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Smoking, Alcohol Use, Obesity, and Overall Survival from Non-Hodgkin Lymphoma: A Population-Based Study

Susan M. Geyer, PhD^{1,2}, Lindsay M. Morton, PhD³, Thomas M. Habermann, MD¹, Cristine Allmer, BS¹, Scott Davis, PhD⁴, Wendy Cozen, MD⁵, Richard K. Severson, PhD⁶, Charles F. Lynch, MD, PhD⁷, Sophia S. Wang, PhD³, Matthew J. Maurer, MS¹, Patricia Hartge, ScD³, and James R. Cerhan, MD, PhD¹

¹College of Medicine, Mayo Clinic, Rochester, Minnesota ²College of Medicine, The Ohio State University, Columbus, Ohio ³National Cancer Institute, Rockville, Maryland ⁴Fred Hutchinson Cancer Research Center, Seattle, Washington ⁵University of Southern California, Los Angeles, California ⁶Wayne State University, Detroit, Michigan ⁷The University of Iowa, Iowa City, Iowa

Abstract

BACKGROUND—Smoking, alcohol use, and obesity appear to increase the risk of developing non-Hodgkin lymphoma (NHL), but few studies have assessed their impact on NHL prognosis.

METHODS—We evaluated the association of pre-diagnosis cigarette smoking, alcohol use, and body mass index (BMI) on overall survival in 1,286 patients enrolled through population-based registries in the United States from 1998–2000. Hazard Ratios (HR) and 95% confidence intervals (CI) were estimated using Cox regression, adjusting for clinical and demographic factors.

RESULTS—Through 2007, 442 patients died (34%), and the median follow-up on living patients was 7.7 years. Compared to never smokers, former (HR=1.59; 95% CI 1.12–2.26) and current (HR=1.50; 95% CI 0.97–2.29) smokers had poorer survival, and poorer survival was positively associated with smoking duration, number of cigarettes smoked per day, pack-years of smoking, and shorter time since quitting (all p-trend<0.01). Alcohol use was associated with poorer survival (p-trend=0.03); compared to non-users, those drinking more than 43.1 grams/week (median of intake among drinkers) had poorer survival (HR=1.55; 95% CI 1.06–2.27) while those drinkers consuming less than this amount showed no survival disadvantage (HR=1.13; 95% CI 0.75–1.71). Greater body mass index was associated with poorer survival (p-trend=0.046), but the survival disadvantage was only seen among obese individuals (HR=1.32 for BMI ≥30 versus 20–24.9 kg/m²; 95% CI 1.02–1.70). These results held for lymphoma-specific survival and were broadly similar for DLBCL and follicular lymphoma.

CONCLUSIONS—NHL patients who smoked, consumed alcohol or were obese prior to diagnosis had a poorer overall and lymphoma-specific survival.

Keywords

alcohol; non-Hodgkin lymphoma; obesity; smoking; survival

Corresponding author: James R. Cerhan, MD, PhD, Division of Epidemiology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

Conflict of Interest Disclosures

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INTRODUCTION

In 2008, the American Cancer Society estimates that 66,120 persons will be diagnosed with non-Hodgkin lymphoma (NHL), and 19,160 will die from this disease.¹ NHL is now the fifth most common cause of cancer among both men and women. NHL incidence rates have been increasing over much of the 20th century and have only recently begun to slow. Five-year relative survival for the time period of 1974–1995 was stable at approximately 50%, but has increased to 66% for the time period 1996–2004.² Of the estimated 10.7 million cancer survivors in the US in 2004, approximately 431,000 had NHL,² making this an important group from a clinical and public health perspective. Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma are the two most common NHL subtypes.

