−/D+ groups when compared to the recipients who were R−/D− for both CMV and EBV.

Discussion

Recipients of a solid organ transplant have an elevated risk of cancer, especially for malignancies caused by viral infections.[1-3] Virus-associated cancers include NHL and Hodgkin lymphoma (both due to EBV) and anogenital cancers (human papillomavirus).

CMV is among the most common viral infections following SOT and has been implicated in the development of PTLD and NHL. However, the relationship between CMV and other malignancies among transplant recipients not been studied.

Here we present the largest investigation of CMV infection as it relates to cancer among SOT recipients. We identified that recipient groups at moderate risk (R+) or high risk (R−/D+) of active CMV infection post-transplant both had decreased incidence of DLBCL and small intestine cancer compared to the group at lowest risk (R−/D−). In contrast, we found an elevated incidence of lung cancer among the moderate-risk group. However, there were no other significant associations between donor/recipient CMV serostatus and incidence of other cancers, including those for which CMV has been hypothesized to play a role.

Overall, recipients who were CMV seronegative at baseline tended to be younger than CMV seropositive recipients. This is consistent with other reports that demonstrate CMV seroprevalence gradually increases with age, such that nearly 70% of individuals 60 years of age and over are CMV seropositive.[27] Additionally, we found greater racial/ethnic diversity among the R+ group and a smaller proportion of individuals who had high SES. These trends are also consistent with other studies showing CMV seroprevalence to be associated with non-White race and lower income.[27,28]

We observed that moderate-risk and high-risk CMV groups had decreased incidence of DLBCL, which is the most common NHL subtype among transplant recipients.[29] This inverse association is contrary to previous findings on PTLD and NHL overall. In a retrospective study of 18,682 kidney transplant recipients, Opelz et al. found no significant differences in lymphoma rates according to CMV serostatus among either EBV seronegative or seropositive recipients.[14] However, hospitalization for CMV disease during the first year post-transplant was associated with increased NHL incidence. Similarly, Desai et al. also reported no association between CMV risk group and subsequent NHL.[15] In contrast, in a retrospective study of 37 liver transplant recipients who seroconverted to EBV, the development of active CMV disease infection post-transplant was associated with significantly increased PTLD risk.[13] All three of these studies were considerably smaller than our current study.

Although the inverse association that we observed between CMV risk group and DLBCL was unexpected, there may be a biological explanation. A retrospective cohort study of 105 kidney transplant recipients by Couzi et al., which included 23 incident cancer cases (13 skin cancers, 8 solid tumors, and 2 lymphomas), reported an inverse association between CMV risk group and cancer incidence.[19] In addition, they found that circulating levels of γδ T-cells were associated with lower cancer incidence. These T-cells are induced by CMV infection and are capable *in vitro* of killing myeloma and carcinoma cell lines.[30] While γδ T-cells may mediate a protective effect of CMV infection on development of DLBCL, it is unclear why such an effect would be limited to DLBCL and not present for other malignancies as well.

EBV infection is the most important risk factor for PTLD (including DLBCL) among transplant recipients.[31] When we restricted our analysis to the CMV low-risk group, we found that recipients who were EBV sero-mismatched (R−/D+) were nearly 3.5 times more likely to develop DLBCL than those who were low-risk for EBV (R−/D−). However, when the recipient had moderate- or high-risk of CMV status, the association of EBV and DLBCL was no longer present.We speculate that one possible explanation for this finding, and for the overall inverse association with CMV serostatus, is that prophylaxis or treatment of CMV infection with valganciclovir or immunoglobulin may have off-target efficacy against EBV infection. In support of this hypothesis, a retrospective cohort study of kidney recipients reported a complete absence of lymphomas in the first year after transplantation among those individuals who received anti-CMV immunoglobulin.[32] Similarly, a case-control study among EBV-seropositive kidney recipients found that ganciclovir prophylaxis was associated with significantly decreased risk of PTLD in the first year post-transplant.[33] In our analysis, we saw a protective effect of moderate- and high-risk CMV on DLBCL in the first two years after transplantation, which might similarly be explained by CMV prophylaxis. Furthermore, based on limited data, the inverse associations that we saw in our primary analysis were stronger for EBV+ DLBCL than EBV− DLBCL, which again supports the hypothesis that the decreased incidence of DLBCL is explained by anti-EBV effects of CMV prophylaxis. Unfortunately, we did not have data on CMV prophylaxis, which prevented us from directly testing this hypothesis in our study. In addition, the inverse associations at 10+ years post-transplant would not be explained by this mechanism.

Among solid tumors that we evaluated, only lung cancer showed an increased incidence in association with CMV risk group. However, the 24% elevation in lung cancer incidence among the moderate-risk CMV group was not accompanied by a parallel increase in the high-risk group. Smoking is the most important risk factor for lung cancer, and the observed association may be due to confounding since we did not have data on smoking status or tobacco use. In the general population, CMV has not been implicated in lung cancer.

