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Blood transfusions and the subsequent risk of cancers in the U.S. elderly

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Abstract

BACKGROUND—Blood transfusions are common in older adults, and also may modulate the immune system. However, the impact of transfusion on cancer risk in the elderly has not been studied.

STUDY DESIGN AND METHODS—Cancer risk after blood transfusion was evaluated in a U.S. population-based case-control study using 552,951 elderly cases identified from cancer registries and 100,000 frequency-matched controls. Transfusions received 0–12 months, 13–30 months and 31–48 months prior to cancer diagnosis or selection date were identified using Medicare claims. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regressions. A Bonferroni correction adjusted for multiple testing.

RESULTS—Transfusions received 0–12 months before cancer diagnosis/selection were associated with significantly elevated risk of cancer overall (OR=2.05; 95% CI: 1.95–2.16), and cancers of the stomach, colon, liver, kidney/renal pelvis/ureter, lymphoma, myeloma and leukemia. No significant associations for cancer overall were observed for the two earlier intervals. No site was associated with transfusions received 13–30 or 31–48 months before diagnosis/selection. Nonetheless, overall cancer risk increased with the number of transfused periods (p-trend < 0.0001).

CONCLUSION—Risk of overall cancer and specific sites was elevated 0–12 months after blood transfusion and associated with multiple transfusions, possibly due to reverse causation, i.e. incipient cancers or cancer precursors causing anemia.

Keywords

Surveillance; Epidemiology and End Results (SEER) registries; SEER-Medicare database; latency periods; transfusion-transmissible infections; transfusion-related immunomodulation (TRIM); reverse causation

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INTRODUCTION

The contributions of inflammation, immune disturbances, and infection to the etiology of cancer are increasingly recognized. The process of cancer-related inflammation is complex, involving numerous cell types and signaling molecules, but it is posited that these pathways lead to chronic tissue damage that, in turn, promotes cancer through the accumulation of genetic changes, cell proliferation, and angiogenesis (1). Immunosuppression, due to infection with human immunodeficiency virus (HIV) or from medications used in organ transplantation, increases the risk for numerous malignancies (2). Worldwide, approximately 16% of all cancers (23% in less developed countries and 7% in developed countries) are attributable to viruses and other infectious agents (3).

In this context, it is important to consider that blood transfusions may be a cause of some malignancies. Receipt of a blood transfusion may increase risk of cancer by causing immune suppressive or proinflammatory changes in the recipient's immune system, a constellation of effects termed "transfusion-related immunomodulation" (TRIM) (4). Blood transfusions might also increase risk by transmitting infectious agents associated with cancer risk, including Epstein-Barr virus, hepatitis C virus (HCV), and HIV, although transfused blood is typically screened now for most of these agents (5, 6).

The incidence of many types of cancer increases with age, and blood transfusions are also disproportionately more common among elderly adults (7, 8, 9). While an assessment of the contribution of blood transfusions to risk of cancer in the elderly is important, it is also possible that the presence of an undiagnosed cancer or a precursor to cancer in an individual causes anemia. These undiagnosed conditions could result in associations between blood transfusion and subsequent risk of cancer due to reverse causation. Along these lines, reverse causation was the explanation Hjalgrim and colleagues (10) gave for a marked increase in cancer risk they found in blood transfusion recipients from Denmark and Sweden, shortly after the transfusion. The overall standardized incidence ratios (SIRs) of cancer 6 months after transfusion were 4.80 (95% CI: 4.69–4.91) for recipients ages 70–79 years and 4.11 (95% CI: 4.01–4.22) for recipients 80 years or older. The SIRs of most cancers decreased with longer time periods since transfusion to near unity. However, the risk of tobacco- and alcohol- related cancers, including cancers of the tongue, mouth, pharynx, esophagus, liver and respiratory and urinary tracts, was still increased 10–20 years after blood transfusion suggesting that lifestyle-related factors correlated with conditions prompting transfusions may cause the observed cancer occurrence.

In the U.S., a detailed assessment of the association of transfusions with cancer risk has so far only been undertaken for hematologic malignancies. Chang et al (11) investigated the risk of hematologic malignancies after blood transfusion among the U.S. elderly using the Surveillance, Epidemiology and End Results (SEER)-Medicare database. They found that 7.9% of hematologic malignancy cases compared to 5.9% controls had a history of transfusion. Blood transfusions were associated with increased risk of multiple hematologic malignancy subtypes and risk following blood transfusion remained elevated for two non-Hodgkin lymphoma (NHL) subtypes, lymphoplasmacytic lymphoma and marginal zone lymphoma, at latency periods of several years, consistent with a possible etiologic relationship. However, Chang at al excluded transfusions occurring within one year of cancer diagnosis, and only studied the impact of latencies of one or more years.

