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Blood Transfusion, Anesthesia, Surgery and Risk of Non-Hodgkin Lymphoma in a Population-Based Case-Control Study

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Abstract

The incidence of NHL has increased dramatically since at least the 1950s, and during this timeframe there has been a major increase in the use of blood transfusions, invasive surgical procedures, and anesthesia, all of which can impact immune function. We evaluated these factors with NHL risk in a population-based study of 759 cases and 589 frequency-matched controls. Risk factor data were collected during in-person interviews. Unconditional logistic regression was used to estimate ORs and 95% CIs, adjusted for the matching factors. History of transfusion was associated with a 26% higher risk of NHL (95% CI 0.91–1.73), and the elevated risk was specific to transfusions first given 5–29 years before the reference date (OR=1.69; 95% CI 1.08–2.62) and transfusions given for a medical condition (OR=2.09; 95% CI 1.03–4.26). The total number of surgeries and dental procedures (OR=1.53 for 26+ surgeries compared to 0–6; 95% CI 1.02–2.29) and to a lesser extent the total number of exposures to general or local/regional anesthesia (OR=1.35 for 24+ times compared to 0–6; 95% CI 0.91–2.02) were positively associated with risk of NHL. Inclusion of transfusion and surgery or transfusion and anesthesia in the same model did not attenuate these associations. All results were broadly consistent for both DLBCL and follicular subtypes. Blood transfusions were associated with NHL risk, but appear to be a marker for underlying medical conditions. Multiple surgical procedures and/or repeated administration of anesthesia have not been previously reported to be associated with risk of NHL and these exposures warrant further evaluation.

Keywords

anesthesia; blood transfusion; non-Hodgkin lymphoma; surgery

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous but closely related group of malignancies of lymphocytes, and is currently the fifth most commonly diagnosed cancer among both men and women in the United States.[1] The incidence of NHL increased dramatically over the 20th century in North America and Europe, with the rates only recently leveling off.[2–4] One of the few established risk factors for NHL is primary or acquired immune suppression, and factors that can alter immunologic function have been suggested

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as potential NHL risk factors.[5] Use of blood transfusions, which can suppress cellular immunity and transmit infectious agents and allogeneic cells,[6] increased dramatically during the timeframe of the rapid increase in NHL incidence.[7] Blood transfusions have been associated with risk of NHL in some but not most studies.[8, 9]

Coincident with the increased use of blood transfusions has been the increased use of invasive surgical procedures, implants, and general and local/regional anesthesia. Anesthetics can impair cellular and humoral immune responses by direct impact on immune cells or indirectly through modulation of the stress response, although impacts vary by type of agent and appear to be transitory.[10] Major surgery affects the immune system in numerous documented ways, including an early hyperinflammatory response (acute phase reaction characterized by release of proinflammatory cytokines including TNF-alpha, IL-6, and IL-1b) followed by upregulation of anti-inflammatory mediators (including prostaglandin E2, IL-10 and TGF-beta) and a shift of the Th1/Th2 balance towards a Th2 cytokine profile and suppression of cell-mediated immunity.[11] Beyond an evaluation of cancer risk in persons undergoing hip or knee arthroplasty[12, 13] or for selected specific surgeries,[14–18] exposure to surgical procedures has had only limited evaluation as an NHL risk factor. Alternatively, more modest immunologic responses to minor surgery or dental work could induce inflammation and chronic antigenic stimulation by exposing tissue to foreign antigens or seeding of the blood stream with bacteria, and this response could lead to an increased risk of NHL.[5] We therefore investigated the associations between transfusions, anesthesia, and surgery (including dental surgeries and procedures) and risk of NHL in a multi-center, population-based case-control study conducted in the United States.

Material and Methods

Study population and data collection

Details of this study have been previously published.[19, 20] Written informed consent was obtained from each participant prior to interview. Human subjects review boards approved the study at the National Cancer Institute and at all participating institutions.

