Published in final edited form as:

Transfusion. 2010 October ; 50(10): 2249–2257. doi:10.1111/j.1537-2995.2010.02692.x.

Blood Transfusions and the Subsequent Risk of Hematologic Malignancies

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Abstract

Background—Blood transfusions are associated with viral transmission and immunomodulation, perhaps increasing subsequent risk of hematologic malignancies (HMs). Prior studies of transfusion recipients have lacked details on specific HM subtypes.

Study Design and Methods—Risk of HM risk following blood transfusion was evaluated in a U.S. population-based case-control study (77,488 elderly HM cases identified through cancer registries, 154,509 controls). Transfusions were identified using linked Medicare hospitalization claims. Polytomous logistic regression was used to calculate odds ratios (ORs) associating transfusion and HM subtypes by features suggestive of a causal relationship.

Results—A history of transfusion was present in 7.9% of HM cases vs. 5.9% of controls. Associations for most HM subtypes suggested reverse causality: ORs were elevated only during the shortest latency periods; ORs for unspecified anemia and gastrointestinal bleeding, which may be related to undiagnosed HM, were stronger than for surgeries, which are unlikely to be related to HM; and/or there was no dose-response. In contrast, risk for lymphoplasmacytic lymphoma (1,397 cases) was elevated at long latency (OR=1.56 at 10+ years following transfusion), following transfusions for surgeries (ORs 1.22–1.47), and in a dose-response relationship with number of transfusion-related hospitalizations (OR=1.53 with 1 hospitalization; OR=1.80 with 2+ hospitalizations, p -trend<0.0001). Risk for marginal zone lymphoma (1,915 cases) was also elevated at 10+ years following transfusion (OR=1.80).

Conclusion—Consistent with prior studies, blood transfusions did not increase risk of most HM subtypes. Patterns of elevated risk for lymphoplasmacytic and marginal zone lymphomas suggest an etiologic role for transfusion.

Keywords

Transfusion Complications- Non Infectious

INTRODUCTION

Hematologic malignancies (HMs) encompass a wide variety of lymphoid and myeloid neoplasms and account for a substantial health burden. In 2008 in the U.S. alone, there were

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Authorship Contribution: C.M.C., E.A.E., and J.L.W. designed the research study; C.M.C. and S.C.Q. performed the statistical analysis; and C.M.C. and E.A.E. analyzed and interpreted the data, and wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

70,000 new cases of lymphoma with 40,000 deaths, 20,000 new cases of myeloma with 11,000 deaths, and over 44,000 new cases of leukemia with 25,000 deaths¹. Most of these malignancies occur disproportionately in the elderly population².

Receipt of an allogeneic blood transfusion has been considered among exposures that may contribute to the development of HMs. In particular, blood transfusion may increase HM risk by causing immune suppressive or pro-inflammatory changes in the recipient's immune system, a constellation of effects that are termed "transfusion-related immunomodulation" (i.e., TRIM)³. This mechanism would be consistent with the observation that other primary and acquired immunodeficiencies are strongly associated with development of lymphomas⁴⁻⁵. Additionally, blood transfusions might increase risk by transmitting infectious agents linked to lymphoma, including Epstein-Barr virus, hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-lymphotropic virus type I6, although screening of transfused blood is now in place for most of these agents.

The potential association between receipt of a blood transfusion and subsequent HM risk has been evaluated in a number of cohort and case-control studies, particularly of non-Hodgkin lymphoma (NHL), with variable results⁷⁻²². While some cohort studies of transfusion recipients suggested an increased risk of NHL, there were few cases in these studies (15 to 229 HM or NHL cases), thus point estimates were imprecise^{9,12,17}. Additionally, in many of the earlier studies NHL subtypes were not always evaluated separately, and studies that reported subtype-specific associations may not have had sufficient cases to give precise results^{9,12-13}. Finally, data are limited with respect to other characteristics of blood transfusions (e.g., dose-response relationship with number of transfusions, latency period following transfusion, and indication for transfusion) that would be helpful in assessing whether transfusions increase HM risk.

The number of blood transfusions continues to rise. In the U.S. in 2006, over 14.6 million units of donor blood were transfused to recipients compared to 14.2 million units in 2004²³. The growing elderly population in the U.S., who comprise over 50% of the transfusion recipients, is likely to further increase the demand for transfusions in the future.

In the present case-control study of elderly U.S. adults, we used population-based cancer registry and Medicare data to evaluate HM risk following a blood transfusion. Strengths of our study include its large size (over 77,000 HM cases), detailed data on HM subtypes, and documentation of receipt of blood transfusions through use of hospital claims data.

MATERIALS AND METHODS

Study design

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program comprises population-based state and metropolitan cancer registries that currently capture the occurrence of malignancies for approximately 26% of the U.S. population²⁴⁻²⁵. Medicare is a federal insurance program that provides primary health insurance for 97% of the U.S. population aged 65 years and older, as well as persons with disability or end-stage renal disease. Ninety-eight percent of Medicare beneficiaries are entitled to Part A which includes coverage for inpatient care, and 96% subscribe to Part B coverage which includes physician and outpatient services²⁵.

As described previously²⁵, the SEER-Medicare dataset contains demographic and clinical information, and Medicare claims data (hospital claims of Part A [beginning in 1986] which covers inpatient care, and Part B claims [beginning in 1991] which cover physician and outpatient care) on newly diagnosed cancer patients through December 2002. Additionally,

Medicare data are available for a 5% random sample of beneficiaries living in SEER regions.