To further characterize the associations of blood transfusion with risk of cancer, we conducted a large case-control study in the U.S. elderly population using SEER-Medicare data. In our study, we addressed the possibility of reverse causation by examining cancer risk in several intervals of time following blood transfusion, and also controlled for

confounding of the associations between transfusion and cancer risk by other diagnosed medical conditions.

MATERIALS AND METHODS

Data

We used the SEER-Medicare database that links data from the National Cancer Institute's SEER program cancer registries and the U.S. government health insurance program Medicare. Currently, the SEER cancer registries cover approximately 26% of the U.S. population. Within their catchment areas, the SEER registries are highly complete, recovering 97–98% of cancer cases (12). Medicare provides health insurance Part A coverage (hospital coverage includes inpatient care) for approximately 97% of people aged 65 or older in the U.S. Medicare Part B covers physician and outpatient services for approximately 96% of beneficiaries (13). Full details about the linkage are described in (14). In brief, the SEER-Medicare data are linked based on a deterministic matching algorithm that has been used by the National Center for Health Statistics to match to the National Death Index. The matching variables include each person's social security number, first name, last name, and date of birth. For the creation of the algorithm, hundreds of records were reviewed to determine the presence of false positives or false negatives. The data are linked every two years. Each linkage includes millions of Medicare beneficiaries, with an overall match rate of 94% for persons age 65 and older.

Selecting cases

Cases were defined as persons diagnosed with a first tumor during 1997–2005 in the SEER database. Solid tumors were defined using the SEER site recode (http://seer.cancer.gov/siterecode/icdo3_d01272003/) based on the International Classification of Diseases for Oncology, 3rd edition (15) site and morphology codes. To ensure that subjects had enough time to provide exposure and confounder information, we included only cases with a minimum of 60 continuous months of Medicare coverage before diagnosis. Due to this restriction, only individuals ages 70 years or older were selected. We excluded cases who were 100 years or older at diagnosis. We excluded cases diagnosed only on death certificate or at autopsy, those with missing month of diagnosis and cases whose diagnosis date was after their date of death. To ensure complete claims were available, cases had to have continuous Part A and B coverage and no health maintenance organization (HMO) enrollment during the 60 month period. After these exclusions, our study was based on a total of 552,951 cases diagnosed with a first cancer during 1997–2005 in SEER.

Selecting controls

A total number of 100,000 controls were selected from a 5% random sample of Medicare beneficiaries living in the SEER catchment areas. Controls were frequency matched to the cases by sex, age in four categories (70–74, 75–79, 80–84, and 85–99 years), and calendar year of selection (in single years). Individuals who were alive and cancer free as of July 1 in the calendar year of selection of the cases were eligible as controls. Similarly to the cases, we included only individuals with a minimum of 60 continuous months of Medicare coverage before selection and continuous Part A and B coverage and no HMO enrollment during the 60 month period. Controls could have been sampled multiple times in different calendar years or could later have become a case.

Blood transfusions

We reviewed Medicare claims from hospitals and physicians and other noninstitutional medical care providers to identify any blood transfusions administered. For Medicare

hospital claims, 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 (BLDPNTS variable) during the hospitalization was greater than zero. For provider claims, we used the Healthcare Common Procedure Codes of P9016, P9021, P9022, P9038, P9039, P9040, P9058, C1020, C1021, C9504, C9505, P9057. The analysis only includes blood that was administered. Blood products that were prepared, but not used, are not included as they cannot be billed to Medicare.

To address the latency of any blood transfusion effect on cancer risk, we investigated the receipt of transfusions in three time periods: 0–12 months, 13–30 months and 31–48 months prior to cancer diagnosis or control selection. If a person had more than one transfusion in a given interval, we selected the transfusion closest to the midpoint of the interval, otherwise we used the actual transfusion date in that interval. For an un-transfused person the index date for each transfusion interval was the midpoint of the interval.

Possible confounders

Using Medicare claims, we identified 96 acute medical diagnoses and chronic conditions, e.g. gastrointestinal hemorrhage, gastric ulcer, duodenal ulcer, bronchopneumonia, and vascular insufficiency of intestine, that were associated with the probability of receiving a blood transfusion based on the following criteria: the condition had to be present in at least 75 transfused cases and the condition had to be associated with transfusion, with an odds ratio larger or equal than 1.4 or smaller or equal than 0.7. These criteria were applied to ensure that the conditions could have reasonably strong confounding effects. We considered medical conditions reported within 12 to 24 months prior to the transfusion/index date to be relevant for the transfusion in that interval.

