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Obesity and Non-Hodgkin Lymphoma Survival in an Ethnically Diverse Population: The Multiethnic Cohort Study

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Abstract

Purpose—Obesity increases mortality for several malignancies, but for non-Hodgkin lymphoma (NHL) the association between body mass index (BMI) and survival is unclear. We examined the association of pre-diagnostic BMI with overall and NHL-specific survival in the Multiethnic Cohort (MEC) study of African Americans, Native Hawaiians, Japanese Americans, Latinos, and Caucasians.

Methods—MEC participants free of NHL at cohort entry and diagnosed with NHL during follow-up were included in the analyses (N=1331). BMI was based on self-reported weight and height at cohort entry and after 6.1 years of cohort entry. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) with BMI as time-varying exposure in relation to all-cause and NHL-specific mortality while adjusting for known confounders.

Results—The mean age at NHL diagnosis was 70.5 (range 45–89) years. After a mean follow-up of 4.3±3.5 years, 667 deaths including 450 NHL-specific deaths occurred. In multivariable models, obese patients (BMI ≥30.0 kg/m²) had higher all-cause (HR=1.46, 95%CI 1.13–1.87) and NHL-specific (HR=1.77, 95%CI 1.30–2.41) mortality compared to patients with high-normal BMI (22.5–24.9 kg/m²). For overweight patients (BMI=25.0–29.9 kg/m²), the respective HRs were 1.21 (95%CI 0.99–1.49) and 1.36 (95%CI 1.06–1.75). Cases with low-normal BMI (<22.5 kg/m²) experienced a significant 45% higher all-cause and a 40% higher NHL-specific mortality. After stratification by NHL type, the adverse effect of BMI was stronger for chronic lymphocytic leukemia/small lymphocytic lymphoma than for diffuse large B-cell lymphoma and follicular lymphoma.

Conclusions—Pre-diagnostic BMI may be a suitable prognostic marker for NHL patients.

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Keywords

Non-Hodgkin Lymphoma; Ethnicity; Obesity; Survival; Prognosis

Introduction

Non-Hodgkin lymphoma (NHL) is the 7th most common cancer in the United States (1) and consists of a heterogeneous group of neoplasms that arise from the malignant transformation of B, T, and natural killer cells of the immune system. With the addition of rituximab to traditional therapies, survival has improved over the past decade (2). In 2009, the 5-year relative survival rate for NHL patients was reported to be as high as 71% (3). Currently, the International Prognostic Index and the Follicular Lymphoma International Prognostic Index are validated prognostic systems used by clinicians to predict treatment outcomes for aggressive diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) (4, 5). Well-established factors that predict a poor prognosis include >60 years of age at diagnosis, stage 3 (nodal involvement on both sides of the diaphragm) or 4 (disseminated disease), elevated serum LDH as a marker of increased tumor burden, poor performance status, and extranodal involvement. Despite the many studies focusing on lifestyle risk factors related to NHL etiology (6, 7), few investigations have examined the impact of modifiable factors on survival after a diagnosis of NHL. Since obesity may increase the risk of NHL and mortality for other malignancies, e.g., breast cancer, weight status in relation to survival after a primary diagnosis of NHL has emerged as an area of interest (7–9).

Previous reports evaluating the influence of BMI on survival in NHL patients are inconsistent. Whereas several studies reported worse survival for obese patients (10), others reported null findings (11, 12) or improved survival (13, 14). Most previous studies did not examine obesity in relation to NHL-specific mortality, which is important as it determines whether BMI has a direct impact on lymphoma outcome after removing deaths secondary to competing causes related to BMI. Among published reports, many retrospective cohort studies and clinical trials excluded patients with comorbidities or were unable to enroll patients with severe disease who died before recruitment. Also, available data are limited for ethnically diverse populations (15–17). Therefore, we examined the relation of self-reported, pre-diagnostic BMI at baseline and after 6 years of follow-up with overall and NHL-specific mortality among African American, Caucasian, Native Hawaiian, Japanese American and Latino NHL patients in Hawaii and Los Angeles who participated in the Multiethnic Cohort (MEC) study. Specifically, we hypothesized that overweight and obesity are associated with poorer overall and NHL-specific survival.

