

Increased Risk for Lymphoid and Myeloid Neoplasms in Elderly Solid-Organ Transplant Recipients

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Abstract

Background: By assessing the spectrum of hematologic malignancies associated with solid-organ transplantation in the elderly, we provide information on the pathogenesis of lymphoid and myeloid neoplasms and the clinical manifestations of immunosuppression.

Methods: Using data from the U.S. Surveillance, Epidemiology, and End Results Medicare database, we identified 83,016 cases with a hematologic malignancy (age 66-99 years) and 166,057 population-based controls matched to cases by age, sex, and calendar year. Medicare claims were used to identify a history of solid-organ transplantation. We used polytomous logistic regression to calculate odds ratios (OR) comparing transplantation history among cases with various hematologic malignancy subtypes and controls, adjusting for the matching factors and race.

Results: A prior solid-organ transplant was identified in 216 (0.26%) cases and 204 (0.12%) controls. Transplantation was associated with increased risk for non-Hodgkin lymphomas [OR, 2.13; 95% confidence interval (95% CI), 1.67-2.72], especially diffuse large B-cell lymphoma (OR, 3.29; 95% CI, 2.28-4.76), marginal zone lymphoma (OR, 2.48; 95% CI, 1.17-5.22), lymphoplasmacytic lymphoma (OR, 3.32; 95% CI, 1.41-7.81), and T-cell lymphoma (OR, 3.07; 95% CI, 1.56-6.06). Transplantation was also associated with elevated risk of Hodgkin lymphoma (OR, 2.53; 95% CI, 1.01-6.35) and plasma cell neoplasms (OR, 1.91; 95% CI, 1.24-2.93). Risks for myeloid neoplasms were also elevated (OR, 1.99; 95% CI, 1.41-2.81).

Conclusion: Solid-organ transplantation is associated with a wide spectrum of hematologic malignancies in the elderly. Risk was increased for four specific non-Hodgkin lymphoma subtypes for which a viral agent has been implicated, supporting an added role for immunosuppression.

Impact: Our results support monitoring for a wide spectrum of hematologic malignancies following solid-organ transplant. *Cancer Epidemiol Biomarkers Prev*; 19(5); 1229-37. ©2010 AACR.

Introduction

Hematologic malignancies are a diverse group of leukemias, lymphomas, and related proliferative disorders characterized by heterogeneity in clinical presentation, pathology and molecular characteristics, and treatment. Although the etiology of many subtypes is not fully understood, one factor that seems to play an etiologic role in multiple hematologic malignancy subtypes is immunodeficiency. Persons infected with HIV are at in-

creased risk of these malignancies, particularly non-Hodgkin lymphomas (NHL), which may result from uncontrolled proliferation of EBV-infected lymphocytes (1, 2). Nonetheless, recent research has shown etiologic heterogeneity among NHL subtypes, and immune dysfunction seems to affect some subtypes more than others (3, 4). In addition, the role of immunodeficiency in the development of other hematologic malignancy subtypes, such as myeloid neoplasms, is less well understood.

Solid-organ transplantation is a life-saving treatment for people with end-stage organ disease. The number of solid-organ transplants performed annually in the United States has increased steadily over the past two decades, with 28,291 transplants performed in 2006 (5). In addition, the number of persons living with a functioning transplanted organ has increased due to improved post-transplant survival (5). Solid-organ transplant recipients have an elevated risk of NHL due to immunosuppressive medications that they receive to prevent rejection of the allograft (1, 6-10). NHLs represent one component of a spectrum of lymphoid proliferations arising in transplant

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doi: 10.1158/1055-9965.EPI-09-1220

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recipients, termed posttransplant lymphoproliferative disorder (PTLD; refs. 11-13). These disorders also include Hodgkin lymphoma and multiple myeloma, as well as nonmalignant lymphoproliferations. Most NHLs in transplant recipients seem to be high-grade subtypes such as diffuse large B-cell lymphoma (DLBCL; refs. 14, 15), and many are EBV positive (13). Nonetheless, due to inclusion of small numbers of NHL cases with limited information, studies have been unable to delineate which NHL subtypes are most strongly increased in incidence. In addition, very little is known about the effect of transplant-related immunosuppression on myeloid neoplasms and lymphoid neoplasms other than NHL.

A systematic evaluation of hematologic malignancy risk following solid-organ transplantation will be helpful in better understanding the role of immunosuppression in lymphomagenesis and leukemogenesis. Furthermore, demonstration of an elevated risk for specific subtypes of hematologic malignancies after transplantation may affect follow-up and treatment of transplant recipients. The Surveillance, Epidemiology, and End Results (SEER)-Medicare data set provides data on elderly cancer patients (including 80,000 cases with hematologic malignancies), including linked claims for medical care before cancer diagnosis, and thus offers a unique resource to expand on prior research in this area. We used these data to conduct a case-control study examining associations between specific hematologic malignancy subtypes and prior solid-organ transplantation among older adults.