Statistical analysis

We used unconditional logistic regression models to estimate odds ratios (ORs) for the associations of cancer overall with transfusions received in the three time periods. To assess the dose-response relationship of blood transfusions and cancer risk, we created a variable defined as having had 0, 1, 2 or 3 periods with blood transfusions. For the analysis of cancers at specific sites, we used polytomous logistic regression models. All models were adjusted for the matching factors sex, age in four categories (70–74, 75–79, 80–84 and 85–99 years), and year of diagnosis or selection (1997–1999, 2000–2001, 2002–2003 and 2004–2005). We further adjusted for race (white, black, Asian, others/unknown) and the summary variable “any conditions”, that was defined to be 1 if any of the 96 conditions associated with blood transfusion was diagnosed and zero otherwise. We accounted for the repeated sampling of controls and the fact that some controls later became cases using a robust variance estimator (13). All models were additionally stratified by sex.

In a sensitivity analysis that we performed for all cancers that were significantly associated with transfusion, we fitted logistic regression models additionally adjusted for each of the individual 96 conditions separately and combinations of the conditions.

Finally, we repeated the selection of controls from the 5% random sample of Medicare beneficiaries, but now used frequency matching to the cases by sex and propensity scores (16). Three propensity scores, defined as the probability of receiving a blood transfusion in the three time intervals (0–12 months, 13–30 months and 31–48 months) given covariates, were computed for each person from the 5% random Medicare sample and for each case, separately for every calendar year and for men and women. The propensity score for each interval was calculated using a logistic regression model that included age, race and any of the 96 transfusion associated conditions identified using stepwise selection. Cases and

controls were then frequency matched by sex and the deciles of the propensity scores for each period, with a matching ratio of 1:0.2. Odds ratios for the association of cancer risk with blood transfusion for the three time periods were estimated using unconditional logistic regression models adjusted for sex, age, year of diagnosis or selection, race and the estimated propensity score, used as a continuous variable. Models that adjusted for the propensity score in deciles with a trend, or in ten separate categories did not yield different results (data not shown).

We present odds ratios (ORs) and 95% confidence intervals (CIs), but we highlight results that are still significant after a Bonferroni adjustment for 129 comparisons (43 sites for 3 time periods) with a type one error rate of 5%. After this correction findings with $p<0.0004$ are considered significant. All analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the study subjects

The characteristics of the 552,951 cases and 100,000 controls are presented in Table 1. There were no significant differences between the cases and controls for the matching variables (sex, age at diagnosis/selection, and selection year). The median age at diagnosis or selection was 78 years. The majority of the study population was white, and cases were slightly more likely to be white or black than controls (Table 1).

The presence of a medical condition associated with blood transfusion was somewhat higher for the time periods closer to diagnosis/selection (Table 1). For the time periods 0–12 and 13–30 months before diagnosis/selection, there were slightly more cases with any condition than controls. The median number of conditions reported for the 0–12 month time period for both cases and controls was five, and for the earlier time periods the median number was four for both groups, although slightly more conditions were reported for cases than controls (Table 1).

Association of transfusion with cancer risk

Among all cases, 3.5% had a blood transfusion within 0–12 months prior to their cancer diagnosis, while within 13–30 and 31–48 months prior to diagnosis, 2.3% and 1.8% of the cases respectively were recipients of a transfusion (Table 2). Among the controls, 1.7%, 2.1% and 1.6% had a transfusion within the three time periods, respectively. Fewer than 1% of cases and controls received blood transfusions in two or all three time periods (Table 2).

Overall cancer risk after blood transfusion was significantly increased during the first 12 months after transfusion (OR=2.05, 95% CI: 1.95–2.16) and then risk decreased to OR=1.04 (95% CI: 0.99–1.09) and OR=1.05 (95% CI: 1.00–1.11) for blood transfusions received 13–30 months and 31–48 months before diagnosis or selection, respectively (Table 3). The number of transfused periods was significantly associated with overall cancer risk, with OR=1.39 (95% CI: 1.35–1.44), OR=1.58 (95% CI: 1.42–1.75) and OR=2.39 (95% CI: 1.66–3.45) for one, two or three transfused periods, respectively (p-trend < 0.0001).

