

# Blood Transfusion and Non-Hodgkin Lymphoma: Lack of Association

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**Background:** Non-Hodgkin lymphoma is the seventh most commonly diagnosed malignant condition worldwide, and its incidence has increased markedly in recent decades. Blood transfusions have been implicated as a possible risk factor for non-Hodgkin lymphoma.

**Objective:** To determine whether blood transfusions are associated with an elevated risk for non-Hodgkin lymphoma.

**Design:** Population-based, nested case-control study.

**Setting:** Nationwide cohort in Sweden.

**Patients:** 361 patients with non-Hodgkin lymphoma and 705 matched controls, nested within a population-based cohort of 96 795 patients at risk for blood transfusion between 1970 and 1983. Prospectively collected information on exposure was retrieved from computerized transfusion registries.

**Measurements:** Odds ratios obtained from conditional logistic regression models were used as measures of relative risks.

**Results:** No association was found between blood transfusions and the risk for non-Hodgkin lymphoma when patients who had received transfusions were compared with patients who had not received transfusions (odds ratio, 0.93 [95% CI, 0.71 to 1.23]). A reduction in risk was seen among persons who received transfusion of blood without leukocyte depletion (odds ratio, 0.72 [CI, 0.53 to 0.97]). Risk was not related to number of transfusions, and no interaction was seen with latency after transfusion.

**Conclusion:** The findings in this study do not support previous observations of an association between blood transfusions and the risk for non-Hodgkin lymphoma.

Non-Hodgkin lymphomas comprise a heterogeneous group of lymphoid neoplasms that vary in terms of cell of origin, pathogenesis, and natural history. Although it is classified with the leukemias in the International Classification of Diseases, chronic lymphocytic leukemia is also part of the spectrum of non-Hodgkin lymphoma (1). Several countries have reported an increase in the incidence of non-Hodgkin lymphomas (2-5) that can be dated in some surveys from the 1930s and 1940s (6-8). This increase is found in all age groups and both sexes (3, 6, 8), but its causes are essentially unknown.

Immunologic dysfunction may predispose patients to the development of non-Hodgkin lymphoma; substantially elevated risks have been reported among persons who have primary and acquired immunodeficiencies (9-15). In addition, the prevalence of some immunodeficient conditions, especially AIDS, has increased. This increased prevalence has contributed in part to recent trends in the incidence of non-Hodgkin lymphoma, but it cannot account for the long-term increase.

Because blood transfusions can induce immunosuppression (16-18) and increase susceptibility to infections, including infections that are caused by blood-borne organisms (19-23), transfusions have been suggested as a possible risk factor for the development of non-Hodgkin lymphoma. The few epidemiologic studies that have tested this hypothesis (24-27) have reported an excessive relative risk for non-Hodgkin lymphoma among persons who received blood transfusions. However, these studies used small numbers of patients with non-Hodgkin lymphoma, and the risk estimates may have been inflated by various biases.

To shed further light on the possible association between blood transfusions and non-Hodgkin lymphoma, we performed a case-control study that was nested within a population-based cohort. We used registry-based sources in Sweden to obtain information on blood transfusion status and a diagnosis of non-Hodgkin lymphoma. Accurate identification and linkage of records among the different registries were made possible by the unique national registration number given to every resident of Sweden.

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## Methods

### Registries

#### *The Inpatient Register*

Since 1965, the National Board of Health and Welfare has collected data on individual hospital discharges in the Inpatient Register, which has been described elsewhere (28, 29). The proportion of the Swedish population covered by this registry increased from 60% in 1969 to 85% in 1983. Each record contains as many as 8 discharge diagnoses, coded during the period of cohort accrual according to the eighth revision of the International Classification of Diseases. Furthermore, each record can contain up to 10 surgical codes, assigned according to the Swedish Classification of Operations and Major Procedures. Patients are identified through their national registration numbers. The registry has been evaluated for validity and completeness, and the codes for the main diagnoses were correct at the 3-digit level for 92% to 94% of records on surgical patients (30, 31). For surgical procedures (excluding endoscopies or biopsies), the codes were incorrect for 2% of records and were missing for 5.3% (31).

#### *The Swedish Cancer Registry*

The Swedish Cancer Registry, established in 1958, receives reports of all new diagnoses of malignant tumors. Notification is mandatory by law, and almost all cases are reported by the physician who made the diagnosis and by the pathologist or cytologist who confirmed it. Almost 98% of all patients with a diagnosis of cancer are reported to the registry, and 97% of these diagnoses are morphologically verified by a pathologist (32). The Cause of Death Registry, which is almost complete and is updated continuously, provides information on all persons who have died; records include such information as underlying and contributing causes of death, date of death, and age at death.