Materials and Methods

SEER-Medicare data set. The National Cancer Institute SEER cancer surveillance program provides population-based data on incident malignancies diagnosed in 1973-2002 for multiple state and metropolitan areas, currently covering approximately 26% of the U.S. population (16). Medicare is a federally funded program providing health insurance for approximately 97% of persons ages 65 y or older in the United States (17). Ninety-eight percent of Medicare beneficiaries receive Part A coverage for inpatient hospital stays, nursing facilities, and home health and hospice care, and 95% of beneficiaries pay for Part B coverage, which covers physician and outpatient services (17). Medicare also provides health insurance for individuals under the age of 65 years with end-stage renal disease (ESRD) or disability.

Details of the SEER-Medicare linked data set are provided elsewhere (17). In summary, incident cancers reported to SEER registries were linked to Medicare enrollment and claims files. The SEER-Medicare database includes demographic and clinical information on all newly diagnosed cancer cases living in SEER areas during 1973-2002. Inpatient hospitalization claims are available for 1986-2002, and physician and outpatient claims for 1991-2002. In addition, Medicare claims data for persons who do not have cancer are available from

a 5% random sample of Medicare beneficiaries living in SEER areas.

Selection of cases and controls. As previously described, the SEER-Medicare Assessment of Hematopoietic Malignancy Risk Traits (SMAHRT) Study is a population-based, case-control study of hematologic malignancies using SEER-Medicare data (18). Individuals diagnosed with a SEER-registered hematologic malignancy as a first malignancy during 1987-2002, ages 66 to 99 years, and with at least 12 months of non-health maintenance organization (HMO) Medicare coverage before diagnosis were included as cases. We required at least 12 months of coverage to ensure that cases had sufficient time to accrue Medicare claims before diagnosis. Non-HMO Medicare coverage was required because HMOs do not routinely submit separate claims for individual diagnoses and procedures.

Lymphoproliferative malignancies were grouped according to a hierarchical system based on the WHO classification (19). NHLs were classified as either nodal or extranodal using International Classification of Diseases for Oncology topography codes (20). Myeloproliferative malignancies were classified as acute myeloid leukemia, chronic myeloid leukemia, myelodysplastic syndrome, or chronic myeloproliferative disorder (18).

For each case, two controls were randomly selected from the 5% random sample of Medicare recipients living in SEER areas. Controls were alive and cancer-free as of July 1 of the calendar year of selection and had at least 12 months of non-HMO Medicare coverage before selection. Controls were frequency matched to cases on calendar year of selection, age in five strata (66-69, 70-74, 75-79, 80-84, and 85-99 years), and gender. Under this sampling scheme, the same person could be selected as a control in different calendar years or as a control in years before being diagnosed with a hematologic malignancy. After selection, cases and controls with Medicare claims evidencing HIV infection were excluded ($n = 97$ cases and $n = 169$ controls).

Ascertainment of history of solid-organ transplant. We reviewed Medicare claims data for the period before diagnosis/selection to determine whether cases and controls had had a history of solid-organ transplantation, based on three types of evidence (i.e., transplant procedure, history of transplant, or complication of transplant). Specifically, a subject was considered to have had a solid-organ transplantation based on a hospital claim indicating the diagnosis-related group code for a transplant procedure (kidney: 302, heart: 103, lung: 495, liver: 480). In addition, we identified people with prior transplants who had at least one hospital, physician, or outpatient claim indicating a prior history or unspecified complication of transplantation (International Classification of Diseases, version 9 codes: kidney V42.0, 996.81; heart V42.1, 996.83; lung V42.6, 996.84; liver V42.7, 996.82; ref. 21). We included Medicare claims before age 65 years, which could have been present if the person was covered at that time due to ESRD or disability.

Statistical analysis. We used polytomous logistic regression to compute odds ratios (OR) and 95% confidence intervals (95% CI) to assess the association of solid-organ transplant with specific subtypes of hematologic malignancies. If no cases of a hematologic malignancy subtype had a transplant history, we used one-sided Fisher's exact test to examine the statistical significance of the association. We also examined the association with solid-organ transplant separately for nodal and extranodal NHL. Additional models evaluated associations with specific organ transplants (kidney, liver, lung, and heart) and the type of Medicare claim evidencing transplant history (claims for transplant procedure, history, or complication). We tested for heterogeneity to determine whether the association with solid-organ transplant varied significantly by hematologic malignancy subtype, NHL topography, or type of transplanted organ using Wald χ^2 tests. We also evaluated associations for specified hematologic malignancy subtypes as a function of time since transplantation for those subjects where the date of the transplant procedure was indicated by a Medicare claim. All analyses were adjusted for the three matching factors (age, sex, calendar year) and race. We accommodated the repeated selection of controls, and the possibility of a control later becoming a case, in the variance computations (see Appendix 1). Observations in which the number of subjects was between 1 and 10 are reported as "<11" to preserve subject confidentiality in accordance with the SEER-Medicare data use agreement.