From July 1998 through June 2000, newly diagnosed NHL cases aged 20 to 74 years with no evidence of HIV infection were rapidly reported from four areas with Surveillance, Epidemiology, and End Results (SEER) cancer registries. In Iowa and Seattle, all consecutive cases were eligible, while in Los Angeles and Detroit all African American cases were eligible, but only a random sample of non-African American cases. Of 2,248 eligible cases, 320 (14%) died before we could conduct an interview, 127 (6%) could not be located, 16 (1%) had moved out of the area, and 57 (3%) had physician refusals. We attempted to contact the remaining 1,728, but 274 (16%) declined to be interviewed, and 133 (8%) never responded or were not interviewed because of illness, impairment or other reasons. This left 1,321 eligible cases who were enrolled into the study, for a participation rate of 76% of the cases we attempted to contact and an overall response rate of 59% of the living and deceased cases presumed to be eligible. Approximately 60% of cases were interviewed within six months of their diagnosis, and 84% were interviewed within one year. NHL subtypes were defined based on SEER Registry codes.

Population controls were identified by random digit dialing (under age 65 years) and from Medicare eligibility files (65 years and older), and were frequency matched to the case distribution on age, sex, race, and study center. Of the 2,409 controls selected, 28 (1%) died before contact, 311 (13%) could not be located, and 24 (1%) had moved out of the geographic area. We attempted to contact a total of 2,046, but 839 (41%) declined to be interviewed and 150 (6%) never completed an interview because of illness, impairment or other reason. Thus, a total of 1,057 eligible controls were interviewed, for a participation

rate of 52% of the controls that we attempted to contact, and a response rate of 44% of all presumed eligible controls.

Exposure assessment

Because the study questionnaire included multiple components and several of these components contained a large number of questions, the study population was divided into two groups, each receiving a different version of the computer-assisted personal interview (CAPI) and a different self-administered questionnaire. Core components of each version of the CAPI contained questions about demographic characteristics, occupational history and pesticide use history. The present analysis is based on 759 cases and 589 controls in the group queried in detail about their medical history as part of the CAPI interview.

Transfusion history was ascertained by asking “before one year ago, did you ever have a blood transfusion?” For a positive response, participants were further queried on conditions and surgical procedures for which they had a transfusion, and for each condition, the number of transfusions, age at first transfusion, and age at last transfusion; the actual number of units of blood transfused or the type of blood transfused was not collected. The indications for a transfusion were reviewed and classified into one of four categories related to the most proximate indication (trauma, obstetric, surgical, or medical) by one of the authors (JRC) blind to case-control status.

Surgical history was queried by asking about any surgery before one year ago on each of 20 sites (as presented in Table IV) or as an open-ended question for any other surgery not previously mentioned, excluding dental surgery. Systematic inquiry regarding surgical history by site of surgery was done to facilitate recall, and thereby increase the validity of the summation of the total number of surgeries. Dental surgeries and procedures were queried separately. For dental surgeries, participants were asked if they ever had any teeth pulled, a root canal, gum surgery, or any other type of dental surgery. For a positive response about a surgery (excluding dental surgeries), further data were collected on the type of surgery, number of surgeries, age at first surgery, age at last surgery, the number of these surgeries for which the participant was “put to sleep” (i.e., general anesthesia), and the number of surgeries for which the participant was “given an injection to numb you without putting you to sleep” (i.e., local/regional anesthesia). For dental procedures, participants were asked how many times they had a cavity filled or a crown or cap put on a tooth and the number of times they had novocaine for these procedures. Dental cleanings were not included as part of dental procedures.

All surgeries were coded according to ICD-9CM and were reviewed by one of the authors (JRC) blind to case-control status. Patients reporting laporoscopic surgery were included as exposed, but patients reporting endoscopy were not considered exposed. To compare with previous literature, we also analyzed hip or knee replacement as an additional exposure category. There were <5 exposed cases or controls for “other chest surgery” and “spleen surgery,” and these data are not reported.