The inverse association between CMV risk and small intestine cancer does not have a clear explanation. Several studies have suggested an association between CMV infection and an increased risk of colorectal cancer or gastrointestinal cancers overall.[34-36] In the general population, small intestine cancer is rare.[37] Transplant recipients have an elevated risk of small intestine cancer,[3] which is unexplained.

There are several strengths of our study. First, the large size of the Transplant Cancer Match Study enabled us to examine CMV and cancer risk in nearly 250,000 recipients, which is the largest study of CMV and cancer to our knowledge. Our study was nearly ten times larger than the study in the United Kingdom by Desai and colleagues,[15] which allowed for more precise estimates for rare cancers. Second, our study population is a representative sample of the US transplant population, so our results are generalizable. Third, CMV serostatus was measured prospectively in recipients and donors at the time of listing and donation, respectively. Lastly, the inclusion of Yost index data allowed us to demonstrate associations of CMV with SES in the transplant population and adjust for SES in our analyses of cancer risk.

The primary limitation of our study is the lack of data for CMV infection or disease following transplantation, which would allow for better characterization of the role of CMV in development of cancer. Follow-up data on CMV serostatus, which were available only for a small minority of recipients (<10%), do not accurately reflect active viral infection as defined by direct measures of CMV (e.g., polymerase chain reaction, culture, or antigen detection). We also did not have follow-up data on clinical illness due to CMV. As a result, we had limited information on CMV seroconversion rates and how they corresponded to CMV risk groups in regard to distinguishing between primary and reactivated infection. We therefore used baseline CMV IgG data for recipients and their donors to classify the recipients according to risk of active CMV infection after transplantation, which follows well-accepted clinical practice. In addition, EBV serostatus was missing for 22.3% of recipients at baseline, which may have affected the results of our DLBCL analyses. As for all studies using registry data, information on some important confounders, such as smoking, was missing. Some cancer outcomes were too rare to examine, including ALL (n=15) or subtypes of brain cancers. Lastly, our study is exploratory, and none of the associations met the Bonferroni p-value cutoff for significance, so some associations that we report could be due to chance.

Based on the findings our study, it appears likely that CMV plays little if any direct role in carcinogenesis after transplantation. Future work to characterize the immunologic profile in transplant recipients following CMV infection and reactivation using prospective data on CMV viremia may help in understanding possible adverse or protective cancer mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported in part by the Intramural Research Program of the National Cancer Institute.

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 Alabama (Justin George), Alaska (David O'Brien), Arkansas (Lunda Lehing), California (Cyllene Morris), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Florida (Brad Wohler), Georgia (Rana Bayakly), Hawaii (Brenda Hernandez), Idaho (Bożena Morawski), Illinois (Lori Koch), Iowa (Charles Lynch), Kentucky (Jaclyn McDowell), Louisiana (Meichin Hsieh), Michigan (Georgetta Alverson), Montana (Heather Zimmerman), Nebraska (Lifeng Li), Nevada (Ben Claassen), New Jersey (Xiaoling Niu), New Mexico (Angela Meisner), New York (Maria Schymura), North Carolina (Chandrika Rao), North Dakota (Yun Zeng), Ohio (Roberta Slocumb), Oklahoma (Espinoza Raffaella), Oregon (Jeff Soule), Pennsylvania (Jim Rubertone), Puerto Rico (Carlos Cintron), Rhode Island (Junhie Oh), South Carolina (Deborah Hurley), Texas (Leticia Nogueria), Utah (Jen Doherty), Virginia (Shuhui Wang), 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 75R60220C00011 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), Idaho (HHSN261201800006I), Illinois (75N91021D00006), Iowa (HSN261201000032C, N01-PC-35143, HHSN261201800012I), Kentucky (HHSN261201800013I), New Jersey (75N91021D00009), New York (75N91018D00005 [Task Order 75N91018F00001]), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN261201800016I). 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), Idaho (1NU58DP006270), Illinois (5U58DP003883-03), Michigan (5U58DP003921-03), New Jersey (5NU58DP006279-02-00), New Mexico (HHSN261201800014I, Task Order HHSN26100001), New York (6NU58DP006309), North Carolina (U58DP003933), North Dakota (NU58DP006317-05-01), Ohio (NU58DP006284), Oregon (NU58DP006288), Texas (5U58DP000824-04), and Utah (NU58DP006320). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, Montana (5 NU58DP006339-05-00), New Jersey, New York (including the Cancer Surveillance Improvement Initiative), Texas, and Fred Hutchinson Cancer Research Center in Seattle, WA.

Funding

Jennifer Geris was supported by a fellowship from the Institute for Molecular Virology Training Program at the University of Minnesota by the National Institute of Health (T32 AI083196). Ajit Limaye was supported by a grant by the National Institute of Allergy and Infectious Diseases (NIAID U0AI163090). This research was supported in part by the Intramural Research Program of the National Cancer Institute.