The present report includes data from the SEER-Medicare Assessment of Hematopoietic Malignancy Risk Traits (SMAHRT) Study, a population-based case-control study of HMs using SEER-Medicare data²⁶. Cases were patients aged 67–99 years diagnosed with a lymphoid or myeloid HM (International Classification of Disease for Oncology [ICD-O, third edition] morphology codes 9590–9989) as a first primary cancer in SEER during 1988–2002. Subtype classification for the lymphoid neoplasms was based on the World Health Organization scheme²⁷. Myeloid neoplasms were classified as acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), and chronic myeloproliferative disease (CMD)²⁸. Cases were required to have had at least 12 months non-health maintenance organization (HMO) Part A and Part B Medicare coverage prior to diagnosis. Cases diagnosed only at autopsy or by death certificate were excluded.

Two controls were selected for each case from the 5% random sample of Medicare beneficiaries, frequency-matched to cases by selection year, age in 5 categories (67–69, 70–74, 75–79, 80–84, 85–99 years), and sex. As of July 1 of the calendar year of selection, controls must have been alive, cancer-free, and have had at least 12 months of Part A, Part B, and non-HMO Medicare coverage. Controls could have been selected multiple times in different calendar years or could later have become a case. Finally, after selection of cases and controls, subjects with HIV infection were excluded (n=263), because HIV is itself a strong risk factor for lymphoma.

We used Medicare claims data to identify any blood transfusions occurring one year or more prior to HM diagnosis/control selection; we excluded transfusions during the one-year prior to HM diagnosis to minimize the possibility that the transfusions were administered to cases due to anemia arising from early undiagnosed disease. Because the majority of blood transfusions occur during hospitalizations (95% according to the 2007 National Blood Collection and Utilization Survey Report)²³, only hospitalization claims (MEDPAR file) were reviewed. Blood transfusions were defined as receipt of packed cells (International Classification of Diseases [version 9, ICD-9] procedure code 9904) or an indication that the number of transfused units during the hospitalization (BLDPNTS variable) was greater than zero. According to the NBCUS 2007 report, 98.7% of all transfusions in US blood centers and hospitals are allogeneic (including those directed to a designated patient), and only 1.3% are autologous²³.

Statistical analysis

Unconditional polytomous logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (CIs), comparing the prevalence of blood transfusions in specific subtypes of HM cases and controls. We accounted for the repeated sampling of controls and the fact that some controls later became cases in the variance calculation²⁹. All analyses were adjusted for age (67–69, 70–74, 75–79, 80–84, 85–89 years), sex, calendar year of HM diagnosis/selection (1988–1993, 1994–1997, 1998–2000, 2001–2002), and race (white, other/unknown).

Further, we used unconditional logistic regression to assess the associations with blood transfusion according to latency (i.e., time from transfusion until HM diagnosis/selection, p-value for trend across latencies of 1–1.99, 2–4.99, 5–9.99, 10 or more years). Blood transfusions are frequently given to patients with certain procedures and diagnoses that are themselves related to cancer. To assess this possibility, we evaluated associations separately for transfusions given during hospitalizations related to unspecified anemia and gastrointestinal bleeding (indicated in discharge diagnoses), two medical conditions

suggestive of pre-clinical HM effects on bone marrow erythrocytes or platelets. For comparison, we evaluated the associations for transfusions given during hospitalizations when coronary artery bypass or hip replacement were performed, procedures for conditions not directly related to HM. Finally, we assessed whether there was a dose-response relationship by estimating ORs associated with an increasing number of hospitalizations with blood transfusion (p-value for trend across categories of no transfusion, 1, or 2 or more hospitalizations).

Based on these analyses, we considered the following three criteria as support for a causal association between blood transfusion and a specific HM subtype, in addition to a significantly elevated overall OR: ORs that remained stable or increased with increasing latency period and were significantly elevated at long latencies; elevated ORs for transfusions during hospitalizations related to coronary artery bypass or hip replacement; and ORs increasing with the number of hospitalizations with transfusions.

RESULTS

Among the 77,488 HM cases and 154,509 controls, roughly half were male and the median age at diagnosis/selection was 77 years (Table 1). The large majority of subjects were white, and cases were more likely than controls to be white. Cases also had a longer duration of Medicare coverage, and the numbers of physician, outpatient, and hospital claims were greater among cases than controls. However, although statistically significant, these differences were small in magnitude (Table 1). The numbers of specific HM subtypes included as cases are presented in Table 2.

Among the 154,509 controls, 4.1% had a hospital claim prior to selection indicating receipt of nonzero blood pints, 2.6% had a claim indicating blood transfusion as a procedure (ICD-9 code 9904), and 5.9% had a claim with either indication of a blood transfusion (Table 2). Among cases of various HM subtypes, the corresponding proportions with a claim for transfusion prior to HM diagnosis ranged from 3.8–10.3% for nonzero blood pints, 1.9–9.5% for transfusion procedure, and 5.2–16.5% for either indication of transfusion. To capture all transfusions during hospitalizations, for the remainder of analyses we considered blood transfusion to be present if either type of Medicare claim was present, although associations were similar using either type of claim separately (Table 2).

Overall, HM risk was increased following a blood transfusion (OR=1.37, Table 2). Among NHL subtypes, risk was elevated for diffuse large B-cell lymphoma (DLBCL, OR=1.18), marginal zone lymphoma (OR=1.22), chronic lymphocytic leukemia (CLL, OR=1.13), lymphoplasmacytic lymphoma (OR=1.59), and T-cell NHL (OR=1.30). Risk was also increased for plasma cell neoplasms (OR=1.35) and Hodgkin lymphoma (OR=1.28). Finally, risk was elevated for all of the myeloid neoplasm subtypes, i.e., AML (OR=1.79), CML (OR=1.80), MDS (OR=2.49), and CMD (OR=1.30).