Data analysis

Transfusion history was *a priori* categorized as ever/never, number transfusions (continuous), time since first transfusion (<5 years, 5–29 years, and 30+ years; categories based on prior publications and to ensure sufficient sample size to provide stable risk estimates), and indication for transfusion (as described above). The total number of surgeries, with and without dental surgeries and procedures, was based on summing across all surgeries, and the quintile cutpoints were based on the distribution among the controls. Site of surgery for each of 21 sites was classified as ever/never, number of surgeries (0, 1,

>1), and time since first surgery (<5 years, 5–29 years, and 30+ years). Use of general, local/regional (including novocaine or lidocaine), and any anesthesia was summed across all procedures, and quintile cutpoints were based on the distribution among the controls.

We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the association of these variables with risk of NHL. For analyses of DLBCL and follicular NHL subtypes, we used polychotomous logistic regression.[21] In regression models, we adjusted for the design variables of study center, age (in decades), sex and race (White versus non-White). Trends were evaluated based on the ordinal scoring (0–4) of the exposure categories (including the lowest category with low and/or no exposure), and included the ordinal OR, 95% CI, and *P*-value for trend based on the 0–4 coded ordinal variable. We further evaluated additional potential confounding by educational level, body mass index, and family history of lymphoma; results were not materially changed (data not reported). Statistical analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

Results

NHL cases were less likely to be African-American compared to controls (13% versus 25%), but the groups were reasonably balanced on sex, study center, education, age and body mass index (Table I). DLBCL and follicular NHL were the two most common NHL subtypes.

Cases (16%) and controls (14%) reported a similar prevalence of ever having received a blood transfusion one year or more before the reference date. Of participants who ever had a transfusion, the mean number of transfusions was similar for cases (2.7) and controls (2.8). After adjustment for age, gender, race and study center, we observed a 26% higher risk of NHL for participants reporting any history of transfusion (OR=1.26; 95% CI 0.91–1.73), although this was not statistically significant at $p<0.05$. There was no association with the total number of transfusions (OR=1.01 per transfusion; 95% CI 0.93–1.10). The increased risk was specific to transfusions first given 5 to 29 years before the reference date (OR=1.69; 95% CI 1.08–2.62) (Table II), and a test for homogeneity was highly significant ($p=0.0025$). Only first transfusions given for a medical condition were associated with risk of NHL (OR=2.09; 95% CI 1.03–4.26), while those given for trauma, obstetric, or surgical care were not associated with risk; the test for homogeneity ($p=0.097$) suggested a potential interaction but did not attain conventional statistical significance. These associations were broadly consistent for both DLBCL and follicular NHL (Table II) and among subgroups defined by age, sex, race, and education (data not shown). Further adjustment for body mass index and family history of NHL did not alter these associations (data not shown). The most common medical conditions were anemia (34%), ulcers (18%), unspecified hemorrhage (9%) and gastrointestinal bleeding (8%), and small numbers precluded estimating ORs for individual conditions. There were too few cases to simultaneously evaluate the time since first transfusion, number of transfusions, and/or indication for first transfusion.

A history of any surgery excluding dental surgeries and procedures (i.e., non-dental surgeries) was reported by 91% of the cases and 88% of the controls, and the mean number of surgeries was similar for cases (4.4) and controls (4.0). There was no association of the number of non-dental surgeries or total number of dental surgeries and procedures with risk of NHL overall, while there was a suggestive positive trend ($p=0.07$) with the combined grouping of the number of surgeries including dental surgeries and procedures with risk of NHL (Table III). Participants reporting 26 or more surgeries or dental procedures one year or more before the reference date were estimated to have a 53% higher risk compared to those with 0–6 surgeries or dental procedures (95% CI 1.02–2.29), and all ORs were all

similarly elevated for more than 6 surgeries (i.e., ORs=1.41, 1.52, 1.56, and 1.53 for increasing numbers of surgeries). The results were similar for DLBCL and follicular lymphoma, with the strongest evidence for increasing ORs with increasing number of surgeries for follicular lymphoma.