Results

The study included 83,016 hematologic malignancy cases and 166,057 controls (127,397 unique control individuals, with repeat sampling). Cases and controls were similar with respect to sex, age, and calendar year of selection (Table 1). Although differences were small, cases were more likely than controls to be non-Hispanic white and had more claims for hospitalization, physician visits, and outpatient care (Table 1).

A total of 216 (0.26%) hematologic malignancy cases and 204 controls (0.12%) had at least one Medicare claim indicating a prior solid-organ transplant (OR, 2.16; 95% CI, 1.75-2.65). In analyses by hematologic malignancy subtype, solid-organ transplant was associated with statistically significant increased risk for lymphoid neoplasms overall (OR, 2.17) and more specifically for NHL (OR, 2.13), plasma cell neoplasms (OR, 1.91), and Hodgkin lymphoma (OR, 2.53; Table 2). Among NHL subtypes, strong associations were observed for DLBCL (OR, 3.29), the most common lymphoma subtype, as well as for lymphoplasmacytic lymphoma (OR, 3.32), marginal zone lymphoma (OR, 2.48), and T-cell lymphoma (OR, 3.07). No significant association was observed with follicular lymphoma or chronic lymphocytic leukemia (Table 2). The association between solid-organ transplant and DLBCL risk was significantly stronger than the asso-

ciation for follicular lymphoma ($P = 0.02$) or for chronic lymphocytic leukemia ($P = 0.0001$). Most plasma cell neoplasms (94.9%) were multiple myelomas, and solid-organ transplant was associated specifically with increased risk of multiple myeloma (OR, 1.91; 95% CI, 1.29-2.83). In addition, transplant history was significantly associated with elevated risk for myeloid neoplasms overall (OR, 1.99). Although we examined specific myeloid neoplasms (Table 2), the association with transplant did not vary significantly across these subtypes ($P = 0.33$).

Thirty-six percent of DLBCLs were extranodal. A stronger association with transplantation ($P = 0.04$) was observed for extranodal DLBCL (OR, 4.58; 95% CI, 3.02-6.97) than for nodal DLBCL (OR, 2.59; 95% CI, 1.70-3.94). Among DLBCLs arising in transplant recipients, fewer than 11 (<1%) were diagnosed in the transplanted organ (e.g., a kidney DLBCL in a kidney recipient). DLBCLs located in the central nervous system (CNS) were rare (3.1% of cases), and none had had a transplant.

We examined associations for the most common hematologic malignancy subtypes with specific transplanted organs (Table 3). DLBCL risk varied by transplanted organ ($P = 0.0006$) and was significantly higher following liver transplant (OR, 6.58) than all other organ transplants ($P = 0.02$). Risk of plasma cell neoplasms did not vary by transplanted organ, either overall ($P = 0.79$) or specifically for kidney transplants compared with all other organ transplants ($P = 0.53$). Risk of myeloid neoplasm did not vary by transplanted organ ($P = 0.11$). We also examined associations for the most common hematologic malignancy subtypes by type of Medicare evidence for transplant (Table 3). DLBCL risk estimates were higher if a claim for the transplant procedure was present (OR, 11.81) compared with other forms of evidence ($P < 0.0001$). The association with transplantation did not vary by type of Medicare evidence for either plasma cell neoplasms ($P = 0.38$) or myeloid neoplasms ($P = 0.76$).

A total of 60 cases and 29 controls had documented transplant dates based on procedure claims. Although based on the limited data for this subset, there was a suggestion of a "U-shaped" pattern for DLBCL risk as a function of time since transplantation (Fig. 1A), with the strongest associations occurring within 2 years following the procedure or more than 10 years after the procedure. For plasma cell neoplasms, we found no cases within the first 2 years of the procedure, but strong associations were present more than 5 years after transplant (Fig. 1B). For myeloid neoplasms, associations were observed both within 2 years of the procedure and, more strongly, more than 10 years after transplant (Fig. 1C).