### *Transfusion Registries*

In the late 1960s and early 1970s, an increasing number of hospitals established transfusion registries. These registries include the national registration number of the transfusion recipient, the date of transfusion, the number of transfusion units given, the type of transfusion, the acute complications encountered, and the national registration number of the donor (33). The registries were in full operation between 1 January 1968 and 1 January 1974 and covered all transfusions given at a hospital. Most of the registries are run by one of two organizations: Databyrån för Informationsbehandling or Kebo Computer (both located in Stockholm, Sweden).

### Patients

#### *Identification of Cohort*

In Sweden, patients must use public hospitals in their county of residence for inpatient care; as a result, private inpatient treatment is almost nonexistent. Therefore, hospital-provided medical services are, in effect, population-based and are referable to the county in which the patient lives. Each hospital has a catchment area that does not overlap with that of other hospitals. For nonacute diseases, patients must use the hospital in the catchment area in which they live. Furthermore, the referral pattern of local hospital to county hospital to university hospital is fixed for each catchment area. Therefore, the likelihood of a study participant receiving a transfusion at a hospital without a transfusion registry was small, particularly because referral patterns were fixed for the areas under study. The study base was defined as the population living in the catchment areas of hospitals in which a transfusion registry had been in full operation since the late 1960s to early 1970s. The starting date for each catchment area was determined by the requirement that the transfusion register had to have been in operation for at least 2 years.

From the Swedish Inpatient Register, we selected all patients in the study base who were hospitalized through 1983 for 11 surgical procedures and benign diseases and who were at risk for blood transfusion. We initially identified 118 671 records with one or more of these 11 diagnoses or procedure codes. By sorting the records according to national registration number, we identified 97 372 patients who had had at least one hospitalization for the aforementioned conditions or procedures. The first hospitalization marked entry into the cohort. National registration numbers that could not be found in the Population, Death, or Migration registers ( $n = 347$ ) were considered coding errors. Because these patients were not available for follow-up, we excluded these records. Of the remaining patients, we ex-

**Table 1. Selected Characteristics of the Study Cohort**

Characteristic	Value
Patients, <i>n</i>	94 788
Mean age at entry into cohort, <i>y</i>	57
Age distribution at entry, %	
<30 years	8.5
30–39 years	9.1
40–49 years	14.9
50–59 years	16.3
60–69 years	22.6
70–79 years	21.3
≥80 years	7.3
Sex, %	
Male	50.1
Female	49.9
Mean follow-up, <i>y</i>	10.7

cluded 2108 who died during the first hospitalization and 129 who had prevalent non-Hodgkin lymphoma at time of entry into the cohort. A total of 96 795 patients were thus available for analysis. Selected characteristics of the cohort are shown in **Table 1**.

### Follow-up

By using the national registration numbers, the cohort file was linked to the Swedish Migration, Death, and Cancer registers. These linkages provided information on the occurrences of emigration, death, or incident cancers. Follow-up began at entry to the cohort and continued until the date of diagnosis of non-Hodgkin lymphoma, death, emigration, or end of follow-up (31 December 1991), whichever occurred first. Follow-up ranged from 1 to 22 years.

### Case-Patients and Controls

For the case-control analysis, we defined the case-patients as cohort members in whom non-Hodgkin lymphoma (including chronic lymphocytic leukemia) was diagnosed during the period from 1 year after enrollment until 31 December 1991. Using the codes for non-Hodgkin lymphoma (200 and 202) and chronic lymphocytic leukemia (204.1) in the International Classification of Diseases, Seventh Revision, we identified 361 case-patients.

For each case-patient, two individually matched controls were randomly selected from the cohort. Controls had to survive at least until the date when their matched case-patient received a diagnosis of non-Hodgkin lymphoma; must not have emigrated before that date; and had to match the case-patient for sex, 5-year age band, diagnosis or procedure at entry, hospital, and date of initial discharge within 2 years. Because we were unable to identify two controls for every case-patient, the total number of controls was 705. Basic demographic data about the case-patients are given in **Table 2**.