In the analysis of surgeries at a specific anatomic site, there were no statistically significant associations for ever/never histories (Table IV), the number of the surgeries (0, 1, 2+), or the time since first surgery (1–4, 5–29, 30+ years) (data not shown). The single exception was for the group "appendix, stomach, or bowel surgery," where there was a 24% increased risk for any history (OR=1.24; 95% CI 0.98–1.58). The latter risk was also elevated for the first surgery 5–29 years (OR=1.45; 95% CI 1.02–2.04) and 30+ years (OR=1.25; 95% CI 0.93–1.69) before the reference date, but not for the surgery 1–4 years before the reference date (OR=0.71; 95% 0.40–1.47). In the analysis of surgeries at a specific anatomic site by NHL subtype, there were suggestive positive associations for DLBCL with any history of "liver, gallbladder, or pancreas surgery" (OR=1.66; 95% CI 0.98–2.80), and for follicular NHL with "throat or neck surgery" (OR=1.37; 95% CI 0.95–1.96), "appendix, stomach, or bowel surgery" (OR=1.36; 95% CI 0.94–1.98), and "bone surgery" (OR=1.39; 95% 0.96–2.01) (Table IV).

For each surgery, including dental surgeries and procedures, use of general or regional/local anesthesia was ascertained. A history of any general anesthesia was reported by 86% of cases and 83% of controls, and the mean number of events was 3.2 for cases and 3.0 for controls. Compared to never having had general anesthesia, there was a 40% higher risk for 3–4 (95% CI 0.96–2.05) and a 27% higher risk for 5 or more (95% CI 0.85–1.88) times having had a general anesthesia, although these point estimates and the trend test were not statistically significant at $p<0.05$ (Table V). Results were similar for DLBCL and follicular NHL. These patterns were also observed for exposure to local/regional anesthesia (which included anesthetic for dental procedures) and all anesthesia (general and local/regional combined) (Table V).

We only queried participants about anesthesia as part of an inquiry on the details of their surgical or dental procedures, and there was a strong correlation between total number of surgeries and total number of anesthesias (r=0.92). For example, nearly all participants reporting a non-dental surgery also reported receiving some type of anesthesia (99.7%), mainly a general anesthesia (91.7%). This high correlation of surgery and anesthesia precluded including these variables in the same model.

Total number of transfusions showed little correlation with total number of surgeries (r=0.07) or with total number of anesthesias (r=0.01). When history of transfusion (no/yes) or time since first transfusion (no transfusion, <5, 5–29, and 30+ years) were included in the same model with total number of surgeries, the ORs remained virtually unchanged for NHL overall and for DLBCL and follicular NHL (data not shown). Similar results were also observed when the transfusion variables and anesthesia were included in the same model (data not shown).

Discussion

In this population-based case-control study of NHL risk, we found some evidence for an association of blood transfusion, which has been reported in other studies, and histories of surgery or anesthesia, which has not been studied previously. We observed independence between the effects of anesthesia and the length of time since the first transfusion, as well as independence between the effects of surgery and the length of time since first transfusion, and we found broadly similar patterns of risk for follicular lymphoma and DLBCL. Finally,

we noted no increased risk for transfusions unless they were given for medical conditions, rather than for trauma, delivery or surgery.

A history of blood transfusion has been inconsistently associated with risk of NHL. In positive studies, the magnitude of the relative risk has been in the range of 1.5–3.0,[22–25] but a majority of studies have found no association.[26–34] This heterogeneity does not appear to be explained by differences in study populations, era of transfusion, method of exposure assessment, age at first transfusion, gender, or assessment of confounding, although a higher percentage of earlier studies and cohort studies have reported a positive association.[8, 9, 35] The role of latency has been evaluated less thoroughly. Transfusions occurring just before NHL diagnosis mostly would not be of etiologic relevance,[36] but some studies have reported that risk remains elevated in the 5–30 year window from first transfusion to NHL diagnosis.[22, 25] Of the null studies with latency data, one reported no association by time from first transfusion,[31] while a second study reported a slight increase in risk of NHL for a first transfusion 11–15 years (OR=1.4; 95% 0.84–2.4) but not >16 years before NHL diagnosis.[30] We restricted the history of transfusions to those reported at least one year before diagnosis. In analyses of time from first transfusion, the period of 5–29 years before diagnosis was specifically associated with risk. Finally, earlier studies reported some evidence for a stronger association with more indolent NHL subtypes, including SLL/CLL and follicular NHL in most [25, 29, 30, 37] but not all[31] studies that reported subtype data.