Associations between HM subtypes and blood transfusion by latency period (i.e., time since transfusion) are presented in Tables 3 and 4. Risk of most HM subtypes was highest in the latency periods closest to blood transfusion. This pattern was especially apparent for myeloid neoplasms (Table 4). Ten or more years after transfusion, risk was significantly elevated for marginal zone lymphoma (OR=1.81), lymphoplasmacytic lymphoma (OR=1.56), and chronic lymphocytic leukemia (OR=1.24). The elevated risk for lymphoplasmacytic lymphoma was relatively stable across latency intervals (Table 3).

HM risk related to specific hospital diagnoses or procedures associated with transfusion is also shown (Tables 3 and 4). Several HM subtypes, particularly plasma cell neoplasms and myeloid neoplasms, appeared more strongly associated with transfusions linked to

unspecified anemia and gastrointestinal bleeding than with transfusions linked to the two surgeries. DLBCL, lymphoplasmacytic lymphoma, T-cell NHL, and Hodgkin lymphoma were weakly or moderately associated with transfusions across all of the diagnoses and procedures (Table 3).

Finally, Tables 3 and 4 also show estimates of HM risk related to number of transfusion-associated hospitalizations. Although several HM subtypes manifested significant trends, a dose-response relationship of increasing risk was most apparent for lymphoplasmacytic lymphoma (ORs of 1.57 for 1 hospitalization, 1.85 for 2+ hospitalizations; p -trend<0.0001) and the myeloid neoplasms (Table 4).

DISCUSSION

In this population-based case-control study among elderly U.S. adults, we evaluated risk for distinct HM subtypes following a blood transfusion. We detected a slightly increased risk of NHL one or more years after a transfusion (OR=1.17). Given our large sample size (42,729 NHL cases), we were better able to detect such an association than other recent case-control studies, which produced similar but inconclusive findings (ORs 1.0–1.3, based on 600–1600 NHL cases each)^{12,16,22}.

In addition to the finding of an overall association, we considered three kinds of evidence as supportive of a causal relationship between receipt of a blood transfusion and subsequent development of HM rather than an association due to reverse causality (i.e., transfusion arising due to anemia caused by an incipient HM). First, we examined whether HM risk increased with increasing time since transfusion, consistent with a biological model in which transfusions act at an early or intermediate stage in a multi-step pathway to HM development. We were therefore alert to instances where HM risk seemed very high immediately after transfusion, which would suggest reverse causality. A recent cohort study of all blood transfusion recipients in Sweden and Denmark found elevated HM risk in the 6 months immediately post-transfusion (a time period we purposefully excluded from analysis)¹⁷, while previous case-control studies did not show a consistent pattern across latency periods^{12,16}. Second, we evaluated diagnoses and procedures occurring with the transfusion on the same hospital claim, as an indication of medical illnesses potentially related to undiagnosed HM (anemia, gastrointestinal bleeding) or unlikely to be related to HM (coronary artery bypass, hip replacement). In prior case-control studies, medical indications for transfusion (anemia and bleeding) were more strongly associated with NHL risk than were transfusions following trauma and obstetric procedures, supporting reverse causality as the explanation^{12,22}. Finally, we examined HM risk as a function of the number of hospitalizations during which a transfusion was administered, considering a positive dose-response relationship to support a causal interpretation. Prior studies of dose-response did not show a strong or consistent pattern for lymphomas¹⁶ or cancers in general¹⁷.

Among NHL subtypes, the evidence for an association with blood transfusion was strongest for lymphoplasmacytic lymphoma. Specifically, risk appeared elevated across latency periods (ORs 1.37–1.77), in association with a procedure unrelated to NHL (hip replacement, OR=1.47), and in a dose-response relationship (OR=1.53 with 1 hospitalization; OR=1.80 with 2+ hospitalizations). There was also a suggested link with marginal zone lymphoma, with strongly elevated risk occurring at 10 or more years after transfusion (OR=1.80). HCV infection has been associated with an elevated risk of these two NHL subtypes in epidemiologic studies^{26,30–31}, and we considered the possibility that risk for these subtypes was due, at least in part, to the transmission of HCV during blood transfusion. Until 1992, when HCV screening of U.S. blood donors was implemented,

transfusion was a common mode of HCV transmission. However, HCV prevalence in U.S. donors is very low (0.26% in first-time donors, 0.006% in repeat donors)³², and the current estimated risk of HCV transmission after screening is 1 per 2 million units transfused³³. Additionally, when we restricted our analysis to blood transfusions occurring in 1992 or later, after screening began, the overall association did not change substantially for either NHL subtype (data not shown). Thus, HCV infection cannot account for the increased risk of lymphoplasmacytic lymphoma or marginal zone lymphoma following transfusion.

Alternatively, blood transfusion may increase the risk of these lymphoma subtypes through a suppressive or stimulating effect on the immune system. Transfusion-related immunomodulation (TRIM) studies have shown that transfusion may cause immunosuppression, possibly due to reduced natural killer (NK) cell activity, or a shift from T-helper type 1 (Th1) to T-helper type 2 (Th2)-dominant response³. Recent studies of TRIM have suggested a pro-inflammatory effect of transfusion, in which bioactive lipids or other soluble molecules accumulated during blood storage prime neutrophils of the transfusion recipient. Other immune stimulating effects of transfusion include development of HLA allo-antibodies and production of allo-reactive T-cells in transfusion recipients^{34–37}. A mechanism whereby blood transfusions would cause lymphoplasmacytic lymphoma and marginal zone lymphoma through chronic immune stimulation is consistent with the proposed pathway for HCV-mediated lymphomagenesis^{38–39}.