### Exposure to Blood Transfusions

Exposure to blood transfusions was determined through records linked to computerized transfusion registries at the local and referral hospitals of case-patients and controls. Each case-patient and his or her matched controls were followed in the transfusion registries for an equal amount of time; the starting point was 2 years before the hospitalization during which the case-patient entered the cohort, and the end point was 1 year before non-Hodgkin lymphoma was diagnosed. The latter restriction was made to avoid including patients whose transfusions were prompted by the development of non-Hodgkin lymphoma. We analyzed the data by focusing on transfusion status at entry into the cohort (including

**Table 2. Selected Characteristics of the Case-Patients\***

Characteristic	Case-Patients (n = 361)
Patients with non-Hodgkin lymphoma, n	
ICD-7 codes 200 and 202	260
ICD-7 code 204.1†	101
Mean age at diagnosis, y	65
Age distribution, %	
<30 years	0.6
30-39 years	1.4
40-49 years	9.1
50-59 years	19.4
60-69 years	30.5
70-79 years	29.6
≥80 years	9.4
Sex, %	
Male	70
Female	30
Mean time from entry into cohort until diagnosis of non-Hodgkin lymphoma, y	7.0
Follow-up distribution, %	
1-3 years	35.5
4-7 years	34.9
8-11 years	23.0
≥12 years	6.6

\* ICD-7 = International Classification of Diseases, Seventh Revision.

† Indicates patients who had chronic lymphocytic leukemia.

the first hospitalization) and evaluating all transfusions recorded in the transfusion registries from 2 years before entry into the cohort until 1 year before the case-patient received a diagnosis of non-Hodgkin lymphoma. Because both analyses yielded almost identical results, we report the results of the latter analysis.

We evaluated the total number of transfusion units given, the total number of transfusion events, and the types of transfusions given according to leukocyte content. A transfusion unit equaled 500 mL of whole blood or derived red cells; a transfusion event was defined as a 14-day period beginning with a first transfusion. For two events to be considered separate transfusion events, at least 2 weeks had to elapse between them. Because leukocytes are likely to induce immunosuppression, the transfusion types were categorized according to the leukocyte content as follows: transfusion without leukocyte reduction (100% leukocytes), leukocyte-reduced transfusion (20% to 50% leukocytes remaining), leukocyte-depleted transfusion (<5% leukocytes remaining), undefined transfusion type, and all transfusion types combined. Patients in the last group were categorized according to the recorded transfusion with the highest leukocyte content.

We evaluated the validity of the transfusion information in the registers by selecting a random sample of 100 case-patients and 100 controls for review of medical records. The records for every recorded inpatient episode were scrutinized in a blinded manner with respect to case-control status and transfusion information. The transfusion status of the patients (received or never received a trans-

**Table 3. Odds Ratios for Non-Hodgkin Lymphoma after Blood Transfusion by Type of Transfusion\***

Variable	Exposed Case-Patients	Exposed Controls	Odds Ratio (95% CI)
	n		
Never had transfusion	198	376	1.00
Had transfusion	163	329	0.93 (0.71-1.23)
100% leukocytes	124	285	0.72 (0.53-0.97)
20%-50% leukocytes	38	75	1.01 (0.64-1.59)
<5% leukocytes	21	41	1.01 (0.59-1.71)
Undefined transfusion	16	11	3.68 (1.48-9.15)

\* Case-patients in each transfusion category are compared with controls who received the same type of transfusion.

fusion, with the information in the record used as the gold standard) showed a sensitivity of 84% and a specificity of 93%. The registers performed equally well for case-patients and controls.

### Statistical Analysis

A logistic regression model was used as the basic model in the analyses, and the parameters of the model were estimated by the conditional maximum likelihood method (34). Models were estimated by using continuous and categorized variables, as well as variables for having received or never having received a transfusion. Likelihood ratio tests were mainly used. Trend tests were done by using models in which ordinal categories, such as those for the number of transfusions and the percentage of leukocytes in the blood products, were assigned the integer values 0, 1, 2, and so on. In addition to univariate models in which the effect of each type of transfusion was considered in isolation, multivariate models in which all four types of transfusions were evaluated simultaneously were also estimated. Because the results of multivariate analyses did not vary measurably from results of the univariate analyses, we present the latter.

### Results

When all types of transfusions were considered, we found no association between transfusion and the risk for non-Hodgkin lymphoma. The odds ratio among persons who had received a transfusion compared with persons who had never received a transfusion was 0.93 (95% CI, 0.71 to 1.23). A significantly decreased risk was associated with transfusion of blood that had no leukocyte reduction (odds ratio, 0.72 [CI, 0.53 to 0.97]). An excessive risk was associated with transfusions that could not be classified; this may represent a chance finding based on small numbers (Table 3). The few case-patients and controls who had three or more transfusion events

did not have a significantly increased risk compared with their matched controls. An increasing number of transfusion events was not associated with a trend toward increased risk ( $P$  for trend = 0.99) (Table 4).