Any association between transfusion and NHL risk may be due to confounding by the indication for transfusion, but few studies have reported data on indication. We found that the transfusion-NHL association was specific to an indication for a medical condition, which is consistent with Zhang et al.[31] who found that anemia but not other indications for transfusion was associated with an increased risk of NHL (OR=2.3; 95% CI 0.9–6.3). Our observation of no effect of blood transfusions given for an obstetric indication agrees with two smaller studies (<2 exposed cases).[27, 33] In our data, the most common specific conditions in the medical condition group were anemia, ulcers, and hemorrhage, and no specific disease processes were clearly identifiable (e.g., process causing anemia; cause of hemorrhage). Anemia itself has been suggested as a NHL risk factor in at least one additional study.[14] Mechanistically, our data support the hypothesis that transfusion history is likely a marker for underlying immune dysfunction impacting diverse medical conditions, and is less likely to be a marker for the immunologic impacts of transfusion per se, given that there were no associations for traumatic, obstetric or surgical indications.

Transfusion may also be a marker for the transmission of an infectious agent. Participants with known HIV infection, which is a strong risk factor for NHL, were excluded from our study. HCV was positively associated with risk in this study,[38] but the prevalence of infection was quite low. We were not able to adjust for HCV infection in this analysis as our HCV data were delinked from the dataset. Nevertheless, HCV infection is not likely to explain the specific associations with time since first transfusion or transfusion for a medical condition.

Our finding of an association with the total number of surgeries and NHL risk has not been reported previously. Major surgery produces an initial state of hyperinflammation (related to the acute phase response) followed by a state of immunosuppression (related to a shift in the Th1/Th2 balance to a Th2 cytokine profile driven in part by IL-6); there is also a down regulation of the innate immune system.[11] This impact is blunted for elective surgery relative to major trauma,[11] and is also weaker for less invasive laparoscopic surgery.[39, 40] In experimental studies, tumor cells grow more aggressively after major surgery compared to minor surgery.[41, 42] We could not assess intensity for all surgeries from our questionnaire, but we did not find especially strong results for procedures that are almost certainly more

intense (e.g., heart or lung surgery). Furthermore, dental surgeries and procedures, a majority likely to be minor in nature, also showed an association with NHL risk. The latter finding, along with the lack of a clear dose response relation for the different measures of surgery, raises the possibility of either false positive findings or confounding by some other factor, although it does not appear that transfusion history, BMI, or education play such a role. However, there could be residual confounding by these factors, or by socioeconomic status in general, for which education is an incomplete surrogate. Alternatively, if the association is real, this would support a mechanism related to low level antigenic stimulation and inflammation rather than the more pronounced immune effects of major surgery.

Few data on specific types of surgery and risk of NHL have been published, but concern has been raised about potential carcinogenic impacts on the lymphatic system by corrosion products from metal implants.[43, 44] At least two studies have found an association with total hip or knee arthroplasty and risk of lymphoma,[45, 46] but two separate meta-analyses of eight studies reported no association for either NHL[12] or lymphoma,[13] which is consistent with our overall results. There are also prior reports linking appendectomy to NHL risk from two case-control [14, 16] and two cohort studies,[15, 17] although one case-control study reported no association.[18] These findings are consistent with our finding of increased risk of “appendix, stomach, bowel” surgery (OR=1.24; 95% CI 0.98–1.58). However, we were not able to estimate the risk for appendectomy specifically.

Our weak positive association of general anesthesia with NHL risk is consistent with a case-control study from Los Angeles, which found that those who had reported ever having undergone general anesthesia experienced an increased risk of NHL (OR=1.52; 95% CI 1.05–2.21).[14] The prevalence of ever exposure among controls in that study (87%) was similar to our study (83%). We also had data on local/regional anesthesia, and higher cumulative exposure (any exposure was nearly universal) also showed a positive association with risk. We were not able to disentangle the effects of anesthesia and surgery. Anesthesia has broad immunosuppressive effects, but these effects are transitory and the specific effects vary greatly by type of agent and route of administration (e.g., inhalation versus intravenous).[10]