Similarly, the association of transfusion with risk of most specific cancer sites was stronger during the first 12 months after blood transfusion and decreased with increasing time since transfusion (Table 3). A statistically significantly higher risk after Bonferroni adjustment during the first 12 months after transfusion was found for cancers of the digestive system overall (OR=3.14, 95% CI: 1.97–4.99) and specifically for cancers of the stomach (OR=3.92, 95% CI: 2.46–6.25), colon (OR=3.73, 95% CI: 2.46–5.65), and liver (OR=3.29, 95% CI: 2.01–5.40); for kidney, renal pelvis, and ureter (OR=2.42, 95% CI: 1.50–3.92) for

myeloma (OR=4.71, 95% CI: 2.72–8.16), leukemia (OR=6.51, 95% CI: 3.81–11.13) and for Hodgkin lymphoma (OR=3.14, 95%CI: 1.75–5.62) and NHL (OR=2.38, 95%CI: 1.51–3.76). Risk for the first 12 months after transfusion was also significantly elevated (but not after multiple comparisons adjustment) for cancers at the following sites: esophagus (OR=1.78, 95% CI: 1.06–2.99), rectum (OR=2.00, 95% CI: 1.24–3.22), pancreas (OR=2.16, 95% CI: 1.34–3.47), respiratory system overall (OR=1.71, 95% CI: 1.04–2.79) and specifically for cancers of the lung (OR=1.72, 95% CI: 1.13–2.64), soft tissue (OR=1.99, 95% CI: 1.07–3.70), the urinary system overall (OR=1.79, 95% CI: 1.06–3.00) lymphoma overall (OR=2.41, 95% CI: 1.43–4.08) and Kaposi sarcoma (OR=3.22, 95% CI: 1.51–6.86).

After Bonferroni adjustment, cancer risk remained significantly elevated 13–30 months after transfusion only for liver cancer, with OR=1.72 (95% CI: 1.27–2.32). None of the site-specific cancers was significantly associated with transfusions after Bonferroni adjustment over a latency period of 31–48 months.

For specific cancers that were significantly associated with transfusions, we adjusted all models additionally for individual medical conditions. In these models, the ORs for association with blood transfusions did not change (Supplemental Table 1). The propensity score based analysis also yielded similar results. The exception was for liver cancer, where the adjusted OR decreased to 1.09 (95%CI: 0.84–1.41) for the 13–30 month period (Supplemental Table 2). The lower estimate for liver cancer was confirmed in the original matched dataset: using a model that adjusted jointly for chronic liver disease and cirrhosis, various types of anemias, iron deficiency, gastrointestinal hemorrhage, disorders of fluid, electrolyte, and acid-base balance, purpura and other hemorrhagic conditions and heart failure, the OR was 2.6 (95%CI: 2.23–3.04) for the 0–12 month period, 0.95 (95%CI: 0.78, 1.15) for the 13–30 month period, and 1.04 (95%CI: 0.83, 1.29) for the latency period of 31–48 months.

Separate analysis for men and women showed similarly increased risks during the first 12 months after blood transfusion for the cancers of the digestive system, stomach, colon, liver, myeloma and leukemia for both males and females. The risks for NHL and Kaposi sarcoma were significantly increased only for men and the risk for Hodgkin lymphoma was significantly increased only for women (Supplemental Tables 3 and 4).

Cancers of the stomach, colon, liver, kidney, renal pelvis, and ureter, myeloma and leukemia were also significantly associated with the number of transfused periods (p-trend<0.0001), as were cancers of the esophagus (p-trend=0.001), lymphoma (p-trend=0.002), respiratory system (p=0.003), pancreas (p-trend=0.004), mouth (p-trend=0.008), tongue (p-trend=0.009) and Kaposi sarcoma (p-trend=0.009).

DISCUSSION

In our case-control study of U.S. adults aged 70 years or older, we found that receipt of a blood transfusions was associated with significantly increased risk in the subsequent 0–12 month period, for cancer overall and (after multiple testing adjustment) risk of cancers of the stomach, colon, liver, kidney, renal pelvis and ureter, myeloma, leukemia and for Hodgkin lymphoma and NHL. Risk was also increased for cancer of the esophagus, rectum, pancreas, soft tissue, Kaposi sarcoma, lung and the urinary system, although the level of statistical significance was lower. There was no elevated overall cancer risk in the latency periods 13–30 months and 31–48 months after a transfusion. In site specific analyses, only the risk of liver cancer remained significantly elevated (after multiple testing adjustment) for the 13–30 month time period, however, this association disappeared after jointly adjusting for all possible confounding conditions, and when controls were matched based on propensity

scores. We also found a significant association of the number of transfused periods with overall cancer risk.