Discussion

This large population-based investigation among older U.S. adults is the first study to systematically examine associations between solid-organ transplant and specific hematologic malignancy subtypes. Among NHLs, 3-fold

Table 1. Hematologic malignancy cases and controls in the SMAHRT Study (1987-2002)

Characteristic	Hematologic malignancy cases (n = 83,016), n (%)	Controls (n = 166,057), n (%)	P*
Sex [†]			
Male	40,983 (49.4)	81,996 (49.4)	0.96
Female	42,033 (50.6)	84,061 (50.6)	
Age, y [†]			
66-69	12,544 (15.1)	25,106 (15.1)	1.00
70-74	20,295 (24.5)	40,611 (24.5)	
75-79	20,864 (25.1)	41,724 (25.1)	
80-84	16,043 (19.3)	32,091 (19.3)	
85-99	13,270 (16.0)	26,525 (16.0)	
Median	77.0	76.0	
Race			
Non-Hispanic white	72,850 (87.7)	140,250 (84.5)	<0.0001
Non-Hispanic black	5,123 (6.2)	11,379 (6.9)	
Asian/Pacific Islander	1,541 (1.9)	5,818 (3.5)	
Hispanic	1,114 (1.3)	3,539 (2.1)	
American Indian/Alaskan Native	141 (0.2)	469 (0.3)	
Other/unknown	2,247 (2.7)	4,602 (2.7)	
Selection/diagnosis year [†]			
1987-1990	12,071 (14.5)	24,148 (14.5)	1.00
1991-1994	16,284 (19.6)	32,566 (19.6)	
1995-1998	18,186 (21.9)	36,387 (21.9)	
1999-2002	36,475 (43.9)	72,956 (43.9)	
Hospital claims, n [‡]			
0	43,456 (52.3)	92,789 (55.9)	<0.0001
1-2	23,831 (28.7)	44,736 (26.9)	
3+	15,729 (19.0)	28,532 (17.2)	
Median	0	0	
Physician claims, n [‡]			
0-4	24,383 (29.4)	51,642 (31.1)	<0.0001
5-40	18,650 (22.5)	41,050 (24.7)	
41-125	21,569 (26.0)	42,259 (25.5)	
126+	18,414 (22.2)	31,106 (18.7)	
Median	37	29	
Outpatient claims, n [‡]			
0-1	37,874 (45.6)	81,661 (49.2)	<0.0001
2-5	15,199 (18.3)	31,125 (18.7)	
6-15	15,709 (18.9)	29,802 (18.0)	
16+	14,234 (17.2)	23,469 (14.1)	
Median	2	2	

*P values are based on χ^2 test.

[†]Gender, age, and selection year were matching factors.

[‡]The number of Medicare claims is for the period before diagnosis/selection, excluding the 12 mo immediately before diagnosis/selection.

increased risks were observed for DLBCL, lymphoplasmacytic lymphoma, and T-cell lymphoma and lower but still elevated risk for marginal zone lymphoma. We also found that transplantation was associated with significantly elevated risk for plasma cell neoplasms and Hodgkin lymphoma. Finally, the association between transplant and myeloid neoplasms was also notable, add-

ing to limited prior evidence suggesting an increased risk of these malignancies in transplant recipients.

Among solid-organ transplant recipients, DLBCL was the most common NHL subtype, and the association with transplantation was especially strong (OR, 3.29). The increased risk for DLBCL was highest following liver transplantation (OR, 6.58), which is consistent with

previous studies showing that the risk of lymphoma is higher after liver transplant compared with kidney transplant (15). Based on data for a limited number of cases, we observed a U-shaped pattern of DLBCL risk after transplant, with the strongest associations apparent within 2 years (when immunosuppression is typically most intense) and more than 10 years after transplant. This finding is consistent with previous reports for PTLTD overall (22, 23). The majority of PTLTDs occurring shortly after transplantation are EBV positive, and EBV-induced lymphoproliferation secondary to intense immunosuppression is implicated (13). Recent work has described that some early DLBCLs in transplant recipients are of donor origin (24), but we could not examine that possibility in our study. In contrast, the etiology of PTLTDs late after transplant is less well understood (13). We also found a particularly strong increase in risk for extranodal

DLBCL associated with transplantation. Although other researchers have reported that extranodal lymphomas tend to arise within the transplanted organ (15, 25), we did not have sufficient numbers of cases to evaluate associations by extranodal site. We did not find a transplant history among any CNS NHLs, although these lymphomas are increased in incidence among people with AIDS in relation to immunosuppression (3) and have been reported in the setting of transplantation (15, 26, 27). Nonetheless, CNS NHL can also occur without obvious immunosuppression, particularly in older adults (28, 29).