Strengths of this study include the multi-center, population-based design with case ascertainment using a SEER cancer registry. We also collected details on the number and indication for transfusions and the number, type and associated anesthetic exposure for surgeries. However these were self-reported and not validated against medical records. Also, by collecting timing of transfusions, we were able to exclude transfusions occurring near or after diagnosis, since these would play no etiologic role in NHL. This also allowed us to assess the window for latency between first exposure and disease. Our participation rate for controls was not optimal, and could introduce bias. However, the associations reported here were broadly similar when considered by strata of age, center or education (which had differing participation rates), providing some indirect evidence that a major bias was not likely. Another strength was our ability to address the more common NHL subtypes of DLBCL and follicular NHL.

In summary, blood transfusions were associated with NHL risk, but appear to be a marker for underlying medical conditions. Our study also provides preliminary new data implicating multiple surgical procedures and/or repeated administration of anesthesia in this malignancy. Beyond replication of these findings, future studies should also focus on the indication and timing of transfusion, medical record validation of these exposures, and interactions of these exposures with host genetic susceptibility. Finally, the current body of literature suggests that the effects of surgery, anesthesia and transfusions occur on pathways of immune dysfunction that affect lymphoma development.

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Abbreviations

CAPI	computer-assisted personal interview
CI	confidence interval
DLBCL	diffuse large B-cell lymphoma
NHL	non-Hodgkin lymphoma
OR	odds ratio
SEER	Surveillance, Epidemiology and End Results

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TABLE I

DESCRIPTIVE CHARACTERISTICS, NCI-SEER INTERDISCIPLINARY CASE-CONTROL STUDY OF NHL, 1998–2000

Variable	Controls (N=589)	Cases (N=759)
	Percent Distribution	
Sex		
Male	52	54
Female	48	46
Race		
African-American	25	13
White	69	80
Other	6	7
Center		
Detroit	23	31
Iowa	21	22
Los Angeles	29	25
Seattle	26	22
Education		
<12 years	10	11
12–15 years	61	62
16+ years	28	27
NHL Subtype		
DLBCL		30
Follicular		23
T-Cell		7
All other		41
	Mean ± SD	
Age (years)	56.9 ± 12.7	56.6 ± 12.4
Body Mass Index (kg/m^2)	27.7 ± 5.5	27.7 ± 5.4

TABLE II

ADJUSTED[†] ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR NHL (ALL, DLBCL, FOLLICULAR) ACCORDING TO HISTORY OF TRANSFUSION, NCI-SEER STUDY, 1998–2000

		All NHL Cases			DLBCL			Follicular NHL		
Variable	**Controls**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**
History of transfusion										
No	507	640	1	reference	194	1	reference	142	1	reference
Yes	82	119	1.26	0.91–1.73	30	1.12	0.70–1.81	30	1.40	0.87–2.26
Time since first transfusion (years)[*]										
<5	15	13	0.81	0.37–1.76	4	0.99	0.31–3.18	2	0.67	0.15–3.03
5–29	34	68	1.69	1.08–2.62	21	1.81	1.00–3.30	13	1.40	0.71–2.77
30+	33	36	0.94	0.57–1.57	5	0.44	0.16–1.18	13	1.47	0.73–2.96
Indication for first transfusion[*]										
Trauma	8	11	1.09	0.43–2.80	4	1.16	0.33–4.09	2	--	
Obstetric	21	19	0.86	0.44–1.67	2	--		7	1.30	0.52–3.27
Surgical	41	59	1.19	0.77–1.83	15	1.10	0.58–2.09	11	1.01	0.50–2.05
Medical	12	27	2.09	1.03–4.26	8	2.32	0.89–6.06	8	3.07	1.18–7.98

[†]Adjusted for age, gender, race, and study center.