Our study is unique in focusing on an elderly population, among whom both blood transfusions and cancer are common. Hjalgrim et al (10) previously studied cancer incidence in Swedish and Danish individuals of all ages who received transfusions between 1968 and 2002. In agreement with our findings, they also observed the strongest associations for cancer diagnoses that occurred shortly after the first transfusion, and weaker effects for longer latency periods. Four years after transfusion, the relative risk for cancer decreased to SIR=1.07 in Hjalgrim's study and to OR=1.05 in our population. Similarly to Hjalgrim we found elevated risks shortly after transfusion for cancers of the esophagus, stomach, colon, rectum, pancreas, lung, and the urinary system, as well as NHL, Hodgkin lymphoma, myeloma and leukemias combined. We did not replicate Hjalgrim's findings of increased risk for cancers of the tongue, mouth and, pharynx. We did also not replicate Hjalgrim's findings of long term elevated risk for cancers of the tongue, mouth, pharynx, esophagus, liver, and respiratory and urinary tracts. Two explanations for these discrepancies are possible. First, we compared transfusion in cancer cases and controls aged 70 years or older, while Hjalgrim (10) studied blood transfusion recipients of all ages. As Hjalgrim found that the association between transfusion and cancer was weaker for a first transfusion received at older ages, one would expect more modest associations in an older population. Second, we were able to adjust our analyses for medical conditions that could confound the relationship of transfusion and cancer risk. Specifically for liver cancer, we found that after careful adjustment for confounding, no long term effect of transfusion on risk was observed, while the short term effect persisted.

Similar to our NHL results, a recent meta-analysis of NHL (17) reported an increased NHL risk after a blood transfusion. However, due to differences in lag time intervals across the studies, transfusion latency periods were not investigated and the risk estimate was somewhat weaker than seen in our data, especially for the 0–12 month period after transfusion. Chang et al (11) investigated the risk of hematologic malignancies in the SEER-Medicare population one or more years after a blood transfusion and found elevated risks for most subtypes only for latency periods closest to cancer diagnosis. However, for two NHL subtypes (lymphoplasmacytic lymphoma and marginal zone lymphoma), associations at longer latency intervals were consistent with an etiologic relationship. Chang et al (11) attributed the elevated risk of these lymphoma subtypes to "transfusion-related immunomodulation" (TRIM) (4) and gave a detailed discussion of the mechanistic underpinnings for a possible relationship.

Reverse causation likely plays a role in our findings, as the associations with cancer risk overall and for specific sites were strongest for transfusions received in the 0–12 months before diagnosis/selection. Many cancers or their precursors can cause anemia, and the work-up of the anemia can lead to the diagnosis of cancer. Cancers of the digestive system, as well as precancerous colon polyps, commonly cause chronic occult blood loss and iron deficiency anemia (18, 19), which would explain our results for cancer of the digestive system overall and for cancers of the stomach and colon. For other cancers that we observed to be associated with transfusion, anemia could have been caused by decreased red cell production which may accompany precursor conditions, such as liver disease (a precursor to liver cancer) or bone marrow disorders (which may precede leukemias and lymphomas) (20, 21). This explanation could also be the reason for the significant association of the number of transfusions with kidney cancer, as renal disease causes anemia, which leads to transfusion and also increases the risk of kidney cancer (19).

While reverse causation is the most likely explanation for our findings, we cannot entirely rule out that blood transfusions could affect or shorten the time of transitions of pre-cancers to cancer through TRIM, for example, the transition of myelodysplasia to detectable AML.

Using Medicare claims, we identified acute medical diagnoses and chronic conditions that potentially could act as confounders, given their frequency of occurrence and strengths of association with blood transfusion among the cases. We did not select conditions in relation to their importance for individual cancers. However our criteria likely ensure that all potentially important confounding conditions were selected. Confounding by documented medical conditions thus does not explain our findings, as ORs for the first latency period remained significantly elevated when we adjusted our models for individual conditions that were selected on the basis of being associated with blood transfusions. We also repeated analyses using a second set of controls that were matched to cases based on propensity scores, defined as the probability for receiving a blood transfusion given other available variables. This matching and analysis approach allowed us to more efficiently control for measured confounding. Results were changed only for liver cancer for the intermediate latency period, but not for any other cancer sites, which reassures us that we did not miss confounding by medical conditions captured by Medicare in the main analysis. In a sensitivity analysis we estimated associations of blood transfusion with overall cancer risk in individuals without any conditions and obtained results as seen for the whole study population.