References

1. Vanichanan J, Udomkarnjananun S, Avihingsanon Y, Jutivorakool K. Common viral infections in kidney transplant recipients. Kidney Res Clin Pract. 2018;37(4):323–337. doi:10.23876/j.krcp.18.0063 [PubMed: 30619688]
2. Vajdic CM, McDonald SP, McCredie MRE, et al. Cancer incidence before and after kidney transplantation. J Am Med Assoc. 2006;296(23):2823–2831. doi:10.1001/jama.296.23.2823
3. Engels EA, Pfeiffer RM, Fraumeni JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA - J Am Med Assoc. 2011;306(17):1891–1901. doi:10.1001/jama.2011.1592
4. Jackson SE, Mason GM, Wills MR. Human cytomegalovirus immunity and immune evasion. Virus Res. 2011;157(2):151–160. doi:10.1016/j.virusres.2010.10.031 [PubMed: 21056604]
5. Dupont L, Reeves MB. Cytomegalovirus latency and reactivation: recent insights into an age old problem. Rev Med Virol. 2016;26(2):75–89. doi:10.1002/rmv.1862 [PubMed: 26572645]
6. Simon DM, Levin S. Infectious complications of solid organ transplantations. Infect Dis Clin North Am. 2001;15(2):521–549. doi:10.1016/S0891-5520(05)70158-6 [PubMed: 11447708]
7. Hughes D, Hafferty J, Fulton L, et al. Donor and recipient CMV serostatus and antigenemia after renal transplantation: An analysis of 486 patients. J Clin Virol. 2008;41(2):92. doi:10.1016/J.JCV.2007.10.006 [PubMed: 18032098]
8. Hirata M, Teraski I, Cho Y. Cytomegalovirus antibody status and renal transplantation: 1987-1994. Transplantation. 1996;62(1):34–37. doi:10.1097/00007890-199607150-00007 [PubMed: 8693540]
9. Humar A, Snydman D. Cytomegalovirus in Solid Organ Transplant Recipients. Vol 9. Am J Transplant; 2009. doi:10.1111/J.1600-6143.2009.02897.X
10. Fishman JA, Emery V, Freeman R, et al. Cytomegalovirus in transplantation - Challenging the status quo. Clin Transplant. 2007;21(2):149–158. doi:10.1111/j.1399-0012.2006.00618.x [PubMed: 17425738]
11. Aucejo F, Rofaiel G, Miller C. Who is at risk for post-transplant lymphoproliferative disorders (PTLD) after liver transplantation? J Hepatol. 2006;44(1):19–23. doi:10.1016/j.jhep.2005.10.008 [PubMed: 16298453]
12. Walker R, Marshall W, Strickler J, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis. 1995;20(5):1346–1353. doi:10.1093/CLINIDS/20.5.1346 [PubMed: 7620022]
13. Mañez R, Breinig MC, Linden P, et al. Posttransplant Lymphoproliferative Disease in Primary Epstein-Barr Virus Infection after Liver Transplantation: The Role of Cytomegalovirus Disease. J Infect Dis. 1997;176(6):1462–1467. doi:10.1086/514142 [PubMed: 9395355]