[*]Sums to less than 119 owing to missing data

TABLE III

ADJUSTED[†] ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR NHL (ALL, DLBCL, FOLLICULAR) ACCORDING TO HISTORY OF SURGERY, NCI-SEER STUDY, 1998–2000

		All NHL Cases			DLBCL			Follicular NHL		
Variable	**Controls**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**
Total number of surgeries, excluding dental surgeries and procedures										
0	66	72	1	reference	29	1	reference	12	1	reference
1	106	106	0.89	0.57–1.39	29	0.59	0.31–1.10	21	0.99	0.45–2.18
2–3	156	211	1.16	0.76–1.76	70	0.99	0.56–1.76	47	1.43	0.69–2.97
4–6	147	204	1.17	0.75–1.81	54	0.80	0.43–1.47	53	1.66	0.79–3.49
7+	114	166	1.22	0.77–1.93	42	0.82	0.43–1.56	39	1.61	0.74–3.51
p-trend			0.2			0.9			0.1	
Trend OR[*]			1.07	0.97–1.18		0.99	0.86–1.15		1.14	0.97–1.34
Total number of dental surgeries and procedures										
0–4	127	121	1	reference	32	1	reference	28	1	reference
5–8	127	163	1.31	0.92–1.86	52	1.60	0.94–2.71	28	0.91	0.50–1.64
9–12	109	141	1.29	0.89–1.87	39	1.37	0.77–2.43	34	1.18	0.65–2.12
13–20	110	169	1.49	1.03–2.15	49	1.74	1.00–3.02	44	1.48	0.84–2.60
21+	116	165	1.32	0.91–1.92	52	1.70	0.97–2.98	38	1.17	0.65–2.10
p-trend			0.3			0.2			0.6	
Trend OR[*]			1.06	0.95–1.29		1.09	0.97–1.23		1.03	0.90–1.20
Total number of surgeries, including dental surgeries and procedures										
0–6	112	98	1	reference	30	1	reference	17	1	reference
7–11	123	148	1.41	0.96–2.06	44	1.48	0.84–2.63	28	1.45	0.73–2.85
12–17	118	170	1.52	1.02–2.25	56	1.78	1.00–3.19	38	1.84	0.94–3.62
18–25	114	166	1.56	1.05–2.33	43	1.45	0.80–2.64	46	2.28	1.18–4.40
26+	122	177	1.53	1.02–2.29	51	1.62	0.89–2.95	43	1.92	0.97–3.78
p-trend			0.07			0.2			0.05	
Trend OR[*]			1.09	0.99–1.19		1.10	0.96–1.25		1.15	1.00–1.32

[†] Adjusted for age, gender, race, and study center.

[*] Per unit change in an ordinal variable scored 0–4.

TABLE IV

ADJUSTED[†] ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR NHL (ALL, DLBCL, FOLLICULAR) ACCORDING TO SITE OF SURGERY, SEER-NCI STUDY, 1998–2000

		All NHL Cases			DLBCL			Follicular NHL		
Variable	**Controls**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**
Skin surgery	204	296	1.10	0.87–1.40	80	0.94	0.67–1.33	75	1.28	0.89–1.84
Eye Surgery	81	102	0.96	0.69–1.33	29	0.93	0.58–1.50	23	0.89	0.53–1.49
Nose or Sinus Surgery	38	63	1.25	0.81–1.92	15	0.97	0.51–1.83	18	1.57	0.86–2.87
Brain Surgery	5	5	0.80	0.23–2.83	0	--		0	--	
Ear Surgery	22	25	0.85	0.47–1.54	6	0.66	0.26–1.68	4	--	
Face or Jaw Surgery	17	23	0.95	0.50–1.83	4	--		6	1.14	0.43–3.01
Throat or Neck Surgery	253	360	1.08	0.86–1.36	106	1.15	0.82–1.60	92	1.37	0.95–1.96
Breast Surgery	69	85	0.86	0.59–1.24	21	0.71	0.40–1.26	24	1.04	0.60–1.80
Heart or Lung Surgery	48	51	0.78	0.50–1.20	16	0.92	0.49–1.72	12	0.90	0.45–1.78
Kidney or Bladder Surgery	27	44	1.18	0.71–1.96	16	1.56	0.80–3.05	12	1.47	0.71–3.03
Vasectomy[*]	74	101	0.82	0.57–1.20	34	1.00	0.59–1.70	26	1.13	0.64–2.01
Prostate, Testis, or Penis Surgery[*]	51	77	1.23	0.81–1.87	17	0.94	0.49–1.79	16	1.23	0.64–2.39
Liver, Gallbladder, or Pancreas Surgery	53	74	1.08	0.73–1.59	28	1.66	0.98–2.80	13	0.80	0.42–1.55
Appendix/Stomach/Bowel Surgery	198	289	1.24	0.98–1.58	75	1.10	0.77–1.57	69	1.36	0.94–1.98
Bone Surgery	169	233	1.10	0.86–1.40	62	0.98	0.69–1.41	61	1.39	0.96–2.01
Hip or Knee Replacement	15	21	1.15	0.58–2.30	5	0.93	0.32–2.67	7	1.65	0.64–4.24
Other Surgery	40	37	0.68	0.42–1.08	11	0.68	0.34–1.38	12	0.99	0.50–1.95
Cesarean section[§]	29	40	1.09	0.64–1.83	13	1.28	0.62–2.66	7	0.71	0.29–1.73
Surgical Sterilization[§]	59	75	0.94	0.62–1.42	17	0.76	0.40–1.44	22	1.17	0.64–2.15
Other Surgery on Female Organs[§]	145	175	0.95	0.68–1.32	40	0.67	0.41–1.09	50	1.39	0.83–2.33

