Blood Transfusions and Risk of Non-Hodgkin's Lymphoma Subtypes and Chronic Lymphocytic Leukemia[1]

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Abstract

Allogeneic blood transfusion has been suggested as a risk factor for non-Hodgkin's lymphoma (NHL), possibly specific to certain NHL subtypes, or chronic lymphocytic leukemia (CLL). Self-reported transfusion history and risk of NHL subtypes and CLL were examined in a cohort of 37,934 older Iowa women, using data from a questionnaire mailed in 1986. Through 1997, 229 cases of NHL and 57 cases of CLL in the cohort were identified through linkage to the Iowa Surveillance, Epidemiology and End Results Cancer Registry. Women who reported ever receiving a blood transfusion were at increased risk for all NHLs [age adjusted relative risk (RR), 1.6; 95% confidence interval (CI), 1.2–2.1). On the basis of the Working Formulation classification, blood transfusion was positively associated with low-grade NHL (RR, 2.7; 95% CI, 1.7–4.5) but not with intermediate-grade NHL (RR, 1.1; 95% CI, 0.7–1.6); there were only 8 cases of high-grade NHL. Blood transfusion was positively associated with follicular (RR, 2.8; 95% CI, 1.6–5.1) and small lymphocytic (RR, 3.4; 95% CI, 1.5–7.9) NHL subtypes but not with diffuse NHL (RR, 1.0; 95% CI, 0.7–1.5). There was also a positive association with CLL (RR, 1.7; 95% CI, 1.0–3.0). Finally, transfusion was associated with nodal (RR, 1.8; 95% CI, 1.3–2.5) but not extranodal (RR, 1.2; 95% CI, 0.7–2.1) NHL. Further adjustment for marital status, farm residence, diabetes, alcohol use, smoking, and red meat and fruit consumption did not alter these associations. In conclusion, prior blood transfusion was associated with NHL and CLL, and the strongest associations were seen for low-grade NHL, particularly follicular and small lymphocytic NHL.

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Introduction

Since the initial reports (1, 2) that blood transfusion was associated with an approximately doubling of risk of NHL,[3] two subsequent reports (3, 4) found positive associations of similar magnitude, four (5–8) reported no association, and one (9) reported an inverse association. Explanations for inconsistent findings are not immediately evident, because there are no systematic differences between positive and null studies on aspects of study design (case-control, nested case-control, cohort), exposure assessment (medical record, self-report), timing of exposure (perinatal, pregnancy, older age), or geographic distribution (United States, Europe).

One potential explanation for this discrepancy is that transfusion might be associated with specific subtypes of NHL, the distribution of which could vary among studies. Brandt *et al.* (4) found the strongest association with transfusion history for low-grade NHL of B-cell CLL or immunocytoma type (OR, 4.2; 95% CI, 1.9–9.0) and extranodal high-grade NHL (OR, 3.3; 95% CI, 1.3–8.2), and Nelson *et al.* (7) found no association for intermediate- or high-grade NHL among HIV− subjects, suggesting that if an association exists, it might be specific to low-grade nodal NHL. Maguire-Boston *et al.* (8) reported no overall association of transfusion with NHL (OR, 0.8; 95% CI, 0.5–1.4), although there was a weak positive association with low-grade NHL (OR, 1.3; 95% CI, 0.5–3.8).

In this report, we update reports published previously of the association of blood transfusion and NHL in the Iowa Women's Health Study, which was based on 5 years (1) and 7 years (10) of follow-up; we now report data based on 12 years of follow-up and an additional 115 NHL cases. Furthermore, we evaluate the association of blood transfusion with the risk of NHL subtypes based on the Working Formulation (11) and present results for CLL because it may be part of the spectrum of NHL (12) and was included in another study (5).

Materials and Methods

The Iowa Women's Health Study Cohort. Methods and early results for the association of transfusion with NHL in the Iowa Women's Health Study have been published previously (1, 10). Briefly, a questionnaire mailed in January 1986 was completed and returned by 41,836 randomly selected women who were 55–69 years of age and had a valid Iowa driver's license in 1985 (42.7% response rate). The questionnaire inquired about medical and reproductive history, anthropomet-

[3] The abbreviations used are: NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; OR, odds ratio; CI, confidence interval; ICD-O, International Classification of Diseases for Oncology; RR, risk ratio; IL, interleukin; HCV, hepatitis C virus; DEHP, di-(2-ethylhexyl)phthalate.