14. Opelz G, Daniel V, Naujokat C, Döhler B. Epidemiology of Pretransplant EBV and CMV Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma. Transplantation. 2009;88(8):962–967. doi:10.1097/TP.0b013e3181b9692d [PubMed: 19855238]
15. Desai R, Collett D, Watson CJE, Johnson PJ, Moss P, Neuberger J. Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk after Organ Transplantation. Transplantation. 2015;99(9):1989–1994. doi:10.1097/TP.0000000000000641 [PubMed: 25706273]
16. Cinatl J, Cinatl J, Vogel J-U, Rabenau H, Kornhuber B, Doerr HW. Modulatory Effects of Human Cytomegalovirus Infection on Malignant Properties of Cancer Cells. Intervirology. 1996;39(4):259–269. doi:10.1159/000150527 [PubMed: 9078467]
17. Cinatl J, Scholz M, Kotchetkov R, Vogel JU, Doerr HW. Molecular mechanisms of the modulatory effects of HCMV infection in tumor cell biology. Trends Mol Med. 2004;10(1):19–23. doi:10.1016/J.MOLMED.2003.11.002 [PubMed: 14720582]
18. Harkins L, Matlaf L, Soroceanu L, et al. Detection of human cytomegalovirus in normal and neoplastic breast epithelium. Herpesviridae. 2010;1(1). doi:10.1186/2042-4280-1-8
19. Couzi L, Levaillant Y, Jamai A, et al. Cytomegalovirus-Induced γδ T Cells Associate with Reduced Cancer Risk after Kidney Transplantation. J Am Soc Nephrol. 2010;21(1):181–188. doi:10.1681/ASN.2008101072 [PubMed: 19713314]
20. Francis SS, Wallace AD, Wendt GA, et al. In utero cytomegalovirus infection and development of childhood acute lymphoblastic leukemia. Blood. 2017;129(12):1680–1684. doi:10.1182/blood-2016-07-723148 [PubMed: 27979823]
21. Wiemels JL, Talbäck M, Francis S, Feychting M. Early Infection with Cytomegalovirus and Risk of Childhood Hematologic Malignancies. Cancer Epidemiol Biomarkers Prev. 2019;28(6):1024–1027. doi:10.1158/1055-9965.EPI-19-0044 [PubMed: 30996022]
22. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC: Lyon 2008.; 2008.
23. Site Recode ICD-O-3/WHO 2008 - SEER Data Reporting Tools. https://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html. Accessed August 25, 2021.
24. Turner J, Morton L, Linet M, et al. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. Blood. 2010;116(20). doi:10.1182/BLOOD-2010-06-289561
25. Azevedo LS, Pierrotti LC, Abdala E, et al. Cytomegalovirus Infection in Transplant Recipients. Vol 70.; 2015:515–523. /pmc/articles/PMC4496754/?report=abstract. Accessed January 21, 2020.
26. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control. 2001;12(8):703–711. doi:10.1023/A:1011240019516 [PubMed: 11562110]
27. Staras SAS, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. Clin Infect Dis. 2006;43(9):1143–1151. doi:10.1086/508173/2/43-9-1143-TBL003.GIF [PubMed: 17029132]
28. Dowd JB, Aiello AE, Alley DE. Socioeconomic disparities in the seroprevalence of cytomegalovirus infection in the US population: NHANES III. Epidemiol Infect. 2009;137(1):58–65. doi:10.1017/S0950268808000551 [PubMed: 18413004]
29. Gibson TM, Engels EA, Clarke CA, Lynch CF, Weisenburger DD, Morton LM. Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States. Am J Hematol. 2014;89(7):714–720. doi:10.1002/ajh.23726 [PubMed: 24753070]
30. Ferrarini M, Ferrero E, Dagna L, Poggi A, Zocchi MR. Human gammadelta T cells: a nonredundant system in the immune-surveillance against cancer. Trends Immunol. 2002;23(1):14–18. doi:10.1016/S1471-4906(01)02110-X [PubMed: 11801449]
31. Preiksaitis JK, Keay S. Diagnosis and management of posttransplant lymphoproliferative disorder in solid-organ transplant recipients. Clin Infect Dis. 2001;33 Suppl 1. doi:10.1086/320903
32. Opelz G, Daniel V, Naujokat C, Fickenscher H, Döhler B. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis. Lancet Oncol. 2007;8(3):212–218. doi:10.1016/S1470-2045(07)70040-2 [PubMed: 17329191]

33. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant. 2005;5(12):2894–2900. doi:10.1111/J.1600-6143.2005.01115.X [PubMed: 16303002]

34. Lv YL, Han FF, An ZL, et al. Cytomegalovirus Infection Is a Risk Factor in Gastrointestinal Cancer: A Cross-Sectional and Meta-Analysis Study. Intervirology. 2020;63(1-6):10–16. doi:10.1159/000506683 [PubMed: 32772018]

35. Zhang L, Guo G, Xu J, et al. Human cytomegalovirus detection in gastric cancer and its possible association with lymphatic metastasis. Diagn Microbiol Infect Dis. 2017;88(1):62–68. doi:10.1016/J.DIAGMICROBIO.2017.02.001 [PubMed: 28238538]

36. Bai B, Wang X, Chen E, Zhu H. Human cytomegalovirus infection and colorectal cancer risk: a meta-analysis. Oncotarget. 2016;7(47):76735. doi:10.18632/ONCOTARGET.12523 [PubMed: 27732934]

37. Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969–2019). National Cancer Institute, DCCPS, Surveillance Research Program. www.seer.cancer.gov/popdata. Published 2021.

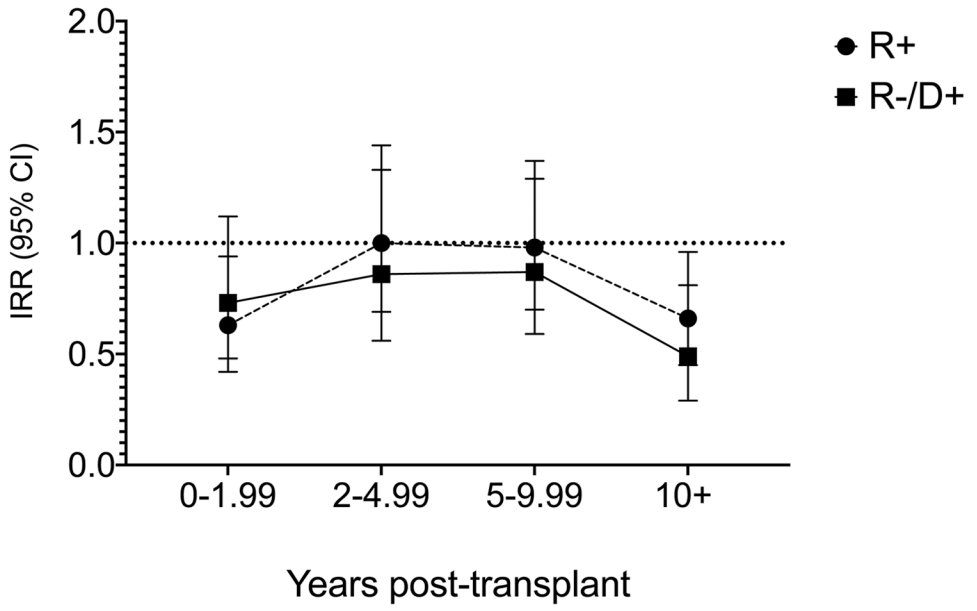

Figure 1: Associations of diffuse large B-cell lymphoma with CMV risk group as a function of time since transplantation.