The strongest and most robust predictors of outcome in NHL are age, stage, number of nodal or extranodal sites, performance status, and certain biochemical measures (e.g., serum LDH and hemoglobin level), and these factors have been aggregated into various clinical prognostic indices including the International Prognostic Index (IPI) for DLBCL³ and the Follicular IPI (FLIPI) for follicular lymphoma.⁴ Multiple tumor biomarkers have also been widely evaluated as predictors of NHL prognosis, although few are used in routine clinical practice.^{5–6} More recently, host genetic background has also been evaluated, including pharmacogenetic markers,^{7–9} genetic markers of general immune function,^{10–11} or genetic markers of DNA repair function.¹² In contrast, there is relatively little data on the impact of lifestyle factors on NHL prognosis. Results from large International Lymphoma Epidemiology Consortium (InterLymph) pooling projects have reported that cigarette smoking appears to slightly increase the risk of NHL overall and follicular lymphoma in particular;¹³ alcohol decreases the risk of NHL across most subtypes;¹⁴ and obesity increases the risk of DLBCL.¹⁵ However, only three studies have evaluated the role of these factors in NHL prognosis, and to date suggest that cigarette smoking,^{16–17} alcohol use,^{16–17} and obesity¹⁸ may be adverse prognostic factors. We therefore evaluated the impact of these factors on overall and lymphoma-specific survival in a series of cases who participated in a population-based case-control study in four regions of the United States.

MATERIALS AND METHODS

Study Population

This study of NHL survival has been previously described.¹⁰ Briefly, subjects with newly diagnosed, histologically-confirmed NHL were enrolled in a population-based case-control study from July 1998 through June 2000;¹⁹ the analyses presented here focus on the cases enrolled in that study. The cases were rapidly reported from four Surveillance, Epidemiology, and End Results (SEER) cancer registries in the Detroit metropolitan area, the state of Iowa, Los Angeles County, and northwestern Washington State. All consecutive NHL patients diagnosed in Iowa and the Seattle area were included in this study, while in Los Angeles and Detroit, all African American NHL patients were included, but only a random sample of non-African American patients. Eligible patients had a first primary diagnosis of NHL between the ages of 20 to 74 years old (inclusive), and were alive and competent to participate in the interview. Any patients known to be HIV-positive were excluded. Local IRB approval was obtained for each of the participating recruitment centers and consent was obtained for all participants.

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 in 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. Response rates were higher for patients with follicular lymphoma (67%) than DLBCL (51%). Approximately 60% of cases were interviewed within six months of their diagnosis, and 84% were interviewed within one year.

Lifestyle Data

In-home interviews were conducted using a computer-assisted personal interview (CAPI). To accommodate a large number of questions, we used a split-sample design, with a core set of questions given to all respondents and the remainder given to participants in either Group A (all African American and 50% of non-African American participants) or Group B (50% of non-African American participants). Prior to the in-person interview, participants were mailed a form for listing residential and job history, and either a family medical history questionnaire (Group A) or a diet and lifestyle questionnaire (Group B). During the interview, the interviewer administered a computer-assisted personal interview (CAPI) that included demographics, height and weight, occupational history, pesticide exposure and hair dye use. The Group A CAPI included an extended medical history and use of illicit drugs, while the Group B CAPI included an abbreviated medical history, cell phone use and sun exposure.

Self-reported height and weight one year before diagnosis was obtained from all participants as part of the CAPI. Alcohol and cigarette smoking (but not other tobacco use) was only collected on Group B participants. Usual intake of beer, white wine, red wine, and liquor one year before diagnosis (and excluding recent changes) were obtained as part of the self-administered modified Block 1995 Health Habits and History Questionnaire.²⁰ Total grams of alcohol intake per week were estimated from the Block database. The smoking history included ever smoking, age start, age stop, and average number of cigarettes smoked per day.

Clinical and Outcome Data

Date of diagnosis, histology, stage, presence of B-symptoms, first course of therapy, date of last follow-up, and vital status were derived from linkage to registry databases at each study site. Histology was coded initially according to the International Classification of Diseases-Oncology (ICD-O), 2nd Edition,²¹ and this was later updated to the 3rd Edition by each registry.²² We grouped cases into NHL subtypes according to the InterLymph guidelines.²³ Data on first course of therapy included use of single or multi-agent chemotherapy, radiation, other therapies exclusive of chemotherapy and/or radiation, and no therapy (presumed to be observation); information on individual agents and doses was not available. The SEER registries collect date and cause of death, but do not collect data on treatment response or disease recurrence or progression. In 2007, we conducted a second linkage to update survival information. Of the 1,321 cases in the original study, we had clinical and follow-up data available for 1286 cases for this analysis.