Methods

Study Population

The MEC is a longitudinal study designed to investigate the associations of dietary, lifestyle, and genetic factors with the incidence of cancer; details have been previously described (18). In brief, the cohort was established in 1993–1996 by mailing a self-administered, 26-page questionnaire to men and women ages 45 to 75 years residing in Hawaii and

California. To obtain a multiethnic sample of African Americans, Caucasians, Native Hawaiians, Japanese Americans, and Latinos, the primary sampling frame included drivers' license records in both states, supplemented with voter registration lists in Hawaii and Medicare files in California. More than 215,000 men and women indicated their consent to participate in the study by returning the questionnaire. The Institutional Review Boards at the University of Hawaii and the University of Southern California approved the study protocol.

Data Collection

The baseline questionnaire (Qx1) included sections on height and body weight that were used to calculate pre-diagnostic BMI, medical history, smoking, demographic information, and a food frequency questionnaire that included use of alcoholic beverages (19). The presence of self-reported co-morbidities, including diabetes, hypertension, and heart attack or angina, was assessed as follows: "Has your doctor ever told you that you had any of the following conditions?" Between 1999 and 2002, approximately 85% of eligible MEC members completed a brief follow-up questionnaire (Qx2) that updated information on body weight.

All participants included in the current analysis were free of a self-reported or registry-detected NHL diagnosis at cohort entry. Case and death ascertainment was available up to December 31, 2007. Following entry into the MEC, incident cases of NHL were identified by linkage with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the state-wide Hawaii Tumor Registry, all part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (20). NHL types were classified into the following categories according to the adaptation of the World Health Organization classification for epidemiologic studies using the International Classification of Disease Oncology version 3 (21, 22): DLBCL (9679, 9680, 9684), FL (9690, 9691, 9695, 9698), chronic lymphocytic leukemia (CLL) (9823) and small lymphocytic lymphoma (SLL) (9670), marginal zone lymphoma (MZL) (9689, 9699), T-cell lymphoma (9700–9719, 9675 (T), 9827, 9831, 9834, 9948), and all other types (9671, 9673, 9675, 9687, 9761, 9826, 9832, 9833, 9835, 9836, 9940). Tumor characteristics were obtained from the cancer registries, including stage at diagnosis and first course of treatment (chemotherapy, radiotherapy, immunotherapy, steroid treatment) within 6 months of diagnosis, but data on recurrence were not available. Stage at diagnosis was coded according to the SEER Coding and Staging Manual 2004 into localized, regional, distant, and unknown (23).

Dates and causes of death were identified by computerized linkages with the databases of the California and Hawaii vital records offices and the National Death Index. The causes of death were registered and coded according to International Classification of Diseases (ICD)-9 or ICD-10. NHL-specific deaths were defined as any ICD code describing NHL or related conditions (2001, 2002, 2021, 2028, 2040, 2041, 2049, 2078, 2080, 2089, 2387, C829-C831, C833, C837, C840, C844, C845, C850, C851, C859, C880, C910, C911, C915, C917, C920, C947, C951, C959). Two deaths due to leukemia in CLL patients were also classified as NHL-specific deaths due to transformation of CLL.

Statistical analysis

After excluding cases with missing BMI and covariate values, 1331 cases were part of the present analysis. BMI was classified into four categories (<22.5, 22.5–24.9, 25.0–29.9, 30 kg/m²). The cutoff of 22.5 kg/m² was used due to the small numbers of cases (N=18) with a BMI <18.5 kg/m² and to maintain consistency with previous analyses (7). Kaplan-Meier survival curves compared survival across ethnic groups, NHL types, and BMI status; log-rank tests were used to test for differences in survival. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using log-linear Cox proportional hazards models with age as the time metric; all-cause mortality and NHL-specific mortality were examined as separate outcomes. For all-cause mortality, survival was modeled starting at the age of diagnosis and ending at age of death from any cause or censored at the end of the study period (12/31/2007). For NHL-specific survival, age of death due to NHL was modeled; everyone else was censored at the time of death from other causes or at the end of the observation period.