Table 1 Distribution of primary site, grade, and subtype of 229 incident NHLs, Iowa Women's Health Study, 1986–1997

	ICD-O codes[a]	Number		%
Primary site				
Nodal		163		71.2%
Lymph nodes	C77		158	
Tonsil	C9.0		1	
Spleen	C42.2		4	
Extranodal		66		28.8%
Stomach	C16		10	
Small intestine	C17		8	
Breast	C50		4	
Brain, central nervous system	C71–72		4	
Thyroid	C73.9		7	
All other			33	
Total		229		100.0%
Working formulation				
Low grade		68		29.7%
Small lymphocytic; plasmacytoid	9670, 9671		27	
Follicular, small cleaved cell	9693, 9695, 9696		20	
Follicular, mixed cell	9691		21	
Intermediate grade		118		51.5%
Follicular, large cell	9698		7	
Diffuse, small cleaved cell	9672, 9673		21	
Diffuse, mixed cell	9675		15	
Diffuse, large cell	9680–9682		75	
High grade		8		3.5%
Large cell, immunoblastic	9684		5	
Lymphoblastic	9685		0	
Small, noncleaved	9686		3	
NOS[b] and other		35		15.3%
Total		229		100.0%
Subtypes				
Small lymphocytic	9670	23		10.0%
Follicular	9690, 9691, 9693, 9695, 9696, 9698	49		21.4%
Diffuse	9595, 9672, 9673, 9675, 9680–9682	114		49.8%
NOS and other		43		18.8%
Total		229		100.0%

[a] Codes from International Classification of Disease-Oncology, Ed. 2 (does not include all possible codes).
[b] NOS, not otherwise specified.

rics, diet, and lifestyle factors. Participants were also asked "have you ever received blood or had a blood transfusion?" If they responded "yes," they were then asked "how old were you when you received your first blood transfusion?" and "what was the reason you had a blood transfusion?" There were only minor demographic differences between respondents and nonrespondents to the baseline survey (13), and compared with nonrepondents, respondents have had somewhat lower cancer incidence mortality rates for smoking-related cancers (14).

Vital status and cancer incidence in the cohort was ascertained through 12 years of follow-up (1986–1997). Follow-up questionnaires were mailed in 1987, 1989, 1992, and 1997 to assess vital status and address changes. Deaths were also ascertained by linkage to Iowa death certificate data and, for survey nonrespondents and emigrants from Iowa, to the National Death Index. Vital status is estimated to be unknown for $<1\%$ of the cohort.

Cancer incidence, except for nonmelanoma skin cancer, was ascertained by annual linkage to the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology and End Results program (15). All participants were linked by a combination of social security number; first, last, and maiden names; birth date; and Zip code. The State Health Registry of Iowa collects cancer data, including identifying information, tumor site, morphology, histological grade, and extent of disease, on all persons who are Iowa residents at the time of their diagnosis. All tumor site and morphology data were derived from pathology reports of the diagnosing pathologist, and there was no centralized review of the tumor material.

Topographic and morphological data were coded using the ICD-O, Ed. 2 (16). The histological subtypes of NHL were grouped according to the Working Formulation (11) into the categories of low-, intermediate-, and high-grade as well as the following subtypes: small lymphocytic, follicular, diffuse, and other (ICD-O codes given in Table 1). We also classified the primary site as nodal (lymph nodes, tonsil, and spleen) or extranodal (all other sites that are not primary lymphoid organs) according to ICD-O definition (16). CLL (ICD-O morphology code 9823) was also analyzed.

Data Analysis. Before data analysis, we excluded women with a self-reported history of cancer or cancer chemotherapy on the baseline (1986) questionnaire ($n = 3{,}903$) to provide a cancer-free, at-risk cohort of 37,934 women. Each woman accumulated person-years of follow-up from the date of receipt of the 1986 baseline questionnaire until the date of NHL or CLL diagnosis, date of emigration from Iowa, or date of death; if none of these events occurred, person-years were accumulated through December 31, 1997.

Age-adjusted and multivariate RRs, along with 95% CIs, were calculated as measures of association between transfusion history and NHL (and CLL) incidence using Cox proportional hazards regression (17). Time since first transfusion to the 1986 baseline survey was *a priori* categorized into <5 years, 5–29 years, and 30+ years to evaluate the influence of recent, distant, and remote transfusions on cancer risk and to ensure sufficient sample size for each category for the subtype analyses; for all NHLs, we also used cutpoints published previously of <5, 5–14, 15–29, and 30+ years (1). Other risk factors for NHL in this dataset, including marital status, red meat and fruit intake (18), farm residence (19), diabetes (10), alcohol use (20), and cigarette smoking (21), were included in a multivariate model with age and transfusion history.