Our study documents elevated risk for certain other NHL subtypes. Prior case reports have described the occurrence of T-cell lymphoma and marginal zone lymphoma following transplant (30-32). The observed increases among transplant recipients could be explained by loss of immune control of oncogenic viruses implicated

Table 2. Associations of hematologic malignancies with solid-organ transplantation

	<i>n</i>	Transplant history (%)	OR (95% CI)*	<i>P</i>
Controls	166,057	204 (0.12)	Reference	Reference
Lymphoid neoplasm	65,897	169 (0.26)	<u>2.17 (1.75-2.70)</u>	<u><0.0001</u>
NHL (overall)	45,824	115 (0.25)	<u>2.13 (1.67-2.72)</u>	<u><0.0001</u>
DLBCL	13,330	52 (0.39)	<u>3.29 (2.28-4.76)</u>	<u><0.0001</u>
Burkitt lymphoma	221	<11 (<5)	2.78 (0.38-20.20)	0.32
Marginal zone lymphoma	1,989	<11 (<1)	<u>2.48 (1.17-5.22)</u>	<u>0.02</u>
Follicular lymphoma	6,142	11 (0.18)	1.50 (0.77-2.92)	0.23
Chronic lymphocytic leukemia [†]	13,124	16 (0.12)	1.08 (0.62-1.89)	0.78
Lymphoplasmacytic lymphoma	1,434	<11 (<1)	<u>3.32 (1.41-7.81)</u>	<u>0.006</u>
B-cell NHL, NOS	2,013	<11 (<1)	0.36 (0.05-2.62)	0.32
T-cell lymphoma	2,362	<11 (<1)	<u>3.07 (1.56-6.06)</u>	<u>0.001</u>
Unknown lineage NHL	3,330	<11 (<1)	<u>2.36 (1.00-5.53)</u>	<u>0.05</u>
Mantle cell lymphoma	1,171	<11 (<1)	1.72 (0.53-5.58)	0.37
Precursor B-cell lymphoma	267	<11 (<5)	2.65 (0.36-19.31)	0.34
Hairy cell leukemia/lymphoma	441	0 (0)	0	0.58 [‡]
Plasma cell neoplasm [§]	14,000	32 (0.23)	<u>1.91 (1.24-2.93)</u>	<u>0.003</u>
Hodgkin lymphoma	1,692	<11 (<1)	<u>2.53 (1.01-6.35)</u>	<u>0.05</u>
Lymphoid neoplasm, NOS	4,381	17 (0.39)	<u>3.72 (2.14-6.48)</u>	<u><0.0001</u>
Myeloid neoplasm	15,116	41 (0.27)	<u>1.99 (1.41-2.81)</u>	<u><0.0001</u>
Acute myeloid leukemia	8,055	15 (0.19)	1.51 (0.85-2.68)	0.16
Chronic myeloid leukemia	2,250	<11 (<1)	2.04 (0.81-5.15)	0.13
Myelodysplastic syndrome	3,366	15 (0.45)	<u>2.75 (1.54-4.88)</u>	<u>0.0006</u>
Chronic myeloproliferative disorder	1,099	<11 (<1)	<u>2.99 (1.28-6.99)</u>	<u>0.01</u>
Myeloid leukemia, NOS	346	0 (0)	0	0.65 [‡]
Hematologic malignancy, NOS	2,003	<11 (<1)	<u>3.10 (1.31-7.32)</u>	<u>0.01</u>

NOTE: Observations in which the number of exposed cancer cases was between 1 and 10 are reported as <11, to preserve subject confidentiality in accordance with the SEER-Medicare data use agreement. Significant associations ($P < 0.05$) are underlined. Abbreviation: NOS, not otherwise specified.

*ORs were adjusted for age in five strata (66-69, 70-74, 75-79, 80-84, and 85-99 y), sex, race (white, non-white), and calendar year of diagnosis/selection (1987-1990, 1991-1994, 1995-1998, and 1999-2002).

[†]This category also includes small lymphocytic lymphoma.

[‡] P value was calculated using one-sided Fisher's exact test.

[§]This category includes multiple myeloma ($n = 13,291$), plasmacytoma ($n = 647$), and plasma cell leukemia ($n = 62$).

Table 3. Associations of hematologic malignancies with specific types of solid-organ transplant and Medicare evidence