We found significant associations between transfusion and several other NHL subtypes, including DLBCL, CLL, and T-cell NHL, but the evidence in Table 3 was less convincing than for lymphoplasmacytic and marginal zone lymphomas. Although NHL subtypes vary by pathologic characteristics, clinical features, and etiology, few previous studies have examined subtype-specific associations with blood transfusions. In one U.S. case-control study, receipt of blood transfusion was non-significantly associated with increased risk of follicular lymphoma, and more weakly DLBCL, but the associations were largely limited to transfusions given for medical illness, suggesting reverse causality¹². Among Connecticut women, neither of these common NHL subtypes was associated with transfusion, while there was a borderline significant association with risk of marginal zone lymphoma (OR=1.3)²². In the Multi-Ethnic Cohort Study, an association between transfusion and DLBCL was reported (HR=1.4), but there were no data on latency or dose-response¹⁰. We also saw an overall increased risk for plasma cell neoplasms and Hodgkin lymphoma following transfusion, but some details in Table 3 were inconsistent with a causal relationship (e.g., for plasma cell neoplasms, elevated risk with transfusions for anemia and gastrointestinal bleeding; for Hodgkin lymphoma, absence of elevated risk with long latency and 2+ transfusion-associated hospitalizations).

Similarly, two aspects of the findings for myeloid neoplasms support the conclusion that the associations that we observed were due to reverse causality. First, the associations were most strongly elevated in the shortest latency periods, dropping off substantially at 10 years or more. Second, the associations for myeloid neoplasms were especially strong for transfusions related to unspecified anemia and gastrointestinal bleeding. These two medical conditions are plausibly related to disturbances in normal bone marrow function due to undiagnosed myelodysplasia or perhaps another precursor of leukemia²⁸. Therefore, it is likely that most myeloid neoplasm cases received a transfusion because of undocumented disease, rather than the transfusion leading to the myeloid neoplasm.

Strengths of our study include the large number of subjects and detailed information on HM subtypes. The large number of cases with each HM subtype allowed us to assess subtype-specific associations with blood transfusions, particularly in terms of latency periods, medical diagnoses and procedures, and dose-response. Our study was based on data

obtained from Medicare and SEER, both of which are population-based sources, thus allowing for fully representative sampling of both cases and controls. In addition, the blood transfusions were documented in Medicare hospital claims, reducing the likelihood that transfusion history would be affected by inaccurate recall. Furthermore, in the U.S., 95% of all transfusions are given in a hospital setting²³.

A limitation to our study is that we could not include transfusions administered before subjects had Medicare benefits and information on claims in the SEER-Medicare database (prior to age 65 years and before 1986). Because cases and controls had similar duration of Medicare coverage, this limitation would result in nondifferential misclassification that is expected to bias the observed associations toward the null⁴⁰. In our data, we were able to assess the effect of transfusion over roughly a 7 to 10-year period after transfusion (based on the duration of Medicare coverage, Table 1). While the latency period for an etiologic effect of transfusion on development of HM is unknown, our study could thus evaluate this association if the effect operated over a short or intermediate time interval. Finally, although we evaluated a large number of HM subtypes, the potential of false positive results arising from multiple comparisons was mitigated by our assessment of several complementary features of transfusion (Tables 3 and 4), which together supported our overall conclusions.

To conclude, we observed elevated risk for a range of lymphoid and myeloid neoplasms following a blood transfusion, but most of these associations could plausibly reflect reverse causality. However, the evidence for lymphoplasmacytic lymphoma and perhaps marginal zone lymphoma was more suggestive of a causal relationship. One possibility is that chronic immune disturbances arising from a blood transfusion could predispose to these lymphoma subtypes. Additional research on the immune-modulating effects of blood transfusions would be informative.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute (NCI); the Office of Research, Development, and Information, Centers for Medicare and Medicaid Services; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The authors thank Winnie Ricker (Information Management Services, Rockville, MD) for assistance with database management. This research was supported by the Intramural Research Program of the National Cancer Institute.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2008. American Cancer Society; Atlanta: 2008.
2. Schottenfeld, D.; Fraumeni, J. Cancer Epidemiology and Prevention. Oxford University Press, Inc; New York: 2006.
3. Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. Blood Rev. 2007; 21:327–48. [PubMed: 17804128]
4. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. JAMA. 2001; 285:1736–45. [PubMed: 11277828]
5. Hoover RN. Lymphoma risks in populations with altered immunity--a search for mechanism. Cancer Res. 1992; 52:5477s–8s. [PubMed: 1394157]
6. Buddeberg F, Schimmer BB, Spahn DR. Transfusion-transmissible infections and transfusion-related immunomodulation. Best Pract Res Clin Anaesthesiol. 2008; 22:503–17. [PubMed: 18831300]
7. Adami J, Nyren O, Bergstrom R, Ekblom A, McLaughlin JK, Hogman C, Fraumeni JF Jr. Glimelius B. Blood transfusion and non-Hodgkin lymphoma: lack of association. Ann Intern Med. 1997; 127:365–71. [PubMed: 9273827]