Results

The mean age of the 37,934 women in this cohort at baseline was 61.7 years; >99% were white, and 39% had completed some school beyond high school. In 1986, 20% resided on a farm, 15% were current smokers, and 44% drank alcohol. At baseline in 1986, 70.8% reported never having received a blood transfusion, 25.5% reported having received one or more transfusions, 3.0% were not sure if they had ever had a transfusion, and 0.7% did not answer the question. Most women (91.4%) who reported ever having a transfusion received their transfusion >5 years before the 1986 survey. The most commonly stated reason for transfusion was blood loss from surgery or bleeding (92%) or decreased blood production because of an illness (5%); the remaining women either did not know why they were transfused or did not answer.

During 418,342 person-years of follow-up (1986–1997), 229 women developed NHL. The mean age at diagnosis was 69.6 years (range, 58–81 years). Approximately 70% of the NHL cases were nodal, and of the extranodal sites, stomach and small intestine were the most common sites (Table 1). After classifying the tumors by the Working Formulation, 30% were low grade, 52% were intermediate grade, 3% were high grade, and 15% could not be classified. The most common subtype was diffuse NHL (50%), followed by follicular NHL (21%). During the same time period, 129 women developed leukemia, of which 57 were CLL.

Compared with women who were never transfused, women who reported ever receiving a blood transfusion had a 60% increased age-adjusted incidence of NHL (95% CI, 1.2–2.1; Table 2). Risk was elevated for a first transfusion within 5 years of the baseline survey (RR, 2.1; 95% CI, 1.0–4.5) and 5–29 years before baseline (RR, 1.7; 95% CI, 1.2–2.4) but only slightly for a transfusion first received 30 or more years before baseline (RR, 1.3; 95% CI, 0.9–2.1). To compare to our previously published categories (1), we also calculated risk for 5–14 years (RR, 2.9; 95% CI, 1.8–4.6) and 15–29 years (RR, 1.3; 95% CI, 0.8–2.0).

Transfusion history was a risk factor for nodal (RR, 1.8; 95% CI, 1.3–2.5) but not extranodal (RR, 1.2; 95% CI, 0.7–2.1) disease (Table 2). When taking time from first transfusion into account, the association with nodal disease was apparent <5 years before baseline (RR, 2.2; 95% CI, 0.9–5.4), 5–29 years before baseline (RR, 1.9; 95% CI, 1.3–2.9), and also for 30+ years before baseline (RR, 1.5; 95% CI, 0.9–2.4), although only the estimate for 5–29 years was statistically significant. In contrast, extranodal disease showed no association with time from first transfusion except for transfusions received within 5 years of the baseline survey (RR, 1.9), and this estimate lacked precision (95% CI, 0.5–7.7) because of the small sample size (2 cases).

When the NHL cases were categorized according to the Working Formulation grades (Table 2), the strongest association was seen for low-grade tumors (RR, 2.7; 95% CI, 1.7–4.5). There was no association for intermediate-grade tumors (RR, 1.1; 95% CI, 0.7–1.6), with a possible exception of transfusions received within 5 years of baseline, but the risk was not statistically significant (RR, 2.0; 95% CI, 0.7–5.5). Although women who had received a transfusion were at elevated risk of high-grade NHL (RR, 1.7), the small sample size (3 exposed cases) made this estimate unstable (95% CI, 0.4–7.2).

Of the common subtypes of NHL, there was no association for transfusion history with diffuse NHL (Table 2), whereas there were strong positive associations with follicular (RR, 2.8; 95% CI, 1.6–5.1) and small lymphocytic (RR, 3.4; 95% CI, 1.5–7.9) NHL. These risks were elevated for transfusions first received >5 years before the baseline survey. There was also a positive association between blood transfusion and risk of CLL (RR, 1.7; 95% CI, 1.0–3.0). When we adjusted for other NHL risk factors in this dataset, there was essentially no effect on the point estimates (Table 2).

Discussion

We found a statistically significant association between a history of blood transfusion and risk of NHL and CLL. The risk was strongest for nodal disease and low-grade disease; we found no association with intermediate-grade disease, and there were too few cases of high-grade disease to make any firm conclusions. We also found a positive association with follicular and small lymphocytic NHL but not diffuse NHL. The association with transfusion history weakened with increasing time from first transfusion to the baseline survey, but there were statistically significant excess risks for transfusions 5–29 years before baseline for all NHL, combined nodal disease, low-grade disease, follicular NHL, and CLL. Multivariate adjustment for the major predictors of NHL in this cohort had little effect on the point estimates, suggesting that our findings are not likely to be a result of confounding by demographic (marital status, farm residence) and lifestyle (smoking and alcohol use) factors, diet (red meat and fruit intake), or other diseases (diabetes).