Although we did not see significant associations with cancer risk for the longer periods following a transfusion, we did observe significant associations for the number of intervals in which transfusions were administered for cancer overall and several specific sites. This finding may point to an especially elevated risk in the small subgroup of people with chronic anemia, who are most likely to have a longstanding precursor condition to cancer or perhaps an undiagnosed malignancy (reverse causation). The possibility of reverse causation is also supported by Edgren et al. (22), who found that in Scandinavian blood donors, for most hematopoietic, lymphopoietic, and gastrointestinal malignancies, hemoglobin concentrations began to decrease two to three years before cancer diagnosis. However, the study was limited to hemoglobin measurements up to five years preceding the cancer diagnosis.

Unmeasured confounding by lifestyle factors, including tobacco and alcohol consumption, could also partially explain the elevated risk for cancer overall. Information on alcohol and tobacco use were not available in our data. Rogers et al (7) found significant associations between blood transfusions and alcohol and tobacco use in a cohort of older Americans. As noted above, liver disease related to alcoholism could cause both anemia and liver cancer (19). Likewise, tobacco use is a risk factor for peptic ulcer disease (23), which is associated with gastrointestinal blood loss and could explain the association we observed between blood transfusions and lung cancer. However, given that we adjusted for conditions associated with alcohol and smoking, additional adjustment for those factors likely would not strongly impact our findings. Transfusion-transmissible infections are an unlikely explanation for the elevated risk of liver cancer, because screening for hepatitis B virus began in 1969 and for hepatitis C virus in the early 1990s (5), leading to an extremely low residual infection risk (6).

A further limitation of our study is that we did not have information on transfusions received before age 65. Also, we lacked information on medical conditions before age 65 that could possibly confound associations. However, as controls were matched to the cases by age and calendar year, any lack of sensitivity in exposure assessment that arises from the limited duration of claims data is non-differential and would bias estimates towards the null.

Strengths of our study are the large population based case-control design and the nearly complete ascertainment of cancer cases from the source population in the SEER catchment areas. In addition, we were able to adjust for confounding by documented medical conditions, which likely impacted the results of earlier studies. We also confirmed our results in sensitivity analyses using a propensity scores based approach to matching and analysis, which more efficiently controlled for confounding. Our findings thus can be generalized to the U.S. elderly population.

In summary, we found that the receipt of a blood transfusion was associated with an increased short-term risk of cancer overall and for specific cancer types. Risk was not elevated over longer time periods, suggesting that transfusions in most patients that were later diagnosed with cancer are prompted by an undiagnosed cancer or a precursor to cancer. Our results do not provide support for a model in which transfusion contributes to the development of cancer over longer intervals, through pathways related to inflammation, immune modulation, or infection. Nonetheless, given the strong associations over shorter intervals, the possibility of an undiagnosed cancer should be considered for elderly patients with unexplained anemia, with further medical evaluation guided by individuals' overall health status (18).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of cases and controls in the SEER-Medicare database from 1997 to 2005

Characteristic	Cases (n = 552 951)		Controls (n = 100 000)		p-value
	N	Percent %	N	Percent %	
Sex					
Male	280 034	50.6	50 644	50.6	1.00
Female	272 917	49.4	49 356	49.4	
Age at diagnosis or selection (years)					
70–74	159 254	28.8	28 800	28.8	1.00
75–79	167 536	30.3	30 299	30.3	
80–84	126 165	22.8	22 817	22.8	
85–99	99 996	18.1	18 084	18.1	
Median (Range)	78 (70–99)		78 (70–99)		
Selection year					
1997–1999	110 534	20.0	19 989	20.0	1.00
2000–2001	153 125	27.7	27 692	27.7	
2002–2003	147 348	26.7	26 648	26.7	
2004–2005	141 944	25.7	25 671	25.7	
Race					
White	482 412	87.2	85 394	85.4	<.0001
Black	39 249	7.1	6 462	6.5	
Asian	13 105	2.4	3 378	3.4	
Other or unknown	18 185	3.3	4 766	4.8	
Any Condition 0–12 months					
No	42 331	7.7	8 488	8.5	<.0001
Yes	510 620	92.3	91 512	91.5	
Any Condition 13–30 months					
No	49 773	9.0	9 496	9.5	<.0001
Yes	503 178	91.0	90 504	90.5	
Any Condition 31–48 months					
No	60 592	11.0	11 153	11.2	0.070
Yes	492 359	89.0	88 847	88.9	