Statistical Analysis

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, and was categorized *a priori* according to WHO categories of <20, 20–24.9, 25.0–29.9, and 30+ kg/m². Alcohol use was categorized as non-drinker, alcohol use ≤median of all alcohol users in this study (43.1 g/week) or alcohol use >median of alcohol users; in secondary analyses, we also modeled alcohol as a continuous variable. Smoking was categorized by status (never, former, current), duration (never smoker, <20 and 20+ years), intensity (never smoker, ≤20 (1 pack) and 21+ cigarettes/day), pack-years (never smoker, <17 and 17+ pack-

years), and time since quitting (never smoker, quit >20 years, quit 10–19 years, quit <10 years, current smokers).

Overall survival was defined as the time from diagnosis to the date of death or last follow-up; patients alive at last follow-up were censored at that time point. Lymphoma-specific survival was defined as death due to lymphoma; other deaths were censored at date of death. We used Cox proportional hazards regression²⁴ to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) after adjusting for clinical and demographic variables (see Table 1 for variables and categories). These analyses were conducted for the entire cohort as well as the subset groups of DLBCL and follicular lymphoma.

RESULTS

There were 1,286 patients with a median age of 58 years old (range: 20–74 years) at diagnosis from 1998–2000. A slight majority of subjects were male (54%). The most common histologies were DLBCL (33%), follicular (26%), CLL/SLL (10%), marginal zone (9%), mantle cell (4%) and peripheral T-cell (3%). As part of their initial therapy, 68% of patients received some type of chemotherapy, while 27% received radiation therapy (treatments not mutually exclusive).

Through 2007, 442 (34%) patients died, including 144 of 420 DLBCL (34%) and 93 of 328 follicular lymphoma (28%) patients. The median follow-up on living subjects was 7.7 years (range: 1.3–9.5). Age over 60 years, male sex, non-white race, lower education, presence of B-symptoms, distant stage, and NHL subtype (DLBCL, mantle cell, peripheral T-cell, CLL/SLL) were associated with poorer survival in univariate analysis for all NHL, although not all were statistically significant at $p < 0.05$ (Table 1).

Data on smoking and alcohol use were only collected on the cases who were part of the Group B arm of the study (N=550). Of the 471 patients from this arm of the study with non-missing smoking data, 34% were former smokers and 19% were current smokers at the time of diagnosis. After adjustment for clinical and demographic factors in Table 1, former (HR=1.59; 95% CI 1.12–2.26) and current smokers (HR=1.50; 95% CI 0.97–2.29) had poorer survival compared to never smokers (Table 2). Poorer survival was positively associated with longer smoking duration ($p < 0.001$), greater number of cigarettes smoked per day ($p = 0.009$), greater pack-years of smoking ($p = 0.0005$), and shorter time since quitting ($p = 0.002$). Of note, compared to never smokers, patients who had quit >20 years before diagnosis did not have a higher risk of death (HR=1.14; 95% CI 0.70–1.86). All of these associations were somewhat weaker for DLBCL and stronger for follicular lymphoma (Table 2).

Of the 458 patients with data on alcohol use from the Group B arm of the study, 49% consumed alcohol one year before diagnosis, and among alcohol users, the median intake was 43.1 grams/week. After multivariable adjustment for demographic and clinical factors, there was poorer survival for drinkers of more than 43.1 grams/week compared to never drinkers (HR=1.55; 95% CI 1.06–2.27), while there was no association for drinkers of ≤ 43.1 grams/week (HR=1.13; 95% CI 0.75–1.71) (Table 2). These trends were evident for DLBCL and follicular lymphoma (Table 2), although the point estimates and trend tests did not reach conventional levels of statistical significance at $p < 0.05$. When we modeled alcohol as a continuous variable, the p-values were 0.038 for all NHL, 0.17 for DLBCL, and 0.008 for follicular lymphoma. When we simultaneously modeled wine, beer, and liquor use, no one specific type of alcohol was associated with NHL survival or DLBCL survival (data not shown); for follicular survival, however, there appeared to be a specific association with

liquor use (HR=2.90; 95% CI 1.19–7.07). However, due to relatively small numbers, these results should be interpreted with caution.