[†] Adjusted for age, gender, race, and study center; reference is not reporting a history of surgery at the given site of surgery.

[*] Males only (N=204 controls and 410 cases)

[§] Females only (N=285 controls and 349 cases)

TABLE V

ADJUSTED[†] ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR NHL (ALL, DLBCL, FOLLICULAR) ACCORDING TO HISTORY OF ANESTHESIA, NCI-SEER STUDY, 1998–2000

		All NHL Cases			DLBCL			Follicular NHL		
Variable	**Controls**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**	**Cases**	**OR**	**95% CI**
General anesthesia, total number										
Never	99	105	1	reference	33	1	reference	21	1	reference
1	119	145	1.10	0.75–1.61	49	1.17	0.68–2.02	34	1.21	0.65–2.26
2	110	135	1.14	0.77–1.69	40	1.15	0.65–2.04	24	0.93	0.47–1.84
3–4	132	204	1.40	0.96–2.05	63	1.49	0.86–2.59	44	1.38	0.74–2.59
5+	129	170	1.27	0.85–1.88	39	1.09	0.60–1.98	49	1.73	0.92–3.28
p-trend			0.1			0.5			0.09	
Trend OR[*]			1.07	0.98–1.17		1.04	0.91–1.19		1.13	0.98–1.31
Local/regional anesthesia, total number										
0–3	120	112	1	reference	35	1	reference	21	1	reference
4–7	133	168	1.27	0.89–1.81	42	1.02	0.60–1.75	30	1.15	0.62–2.14
8–11	101	154	1.52	1.03–2.23	51	1.69	0.98–2.93	42	2.08	1.12–3.85
12–19	120	165	1.30	0.89–1.89	49	1.35	0.78–2.33	44	1.73	0.94–3.17
20+	115	160	1.35	0.92–1.98	47	1.39	0.80–2.44	35	1.43	0.76–2.70
p-trend			0.2			0.09			0.2	
Trend OR[*]			1.06	0.97–1.15		1.11	0.98–1.26		1.08	0.95–1.24
Any Anesthesia, total number										
0–6	120	113	1	reference	32	1	reference	20	1	reference
6–10	121	167	1.46	1.01–2.11	52	1.73	1.00–2.98	30	1.39	0.73–2.64
11–15	123	173	1.37	0.94–2.01	53	1.72	0.97–3.04	46	1.99	1.06–3.73
16–23	111	151	1.33	0.90–1.97	40	1.47	0.81–2.64	43	2.03	1.08–3.82
24+	114	155	1.35	0.91–2.02	47	1.75	0.97–3.17	33	1.49	0.76–2.91
p-trend			0.3			0.1			0.3	
Trend OR[*]			1.04	0.95–1.14		1.10	0.97–1.26		1.08	0.94–1.25

[†]Adjusted for age, gender, race, and study center.

[*]Per unit change in an ordinal variable scored 0–4.