8. Vamvakas EC. Allogeneic blood transfusion as a risk factor for the subsequent development of non-Hodgkin's lymphoma. *Transfus Med Rev.* 2000; 14:258–68. [PubMed: 10914420]
9. Brandt L, Brandt J, Olsson H, Anderson H, Moller T. Blood transfusion as a risk factor for non-Hodgkin lymphoma. *Br J Cancer.* 1996; 73:1148–51. [PubMed: 8624279]
10. Erber E, Lim U, Maskarinec G, Kolonel LN. Common immune-related risk factors and incident non-Hodgkin lymphoma: the multiethnic cohort. *Int J Cancer.* 2009; 125:1440–5. [PubMed: 19444913]
11. Blomberg J, Moller T, Olsson H, Anderson H, Jonsson M. Cancer morbidity in blood recipients--results of a cohort study. *Eur J Cancer.* 1993; 29A:2101–5. [PubMed: 8297647]
12. Cerhan JR, Engels EA, Cozen W, Davis S, Severson RK, Morton LM, Gridley G, Hartge P, Linet M. Blood transfusion, anesthesia, surgery and risk of non-Hodgkin lymphoma in a population-based case-control study. *Int J Cancer.* 2008; 123:888–94. [PubMed: 18506687]
13. Cerhan JR, Wallace RB, Dick F, Kemp J, Parker AS, Zheng W, Sellers TA, Folsom AR. Blood transfusions and risk of non-Hodgkin's lymphoma subtypes and chronic lymphocytic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2001; 10:361–8. [PubMed: 11319177]
14. Cerhan JR, Wallace RB, Folsom AR, Potter JD, Munger RG, Prineas RJ. Transfusion history and cancer risk in older women. *Ann Intern Med.* 1993; 119:8–15. [PubMed: 8498768]
15. Chow EJ, Holly EA. Blood transfusions and non-Hodgkin's lymphoma. *Epidemiol Rev.* 2002; 24:269–79. [PubMed: 12762097]
16. Chow EJ, Holly EA. Blood transfusions as a risk factor for non-Hodgkin's lymphoma in the San Francisco Bay Area: a population-based study. *Am J Epidemiol.* 2002; 155:725–31. [PubMed: 11943690]
17. Hjalgrim H, Edgren G, Rostgaard K, Reilly M, Tran TN, Titlestad KE, Shanwell A, Jersild C, Adami J, Wikman A, Gridley G, Wideroff L, Nyren O, Melbye M. Cancer incidence in blood transfusion recipients. *J Natl Cancer Inst.* 2007; 99:1864–74. [PubMed: 18073377]
18. Maguire-Boston EK, Suman V, Jacobsen SJ, Moore SB, Habermann TM, Cerhan JR, Folsom AR. Blood transfusion and risk of non-Hodgkin's lymphoma. *Am J Epidemiol.* 1999; 149:1113–8. [PubMed: 10369505]
19. Memon A, Doll R. A search for unknown blood-borne oncogenic viruses. *Int J Cancer.* 1994; 58:366–8. [PubMed: 8050819]
20. Nelson RA, Levine AM, Bernstein L. Blood transfusions and the risk of intermediate- or high-grade non-Hodgkin's lymphoma. *J Natl Cancer Inst.* 1998; 90:1742–3. [PubMed: 9827530]
21. Tavani A, Soler M, La Vecchia C, Franceschi S. Re: Blood transfusions and the risk of intermediate- or high-grade non-Hodgkin's lymphoma. *J Natl Cancer Inst.* 1999; 91:1332–3. [PubMed: 10433627]
22. Zhang Y, Holford TR, Leaderer B, Boyle P, Zahm SH, Owens PH, Morton LM, Zhang B, Zou K, Flynn S, Tallini G, Zheng T. Blood transfusion and risk of non-Hodgkin's lymphoma in Connecticut women. *Am J Epidemiol.* 2004; 160:325–30. [PubMed: 15286017]
23. Whitaker, BI.; Green, J.; King, MR.; Leibeg, LL.; Mathew, SM.; Schlumpf, KS.; Schreiber, GB. The 2007 National Blood Collection and Utilization Survey Report. AABB; Bethesda: 2007.
24. <http://seer.cancer.gov>
25. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care.* 2002; 40:IV-3–18.
26. Anderson LA, Pfeiffer R, Warren JL, Landgren O, Gadalla S, Berndt SI, Ricker W, Parsons R, Wheeler W, Engels EA. Hematopoietic malignancies associated with viral and alcoholic hepatitis. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:3069–75. [PubMed: 18957521]
27. Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, Clarke CA, Jack A, Cozen W, Maynadie M, Spinelli JJ, Costantini AS, Rudiger T, Scarpa A, Zheng T, Weisenburger DD. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood.* 2007; 110:695–708. [PubMed: 17389762]
28. Jaffe, ES.; Harris, NL.; Stein, H.; Vardiman, JW., editors. *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.* IARCPress; Lyon: 2001.