The strengths of this study include the prospective cohort design with virtually complete follow-up, use of a Surveillance, Epidemiology and End Results cancer registry for case ascertainment, and extensive data on potential confounding factors. Limitations are mainly related to the assessment of transfusion exposure, which was based on self-report, included no other details on the transfusion event(s), and may be confounded by the indication for transfusion. However, the study design does not allow differential recall bias, and the lifetime history of transfusion is consistent with other studies (Table 3). Although we did not have data on whether the blood transfused was autologous *versus* allogeneic, before 1986 autologous blood transfusion was extremely uncommon in the United States (*e.g.*, only 0.25% of total donations in 1980 were autologous; Ref. 22), and therefore it is reasonable to assume that the vast majority of transfusions in this cohort were allogeneic. Another limitation is that the subtypes of NHL relied on the report of local pathologists, and there was no central review. Nevertheless, for the broad classification of NHL grade and subtype reported here, this method is probably sufficient for the broad categorization needed in an epidemiological study (23). A

Table 2 Age and multivariate[a] adjusted RR of NHL according to transfusion history, Iowa Women's Health Study, 1986–1997

	Transfusion history		Year of first transfusion (time to the 1986 baseline)		
	Never	Ever	1982–1986 (<5 yr)	1957–1981 (5–29 yr)	<1957 (30+ yr)
All					
Number	26,865	9,679	650	5,259	3,589
Person-years	297,970	105,269	6,902	57,568	38,924
Cases	141	80	7	46	25
Age RR (95% CI)	1.0 (referent)	1.6 (1.2–2.1)	2.1 (1.0–4.5)	1.7 (1.2–2.4)	1.3 (0.9–2.1)
Multivariate RR (95% CI)	1.0 (referent)	1.6 (1.2–2.1)	2.1 (1.0–4.4)	1.7 (1.2–2.4)	1.3 (0.8–2.0)
Primary site					
Nodal					
Cases	97	61	5	36	19
Age RR (95% CI)	1.0 (referent)	1.8 (1.3–2.5)	2.2 (0.9–5.4)	1.9 (1.3–2.9)	1.5 (0.9–2.4)
Multivariate RR (95% CI)	1.0 (referent)	1.8 (1.3–2.4)	2.2 (0.9–5.4)	2.0 (1.3–2.8)	1.4 (0.9–2.4)