All 1286 patients were asked to provide height and weight 1 year before diagnosis, and 1189 had useable data. Based on BMI, 5% of patients were classified as underweight, 31% normal weight, 39% overweight, and 26% as obese. As shown in Table 2, after adjustment for clinical and demographic factors, only obese patients showed a survival disadvantage (HR=1.32 compared to normal weight; 95% CI 1.02–1.70). These associations were similar for the patients only in the Group B arm (who had smoking and alcohol data), and were also similar for DLBCL and follicular lymphoma (Table 2). There were no associations with height or weight for NHL overall or by subtype (all p-trend >0.15; data not shown).

We next re-analyzed the associations in Table 2 based on death due to lymphoma (N=273), and the patterns of association were very similar, with the major exceptions that the associations for smoking and survival strengthened for follicular lymphoma and the associations for BMI with survival strengthened for all outcomes (data not shown).

When we included pack-years of smoking, alcohol use and BMI in the same model along with the clinical and demographic variables, the HR smoking remained unchanged for smoking (HR=1.87 for 17+ pack-years versus never smoker; 95% CI 1.29–2.72), nearly identical for BMI (HR=1.38 for BMI >30 versus 20–24.9 kg/m²; 95% CI 0.89–2.15), and slightly attenuated for alcohol use (HR=1.41 for >43.1 grams/week versus no alcohol; 95% CI 0.93–2.15). Similar results were observed for DLBCL and follicular lymphoma (data not shown). These results provide some evidence that these associations were independent of each other, although a much larger sample size would be required to provide a more definitive assessment with respect to statistical significance.

DISCUSSION

In this analysis of a large, population-based sample of NHL cases, we found that smoking cigarettes, drinking more than 43.1 grams of alcohol per week – approximately 3.3 cans (355 mL) of beer, 4.6 glasses (118 mL) of wine, or 2.7 shots (44 mL) of liquor per week – and being obese prior to diagnosis each had a negative impact on overall survival after accounting for clinical and demographic variables. Associations remained after simultaneous inclusion of all three variables in the same statistical model, although some of the associations were no longer statistically significant, and therefore the latter observation is only preliminary. Finally, these associations held for lymphoma-specific survival, and were broadly similar for both DLBCL and follicular lymphoma, with the exception that the associations with smoking were stronger for follicular lymphoma.

This is the first report to simultaneously assess these associations on survival, and to evaluate them in a North American population, and replication is needed. While based on observational data, there does not appear to be obvious explanations for these findings due to bias, confounding or chance, although there may be residual confounding that we have not been able to fully address with the clinical and demographic variables that were measured. Furthermore, there may also be unmeasured confounding by lifestyle and other factors that are closely correlated with smoking, alcohol use and obesity. Alternatively, these associations could have biological plausibility in this context, and could represent a causal association.

Smoking

Our results for smoking are broadly consistent with two prior studies from Italy.^{16, 17} In a population-based study of 1138 patients diagnosed from 1991–1993 and followed through