More detailed analysis did not reveal a dose-risk trend for amount of blood given (Table 5): The odds ratio was 1.03 (CI, 0.44 to 2.44) for patients in the highest category (patients who received >20 units of blood) compared with patients who did not receive transfusion. A significant trend toward risk reduction was seen as the number of leukocyte-rich transfusion units increased. The risk associated with transfusions of blood with reduced or depleted leukocytes did not differ from the risk associated with other types of transfusions.

Analyses done on the basis of the type of transfusion and the amount of blood given at entry into the cohort (that is, during the first hospitalization only) produced similar results (data not shown). Stratification done on the basis of the time between entry into the cohort and the time of diagnosis or the corresponding time point for controls (<5 years compared with  $\geq 5$  years) produced similar risk estimates in both strata, indicating no interaction between the latency period and transfusion (data not shown).

### Discussion

Our results do not support previous observations of an increased risk for non-Hodgkin lymphoma after blood transfusion (24-27). Despite the use of reliable, prospectively collected data on exposure, we found no association between the amount of blood given or the type of transfusion and the risk for non-Hodgkin lymphoma. The large number of patients in our study who had received transfusions permitted various stratifications of the data, but no subgroups with a defined type of blood transfusion showed an increased risk.

Transfusion of human blood products involves

**Table 4. Odds Ratios for Non-Hodgkin Lymphoma by Number of Transfusion Events\***

Transfusion Events	Exposed Case-Patients	Exposed Controls	Odds Ratio (95% CI)
	n		
0	198	376	1.00
1	119	238	0.94 (0.70-1.26)
2	26	68	0.73 (0.44-1.21)
3	12	15	1.46 (0.67-3.20)
4-9	6	8	1.35 (0.46-3.97)

\* One transfusion event equals a 14-day period beginning with a first transfusion.

transfer of biologically active components, including various blood cells; proteins; and, perhaps, infectious agents. Potential hazards include prolonged immunosuppression and increased susceptibility to infections (16-23). In recent decades, such techniques as testing for transmissible viruses and separation of leukocytes have substantially reduced the overall risks associated with blood transfusions. However, recent reports that hepatitis C virus infection may predispose persons to non-Hodgkin lymphoma have created concern about transmissible oncogenic agents (35-37). Because blood transfusions are commonly used worldwide, a carcinogenic hazard would have major clinical and public health implications.

Previous studies that found an association between blood transfusions and non-Hodgkin lymphoma have some limitations. Cerhan and colleagues (25) conducted a prospective cohort study among 37 337 women in Iowa who reported the occurrence of previous transfusions at entry into the cohort. Data from 66 patients in that study indicated that the risk for non-Hodgkin lymphoma was increased twofold among patients who reported a history of transfusions. Because none of the women were followed for more than 5 years, some cases of non-Hodgkin lymphoma may have been at a pre-clinical stage at the time of baseline survey; this raises the possibility of differential misclassification of transfusion status. Because the study was not primarily designed to investigate the association between blood transfusion and risk for non-Hodgkin lymphoma, no details were given about the type or amount of blood products used. The results may have been a chance occurrence that resulted from the multiple comparisons made.

Blomberg and associates (24) also reported an elevated risk for non-Hodgkin lymphoma in a cohort of 6323 blood transfusion recipients compared with the general population in Sweden. This result was based on only seven cases, and the statistical power of the study was too low to allow firm conclusions. More recently, a Swedish case-control study (27) suggested that transfusions were linked to risk for non-Hodgkin lymphoma, but the self-reported exposure information lacked details and was not validated. Finally, Memon and Doll (26) identified about 13 000 infants in Great Britain who received blood transfusions during the postnatal period and reported a nonsignificant twofold increase in risk on the basis of four cases of non-Hodgkin lymphoma.

A major strength of our study is the case-control design nested within a well-defined study base. The individually matched controls were selected from the same study population as the case-patients (38-40). Because all patients had conditions that were