BMI was treated as a time-varying exposure. Any survival time between baseline and Qx2 was assigned the BMI value at baseline, while any survival time after Qx2 was assigned the BMI value at Qx2. That is, BMI at baseline was modeled for participants who never completed or died before Qx2, BMI at Qx2 was modeled for participants who were diagnosed after Qx2, and both BMI values were modeled for participants who were diagnosed prior to Qx2, completed Qx2, and died or were censored after Qx2. The models were adjusted for age at diagnosis as a continuous variable, sex, SEER summary stage (local, regional, distant, and unstaged/unknown), education status (<12, ≥12 years), NHL type (DLBCL, FL, CLL/SLL, MZL, T-cell, others), radiotherapy, chemotherapy, immunotherapy, i.e., interferon, interleukin, or monoclonal antibodies, and steroid treatment (yes, no/unknown for all treatment variables). The models were also adjusted for smoking status (never, former, current), alcohol use (0, <14, 14–28, ≥28 g/day), and comorbidity (hypertension, diabetes, heart attack/angina) in three categories (0, 1, 2+) as these behaviors and conditions are associated with BMI and overall survival (24).

To examine differential effects of BMI status according to NHL type, stratified analyses for the three most common NHL types DLBCL, FL, and CLL/SLL were performed. In addition, we examined potential interactions of BMI and ethnicity on the risk of mortality by including cross-product terms in the multivariable models. To assess the possible influence of rituximab, we included an indicator for the era before and after the introduction of rituximab defined as 1993–2001 vs. 2002 onwards and performed stratified analyses based on a landmark study demonstrating that rituximab improved survival in DLBCL patients (25). As rituximab was coded as immunotherapy prior to 2005 but as cytostatic chemotherapy starting in 2005, its use could not be adequately identified from the SEER data.

In addition, the following sensitivity analyses were performed: stratification by age (<70 vs ≥70 years) and years of follow-up before diagnosis (<5 vs ≥5 years), excluding deaths during the first 3 years after cohort entry, limiting cases to never smokers, limiting patients to CLL/SLL and FL cases who did not receive any treatment, and using redefined treatment and comorbidity variables. The proportional hazards assumptions were assessed by

examining $\log(-\log(\text{survival function}))$ plots for diverging or crossing survival curves over time, testing the statistical significance of time-by-covariate interaction terms, and assessing the scaled Schoenfeld residuals. All statistical computing was conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) with a p-value <0.05 considered to be significant.

Results

For the 1331 cases included in this analysis, the mean time from cohort entry to NHL diagnosis was 7.2 ± 3.9 years and the mean age at diagnosis was 70.5 ± 8.5 years. A total of 667 deaths and 450 NHL-specific deaths were observed over a mean follow-up period of 4.3 ± 3.5 years (Table 1). Caucasians, African Americans, Japanese Americans, Latinos, and Native Hawaiians comprised 29.3, 14.8, 25.7, 24.3, and 5.9% of the study population, respectively. The mean BMI was 26.5 ± 4.7 kg/m² at baseline and 26.3 ± 4.9 kg/m² for the 961 participants who completed Qx2 after 6.1 ± 0.9 years. Among these, 289 cases were diagnosed before Qx2 (2.6 ± 1.9 years) and 672 cases after Qx2 (3.8 ± 2.3 years). Smoking and alcohol use were significantly associated with BMI ($p = 0.007$ and 0.02). The lowest BMI category included higher proportions of Japanese, Caucasians, never smokers, non-drinkers, and participants with fewer comorbidities and better education, but the stage distribution and NHL types did not differ. Hypertension was the most frequently reported comorbidity ($N = 545$), followed by diabetes ($N = 176$) and a history of heart attack ($N = 150$). DLBCL was the most common type diagnosed for all ethnic groups except African Americans and Caucasians who had a higher proportion of CLL/SLL, whereas Japanese Americans had the lowest proportion of CLL/SLL. For 532 (40%) cases, no treatment was recorded with the highest proportion among CLL/SLL (67%) and the lowest among DLBCL (23%) patients.