Extranodal					
Cases	44	19	2	10	6
Age RR (95% CI)	1.0 (referent)	1.2 (0.7–2.1)	1.9 (0.5–7.7)	1.2 (0.6–2.4)	1.0 (0.4–2.4)
Multivariate RR (95% CI)	1.0 (referent)	1.2 (0.7–2.1)	1.8 (0.4–7.4)	1.2 (0.6–2.5)	0.9 (0.3–2.2)
Grade					
Low					
Cases	32	31	3	18	9
Age RR (95% CI)	1.0 (referent)	2.7 (1.7–4.5)	3.9 (1.2–12.9)	3.0 (1.7–5.3)	2.1 (1.0–4.5)
Multivariate RR (95% CI)	1.0 (referent)	2.7 (1.6–4.5)	3.8 (1.2–12.4)	2.8 (1.5–5.1)	2.2 (1.0–4.6)
Intermediate					
Cases	84	31	4	17	10
Age RR (95% CI)	1.0 (referent)	1.1 (0.7–1.6)	2.0 (0.7–5.5)	1.1 (0.6–1.8)	0.9 (0.5–1.7)
Multivariate RR (95% CI)	1.0 (referent)	1.0 (0.7–1.6)	2.0 (0.7–5.5)	1.1 (0.6–1.8)	0.8 (0.4–1.7)
High					
Cases	5	3	0	2	1
Age RR (95% CI)	1.0 (referent)	1.7 (0.4–7.2)		2.1 (0.4–11)	1.5 (0.2–13)
Multivariate RR (95% CI)	1.0 (referent)	2.0 (0.5–8.5)		2.4 (0.5–13)	1.9 (0.2–17)
No grade					
Cases	20	15	0	9	5
Age RR (95% CI)	1.0 (referent)	2.1 (1.1–4.2)		2.4 (1.1–5.4)	1.9 (0.7–5.0)
Multivariate RR (95% CI)	1.0 (referent)	2.1 (1.0–4.1)		2.6 (1.2–5.7)	1.5 (0.5–4.5)
Subtypes					
Diffuse					
Cases	82	29	2	17	10
Age RR (95% CI)	1.0 (referent)	1.0 (0.7–1.5)	1.0 (0.3–4.2)	1.1 (0.7–1.8)	0.9 (0.5–1.8)
Multivariate RR (95% CI)	1.0 (referent)	1.0 (0.6–1.5)	1.0 (0.3–4.2)	1.1 (0.6–1.9)	0.9 (0.4–1.7)
Follicular					
Cases	23	23	4	15	4
Age RR (95% CI)	1.0 (referent)	2.8 (1.6–5.1)	7.4 (2.6–21)	3.4 (1.8–6.6)	1.3 (0.5–3.8)
Multivariate RR (95% CI)	1.0 (referent)	2.8 (1.5–4.9)	7.0 (2.4–21)	3.4 (1.8–6.5)	1.3 (0.4–3.6)
Small lymphocytic					
Cases	10	12	1	5	5
Age RR (95% CI)	1.0 (referent)	3.4 (1.5–7.9)	4.2 (0.5–33)	2.6 (0.9–7.6)	3.8 (1.3–11)
Multivariate RR (95% CI)	1.0 (referent)	3.4 (1.4–8.2)	4.4 (0.6–35)	2.2 (0.7–7.1)	4.2 (1.4–13)
All other					
Cases	26	16	0	9	6
Age RR (95% CI)	1.0 (referent)	1.8 (0.9–3.3)		1.9 (0.9–4.0)	1.7 (0.7–4.2)
Multivariate RR (95% CI)	1.0 (referent)	1.8 (0.9–3.3)		2.0 (0.9–4.3)	1.5 (0.6–4.0)
CLL					
Cases	33	20	3	12	5
Age RR (95% CI)	1.0 (referent)	1.7 (1.0–3.0)	3.7 (1.1–12)	1.9 (1.0–3.8)	1.1 (0.4–2.9)
Multivariate RR (95% CI)	1.0 (referent)	1.9 (1.1–3.4)	4.4 (1.3–14)	2.2 (1.1–4.3)	1.2 (0.5–3.2)