**Table 5. Odds Ratios for Non-Hodgkin Lymphoma by Type and Amount of Transfusion\***

Type and Number of Transfusion Units	Exposed Case-Patients	Exposed Controls	Odds Ratio (95% CI)	P Value for Trend
<i>n</i>				
100% leukocytes				
Never received transfusion	198	376	1.0	0.032
0 units	39	44	1.80 (1.08-3.00)	
1-2 units	54	123	0.77 (0.52-1.14)	
3-5 units	42	88	0.85 (0.55-1.31)	
6-10 units	19	46	0.73 (0.40-1.31)	
≥11 units	9	28	0.54 (0.24-1.21)	
20%-50% leukocytes				
Never received transfusion	198	376	1.0	>0.2
0 units	125	254	0.92 (0.67-1.26)	
1-2 units	14	26	1.04 (0.52-2.07)	
3-5 units	12	27	0.84 (0.41-1.74)	
6-10 units	7	13	1.05 (0.40-2.75)	
≥11 units	5	9	1.07 (0.34-3.34)	
<5% leukocytes				
Never received transfusion	198	376	1.0	>0.2
0 units	142	288	0.92 (0.69-1.24)	
1-2 units	12	23	0.99 (0.48-2.04)	
≥3 units	9	18	0.96 (0.42-2.19)	
Undefined transfusion				
Never received transfusion	198	376	1.0	0.029
0 units	147	318	0.83 (0.62-1.11)	
1-5 units	11	5	6.30 (1.73-22.96)	
≥6 units	5	6	1.84 (0.52-6.45)	
All transfusion types				
Never received transfusion	198	376	1.00	>0.2
1-2 units	65	120	1.01 (0.70-1.47)	
3-5 units	48	97	0.94 (0.62-1.42)	
6-10 units	25	64	0.74 (0.44-1.23)	
11-20 units	16	31	1.05 (0.55-2.01)	
≥21 units	9	17	1.03 (0.44-2.44)	

\* One transfusion unit equals 500 mL of whole blood or red cells derived from whole blood.

not related to non-Hodgkin lymphoma and because follow-up was stopped 1 year before non-Hodgkin lymphoma was diagnosed, confounding by indication was essentially excluded. Losses to follow-up were minimal. In addition, exposure information, including dose, timing, and type of blood product, was collected before identification of case-patients and controls. This precludes differential misclassification of transfusion status, a serious problem in many case-control studies (38-40).

The sensitivity and specificity of the transfusion registries do not explain the negative findings in our study. On the basis of the observed number of exposed and unexposed patients and the estimated sensitivity and specificity in the validation study, we can calculate the expected true distribution of exposed and unexposed case-patients and controls. The odds ratio obtained by using that distribution is consistent with our results (data not shown).

Because the computerized transfusion registries that we used did not cover transfusions given at hospitals outside the study base or before the late 1960s, some exposed patients may have been misclassified as unexposed according to transfusion sta-

tus. However, because patients had to use hospitals in their catchment areas, this misclassification should be minor.

Another possible limitation of our study is that cases of non-Hodgkin lymphoma could not be subtyped by using data from the Swedish Cancer Registry; however, we are not aware of any data suggesting that the risk for non-Hodgkin lymphoma is not confined to patients who have received transfusions. Moreover, we found no differences in risk between cases registered as typical non-Hodgkin lymphoma and those reported as chronic lymphocytic leukemia. The composition of our cohort did not allow us to evaluate the potential risk generated by postnatal exposure to transfusions, as suggested by Memon and Doll (26).

Most patients in the study by Cerhan and coworkers (25) received transfusions much earlier than did the patients in our study. These early transfusions had a much higher leukocyte content than did those given in the 1970s and 1980s in Sweden. Since the mid-1970s, the buffy coat has been routinely depleted from the blood products in many European countries, including Sweden. It is conceivable that our patients were, on average, not sufficiently exposed to leukocytes to induce the immunosuppression required for development of non-Hodgkin lymphoma. However, if the discrepancy between our results and those of Cerhan and colleagues (25) can be explained by the difference in leukocyte content, we should have found a trend toward higher risk among patients who received leukocyte-rich transfusions. Rather, we found that the risk tended to decrease with the total number of transfused units, particularly when leukocyte-rich blood was given.

In our study, with its large cohort and design advantages, we did not find an association between blood transfusions given during the 1970s and 1980s and subsequent risk for non-Hodgkin lymphomas. Our findings are reassuring for recipients of blood transfusions because they do not support earlier reports of an excess risk for non-Hodgkin lymphomas.

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## AD LIBITUM

"A singularity is a mathematical point at which space and time are infinitely distorted, where matter is infinitely dense . . ."

*The New York Times*, 12 February 1997

### Sunset on the Turnpike

Black holes and naked singularity  
 Keep me in constant awe of outer space—  
 I haven't felt the force of gravity  
 Collapse my inner sense of time or place.  
 Perhaps my limited trajectory  
 Protects me from the rims of galaxies  
 Or this confining earthbound entropy  
 Defies extremes of griefs or ecstasies.  
 Sunset on the Turnpike describes my state—  
 Not truly glacial, but perhaps devoid  
 Of cosmic movement, blending slow and late  
 Into a kind of twilight trapezoid—  
 Sky above, earth below, the sides as stark  
 As the event horizon, and as dark.

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