The overall 5-year survival rate was 56.1% (Table 1), while the relative rate due to NHL was 66.9%. Kaplan-Meier analysis indicated higher overall ($p = 0.03$) and NHL-specific ($p = 0.01$) mortality among low-normal, overweight, and obese patients (Figure 1). In an adjusted model (Table 2), obese patients had a statistically significant higher all-cause mortality (HR = 1.46, 95% CI 1.13–1.87) relative to patients with high-normal BMI. The corresponding value for overweight was HR = 1.21 (95% CI 0.99–1.49). For patients with low-normal BMI, a 45% (95% CI 1.13–1.85) higher risk of all-cause mortality was observed. The results were similar for NHL-specific deaths: low-normal (HR = 1.40, 95% CI 1.03–1.91), overweight (HR = 1.36, 95% CI 1.06–1.75), and obese (HR = 1.77, 95% CI 1.30–2.41) BMI status.

Among the three common types of NHL (Table 3), significant associations of survival with BMI were only detected for CLL/SLL patients with HRs of 3.89 and 4.99 for low-normal and obese BMI. However, CIs were imprecisely estimated and the point estimates were also in the direction of lower overall and NHL-specific mortality for DLBCL. When the analysis was restricted to the 67% of CLL/SLL cases without recorded treatment, the risk estimates for low-normal, overweight, and obese BMI remained elevated with HRs of 4.06, 1.90, and 4.48 (significant for obesity). The interaction between BMI and ethnicity was not significant. Also, no difference in all-cause or NHL-specific mortality by ethnicity was observed for all cases (Table 2) or by NHL type (Table 3) except for poorer NHL-specific survival of Japanese Americans with CLL/SLL (HR = 3.12, 95% CI 1.39–6.97). However,

the numbers were small, 14 NHL-specific deaths among 32 cases. In a similar pattern, current smokers had statistically higher overall (HR = 1.67, 95% CI 1.31–2.12) and NHL-specific mortality (HR = 1.47, 95% CI 1.10–1.97) than never smokers (Table 2) with the strongest association in CLL/SLL patients (Table 3).

Cox models adjusted for an indicator of rituximab era detected a non-significant survival advantage after rituximab was introduced in 2002 (HR = 0.83, 95% CI 0.66–1.04). In stratified analyses for cases diagnosed before 2002 (687 cases and 293 deaths), the respective HRs for low-normal weight, overweight, and obesity were 1.33 (95% CI 0.89–1.58), 1.47 (95% CI 1.07–2.01), and 1.89 (95% CI 1.28–2.79). In the rituximab era (644 cases and 157 deaths), the HRs were attenuated and did not reach statistical significance: 1.49 (95% CI 0.88–2.54), 1.12 (95% CI 0.72–1.75), and 1.68 (95% CI 0.99–2.84).

After stratification by age at diagnosis (<70 vs. ≥70 years), the association of BMI with survival was stronger and only significant for in the younger group. The respective HRs for low-normal, overweight, and obesity were 1.89 (95% CI 1.03–3.48), 2.60 (95% CI 1.59–4.24), and 2.86 (95% CI 1.67–4.92) as compared to 1.26 (95% CI 0.87–1.81), 1.08 (95% CI 0.79–1.46), and 1.45 (95% CI 0.96–2.18). Also, the risk estimates were slightly greater for cases diagnosed >5 years after cohort entry than for the earlier group. After excluding the 46 deaths during the first 3 years after cohort entry, the HRs for NHL-specific mortality remained 1.31 (95% CI 0.95–1.82), 1.33 (95% CI 1.02–1.72), and 1.93 (95% CI 1.41–2.66). Restricting the analysis to 560 never smokers modified the risk estimates to a small degree. The respective HRs for the three BM categories were 1.56 (95% CI 0.99–2.48), 1.73 (95% CI 1.14–2.63), and 2.14 (95% CI 1.28–3.58). Combining the four treatment modalities into one variable or modeling comorbidity as separate conditions did also not substantially affect the risk estimates.