[a] Adjusted for age, marital status (never, former, current), residence (farm *versus* nonfarm), diabetes, smoking (never, former, current), alcohol use, and intake of red meat (servings/week) and fruit (servings/week).

final limitation is the small sample size for many of the subtypes.

Transfusion and Overall Risk of NHL. There have now been nine reports on the association between transfusion history and risk of NHL (summarized in Table 3): four positive (1–4), four null (5–8), and one inverse (9); one of the null studies (5) included CLL along with NHL in the case group. The only study to report an inverse association (9) was a hospital-based case-control study, and the use of hospital controls raises the concern of a biased association attributable to the likely overrepresentation of a history of transfusion in hospitalized patients. Of the four null studies, two were nested case-control studies (5, 6) and two were population-based case-control studies (7, 8). However, the study by Anderson *et al.* (6) was

Table 3 Comparison of studies of transfusion history and NHL risk

	Current report	Blomberg *et al.* (2)		Memon and Doll (3)	Brandt *et al.* (4)	Adami *et al.* (5)	Anderson *et al.* (6)	Nelson *et al.* (7)	Maguire-Boston *et al.* (8)	Tavani *et al.* (9)
Location	Iowa	Lund, Sweden	Lund, Sweden	United Kingdom	Lund, Sweden	Southern Sweden	Sweden	Los Angeles, CA	Olmsted County, MN	Northern Italy
Design	Cohort	Cohort 1	Cohort 2	Cohort	Population-based case-control	Nested case-control	Nested case-control	Population-based case-control	Population-based case-control	Hospital-based case-control
Time	1986–1997	1981–1990	1981–1990	1942–1991	Early 1990s	1970–1991	1973–1991	1989–1992	1975–1993	1984–1998
Study details	37,934 cancer-free subjects followed for 12 years; 229 cases of NHL and 57 cases of CLL	3,177 recipients of blood from 1981–1982 and with no prior cancer followed for 9 yr; 13 cases of malignant lymphoma	29,910 patients hospitalized from 1981 to 1982 and with no prior cancer followed for 9 yr; 29 cases of NHL	12,690 infants transfused between 1942 and 1970 and followed through 1990; 5 cases of NHL	280 NHL cases (HIV unlikely); 1827 controls matched on age, sex, and residence	96,795 in-patients from 1970 to 1983 and followed 1–22 yr (mean, 7.0); 260 cases of NHL and 101 cases of CLL; 705 matched controls	77,928 women with bleeding complications during delivery from 1973 to 1986 and followed to 1991; 15 cases of NHL; 136 matched controls	378 HIV− cases with intermediate or high-grade NHL; 378 age, sex, and race matched controls	221 cases and 221 age- and sex-matched controls	385 cases and 1297 controls
Age and sex	55–69 years in 1986; 100% female	Up to age 80 yr; both sexes	Up to age 80 yr; both sexes	Infants; both sexes	17–92 yr (median, 63); both sexes	Mean age at diagnosis, 65 yr; 30% female	Median age at diagnosis, 41 yr; 100% female	18–75 yr; 51% female	20–95 yr (median, 71); 60% female	18–79 yr (median, 43); 42% female
Assessment of transfusion	Self-report	Transfusion registry	Transfusion registry	Medical records	Self-report	Transfusion registry	Medical record	Self-report	Medical record	Self-report
Prevalence of transfusion[a]	25% transfused	100% transfused	5.3% transfused	100% transfused	19% cases; 13% controls	45% cases; 47% controls	0% cases; 23% controls	15% cases; 13% controls	18% cases; 20% controls	7% cases; 10% controls
Analysis	RR	SMR	RR	SMR	OR	OR	OR	OR	OR	OR
Confounding	Demographic, lifestyle, diet, medical history	Age	Age	Age	Age	Age, sex	Age	Age, race, sex, and recreational drugs	Age, sex	Age, sex, residence, and education
Risk of NHL	1.6 (1.2–2.1)	2.7 (1.4–4.6)	3.5 (1.5–7.9)	2.2 (0.6–5.5)	1.7 (1.2–2.4)	0.9 (0.7–1.2)[b]		NA[c]	0.8 (0.5–1.4)	0.6 (0.4–1.0)

[a] At baseline for cohort studies and before diagnosis for case-control studies.
[b] Estimate is for NHL and CLL combined.
[c] NA, not applicable.

extremely small (15 cases of NHL, none of whom were transfused), and the study by Nelson *et al.* (7) was based on only intermediate- and high-grade NHL.

In the third null study, Adami *et al.* (5) reported data from a case-control study nested in a cohort of nearly 100,000 persons who were first hospitalized from 1970 to 1983 with ICD codes that had a high likelihood of having received a transfusion (11 surgical procedures and benign diseases; actual codes were not reported); from this cohort, 260 cases of NHL and 101 cases of CLL were compared with 705 matched controls. Transfusion, as documented in a transfusion registry from two years before entry into the cohort up until 1 year before diagnosis of NHL, was nearly identical in cases (45%) and controls (47%), and there was no association with transfusion history and risk of NHL and CLL combined (OR, 0.9; 95% CI, 0.7–1-2) or individually. Although a strength of this study was that transfusion was identified in a transfusion registry, this is also a potential limitation because any transfusions >2 years before entering the cohort would not have been identified. In addition, only transfusions that occurred in the catchment area (district) where the subject was hospitalized were identified; a transfusion received outside of the area would also not be identified. Finally, by designing the study so that cases and controls were chosen on the basis of the procedures (mainly surgical procedures for noncancer conditions) that they were undergoing, there is a potential concern of confounding by medical history factors. However, as discussed by Alexander (24), the net effect of such selection is difficult to predict, and our data (10) suggest little confounding by the few identified medical history risk factors for NHL.

The final null study, conducted by Maguire-Boston *et al.* (8), was a population-based case-control study using the Rochester Epidemiology Project and was based on 221 age- and sex-matched NHL cases and controls from Olmsted County, Minnesota. Transfusion history was abstracted from the medical record, and there was no association with transfusion history (OR, 0.8; 95% CI, 0.5–1.4) and no evidence for heterogeneity in risk based on age or sex. Although transfusions outside the Mayo system could not be systematically identified in the medical record, the median time in the Mayo system was 37 years for both cases and controls, and analyses based on routinely collected self-reported history of transfusion in the medical chart yielded similar results to those based on the medical record.