2002, Battaglioli and colleagues¹⁶ reported that the number of years smoked (HR=1.26 for >39 years versus ≤25 years, 95% CI 0.94–1.70) and number of pack-years (HR=1.60 for >31 pack-years versus ≤14 pack-years, 95% CI 1.18–2.18) were associated with poorer survival after adjustment for gender, age, and education, although there was no association by smoking status (never, former, current) or years since quitting smoking. These associations were similar when the outcome was restricted to death due to lymphoma. In a second study of 268 NHL patients enrolled from 1983 to 2002, Talamini and colleagues¹⁷ reported that number of cigarettes per day (HR=1.80 for ≥20 versus never smoked, 95% CI 1.06–2.73) and to a lesser extent duration of smoking (HR=1.32 for ≥30 years versus never smoked, 95% CI 0.85–2.05) were associated with poorer survival after adjustment for age, sex, B-symptoms and the IPI. With respect to NHL subtypes, the first study reported stronger associations for follicular lymphoma¹⁶ while the second smaller study reported stronger associations for follicular lymphoma and CLL/SLL.¹⁷ These findings for follicular lymphoma are consistent with our results; we had too few CLL/SLL cases in our study to evaluate survival.

Cigarette smoking could negatively influence NHL survival through multiple mechanisms,^{13, 25} including a direct carcinogen impact; activation of other carcinogens through induction of metabolizing enzymes; influence on immunologic function, including increasing pro-inflammatory cytokines and T-cell function; and impact on the prevalence of the t(14;18) translocation and subsequent overexpression of bcl-2, which can inhibit apoptosis. Smoking may also impact treatment efficacy, and smokers also tend to have more comorbidities that can also impact survival.²⁵

Alcohol Use

Both of the Italian studies also reported positive associations with alcohol use. Compared to non-drinkers, drinkers of any alcohol (HR=1.41; 95% CI 1.10–1.81), drinking >32 versus ≤13 grams of alcohol per day (HR=1.41; 95% CI 1.05–1.90), and longer duration of drinking (HR=1.55 for >43 years versus ≤10; 95% CI 1.13–2.14) were all associated with poorer survival in one study,¹⁶ while a greater number of drinks per day (HR=1.69 for ≥4 versus <2; 95% CI 1.04–2.76) was associated with poorer survival in the other study.¹⁷ These associations were broadly elevated for the common subtypes. The poorer survival associated with any use of alcohol is consistent with our findings, although it must be noted that the Italian studies had a much higher level of alcohol use than our study, raising concerns about the nature of any dose-response biologic effect. With respect to risk of developing NHL, light to moderate alcohol use appears to be protective for NHL overall and for the major subtypes,¹⁴ which is the opposite of its association with outcome observed to date. The reasons for this are not clear, but if real, would suggest different biologic mechanisms for the two associations. Alcohol can act as both a direct and indirect carcinogen,²⁶ and may also impact treatment efficacy.²⁷ In contrast, alcohol has immunomodulatory effects²⁸ that have been hypothesized to protect against the development of NHL at light to moderate levels of intake,²⁹ complicating interpretation of these findings.

Obesity

Only a single study has evaluated the role of obesity in NHL prognosis. Tarella and colleagues¹⁸ reported on 121 lymphoma patients enrolled in Italy from 1990–1997 who received high-dose chemotherapy and autograft and were followed for a median of 3 years. Patients with a BMI ≥28 kg/m² had a poorer event-free (HR=2.8; 95% CI 1.5–5.3) and overall survival (RR=2.9; 95% CI: 1.3–6.2) compared to patients with a BMI of <28 kg/m² after adjustment for gender, IPI, bone marrow infiltration, and histology; histology-specific results were not provided.

In this study, when smoking, alcohol and obesity were included in the same model that also adjusted for clinical and demographic factors, the associations were largely unchanged, suggesting that these may be independent prognostic factors. Both Battaglioli et al.¹⁶ and Talamini et al.¹⁷ reported a similar result when they simultaneously adjusted for smoking and alcohol use; however, no other study has simultaneously assessed all three factors.

Obesity can affect cancer through multiple mechanisms, including an impact on estrogen, androgen, insulin and growth factor pathways.³⁰ Obesity is associated with a pro-inflammatory state in general and the release of TNF α in particular, both of which have been suggested as NHL risk^{31, 32} and prognostic factors.^{10, 11} There is also the potential for underdosing of chemotherapy in obese individuals.³³ While all of these factors can negatively impact existing comorbidities in NHL patients and therefore decrease overall survival, our finding that these associations remain when assessing lymphoma-specific survival suggest a more direct impact of these factors on lymphoma and/or its treatment.