Discussion

In this ethnically diverse cohort of patients diagnosed with NHL, low-normal weight, overweight and obese patients had 40%, 36% and 77% higher NHL-specific mortality than patients with high-normal BMI. In agreement with the previous studies, the association of pre-diagnostic BMI with all-cause mortality in our cohort was J-shaped with 45% higher mortality for patients with low-normal BMI and 21% and 46% higher mortality for overweight and obese patients, respectively, as compared to high-normal BMI (26). After stratification by NHL type, the elevated mortality risk was most pronounced in CLL/SLL patients; however, our ability to detect associations for specific NHL types was limited by the sample size. Survival showed little difference by ethnicity except for Japanese Americans with CLL/SLL. Our finding of worse overall survival associated with smoking prior to NHL diagnosis agrees with previous reports (10, 27, 28) possibly due to creating a microenvironment that promotes tumor growth.

Our results are consistent with the lower survival of obese patients in two previous reports (10, 29), which assessed self-reported height and weight at least 1 year before diagnosis. A study that had information on weight near the time of diagnosis found no association between obesity and survival or even improved survival (13). The discordant findings are

thought to reflect a loss of weight occurring nearer to diagnosis, especially among patients experiencing B symptoms, i.e., fever, night sweats, and weight loss. However, contrary to this argument, the excess risk in our study was seen in models that included two BMI values 6 years apart and were very similar and relatively close to diagnosis. Exclusion of deaths during the first 3 years of follow-up also did not change the findings substantially. For future studies, it would be desirable to record the weight at time of diagnosis and in subsequent years.

Our finding that overweight and obese individuals have a higher risk of NHL-specific death is of importance; it suggests that obesity may have a direct impact on lymphoma progression and death, apart from being a risk factor for overall mortality (30). Most studies in NHL patients to date reported on overall mortality only (11, 13, 14, 29) although one report detected similar patterns of association for the 273 deaths due to lymphoma (10). Previous cohort studies detected higher NHL-related mortality in their participants with excess body weight but did not examine survival specifically in cases (15–17).

When stratified by common NHL types, obesity was primarily associated with poorer NHL-specific survival for CLL/SLL patients. Previous studies mostly showed non-significant associations between obesity and poorer overall survival for DLBCL, CLL/SLL, and FL (10, 29). A retrospective study on United States Veterans with DLBCL (14) indicated a protective effect of overweight and obesity, but only 70% of all cases were included in the analysis and the inability to obtain information for all cases may have biased the results. Although our findings indicated lower survival for several NHL types, pooled studies are warranted to obtain adequately powered type specific effect estimates.

Obesity can affect cancer through various mechanisms, including inflammatory, estrogen, androgen, insulin and growth factor pathways (31). The pro-inflammatory state associated with obesity (32, 33) may lead to higher levels of pro-inflammatory adipokines that promote cell proliferation or higher levels of adiponectin that inhibit proliferation (34). Obesity-induced insulin resistance may fuel growth through the production of insulin and insulin-like growth factor (35). As suggested by clinical studies, chemotherapy may be underdosed in obese individuals and be responsible for poorer survival due to variations in dose calculations and adverse effects (36).