29. Quinlan, S.; Morton, L.; Pfeiffer, R.; Anderson, L.; Landgren, O.; Warren, J.; Engels, E. Increased risk for lymphoid and myeloid neoplasms following solid organ transplant submitted.
30. de Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, Spinelli JJ, Zheng T, Zhang Y, Franceschi S, Talamini R, Holly EA, Grulich AE, Cerhan JR, Hartge P, Cozen W, Boffetta P, Brennan P, Maynadie M, Cocco P, Bosch R, Foretova L, Staines A, Becker N, Nieters A. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol*. 2008; 6:451–8. [PubMed: 18387498]
31. Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El-Serag H, Engels EA. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA*. 2007; 297:2010–7. [PubMed: 17488966]
32. Zou S, Notari EPT, Stramer SL, Wahab F, Musavi F, Dodd RY. Patterns of age- and sex-specific prevalence of major blood-borne infections in United States blood donors, 1995 to 2002: American Red Cross blood donor study. *Transfusion*. 2004; 44:1640–7. [PubMed: 15504171]
33. Dodd RY, Notari EPT, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion*. 2002; 42:975–9. [PubMed: 12385406]
34. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. The Trial to Reduce Alloimmunization to Platelets Study Group. *N Engl J Med*. 1997; 337:1861–9. [PubMed: 9417523]
35. Claas FH, Roelen DL, van Rood JJ, Brand A. Modulation of the alloimmune response by blood transfusions. *Transfus Clin Biol*. 2001; 8:315–7. [PubMed: 11499985]
36. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. *Anesth Analg*. 2009; 108:759–69. [PubMed: 19224780]
37. Vandekerckhove BA, Datema G, Zantvoort F, Claas FH. An increase of donor-specific T helper precursors resulting from blood transfusions. *Transplantation*. 1990; 49:987–91. [PubMed: 2139988]
38. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. *J Intern Med*. 2008; 264:537–48. [PubMed: 19017178]
39. Kristinsson SY, Koshiol J, Goldin LR, Bjorkholm M, Turesson I, Gridley G, McMaster ML, Landgren O. Genetics- and immune-related factors in the pathogenesis of lymphoplasmacytic lymphoma/ Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma*. 2009; 9:23–6. [PubMed: 19362964]
40. Rothman, KJ.; Greenland, S. *Modern Epidemiology*. 2nd ed.. Lipponcott-Raven Publishers; Philadelphia: 1998.

Table 1

Characteristics of cases with hematologic malignancy and controls in the SMAHRT Study (1988–2002)

Characteristic	Cases (n=77,488)		Controls (n=154,509)		P-value
	N	%	N	%	
Gender					0.870
Male	38,063	49.1	75,841	49.1	
Female	39,425	50.9	78,668	50.9	
Age at diagnosis/selection, years					0.463
67–69	9,371	12.1	18,268	11.8	
70–74	19,524	25.2	39,069	25.3	
75–79	20,205	26.1	40,406	26.2	
80–84	15,508	20.0	31,021	20.1	
85+	12,880	16.6	25,745	16.7	
Median	77		77		
Selection year					0.987
1988–1993	20,177	26.0	40,199	26.0	
1994–1997	17,385	22.4	34,588	22.4	
1998–2000	18,431	23.8	36,836	23.8	
2001–2002	21,495	27.7	42,886	27.8	
Race/ethnicity					<0.0001
White	67,984	87.7	130,352	84.4	
Black	4,754	6.1	10,577	6.9	
Asian	1,494	1.9	5,552	3.6	
Hispanic	1,079	1.4	3,388	2.2	
Native American Indian	136	0.2	437	0.3	
Other/unknown	2,041	3.6	4,203	2.7	
Duration of Medicare coverage, mo					<0.0001
12–54	19,930	25.7	43,610	28.2	
55–90	19,000	24.5	38,613	25.0	
91–134	18,965	24.5	34,344	22.2	
135+	19,593	25.3	37,942	24.6	

Characteristic	Cases (n=77,488)		Controls (n=154,509)		P-value
	N	%	N	%	
Median	90		90		
No. physician claims					<0.0001
0-3	18,840	24.3	39,653	25.7	
4-38	17,917	23.1	39,980	25.9	
39-109	19,487	25.2	38,433	24.9	
110+	21,244	27.4	36,443	23.6	
Median	44		36		
No. outpatient claims					<0.0001
0	26,250	33.9	56,876	36.8	
1-2	11,386	14.7	24,061	15.6	
3-10	19,923	25.7	39,418	25.5	
11+	19,929	25.7	34,154	22.1	
Median	3		2		
No. hospital claims					<0.0001
0	38,303	49.4	81,915	53.0	
1	14,825	19.1	28,170	18.2	
2-3	13,885	17.9	25,163	16.3	
4+	10,475	13.5	19,261	12.5	
Median	1		0		