Incidence rate ratios and 95% confidence intervals of CMV risk groups compared to R−/D− group. Abbreviations: CI – confidence interval; IRR – incidence rate ratio;

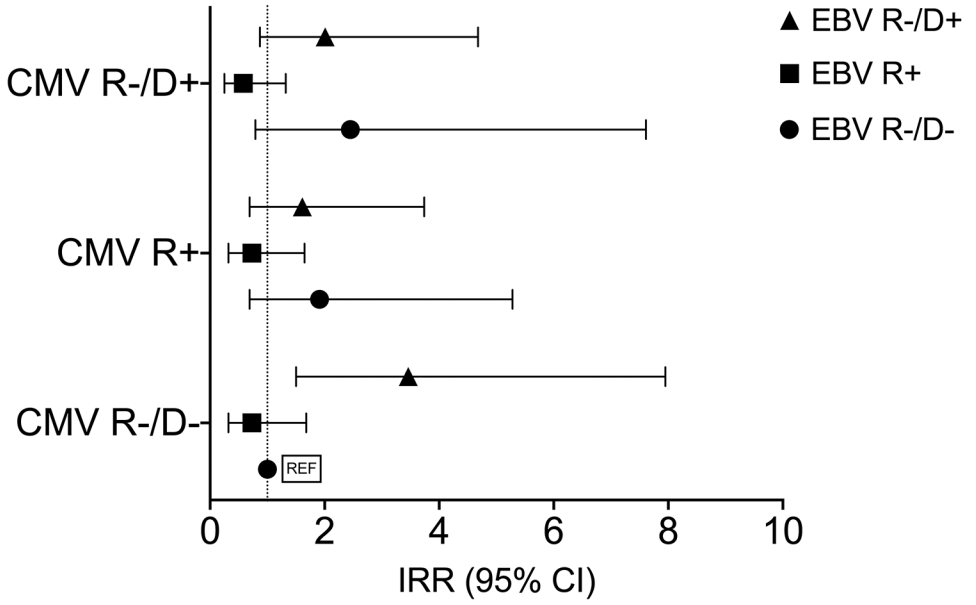

Figure 2: Interaction between CMV and EBV risk groups and the risk of DLBCL.

The model is adjusted for recipient sex, age (0-17, 18-34, 35-49, 50-64, 65+ years), race/ethnicity, organ type (kidney, liver, other/multiple), and SES quintile. Abbreviations:CI – confidence interval; EBV – Epstein-Barr virus; IRR – incidence rate ratio; REF – reference;

Table 1:

Characteristics of US solid organ transplant recipients, according to recipient and donor CMV serostatus

		CMV status (recipient/donor)			
Characteristic	**Total**	**R+**	**R−/D+**	**R−/D−**	**p-value**
Total	247,318 (100%)	155,666 (62.9%)	50,134 (20.3%)	41,518 (16.8%)	
Sex					<0.0001
Male	151,418 (61.2%)	89,912 (57.8%)	33,763 (67.4%)	27,743 (66.8%)	
Female	95,900 (38.8%)	65,754 (42.2%)	16,371 (32.7%)	13,775 (33.2%)	
Age at transplant, years					<0.0001
0-17	16,931 (6.9%)	6,536 (4.2%)	5,458 (10.9%)	4,937 (11.9%)	
18-34	31,215 (12.6%)	17,237 (11.1%)	7,417 (14.8%)	6,561 (15.8%)	
35-49	65,203 (26.4%)	40,006 (25.7%)	13,694 (27.3%)	11,503 (27.7%)	
50-64	100,690 (40.7%)	67,639 (43.4%)	18,405 (36.7%)	14,646 (35.3%)	
65 - 96	33,279 (13.5%)	24,248 (15.6%)	5,160 (10.3%)	3,871 (9.3%)	
Median age, years (IQR)	51 (21)	53 (19)	48 (24)	47 (25)	<0.0001
Race/ethnicity					<0.0001
Non-Hispanic White	139,662 (56.5%)	73,556 (47.3%)	34,842 (69.5%)	31,264 (75.3%)	
Non-Hispanic Black	48,700 (19.7%)	35,704 (22.9%)	7,668 (15.3%)	5,328 (12.8%)	
Hispanic	41,275 (16.7%)	31,373 (20.2%)	6,032 (12.0%)	3,870 (9.3%)	
Asian/Pacific Islander	14,959 (6.0%)	13,104 (8.4%)	1,117 (2.2%)	738 (1.8%)	
Other/unknown	2,722 (1.1%)	1,929 (1.2%)	475 (1.0%)	318 (0.8%)	
Transplanted *o*rgan					<0.0001
Kidney	151,781 (61.4%)	97,980 (62.9%)	27,842 (55.5%)	25,959 (62.5%)	
Liver	41,027 (16.6%)	26,438 (17.0%)	8,641 (17.2%)	5,948 (14.3%)	
Other/multiple	54,510 (22.0%)	31,248 (20.1%)	13,651 (27.2%)	9,611 (23.2%)	
Calendar *y*ear of transplant					<0.0001
2000-2004	68,520 (27.1%)	43,301 (27.8%)	13,402 (26.7%)	11,817 (28.5%)	
2005-2009	76,317 (30.9%)	48,330 (31.1%)	15,748 (31.4%)	12,239 (29.5%)	
2010-2014	66,930 (27.1%)	42,053 (27.0%)	13,642 (27.2%)	11,235 (27.1%)	
2015-2017	35,551 (14.4%)	21,982 (14.1%)	7,342 (14.6%)	6,227 (15.0%)	
Education *s*tatus (for recipients >21 years old)					<0.0001
None	1,008 (0.4%)	864 (0.6%)	97 (0.2%)	47 (0.1%)	
Grade school	11,767 (5.2%)	10,141 (6.9%)	1,005 (2.3%)	621 (1.7%)	
High school	85,025 (37.5%)	57,267 (38.9%)	15,523 (35.5%)	12,235 (34.2%)	
Attended college/technical school	51,633 (22.8%)	31,869 (21.6%)	10,909 (24.9%)	8,855 (24.7%)	