	Control (n = 166,057)		DLBCL (n = 13,300)		Plasma cell neoplasm (n = 14,000)		Myeloid neoplasm (n = 15,116)	
	n (%)	n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	
Organ transplanted								
Kidney	113 (0.07)	34 (0.26)	<u>4.00 (2.68-5.96)</u>	20 (0.14)	<u>2.13 (1.31-3.48)</u>	15 (0.10)	1.35 (0.78-2.34)	
Liver	31 (0.02)	16 (0.12)	<u>6.58 (3.48-12.45)</u>	<11 (<1)	1.62 (0.56-4.69)	11 (0.07)	<u>3.44 (1.68-7.01)</u>	
Heart	52 (0.03)	14 (0.11)	<u>3.45 (1.90-6.29)</u>	<11 (<1)	1.49 (0.63-3.51)	16 (0.11)	<u>2.88 (1.63-5.11)</u>	
Lung	25 (0.02)	<11 (<1)	1.43 (0.41-4.97)	<11 (<1)	1.48 (0.44-4.99)	<11 (<1)	1.61 (0.55-4.70)	
Medicare evidence of transplant								
Procedure	29 (0.02)	25 (0.19)	<u>11.81 (6.69-20.85)</u>	<11 (<1)	<u>3.75 (1.72-8.19)</u>	<11 (<1)	<u>2.79 (1.28-6.10)</u>	
History	177 (0.11)	51 (0.38)	<u>3.76 (2.71-5.20)</u>	27 (0.19)	<u>1.88 (1.24-2.85)</u>	37 (0.24)	<u>2.07 (1.43-2.97)</u>	
Complication	72 (0.04)	31 (0.23)	<u>5.68 (3.65-8.83)</u>	14 (0.10)	<u>2.41 (1.35-4.31)</u>	14 (0.09)	<u>1.91 (1.07-3.41)</u>	

NOTE: Observations in which the number of exposed cancer cases was between 1 and 10 are reported as "<11" in accordance with the SEER-Medicare data use agreement.

*ORs were adjusted for age in five strata (66-69, 70-74, 75-79, 80-84, and 85-99 y), sex, race (white, non-white), and calendar year of diagnosis/selection (1987-1990, 1991-1994, 1995-1998, and 1999-2002). ORs significantly different from 1.00 are underlined.

in these lymphoma subtypes (hepatitis C virus for lymphoplasmacytic and marginal zone lymphomas and EBV for T-cell lymphoma; refs. 33-35). In contrast, we did not observe increased risks for two common lymphoma subtypes, follicular lymphoma and chronic lymphocytic leukemia. Of note, we found elevated risk of Hodgkin lymphoma associated with transplantation, which is consistent with previous studies in transplant recipients (1, 12) and likely reflects the important etiologic role of EBV. Elevated risk of Hodgkin lymphoma is also reported in people with AIDS (1, 36).

Plasma cell neoplasms are not common after transplant, leading to variability of risk estimates in previous studies (1, 8, 9, 37). Although multiple myeloma is a cause of ESRD and thus kidney transplantation, we did not find significantly higher risk for plasma cell neoplasms related to kidney transplants over other organ types. Also, the risk for plasma cell neoplasms was highest more than 5 years after transplantation, suggesting that prolonged disturbances in immune function could account for late development of plasma cell neoplasms among transplant recipients. A modest elevation in multiple myeloma risk is also observed among people with AIDS (1, 38).

The increased risk that we observed for myeloid neoplasms as a group is somewhat supported by prior research pointing to elevated risk for myelodysplastic syndrome and acute myeloid leukemia following transplantation (39-41). DNA damage resulting from prolonged exposure to azathioprine has been implicated (11, 39), which would be consistent with our observation that risk is greatest more than 10 years after transplantation. Nonetheless, we also observed increased risk earlier following transplantation, and cases of myeloid neoplasms have also been reported in transplant recipients not receiving azathioprine (41).

We note that our relative risk estimates for some hematologic malignancies following transplant seemed lower than those of prior reports. In comparison with results in a recent meta-analysis (1), we found a more modest association for NHL (OR of 2.13 in our study versus a standardized incidence ratio of 8.07 in the meta-analysis) and Hodgkin lymphoma (2.53 versus 3.89), but results were more similar for multiple myeloma (1.91 versus 3.12) and myeloid neoplasms (1.99 versus 2.38 for leukemia). One possible explanation for these differences is that our study was restricted to elderly adults. The effect of transplantation on risk of some hematologic malignancies may be smaller in elderly adults than in younger individuals, perhaps reflecting the age-related increase in incidence of these malignancies in the general population, changes in the immune system with age, or differences in the immunosuppressive protocols used in older transplant recipients.

Alternatively, the weaker associations in our study could arise because our use of Medicare claims data likely resulted in some underascertainment of transplantation, particularly for procedures performed before age 65 years. Associations were strongest when a procedure claim for transplant was present, perhaps relating to a greater specificity in these claims or stronger immunosuppression due to more recent transplantation than when claims indicating a prior history of transplantation were used. Nonetheless, few of our subjects had documented dates of transplantation based on these claims, and we believe that the sensitivity of our overall approach was improved by also considering claims indicating either a history or complication of prior transplantation. In the end, any misclassification of transplantation status would likely have been nondifferential between hematologic malignancy cases and controls, which would have conservatively biased