Patients with BMI $<22.5 \text{ kg/m}^2$ at baseline had significantly lower all-cause and NHL-specific survival primarily evident in CLL/SLL cases. The association was attenuated but did not disappear when the models were limited to patients 70 years and older, never smokers, deaths that occurred more than 3 years of cohort entry, and the rituximab era. The finding of higher mortality with low BMI agrees with a large body of evidence describing U-shaped mortality patterns that become J-shaped after longer follow-up (37–39). The characteristics of MEC participants in this BMI category did not explain their unfavorable outcome. Although a compromised immune system, affecting tumor-immune system interactions (40) and resulting in greater toxicity from systemic chemotherapy and overdosing (41), has been proposed for low-weight individuals, we have no evidence to that effect. Other possible reasons suggested for this observation in the general population include reverse causation with weight loss in smokers and respiratory disease, residual

confounding due to risk factors and conditions that were not assessed, loss in muscle mass, and lower body reserves to withstand treatment (37, 42). The results for low-normal BMI could also simply represent a chance finding.

No ethnic differences in survival were observed with the exception of a higher rate of NHL-specific mortality in the small group of Japanese Americans with CLL/SLL. The poorer prognosis may be due to a higher proportion of atypical CLL with a higher percentage of large lymphocytes or prolymphocytes in Japanese than in Western populations as described in a Japanese report (43).

Strengths of the current study include a population-based prospective design with a large number of ethnically diverse individuals. The 5-year relative survival rate of 67% in the MEC cases was very similar to rates reported by SEER, which ranged from 59–71% between 1996 and 2010 (3). Most of the previous reports were based on case-control studies (10, 11, 29), which may not have enrolled a sufficient numbers of patients with advanced stage disease and more aggressive NHL types. Further, previous clinical studies may not be representative of all NHL cases due to strict inclusion criteria (13, 14, 44, 45). The prospective cohort design has the advantage of including all NHL cases even those with a short time interval between diagnosis and death. Our study is also more generalizable to the largest ethnic groups in the US population than previous studies of primarily white individuals. The MEC is well characterized with respect to covariates of interest, allowing for adjustment of potential confounding factors, such as smoking, and comorbidities. An additional strength is the ascertainment of incident NHL diagnoses through linkage with high-quality population-based tumor registries that provided detailed information on tumor characteristics as well as treatment within 6 months of diagnosis. Given the reliability of the National Death Index linkage, misclassification of vital status is unlikely. The validity of cause of death codes for cancer appears to be high. As shown in a recent analysis (46), the concordance of diagnoses from death certificates and cancer registries is >90% for NHL although some underreporting for CLL was detected.

Several limitations should be considered. The relatively short follow-up period is a concern and the power for the analysis of NHL types was limited. Self-reported weight and height may have been subject to reporting bias. Information for BMI at diagnosis, Ann Arbor staging, performance status, B symptoms, and laboratory parameters, such as LDH, was not available. However, the stability of the BMI reported >6 years after baseline and closer to diagnosis increases confidence in its accuracy. The lack of more detailed treatment data is a another weakness, in particular the fact that SEER registries provide treatment data only for the first 6 months and that rituximab use cannot be adequately identified due to coding changes. Nevertheless, we found no significant survival advantage during the rituximab era and similar associations of BMI with mortality before and after the introduction of rituximab.

This study found that being overweight or obese at cohort entry was related to lower overall survival and NHL-specific survival. Therefore, prediagnostic BMI may be a suitable marker to stratify patients by prognosis. Potentially, BMI can be included as part of clinical prognostic assessment among NHL patients, but more information on the association of

post-diagnostic BMI or weight change with survival and a better biologic understanding of the mechanisms how obesity affects NHL survival are needed. Stratification by NHL type suggested higher NHL-specific mortality risk for CLL/SLL compared to other NHL types, but further studies with larger sample sizes and longer follow-up are warranted to examine differences in the association by specific NHL type.

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A. All-cause survival by BMI

D. NHL-specific survival by BMI

B. All-cause survival by ethnicity

E. NHL-specific survival by ethnicity

C. All-cause survival by NHL type

F. NHL-specific survival by NHL type

Figure 1.