		CMV status (recipient/donor)			
Characteristic	**Total**	**R+**	**R−/D+**	**R−/D−**	**p-value**
Associate's/bachelor's degree	35,904 (15.8%)	20,633 (14.0%)	8,060 (18.4%)	7,211 (20.1%)	
Post-graduate degree	15,088 (6.6%)	8,497 (5.8%)	3,410 (7.8%)	3,181 (8.9%)	
Unknown	26,440 (11.7%)	18,066 (12.3%)	4,730 (10.8%)	3,644 (10.2%)	
Yost SES quintile					p<0.0001
1: Lowest	46,236 (18.7%)	32,573 (20.9%)	7,952 (15.9%)	5,711 (13.8%)	
2: Low	46,313 (18.7%)	30,145 (19.4%)	8,976 (17.9%)	7,192 (17.3%)	
3: Mid	48,147 (19.5%)	30,676 (19.7%)	9,652 (19.3%)	7,819 (18.3%)	
4: High	48,492 (19.6%)	29,127 (18.7%)	10,480 (20.9%)	8,885 (21.4%)	
5: Highest	46,458 (18.8%)	26,570 (17.1%)	10,527 (21.0%)	9,361 (22.6%)	
Unknown	11,672 (4.7%)	6,575 (4.2%)	2,547 (5.1%)	2,550 (6.1%)	
Induction regimen					<0.0001
Any induction therapy	200,870 (81.2%)	127,342 (81.8%)	39,975 (79.7%)	33,553 (80.8%)	
Polyclonal antibody	79,172 (32.1%)	51,057 (32.8%)	15,117 (30.2%)	12,998 (31.3%)	
Monoclonal antibody	1,329 (0.5%)	832 (0.5%)	274 (0.6%)	223 (0.5%)	
IL2 receptor antagonist	69,336 (28.0%)	43,297 (27.8%)	14,358 (28.6%)	11,681 (28.1%)	
Alemtuzumab	16,320 (6.6%)	10,130 (6.5%)	3,156 (6.3%)	3,034 (7.3%)	
Rituximab	1,169 (0.5%)	817 (0.5%)	191 (0.4%)	161 (0.4%)	
Corticosteroids	159,714 (64.6%)	101,768 (65.4%)	31,659 (63.2%)	26,287 (63.3%)	
Maintenance immunosuppression					0.0001
Tacrolimus and/or MMF	204,673 (82.8%)	129,657 (83.3%)	40,993 (81.8%)	34,023 (82.0%)	
Cyclosporine and/or azathioprine	8,840 (3.6%)	5,131 (3.3%)	2,064 (4.1%)	1,645 (4.0%)	
Other CNI/antimetabolite combination	33,805 (13.7%)	20,878 (13.4%)	7,077 (14.1%)	5,850 (14.1%)	
mTOR inhibitor	15,453 (6.3%)	9,190 (5.9%)	3,265 (6.5%)	2,998 (7.2%)	
Corticosteroids	193,151 (78.1%)	122,479 (78.7%)	39,228 (78.3%)	31,444 (74.7%)	
EBV serostatus (recipient)					0.0001
Positive	161,715 (65.4%)	104,973 (67.4%)	30,928 (61.7%)	25,814 (62.2%)	
Negative	30,561 (12.4%)	14,013 (9.0%)	8,839 (17.6%)	7,709 (18.6%)	
Unknown	55,042 (22.3%)	36,680 (23.6%)	10,367 (20.7%)	7,995 (19.3%)	
EBV serostatus (donor)					0.0001
Positive	143,044 (57.8%)	89,392 (57.4%)	30,046 (59.9%)	23,606 (56.9%)	
Negative	12,559 (5.1%)	7,098 (4.6%)	1,770 (3.5%)	3,691 (8.9%)	
Unknown	91,715 (37.1%)	59,176 (38.0%)	18,318 (36.5%)	14,221 (34.3%)	

All entries are N (%) unless otherwise noted. All percentages are column percentages except for totals (row percentages). Abbreviations: CNI – calcineurin inhibitor; MMF - mycophenolate mofetil; P-values calculated by Pearson's Chi-Square test.