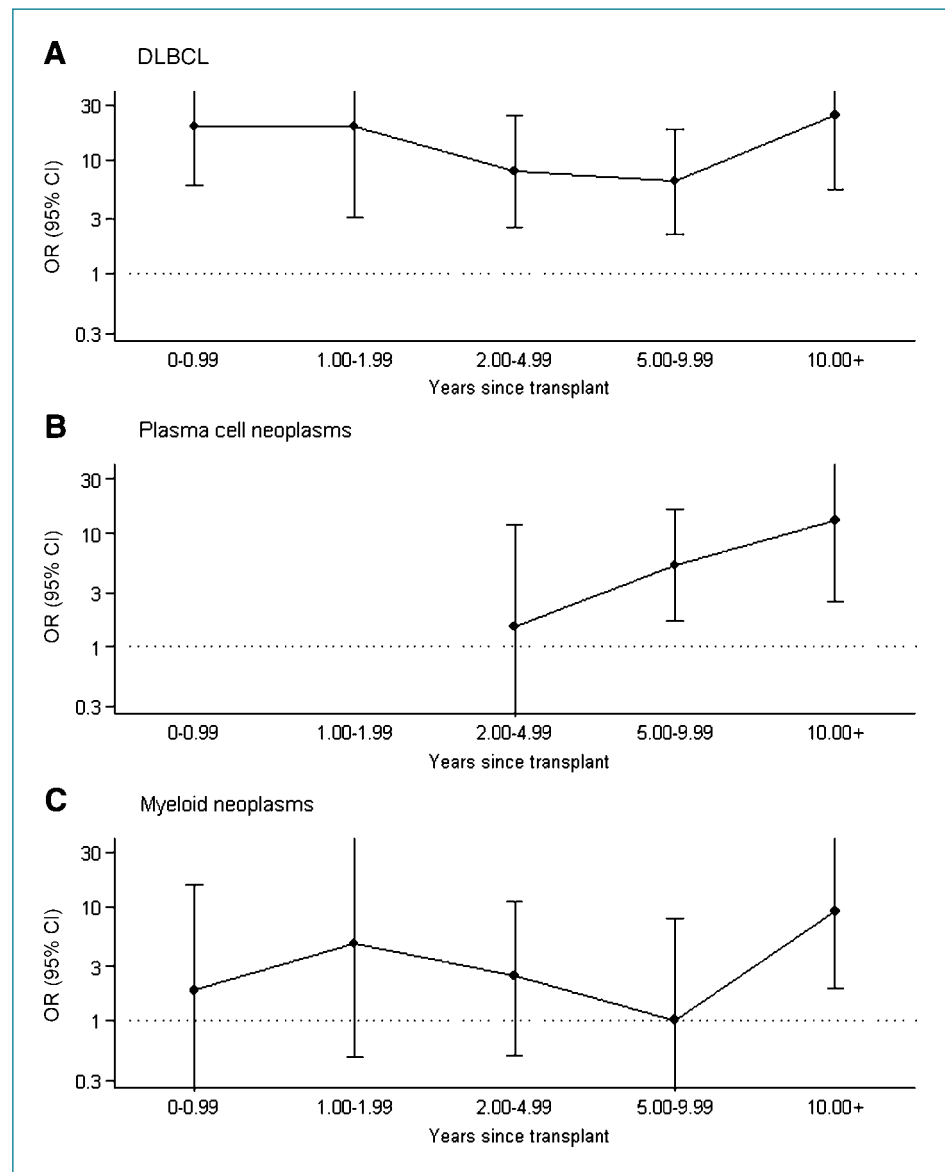
measures of association toward the null. However, the similar results in our study and the Grulich meta-analysis for plasma cell neoplasms and myeloid neoplasms argue against a large artifact.

Our study has several important strengths. First, the large number of hematologic malignancy cases and systematic information on histology allowed us to examine specific subtypes of hematologic malignancy, particularly NHL, in greater detail than in previous research in this area. Further, our population-based sampling ensured that hematologic malignancy cases and controls were representative of the general elderly population in the United States. Limitations to our study also need to be considered. As noted above, our study was restricted to older-aged adults, and the results may not be generalizable to other age groups. A further limitation of our

study was the rarity of solid-organ transplant history (0.12% among control subjects), which limited our ability to detect associations for less common hematologic malignancy subtypes. Finally, we did not formally adjust for multiple comparisons, and some associations could have been due to chance. Nonetheless, the associations between transplantation and DLBCL, T-cell lymphoma, and myelodysplastic syndrome remained significant even after applying a Bonferroni correction for ~25 comparisons ($P < 0.002$; Table 2).