Table 2

Associations of hematologic malignancy subtypes with blood transfusions

	Total			Nonzero blood pints			Transfusion procedure			Either nonzero blood pints or transfusion procedure		
	N	N	%	OR (95% CI)*	N	%	OR (95% CI)*	N	%	OR (95% CI)*	N	%
Controls	154,509	6,283	4.1%	ref.	3,968	2.6%	ref.	9,095	5.9%	ref.		
Cases	77,488	4,120	5.3%	<u>1.33 (1.28–1.39)</u>	2,813	3.6%	<u>1.44 (1.37–1.52)</u>	6,091	7.9%	<u>1.37 (1.33–1.43)</u>		
Lymphoid neoplasms	61,348	2,909	4.7%	<u>1.20 (1.14–1.26)</u>	1,795	2.9%	<u>1.19 (1.12–1.27)</u>	4,195	6.8%	<u>1.21 (1.16–1.26)</u>		
Non-Hodgkin lymphoma	42,729	1,996	4.7%	<u>1.18 (1.12–1.25)</u>	1,175	2.7%	<u>1.11 (1.03–1.18)</u>	2,842	6.7%	<u>1.17 (1.12–1.23)</u>		
DLBCL	12,526	612	4.9%	<u>1.22 (1.12–1.34)</u>	353	2.8%	<u>1.08 (0.96–1.22)</u>	859	6.9%	<u>1.18 (1.09–1.27)</u>		
Burkitt lymphoma	213	<11	<5%	<u>0.96 (0.47–1.94)</u>	<11	<5%	<u>0.64 (0.23–1.73)</u>	11	5.2%	<u>0.85 (0.46–1.57)</u>		
Marginal zone lymphoma	1,915	100	5.2%	<u>1.27 (1.03–1.56)</u>	69	3.6%	<u>1.10 (0.86–1.41)</u>	151	7.9%	<u>1.22 (1.03–1.45)</u>		
Follicular lymphoma	5,661	228	4.0%	<u>1.11 (0.97–1.28)</u>	117	2.1%	<u>0.89 (0.74–1.08)</u>	305	5.4%	<u>1.02 (0.90–1.15)</u>		
CLL	13,227	599	4.5%	<u>1.12 (1.02–1.23)</u>	354	2.7%	<u>1.09 (0.97–1.22)</u>	861	6.5%	<u>1.13 (1.05–1.22)</u>		
LPL	1,397	84	6.0%	<u>1.49 (1.19–1.87)</u>	60	4.3%	<u>1.69 (1.29–2.20)</u>	128	9.2%	<u>1.59 (1.32–1.92)</u>		
B-cell NHL, NOS	1,927	95	4.9%	<u>1.24 (1.00–1.53)</u>	72	3.7%	<u>1.37 (1.08–1.75)</u>	148	7.7%	<u>1.31 (1.10–1.56)</u>		
T-cell NHL	2,222	114	5.1%	<u>1.34 (1.10–1.62)</u>	63	2.8%	<u>1.16 (0.89–1.50)</u>	160	7.2%	<u>1.30 (1.10–1.54)</u>		
NHL, NOS	2,985	129	4.3%	<u>1.12 (0.94–1.35)</u>	66	2.2%	<u>1.19 (0.92–1.53)</u>	180	6.0%	<u>1.18 (1.01–1.39)</u>		
Plasma cell neoplasms	12,974	633	4.9%	<u>1.25 (1.14–1.37)</u>	445	3.4%	<u>1.46 (1.31–1.62)</u>	964	7.4%	<u>1.35 (1.26–1.46)</u>		
Hodgkin lymphoma	1,543	74	4.8%	<u>1.32 (1.04–1.68)</u>	41	2.7%	<u>1.20 (0.88–1.65)</u>	102	6.6%	<u>1.28 (1.04–1.57)</u>		
LN, NOS	4,102	206	5.0%	<u>1.19 (1.03–1.38)</u>	134	3.3%	<u>1.30 (1.08–1.56)</u>	287	7.0%	<u>1.17 (1.03–1.33)</u>		
Myeloid neoplasms	14,267	1,050	7.4%	<u>1.78 (1.66–1.91)</u>	890	6.2%	<u>2.24 (2.07–2.42)</u>	1,641	11.5%	<u>1.93 (1.82–2.04)</u>		
AML	7,574	493	6.5%	<u>1.63 (1.47–1.80)</u>	399	5.3%	<u>2.11 (1.89–2.37)</u>	765	10.1%	<u>1.79 (1.65–1.95)</u>		
CML	2,052	137	6.7%	<u>1.68 (1.40–2.01)</u>	99	4.8%	<u>2.07 (1.68–2.56)</u>	203	9.9%	<u>1.80 (1.55–2.10)</u>		
MDS [†]	2,471	274	11.1%	<u>2.45 (2.13–2.81)</u>	265	10.7%	<u>1.70 (2.35–3.10)</u>	446	18.0%	<u>2.56 (2.29–2.87)</u>		
CMD [‡]	1,017	55	5.4%	<u>1.25 (0.94–1.65)</u>	61	6.0%	<u>1.53 (1.17–2.00)</u>	94	9.2%	<u>1.29 (1.04–1.61)</u>		
MN, NOS	312	27	8.7%	<u>2.08 (1.39–3.11)</u>	20	6.4%	<u>2.54 (1.59–4.07)</u>	37	11.9%	<u>2.04 (1.43–2.91)</u>		
Hematologic malignancies, NOS	1,873	161	8.6%	<u>1.95 (1.65–2.31)</u>	128	6.8%	<u>2.70 (2.23–3.27)</u>	255	13.6%	<u>2.31 (2.00–2.65)</u>		

Numbers of exposed cancer cases between 1 and 10 are reported as "<11" in accordance with the SEER-Medicare data use agreement.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; LPL, lymphoplasmacytic lymphoma; B-NHL, NOS, NHL B-cell, not otherwise specified; T-NHL, T-cell NHL; NHL NOS, NHL of unknown lineage; LN, NOS, lymphoid neoplasm, not otherwise specified; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; CMD, chronic myeloproliferative disease; MN NOS, myeloid neoplasm, not otherwise specified.

* Odds ratios are adjusted for age, race, sex, and selection year.

† Analyses were restricted to 2001–2002, the only years these subtypes were reportable to SEER.

Table 3

Associations of selected hematologic malignancy subtypes with characteristics of blood transfusion