Of the positive studies, three were cohort studies (1–3), and one was a population-based case-control study (4). Assessment of transfusion was based on a transfusion registry in two of the cohorts (2, 3) and on self-report in the two other studies (1, 4). Overall, risk estimates were strikingly similar, with all studies suggesting approximately a doubling of risk of NHL with transfusion history. Although limited sample size has been raised as a concern previously (5, 24), there are now 556 NHL cases in all of the positive studies and 874 in the null studies, suggesting that this is not a likely explanation. In addition to the number of studies and sample size, the striking consistency of the transfusion association across cohort studies warrants comment. Both the Iowa cohort (1), the two cohorts in the report from Sweden (2), and the United Kingdom infant cohort (3) assessed multiple cancer end points, and NHL was the only site elevated across all studies.

Latency, Number, and Type of Transfusion. After 12 years of follow-up of the Iowa Women's Health Study cohort, report of a blood transfusion in 1986 remains a statistically significant predictor of overall NHL risk (RR, 1.6; 95% CI, 1.2–2.1), although the association has attenuated from previous reports at 5 years (RR, 2.2; 95% CI, 1.4–2.6) and 7 years (RR, 2.0; 95% CI, 1.3–2.9) of follow-up (1, 10). This attenuation with increasing follow-up is also apparent when time from first transfusion to baseline survey in 1986 is taken into account; transfusions given >30 years before baseline are now only associated with a slightly elevated risk of NHL (RR, 1.3), which is not statistically significant (95% CI, 0.9–2.1). However, transfusions given 5–30 years before baseline remain significant predictors of NHL risk (albeit attenuated from previous reports). For all NHLs, when more specific time categories were used, the excess risk was greatest for transfusions <5 years and 5–14 years before baseline, with NHL developing a median of 7.4 years after baseline. Thus, our data suggest a latency period of <30 years.

In the study by Brandt *et al.* (4), the greatest risk of NHL was for transfusions received 6–15 years before diagnosis (OR, 2.8; 95% CI, 1.6–5.0), although risks were also elevated for transfusions received 1–5 years before diagnosis (OR, 1.7; 95% CI, 0.9–3.2) and 16–25 years before diagnosis (OR, 1.6; 95% CI, 0.8–3.0). The cohort study by Memon and Doll (3) reported the excess risk for NHL occurred 15–49 years after transfusion as an infant but not 1–14 years after transfusion, whereas the elevated risk in the two cohort studies reported by Blomberg *et al.* (2) occurred 3–9 years after transfusion. In contrast, in the null study by Adami *et al.* (5), there was no association for transfusions received 1–5 years or 5–21 years before diagnosis of NHL/CLL.

Three studies have evaluated the number of distinct transfusion events with risk of NHL. The studies by Adami *et al.* (OR, 1.4; 95% CI, 0.5–4.0) and Boston-Maguire *et al.* (OR, 1.6; 95% CI, 0.7–3.6) both reported nonsignificant elevated risk of NHL for more than three transfusions compared with no transfusion (Table 3), whereas overall they found no effect for transfusion history (5, 8). The study of intermediate- and high-grade NHL by Nelson *et al.* (7) found no association with number of transfusion events.

The only study to evaluate type of transfusion was that by Adami *et al.* (5). They found an inverse association of NHL for persons who had received a transfusion with no leukocyte depletion (OR, 0.7; 95% CI, 0.5–1.0) but no association for leukodepleted transfusions (OR, 1.0; 95% CI, 0.6–1.7).

NHL Subtypes. Another potential explanation for a discrepancy among studies is that transfusion is associated with only certain subsets of NHL, and these may be distributed differently across studies. Brandt *et al.* (4) first raised this issue in their population-based case-control study. They found an overall association between transfusion and NHL risk (OR, 1.7; 95% CI, 1.2–2.4), but there was heterogeneity major subgroups of the Kiel classification. There were specific associations with lymphocytic or lymphoplasmacytic (immunocytoma) NHL (OR, 2.0; 95% CI, 1.2–3.5) and high-grade extranodal NHL (OR, 3.2; 95% CI, 1.3–8.2) but no associations for follicular NHL, low-grade extranodal NHL, or high-grade nodal NHL. Nelson *et al.* (7) found no association between transfusion history and risk of intermediate- or high-grade NHL in HIV-negative persons (risks for each grade not separately reported, but intermediate grade likely to dominate) and further raised the issue that the transfusion association may be specific to low-grade NHL. Our data are broadly consistent with the previous findings; we found a strong positive association for low-grade NHL and no association for intermediate-grade NHL, whereas small numbers limited our ability to evaluate high-grade NHL. The Mayo Clinic study, which was null overall, did show a

slightly elevated risk for low-grade NHL (OR, 1.3), although this was not statistically significant (95% CI, 0.5–3.8).