Strengths and Limitations

Strengths of this study include the relatively large sample size, population-based case ascertainment, and relatively long-term and nearly complete follow-up. Our results should be generalizable to community patients. There are also limitations. Data on smoking, alcohol and BMI were self-reported, but were reported prior to outcome. We also only collected smoking and alcohol data on a subset of cases, limiting sample size for multivariate models. Alcohol use was light, and we could not assess heavier use such as that seen in the Italian studies. We were unable to assess event-free survival, rarer NHL subtypes, or to adjust for standard prognostic factors such as the IPI or FLIPI, or detailed treatment. Nevertheless, these clinical and demographic factors have been shown to predict outcome similar to the IPI or FLIPI in this dataset.^{10, 11} Additional limitations include the lack of data on change in these factors after diagnosis; diagnosis and initial treatment of cases from 1998–2000, prior to the widespread use of rituximab as standard of therapy for B-cell lymphoma;^{34, 35} and a largely white study population. Future studies should address these limitations.

Conclusions

In conclusion, our findings for an adverse impact of smoking, alcohol use, and obesity are consistent with data from three smaller studies from Italy, and thus supports investigating whether smoking cessation, decrease in alcohol intake, or weight loss after diagnosis of NHL can improve outcomes.

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Table 1
Univariate Associations of Demographic and Clinical Factors, NCI-SEER NHL Survival Study, 1998–2007

Factor	All NHL			DLBCL			Follicular Lymphoma		
	N	% Dead	HR (95% CI)	N	% Dead	HR (95% CI)	N	% Dead	HR (95% CI)
Age (years)									
≤60	714	25.4%	1.00 (reference)	247	23.5%	1.00 (reference)	192	21.4%	1.00 (reference)
>60	572	45.6%	1.98 (1.63–2.39)	173	49.7%	2.41 (1.72–3.36)	136	38.2%	1.86 (1.23–2.80)
Sex									
Female	595	31.9%	1.00 (reference)	189	33.3%	1.00 (reference)	165	29.7%	1.00 (reference)
Male	691	36.5%	1.17 (0.97–1.41)	231	35.1%	1.03 (0.74–1.43)	163	27.0%	0.93 (0.62–1.39)
Race									
White	1097	33.5%	1.00 (reference)	368	33.7%	1.00 (reference)	287	27.5%	1.00 (reference)
Non-white	189	39.7%	1.24 (0.97–1.59)	52	38.5%	1.20 (0.75–1.92)	41	34.1%	1.33 (0.76–2.36)
Education Level (years)									
<12	127	49.6%	1.00 (reference)	45	53.3%	1.00 (reference)	25	32.0%	1.00 (reference)
12–15	796	33.2%	0.58 (0.44–0.77)	252	30.2%	0.45 (0.29–0.72)	213	28.6%	0.89 (0.43–1.87)
16+	362	31.8%	0.57 (0.42–0.77)	122	36.1%	0.59 (0.36–0.96)	90	26.7%	0.83 (0.37–1.84)
B Symptoms									
No	496	29.6%	1.00 (reference)	146	28.8%	1.00 (reference)	160	25.6%	1.00 (reference)
Yes	254	41.7%	1.62 (1.26–2.08)	118	39.0%	1.54 (1.01–2.34)	47	29.8%	1.24 (0.67–2.27)
Unknown	536	35.3%	1.25 (1.01–1.55)	156	35.9%	1.34 (0.90–2.00)	121	36.4%	1.26 (0.81–1.96)
Stage of Disease									
Local/Regional	556	26.4%	1.00 (reference)	240	30.8%	1.00 (reference)	130	18.5%	1.00 (reference)
Distant	663	42.2%	1.80 (1.48–2.20)	167	38.9%	1.39 (0.99–1.94)	181	35.4%	2.07 (1.29–3.30)
Unknown	67	22.4%	0.81 (0.48–1.38)	13	38.5%	1.27 (0.52–3.15)	17	29.4%	1.51 (0.57–3.95)
Histologic Subtype									
DLBCL	420	34.3%	1.00 (reference)						
Follicular	328	28.4%	0.77 (0.59–1.00)						
Mantle Cell	54	63.0%	2.36 (1.62–3.43)						
Marginal Zone	115	25.2%	0.65 (0.43–0.96)						
Peripheral T-cell	42	40.5%	1.31 (0.79–2.17)						