Table 2:

Risk of hematologic malignancies according to CMV recipient/donor status

	CMV status (recipient/donor)									
	Total		R−/D− (Reference)		R+			R−/D+		
Cancer group	**N**	**IR**	**N**	**IR**	**N**	**IR**	**Adjusted IRR (95% CI)**	**N**	**IR**	**Adjusted IRR (95% CI)**
Hodgkin lymphoma	61	4.9	19	8.8	21	2.69	0.47 (0.19-1.18)	21	8.5	0.75 (0.29-1.96)
Non-Hodgkin lymphoma	270	21.7	48	22.2	164	21	1.36 (0.66-2.80)	58	23.5	1.56 (0.74-3.30)
DLBCL	1193	95.8	267	123.6	680	86.9	0.83 (0.69-1.00)	246	99.5	0.74 (0.59-0.91)
EBV+ DLBCL	274	22.0	76	35.2	137	17.5	0.74 (0.52-1.08)	61	24.7	0.66 (0.44- 1.01)
EBV− DLBCL	115	9.2	27	12.5	67	8.6	0.94 (0.51-1.74)	21	8.5	0.90 (0.45-1.81)
Burkitt lymphoma	101	8.1	22	10.2	53	6.8	1.36 (0.66-2.80)	26	10.5	1.56 (0.74-3.30)
Follicular lymphoma	39	3.1	9	4.2	21	2.7	0.94 (0.29-3.01)	9	3.6	1.48 (0.43-5.09)
Lymphoplasmacytic lymphoma	12	1.0	1	0.5	11	1.4	-	0	-	-
Mantle cell lymphoma	10	0.8	2	0.9	7	0.9	-	1	0.4	-
Marginal zone lymphoma	61	4.9	11	5.1	39	5.0	0.79 (0.34-1.82)	11	4.4	0.53 (0.17-1.64)
Peripheral T-cell lymphoma	49	3.9	10	4.6	26	3.3	0.71 (0.28-1.80)	13	5.3	0.98 (0.35-2.73)
ALCL	23	1.8	5	2.3	10	1.3	0.70 (0.13-3.73)	8	3.2	1.62 (0.30-8.90)
Mycosis fungoides/ Sézary's syndrome	16	1.3	3	1.4	9	1.2	0.92 (0.17-4.88)	4	1.6	0.82 (0.11-5.87)
Precursor B- or T-cell lymphoblastic leukemia/lymphoma	12	1.0	4	1.9	6	0.8	0.60 (0.13-2.71)	2	0.8	0.23 (0.02-2.19)
Lymphoid leukemia	67	5.4	14	6.5	40	5.1	0.97 (0.42-2.24)	13	5.3	0.65 (0.23-1.89)
ALL	15	1.2	4	1.9	11	1.4	0.95 (0.23-3.85)	0	-	-
CLL/SLL	52	4.2	10	4.6	29	3.7	0.98 (0.35-2.79)	13	5.3	1.06 (0.32-3.49)
Myeloid leukemia	171	13.7	25	11.6	116	14.8	1.39 (0.79-2.43)	30	12.1	1.08 (0.56-2.07)
AML	112	9.0	13	6.0	76	9.7	1.83 (0.84-3.95)	23	9.3	1.58 (0.67-3.70)
CML	59	4.7	12	5.6	40	5.1	0.93 (0.41-2.14)	7	2.8	0.54 (0.18-1.66)
Other leukemia	18	1.4	3	1.4	11	1.4	3.02 (0.37-24.93)	4	1.6	1.72 (0.16-19.03)
Aleukemic, subleukemic and NOS	20	1.6	4	1.9	10	1.3	0.55 (0.16-1.92)	6	2.4	0.76 (0.19-3.06)
Myeloma	216	17.3	32	14.8	145	18.5	0.94 (0.59-1.51)	39	15.8	0.82 (0.46-1.46)

Incidence rates are per 100,000 person-years. Adjusted IRR models include adjustment for recipient sex, age (0-17, 18-34, 35-49, 50-64, 65+ years), race/ethnicity, organ type (kidney, liver, other/multiple), EBV recipient/donor status (EBV R−/D−, EBV R+, EBV R−/D+), and SES quintile. Significant associations are underlined.

Abbreviations: ALCL – anaplastic large cell lymphoma; ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CI - confidence interval; CLL/SLL - chronic lymphocytic leukemia / small lymphocytic lymphoma; CML – chronic myeloid leukemia ; DLBCL – diffuse B cell lymphoma; IR- incidence rate; IRR – incidence rate ratio; NOS- not otherwise specified.