Consistent with Brandt *et al.* (4), we found a positive association of transfusion with small lymphocytic/plasmacytoid NHL. We also found a positive association with follicular NHL (RR, 2.8), although Brandt *et al.* (4) reported no overall association for this subtype (OR, 0.9). However, when time from transfusion was taken into account, they did report a suggestive positive association with follicular NHL for transfusions received 6–15 years before diagnosis (OR, 2.9; 95% CI, 0.9–10), consistent with our finding of a RR of 3.4 (95% CI, 1.8–6.6) for transfusions received 5–29 years before baseline. Although we found a positive association of transfusion with CLL, the two other studies to assess it found no association (2, 5).

Mechanisms. Several biological mechanisms have been proposed that could explain a putative association between allogeneic blood transfusion and NHL risk but the most plausible include immunomodulation, viral transmission, and transfusion of a chemical carcinogen (1). Although the exact mechanisms responsible for the immunomodulatory effects of allogeneic blood transfusion are not known, current evidence strongly suggests that allogeneic transfusion shifts the immune response toward a Th2-type response (secretion of IL-4, IL-5, IL-6, and IL-10) and away from a Th1-type response (secretion of IL-2, IFN-γ, and lymphotoxin), which overall decreases the proinflammatory, cell-mediated immunity response and promotes up-regulation of the humoral immune system (antibody production; Refs. 25 and 26). This immunomodulatory effect appears to be somewhat stronger with whole blood transfusion, does not occur with autologous transfusion, and has been most closely associated with the leukocyte fraction (25).

Suppression of cellular immunity, particularly in the setting of chronic antigenic stimulation, is thought to play an important role in the etiopathogenesis of NHL (27) and thus is consistent with an etiological role for blood transfusion. Persons with primary immunodeficiencies, iatrogenic suppression, and immunosuppression from AIDS are all at elevated risk of NHL (27), and the immunosuppression associated with transfusion might represent a lower level of a dose-response relationship. However, most of the lymphomas that develop in the clinical setting of severe immunosuppression tend to be aggressive, extranodal, high-grade immunoblastic NHL and small noncleaved cell NHL as well as the intermediate-grade diffuse large cell NHL (28, 29) and not the low-grade small lymphocytic NHL, CLL, or follicular NHL most associated with transfusion history in this study. In addition, the only study to evaluate type of transfusion (5) found that although there was no association of NHL with leukodepleted blood, persons receiving transfusions with leukocytes actually had a lower risk of NHL (OR, 0.7; 95% CI, 0.5–1.0). Although there is potential for confounding by indication for leukodepleted blood in the latter study, all of these observations taken together do not provide much support for transfusion-induced immunosuppression as a mechanistic explanation, although it must be acknowledged that data are limited, and this effect has by no means been ruled out.

Transfusion as a vector for viral transmission is also plausible, and EBV has been linked to some forms of NHL, including endemic Burkitt lymphoma and posttransplant lymphoproliferative disease (30). In contrast, EBV overall appears to play a minor role in sporadic NHL, and the subtypes for which a role is most strongly hypothesized are the T-cell NHLs. To date, although no specific infectious agents have been associated with low-grade NHL, there is growing evidence that HCV may play an important role in essential mixed cryoglobulinemia (a lymphoproliferative disorder that has been linked to low-grade NHL) and certain subtypes of NHL, including low-grade B-cell NHLs such as small lymphocytic NHL and follicular NHL. Risk of HCV transmission from transfusion is estimated to have been quite high prior to 1983, at which time donor screening criteria changed in response to the HIV epidemic (22). Since 1983, this risk has declined dramatically with the implementation of screening for HIV antibody in 1985, surrogate testing for non-A, non-B hepatitis in 1986–1987, and HCV antibody screening in 1990 (22).

Transfer of a chemical contaminant through blood transfusion has received less attention. Beyond DEHP, however, few chemicals have been implicated as potential carcinogens. DEHP is a plasticizer that is found in significant quantities in stored blood (31) and is a hepatocarcinogen in rats (32). However, there is little evidence for carcinogenicity in humans (33). In addition, the highest DEHP exposure occurs in dialysis patients, but cancer risk in these patients appears to only be elevated after transplantation (34). The latter finding might also suggest that identification of a carcinogenic chemical in plastic equipment used in blood transfusion is not particularly likely.

In conclusion, prior blood transfusion was associated with NHL and CLL, and the strongest associations were seen for low-grade NHL, particularly follicular and small lymphocytic NHL.

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Blood Transfusions and Risk of Non-Hodgkin's Lymphoma Subtypes and Chronic Lymphocytic Leukemia

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