Factor	All NHL			DLBCL			Follicular Lymphoma		
	N	% Dead	HR (95% CI)	N	% Dead	HR (95% CI)	N	% Dead	HR (95% CI)
CLL/SLL	128	50.8%	1.37 (1.03–1.82)						
Other Subtypes	199	30.2%	0.91 (0.66–1.24)						

Multivariate Adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI)¹ for the Association of Smoking, Alcohol Use and Body Mass Index with Overall Survival for all NHL and for DLBCL and Follicular Lymphoma, NCI-SEER NHL Survival Study, 1998–2007

Table 2

	All NHL				DLBCL				Follicular Lymphoma			
	N	% Dead	HR (95% CI)		N	% Dead	HR (95% CI)		N	% Dead	HR (95% CI)	
Smoking and alcohol use for Group B subjects												
Smoking status												
Never smoker	220	30.0%	1.00 (reference)		86	32.6%	1.00 (reference)		58	22.4%	1.00 (reference)	
Former smoker	162	38.3%	1.59 (1.12–2.26)		54	40.7%	1.36 (0.77–2.40)		40	25.0%	1.98 (0.81–4.80)	
Current smoker	89	37.1%	1.50 (0.97–2.29)		30	33.3%	1.22 (0.58–2.58)		26	42.3%	2.95 (1.27–6.81)	
Smoking duration												
Non-smoker	220	30.0%	1.00 (reference)		86	32.6%	1.00 (reference)		58	22.4%	1.00 (reference)	
Smoker, <20 years	87	31.0%	1.09 (0.67–1.78)		29	31.0%	1.01 (0.47–2.17)		24	25.0%	2.04 (0.74–5.67)	
Smoker, 20+ years	159	44.0%	1.76 (1.25–2.47)	p-trend=0.0009	52	42.3%	1.53 (0.87–2.69)	p-trend=0.16	41	34.1%	2.48 (1.11–5.52)	p-trend=0.03
Smoking Intensity (cigarettes/day)												
Non-smoker	220	30.0%	1.00 (reference)		86	32.6%	1.00 (reference)		58	22.4%	1.00 (reference)	
Smoker ≤1 pack/day	151	35.1%	1.43 (1.00–2.06)		46	37.0%	1.17 (0.64–2.14)		42	28.6%	2.02 (0.88–4.61)	
Smoker >1 pack/day	99	40.4%	1.65 (1.11–2.45)	p-trend=0.009	38	36.8%	1.39 (0.72–2.66)	p-trend=0.32	22	31.8%	2.49 (0.93–6.64)	p-trend=0.04
Smoking pack-years												
Non-smoker	220	30.0%	1.00 (reference)		86	32.6%	1.00 (reference)		58	22.4%	1.00 (reference)	
<17 pack-years	93	24.7%	0.96 (0.59–1.54)		29	27.6%	0.82 (0.37–1.82)		23	17.4%	1.29 (0.40–4.11)	
17+ pack-years	150	44.7%	1.88 (1.33–2.66)	p-trend=0.0005	50	44.0%	1.68 (0.95–2.95)	p-trend=0.10	41	41.5%	2.61 (1.19–5.74)	p-trend=0.02
Time since quitting smoking (to diagnosis)												
Never smoker	220	30.0%	1.00 (reference)		86	32.6%	1.00 (reference)		58	22.4%	1.00 (reference)	
Quit >20 years	70	31.4%	1.14 (0.70–1.86)		21	42.9%	1.16 (0.54–2.49)		17	17.6%	1.19 (0.33–4.27)	
Quit 10–19 years	51	37.3%	1.41 (0.85–2.36)		21	42.9%	1.41 (0.66–3.00)		10	20.0%	1.79 (0.38–8.40)	
Quit <10 years	39	51.3%	3.56 (2.12–5.97)		11	36.4%	2.24 (0.76–6.62)		12	33.3%	3.73 (1.07–13.0)	
Current smoker	89	37.1%	1.51 (0.99–2.32)		30	33.3%	1.22 (0.58–2.59)		26	42.3%	3.01 (1.30–7.00)	