From a clinical perspective, our results suggest that there are a wide variety of hematologic malignancies linked to immunosuppression. Following solid-organ transplantation, recipients should be closely monitored for symptoms and findings consistent with these neoplasms, even though these events are rare. Some subtypes (e.g., extranodal

Figure 1. Risk of DLBCL (A), plasma cell neoplasms (B), and myeloid neoplasms (C) associated with solid-organ transplantation as a function of time since transplantation. The figure presents ORs and 95% confidence intervals for 0-0.99, 1.00-1.99, 2.00-4.99, 5.00-9.99, and more than 10 years after a transplant procedure. For plasma cell neoplasms (B), the ORs were 0 for the first two time points and are not presented.



DLBCL) can have a quite aggressive clinical course, and as our data show, risk for these malignancies persists for years following a transplant. Given that immunosuppression may play a role in their etiology, reduction of the intensity of the immunosuppressive regimen might be considered as part of the clinical management of patients with these malignancies. These possibilities need to be further evaluated in clinical studies.

In conclusion, our results provide a comprehensive picture of the risk of hematologic malignancy following solid-organ transplantation for elderly transplant recipients. We found an association between solid-organ transplantation and four specific NHL subtypes (DLBCL and marginal zone, lymphoplasmacytic, and T-cell lymphomas) as well as for myeloid neoplasms. We also observed increased risks of Hodgkin lymphoma and plasma cell neoplasms following transplantation. Additional research on the etiologic roles of disturbed immunity, viral infections, and medications in the development of these malignancies is warranted.

Statistical Appendix

Let $Y = (Y_0, Y_1, Y_2, \dots, Y_K)$ denote the outcome variable in a nested case-control study composed of one control group and K case groups. We use indicator notation, that is $Y_0 = 1$ if the person is a control and 0 otherwise, and $Y_i = 1$ if the person is a case of type i and 0 otherwise, $i = 1, \dots, K$. We use polytomous logistic regression to compare each case group to the controls, by modeling

$$P(Y_i = 1|X) = p(X, \theta_i) = \exp(X' \theta_i) / \sum_{s=1}^K \{1 + \exp(X' \theta_s)\},$$

for the covariate vector $X = [1, X_1, \dots, X_m]$, which includes a one for the intercept term. As $\sum_{i=1}^K P(Y_i = 1) = 1$, we assume $\theta_0 = [0, \dots, 0]$. We then use maximum likelihood estimation and obtain the log OR estimates $\theta_j = [\theta_{j1}, \theta_{j2}, \dots, \theta_{jm}]$, $j = 1, \dots, K$, for the j th outcome in the polytomous logistic model.

Although the corresponding covariance estimator accounts for the fact that the same control group is used for each disease subtype comparison, we additionally need to consider that due to constraints in our cohort, a substantial number of healthy individuals were sampled multiple times as controls and that some case individuals were sampled as controls before developing disease. We accommodate this issue adapting an approach by Anderson (18) as follows. Let the covariance matrix of the maximum likelihood estimates of the log OR para-

meters be denoted by Σ . For each study subject, we obtain the scores $S_i = (S_{i1}, \dots, S_{iK})$, from each of the K polytomous logistic regression models. For example, for subject i the score for model j , or equivalently, θ_j , is given by $S_{ij} = -X_{ij}[Y_{ij} - P(Y_{ij} = 1 | X_{ij}, \theta_j)]$. We define the matrix of scores for n subjects as

$$S = \begin{pmatrix} S_{11} & S_{12} & \dots & S_{1K} \\ S_{21} & S_{22} & \dots & S_{2K} \\ \dots & \dots & \dots & \dots \\ S_{(n-1)1} & \dots & S_{(n-1)(K-1)} & S_{(n-1)K} \\ S_{n1} & S_{n2} & S_{n(K-1)} & S_{nK} \end{pmatrix}$$

Control subjects have entries in every column of the score matrix because they contribute to all logistic models. Some individuals served as controls before they were selected as cases and thus could also contribute to several logistic models. If there is no overlap between cases and controls, S simplifies to

$$S = \begin{pmatrix} S_1 & 0 & \dots & 0 \\ 0 & S_2 & \dots & 0 \\ \dots & \dots & \dots & \dots \\ 0 & \dots & S_{K-1} & 0 \\ S_1 & S_2 & S_{K-1} & S_K \end{pmatrix}$$

Using the above notation, the asymptotic variance of the estimates $(\theta_1, \dots, \theta_K)$ is given by $\Sigma B \Sigma'$. B is estimated by

$$\hat{B} = \sum_i (\sum S_{ik})(\sum S_{ik})'$$

where i denotes the sum over individuals, and the second sum inside refers to the repeated measurements on the same person.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Winnie Ricker (Information Management Services, Rockville, MD) for assistance with database management.

Grant Support

Intramural Research Program of the National Cancer Institute. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 12/04/2009; revised 02/09/2010; accepted 02/25/2010; published OnlineFirst 04/20/2010.

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