Characteristic	Cases (n = 552 951)		Controls (n = 100 000)		p-value
	N	Percent %	N	Percent %	
Total number of conditions 0–12 months					
0	42 331	7.7	8 488	8.5	<.0001
1	40 163	7.3	7 537	7.5	
2	50 909	9.2	9 711	9.7	
3+	419 548	75.9	74 264	74.3	
Median (Range)	5 (0–44)		5 (0–36)		
Total number of conditions 13–30 months					
0	49 773	9.0	9 496	9.5	<.0001
1	46 054	8.3	8 570	8.6	
2	56 767	10.3	10 657	10.7	
3+	400 357	72.4	71 277	71.3	
Median (Range)	4 (0–40)		4 (0–34)		
Total number of conditions 31–48 months					
0	60 592	11.0	11 153	11.2	0.006
1	54 677	9.9	9 923	9.9	
2	64 258	11.6	11 913	11.9	
3+	373 424	67.5	67 011	67.0	
Median (Range)	4 (0–38)		4 (0–31)		

Table 2

Number of recipients of blood transfusions for cases and controls according to the three time periods

Characteristics	Cases (n = 552 951)		Controls (n = 100 000)		OR (95% CI)
	N	Percent %	N	Percent %	
Blood transfusions 0–12 months					
No	533 536	96.49	98 265	98.27	2.05 (1.95–2.16)
Yes	19 415	3.51	1 735	1.74	
Blood transfusions 13–30 months					
No	540 050	97.67	97 936	97.94	1.04 (0.99–1.09)
Yes	12 901	2.33	2 064	2.06	
Blood transfusions 31–48 months					
No	542 970	98.19	98 376	98.38	1.05 (1.00–1.11)
Yes	9 981	1.81	1 624	1.62	
Number of transfused periods					
0	514 930	93.12	95 046	95.05	Reference
1	34 147	6.18	4 516	4.52	1.39 (1.35–1.44)
2	3 472	0.63	407	0.41	1.58 (1.42–1.75)
3	402	0.07	31	0.03	2.39 (1.66–3.45)

Table 3

Associations of blood transfusions with cancer risk, overall and for specific sites and subtypes