	All NHL			DLBCL			Follicular Lymphoma		
	N	% Dead	HR (95% CI)	N	% Dead	HR (95% CI)	N	% Dead	HR (95% CI)
Alcohol use			p-trend=0.002			p-trend=0.312			p-trend=0.005
None	234	33.3%	1.00 (reference)	83	37.3%	1.00 (reference)	66	28.8%	1.00 (reference)
≤43.1 g/week ²	112	30.4%	1.13 (0.75–1.71)	45	33.3%	1.24 (0.65–2.35)	30	10.0%	0.35 (0.10–1.20)
>43.1 g/week	112	39.3%	1.55 (1.06–2.27)	38	34.2%	1.48 (0.75–2.94)	26	42.3%	2.16 (0.98–4.77)
			p-trend=0.03			p-trend=0.25			p-trend=0.16
BMI for Group A and B subjects combined									
BMI Continuous ³	1189	33.9%	1.09 (1.00–1.20)	391	33.8%	1.07 (0.93–1.23)	299	31.1%	1.14 (0.92–1.41)
BMI WHO Categories:									
Underweight (<20 kg/m ²)	55	29.1%	1.00 (0.59–1.68)	17	23.5%	1.20 (0.42–3.42)	15	26.7%	0.76 (0.26–2.23)
Normal (20–24.9 kg/m ²)	368	31.3%	1.00 (reference)	108	30.6%	1.00 (reference)	107	23.4%	1.00 (reference)
Overweight (25–29.9 kg/m ²)	462	33.8%	1.03 (0.81–1.31)	143	32.2%	1.05 (0.67–1.64)	114	30.7%	1.23 (0.73–2.08)
Obese (≥30 kg/m ²)	304	38.2%	1.32 (1.02–1.70)	123	39.8%	1.37 (0.88–2.14)	63	30.2%	1.49 (0.81–2.72)
			p-trend=0.046			p-trend=0.20			p-trend=0.11
BMI for Group B subjects only									
BMI Continuous ³	459	33.1%	1.08 (0.93–1.25)	167	35.3%	1.05 (0.85–1.30)	122	26.2%	1.05 (0.77–1.44)
BMI WHO Categories:									
Underweight (<20 kg/m ²)	21	28.6%	1.01 (0.43–2.36)	5	40.0%	1.87 (0.42–8.22)	8	12.5%	0.38 (0.05–3.04)
Normal (20–24.9 kg/m ²)	158	32.3%	1.00 (reference)	52	32.7%	1.00 (reference)	48	27.1%	1.00 (reference)
Overweight (25–29.9 kg/m ²)	185	31.4%	0.88 (0.60–1.28)	64	34.4%	0.93 (0.49–1.77)	46	23.9%	1.01 (0.44–2.30)
Obese (≥30 kg/m ²)	95	38.9%	1.33 (0.86–2.03)	46	39.1%	1.24 (0.63–2.46)	20	35.0%	1.29 (0.51–3.27)
			p-trend=0.29			p-trend=0.78			p-trend=0.33

¹ Adjusted for age at diagnosis (≤60 vs. >60 years), gender, race, education, study site, stage (distant vs. not), chemotherapy, radiation, B symptoms, and histology (for the All NHL group only).

² Median intake of users; approximately equal to 3.3 cans (355 mL) of beer, 4.6 glasses (118 mL) of wine, or 2.7 shots (44 mL) of liquor per week.

³ One SD (5 kg/m²) change.