Table 3:

Risk of solid cancers according to CMV recipient/donor status

	CMV status (recipient/donor)									
	Total		R−/D− (Reference)		R+			R−/D+		
Cancer group	**N**	**IR**	**N**	**IR**	**N**	**IR**	**Adjusted IRR (95% CI)**	**N**	**IR**	**Adjusted IRR (95% CI)**
Lip	104	8.4	25	11.6	45	5.8	0.66 (0.37-1.18)	34	13.8	1.03 (0.56-1.92)
Tongue	140	11.2	27	12.5	77	9.9	1.03 (0.59-1.80)	36	14.6	0.90 (0.47-1.74)
Salivary gland	60	4.8	12	5.6	39	5.0	0.87 (0.37-2.02)	9	3.6	0.74 (0.27-2.05)
Other oral cavity and pharynx	205	16.5	33	15.3	124	15.90	1.11 (0.67-1.84)	48	19.4	1.17 (0.66-2.06)
Esophagus	151	12.1	34	15.7	94	12.0	0.78 (0.45-1.34)	23	9.3	0.78 (0.41-1.50)
Stomach	223	17.9	21	9.7	167	21.4	1.73 (0.96-3.12)	35	14.2	1.13 (0.56-2.30)
Small intestine	103	8.3	19	8.8	72	9.2	0.65 (0.37-1.16)	12	4.9	0.23 (0.09-0.63)
Colorectum	674	54.1	102	47.2	434	55.5	1.17 (0.88-1.56)	138	55.8	1.23 (0.89-1.70)
Anus	119	9.6	12	5.6	86	11.0	1.24 (0.60-2.59)	21	8.5	1.05 (0.44-2.50)
Liver	296	23.8	31	14.4	217	27.8	1.37 (0.86-2.17)	48	19.4	0.81 (0.46-1.45)
Intrahepatic Bile Duct	75	6.0	9	4.2	43	5.5	1.38 (0.52-3.67)	23	9.3	2.13 (0.76-6.00)
Pancreas	300	24.1	47	21.8	202	25.8	1.06 (0.70-1.62)	51	20.6	0.98 (0.59-1.61)
Nose, middle ear, and larynx	164	13.2	19	8.8	110	14.1	1.62 (0.84-3.09)	35	14.2	1.22 (0.57-2.61)
Lung	1932	155.1	274	126.8	1347	172.2	1.24 (1.05-1.46)	311	125.8	0.94 (0.77-1.14)
Soft tissue and heart	109	8.8	13	6.0	68	8.7	1.24 (0.63-2.44)	28	11.3	1.50 (0.72-3.15)
Melanoma	557	44.7	125	57.9	308	39.4	0.86 (0.67-1.11)	124	50.2	0.83 (0.61-1.12)
Skin (non-melanoma, non-epithelial)	254	20.4	51	23.6	157	20.1	0.94 (0.61-1.43)	46	18.6	0.89 (0.54-1.47)
Breast	663	53.2	103	47.7	464	59.3	0.86 (0.65-1.14)	96	38.8	0.75 (0.52-1.07)
Genital sites	136	10.9	19	8.8	98	12.5	1.19 (0.64-2.19)	19	7.7	0.90 (0.42-1.92)
Prostate	1578	126.7	262	121.3	1044	133.5	1.12 (0.93-1.34)	272	110.0	0.86 (0.69-1.08)
Bladder	314	25.2	42	19.4	194	24.8	1.43 (0.92-2.22)	78	31.6	1.58 (0.97-2.57)
Kidney	1316	105.7	196	90.7	895	114.4	1.01 (0.83-1.24)	225	91.0	0.89 (0.70-1.13)
Brain and nervous system	89	7.2	17	7.9	58	7.4	0.89 (0.46-1.69)	14	5.7	0.60 (0.25-1.40)
Thyroid	387	31.1	69	31.9	248	31.7	0.95 (0.66-1.37)	70	28.3	1.07 (0.70-1.62)

	CMV status (recipient/donor)									
	Total		R−/D− (Reference)		R+			R−/D+		
Cancer group	**N**	**IR**	**N**	**IR**	**N**	**IR**	**Adjusted IRR (95% CI)**	**N**	**IR**	**Adjusted IRR (95% CI)**
Kaposi sarcoma	93	7.5	5	2.3	80	10.2	2.13 (0.84-5.44)	8	3.2	0.80 (0.23-2.76)
Miscellaneous	1789	143.7	295	136.6	1109	141.8	0.98 (0.83-1.15)	385	155.7	0.98 (0.81-1.18)

Adjusted IRR models include adjustment for recipient sex, age (0-17, 18-34, 35-49, 50-64, 65+ years), race/ethnicity, organ type (kidney, liver, other/multiple), EBV recipient/donor status (EBV R−/D−, EBV R+, EBV R−/D+), and SES quintile. Significant associations are underlined.

Abbreviations: IR – incidence rate; IRR – incidence rate ratio.