		OR[1] (95% CI)		
	Total[2]	0–12 months	13–30 months	31–48 months
All cancers	552 951	**2.05 (1.95–2.16)** [3]	1.04 (0.99–1.09)	1.05 (1.00–1.11)
Oral Cavity and Pharynx	8 897	1.38 (0.77–2.49)	**1.44 (1.04–1.98)**	1.18 (0.83–1.68)
Lip	1 119	1.06 (0.54–2.10)	1.33 (0.85–2.08)	1.13 (0.67–1.90)
Tongue	2 042	1.29 (0.72–2.30)	**1.58 (1.11–2.25)**	1.32 (0.87–1.98)
Salivary Gland	1 262	1.54 (0.84–2.85)	1.37 (0.90–2.08)	0.82 (0.48–1.41)
Mouth	2 418	1.55 (0.89–2.72)	1.38 (0.97–1.95)	1.27 (0.85–1.90)
Pharynx	2 056	1.34 (0.75–2.39)	**1.49 (1.03–2.15)**	1.19 (0.77–1.84)
Digestive System	125 386	**3.14 (1.97–4.99)** [3]	1.08 (0.85–1.38)	1.04 (0.80–1.35)
Esophagus	5 581	**1.78 (1.06–2.99)**	1.30 (0.96–1.77)	**1.40 (1.00–1.96)**
Stomach	10 961	**3.92 (2.46–6.25)** [3]	1.16 (0.88–1.55)	1.29 (0.94–1.76)
Colon	58 480	**3.73 (2.46–5.65)** [3]	1.11 (0.88–1.38)	0.95 (0.73–1.22)
Rectum	17 608	**2.00 (1.24–3.22)**	**0.72 (0.54–0.95)**	0.86 (0.63–1.16)
Anus	1 281	1.79 (0.98–3.25)	0.75 (0.45–1.24)	1.33 (0.83–2.14)
Liver	5 039	**3.29 (2.01–5.40)** [3]	**1.72 (1.27–2.32)** [3]	**1.65 (1.18–2.31)**
Pancreas	17 114	**2.16 (1.34–3.47)**	0.95 (0.73–1.24)	1.03 (0.77–1.39)
Respiratory System	92 639	**1.71 (1.04–2.79)**	1.18 (0.92–1.52)	1.24 (0.95–1.62)
Lung	88 275	**1.72 (1.13–2.64)**	1.17 (0.95–1.45)	1.24 (0.98–1.57)
Bones and Joints	396	1.26 (0.52–3.09)	1.27 (0.64–2.52)	1.00 (0.44–2.29)
Soft Tissue	2 504	**1.99 (1.07–3.70)**	0.94 (0.62–1.42)	0.99 (0.63–1.55)
Skin excluding Basal and Squamous	16 520	1.05 (0.59–1.87)	0.96 (0.70–1.30)	1.04 (0.75–1.45)
Melanoma	14 259	1.04 (0.62–1.72)	0.91 (0.69–1.19)	1.03 (0.76–1.39)
Breast [4]	64 701	0.94 (0.36–2.46)	0.83 (0.52–1.33)	0.93 (0.54–1.59)
Female Genital System	24 812	1.53 (0.57–4.14)	0.89 (0.53–1.49)	0.97 (0.54–1.75)
Cervix	1 727	1.69 (0.61–4.68)	1.29 (0.73–2.28)	1.30 (0.66–2.53)
Uterus	12 210	1.15 (0.44–3.02)	0.81 (0.49–1.32)	0.88 (0.50–1.56)
Ovary	7 940	1.96 (0.75–5.14)	0.83 (0.49–1.38)	0.96 (0.53–1.74)
Vagina/Vulva	2 221	1.52 (0.55–4.24)	1.17 (0.67–2.03)	1.28 (0.67–2.43)
Male Genital System	91 147	0.89 (0.36–2.22)	0.80 (0.48–1.36)	0.81 (0.47–1.40)
Prostate	90 546	0.89 (0.40–1.96)	0.81 (0.51–1.27)	0.81 (0.50–1.32)
Urinary System	45 343	**1.79 (1.06–3.00)**	1.05 (0.80–1.39)	1.09 (0.81–1.47)
Urinary Bladder	31 799	1.53 (0.96–2.44)	1.05 (0.82–1.34)	1.10 (0.84–1.45)
Kidney, Renal Pelvis, and Ureter	13 166	**2.42 (1.50–3.92)** [3]	1.04 (0.78–1.37)	1.07 (0.79–1.46)
Eye and Orbit	728	0.74 (0.3–1.79)	0.79 (0.42–1.52)	1.03 (0.53–1.98)
Brain and Other Nervous System	4 824	1.08 (0.58–2.00)	0.95 (0.66–1.37)	0.83 (0.55–1.24)
Endocrine System	3 236	1.24 (0.67–2.32)	0.70 (0.46–1.06)	0.85 (0.55–1.33)
Thyroid	2 871	1.12 (0.63–1.97)	0.68 (0.45–1.01)	0.81 (0.53–1.25)
Lymphoma	29 991	**2.41 (1.43–4.08)**	0.96 (0.71–1.29)	1.09 (0.79–1.49)

		OR[1] (95% CI)		
	Total[2]	0–12 months	13–30 months	31–48 months
Hodgkin Lymphoma	909	**3.14 (1.75–5.62)** [3]	1.05 (0.63–1.74)	0.96 (0.54–1.73)
NHL, including CLL[5]	29 082	**2.38 (1.51–3.76)** [3]	0.95 (0.74–1.22)	1.09 (0.82–1.43)
Myeloma	7 792	**4.71 (2.72–8.16)** [3]	1.15 (0.81–1.64)	1.08 (0.74–1.59)
Leukemia	8 863	**6.51 (3.81–11.13)** [3]	**1.66 (1.19–2.32)**	1.38 (0.95–1.99)
Mesothelioma	1 703	1.83 (0.95–3.52)	0.87 (0.54–1.39)	1.08 (0.66–1.78)
Kaposi Sarcoma	293	**3.22 (1.51–6.86)**	1.60 (0.83–3.09)	0.64 (0.21–1.88)

Results in boldfaced font are significant at the alpha=0.05 level

[1]The OR for overall cancer risk is adjusted for sex, age, race, selection year and any condition as categorical variables. The ORs for the site specific cancer groups like digestive system are adjusted for sex, age, race and any condition as categorical variables and selection year as continuous variable. The ORs for subtypes of the site specific cancer groups are adjusted for sex and race as categorical variables and age, selection year and any condition as continuous variables.

[2]The number of cases may not add up to the totals for cancer specific sites and for cancer overall because miscellaneous cancers were excluded.

[3]Association is significant at p<0.0004 (Bonferroni correction for all 129 comparisons, 43 sites for 3 time periods).

[4]Women only (537 males are excluded from analysis).

[5]CLL = chronic lymphocytic leukemia