Transfusion exposure	DLBCL	Marginal zone lymphoma	Follicular lymphoma	Chronic lymphocytic leukemia	Lymphoplasmacytic lymphoma	T-cell NHL	Plasma cell neoplasms	Hodgkin lymphoma
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
Latency period, years								
1–1.99	1.26 (1.05–1.50)	1.33 (0.86–2.05)	0.91 (0.67–1.23)	1.04 (0.86–1.25)	1.74 (1.13–2.70)	1.71 (1.20–2.44)	1.81 (1.56–2.10)	0.83 (0.46–1.50)
2–4.99	1.19 (1.05–1.34)	1.04 (0.76–1.42)	0.94 (0.77–1.15)	1.12 (1.00–1.27)	1.77 (1.33–2.37)	1.14 (0.85–1.52)	1.34 (1.19–1.50)	1.65 (1.23–2.20)
5–9.99	1.15 (1.02–1.30)	1.08 (0.81–1.45)	1.11 (0.91–1.34)	1.14 (1.01–1.29)	1.37 (0.99–1.89)	1.37 (1.05–1.78)	1.24 (1.09–1.40)	1.31 (0.93–1.84)
10+	1.14 (0.94–1.38)	1.80 (1.31–2.48)	1.25 (0.93–1.68)	1.24 (1.03–1.48)	1.56 (0.98–2.47)	1.16 (0.74–1.81)	1.18 (0.97–1.44)	0.80 (0.40–1.61)
P-trend	0.409	0.142	0.060	0.206	0.387	0.382	0.0002	0.731
Indication								
Coronary artery bypass	1.24 (1.04–1.49)	1.31 (0.88–1.94)	1.01 (0.76–1.35)	1.01 (0.84–1.22)	1.22 (0.76–1.96)	1.27 (0.86–1.86)	0.91 (0.74–1.12)	1.38 (0.87–2.19)
Hip replacement	1.15 (0.97–1.36)	1.09 (0.75–1.58)	1.04 (0.81–1.35)	1.11 (0.93–1.32)	1.47 (0.97–2.23)	1.16 (0.78–1.72)	1.19 (1.00–1.42)	1.19 (0.74–1.90)
Unspecified anemia	1.16 (1.04–1.31)	1.34 (1.05–1.69)	1.01 (0.84–1.22)	1.16 (1.04–1.31)	1.61 (1.22–2.12)	1.23 (0.96–1.59)	1.39 (1.24–1.55)	1.22 (0.89–1.69)
GI bleeding	1.22 (0.98–1.53)	0.95 (0.53–1.69)	0.96 (0.66–1.40)	1.03 (0.91–1.31)	1.71 (1.01–2.87)	1.35 (0.84–2.18)	1.33 (1.08–1.65)	1.50 (0.86–2.62)
No. of hospitalizations with transfusion								
1	1.17 (1.08–1.28)	1.23 (1.02–1.50)	1.00 (0.87–1.15)	1.11 (1.02–1.21)	1.53 (1.24–1.90)	1.31 (1.09–1.58)	1.34 (1.24–1.46)	1.32 (1.05–1.65)
2+	1.19 (1.03–1.38)	1.22 (0.88–1.69)	1.12 (0.89–1.41)	1.20 (1.04–1.38)	1.80 (1.28–2.55)	1.32 (0.95–1.84)	1.41 (1.23–1.62)	1.20 (0.78–1.84)
P-trend	<0.0001	0.026	0.451	0.0007	<0.0001	0.002	<0.0001	0.0321

Abbreviations: DLBCL, diffuse large B-cell lymphoma; GI, gastrointestinal

* Odds ratios are adjusted for age, race, sex, and selection year.

Table 4

Associations of selected hematologic malignancy subtypes with characteristics of blood transfusion

	<u>Acute myeloid leukemia</u>	<u>Chronic myeloid leukemia</u>	<u>Myelodysplastic syndrome</u>	<u>Chronic myeloproliferative disease</u>
	<u>OR (95% CI) *</u>	<u>OR (95% CI) *</u>	<u>OR (95% CI) †</u>	<u>OR (95% CI) †</u>
Latency period, years				
1–1.99	<u>2.58 (2.20–3.04)</u>	<u>2.07 (1.49–2.87)</u>	<u>4.25 (3.32–5.44)</u>	<u>2.30 (1.46–3.62)</u>
2–4.99	<u>2.00 (1.77–2.26)</u>	<u>2.09 (1.67–2.60)</u>	<u>2.82 (2.33–3.40)</u>	1.11 (0.73–1.68)
5–9.99	<u>1.43 (1.24–1.65)</u>	<u>1.68 (1.31–2.17)</u>	<u>2.32 (1.93–2.79)</u>	0.95 (0.63–1.44)
10+	<u>1.31 (1.05–1.65)</u>	0.93 (0.54–1.58)	<u>1.88 (1.49–2.36)</u>	<u>1.49 (1.00–2.20)</u>
P-trend	<0.0001	0.008	<.0001	0.2884
Indication				
Coronary artery bypass	1.19 (0.96–1.49)	0.99 (0.62–1.56)	<u>1.87 (1.43–2.43)</u>	0.88 (0.48–1.60)
Hip replacement	<u>1.25 (1.02–1.54)</u>	1.11 (0.74–1.67)	<u>2.08 (1.64–2.63)</u>	0.95 (0.56–1.59)
Unspecified anemia	<u>2.00 (1.77–2.25)</u>	<u>1.96 (1.58–2.45)</u>	<u>2.79 (2.41–3.23)</u>	<u>1.54 (1.16–2.04)</u>
GI bleeding	<u>1.67 (1.31–2.13)</u>	<u>2.18 (1.49–3.20)</u>	<u>2.28 (1.64–3.16)</u>	1.58 (0.86–2.89)
No. of hospitalizations with transfusion				
1	<u>1.57 (1.42–1.72)</u>	<u>1.63 (1.37–1.95)</u>	<u>2.09 (1.82–2.39)</u>	1.11 (0.85–1.45)
2+	<u>2.53 (2.21–2.90)</u>	<u>2.34 (1.80–3.04)</u>	<u>3.97 (3.33–4.72)</u>	<u>1.81 (1.27–2.57)</u>
P-trend	<0.0001	<0.0001	<.0001	0.003

Abbreviations: GI, gastrointestinal

* Odds ratios are adjusted for age, race, sex, and selection year.

† Analyses were restricted to 2001–2002, the only years these subtypes were reportable to SEER.