Kaplan-Meier curves for all-cause and NHL-specific survival, Multiethnic Cohort Study, 1993–2007

Table 1

Characteristics of NHL cases in the Multiethnic Cohort Study diagnosed 1993–2007

Characteristic ^a	All cases	African American	Caucasian	Native Hawaiian	Japanese American	Latino	<i>p</i> ^b
Cases, n (%)	1331	197 (14.8)	390 (29.3)	78 (5.9)	342 (25.7)	324 (24.3)	<0.0001
Deaths, n (%)							
All-cause	667	115 (17.3)	171 (25.6)	43 (6.5)	171 (25.6)	167 (25.0)	0.01
NHL-specific	450	76 (17.0)	110 (24.4)	27 (6.0)	127 (28.2)	110 (24.4)	0.06
Age at cohort entry, years	63.3	63.7	63.0	60.4	64.9	62.5	<0.0001
Age at diagnosis, years	70.5	70.7	70.2	67.8	72.1	69.9	<0.0001
Sex, n (%)							
Male	729 (54.8)	94 (47.7)	218 (55.9)	45 (57.7)	194 (56.7)	178 (54.9)	
Female	602 (45.2)	103 (52.3)	172 (44.1)	33 (42.3)	148 (43.3)	146 (45.1)	0.29
5 year survival, n (%)	56.1	54.3	64.5	49.4	53.0	52.0	0.003
BMI, kg/m ² , n (%)							
<22.5	220 (16.6)	16 (8.1)	75 (19.2)	6 (7.7)	91 (26.6)	32 (9.9)	
22.5–24.9	337 (25.3)	47 (23.9)	111 (28.5)	14 (17.9)	113 (33.0)	52 (16.0)	
25.0–29.9	530 (39.8)	82 (41.6)	142 (36.4)	35 (44.9)	120 (35.1)	151 (46.6)	
30.0	244 (18.3)	52 (26.4)	62 (15.9)	23 (29.5)	18 (5.3)	89 (27.5)	<0.0001
BMI at Qx2, kg/m ² , n (%)							
<22.5	176 (13.2)	24 (12.2)	53 (13.6)	6 (7.7)	72 (21.1)	21 (6.5)	
22.5–24.9	251 (18.9)	27 (13.7)	89 (22.8)	13 (16.7)	84 (24.6)	38 (11.7)	
25.0–29.9	365 (27.4)	44 (22.3)	122 (31.3)	20 (25.6)	87 (25.4)	92 (28.4)	
30.0	169 (12.7)	37 (18.8)	41 (10.5)	17 (21.8)	11 (3.2)	63 (19.4)	
Missing	370 (27.8)	65 (33.0)	85 (21.8)	22 (28.2)	88 (25.7)	110 (34.0)	<0.0001
Education, n (%)							
12 years	595 (44.7)	80 (40.6)	100 (25.6)	46 (59.0)	159 (46.5)	210 (64.8)	
>12 years	736 (55.3)	117 (59.4)	290 (74.4)	32 (41.0)	183 (53.5)	114 (35.2)	<0.0001
Comorbidity, n (%) ^c							
None	661 (49.7)	73 (37.1)	242 (62.1)	35 (44.9)	129 (37.7)	182 (56.2)	
1	494 (37.1)	83 (42.1)	109 (27.9)	36 (46.2)	164 (48.0)	102 (31.5)	
2	176 (13.2)	41 (20.8)	39 (10.0)	7 (9.0)	43 (14.3)	40 (12.3)	<0.0001

Characteristic ^a	All cases	African American	Caucasian	Native Hawaiian	Japanese American	Latino	P ^b
Smoking status, n (%)							
Never	560 (42.1)	60 (30.5)	144 (36.9)	32 (41.0)	170 (49.7)	154 (47.5)	
Former	578 (43.4)	93 (47.2)	188 (48.2)	32 (41.0)	136 (39.8)	129 (39.8)	
Current	193 (14.5)	44 (22.3)	58 (14.9)	14 (18.0)	36 (10.5)	41 (12.7)	<0.0001
Alcohol intake, g/day							
None	655 (49.2)	108 (54.8)	117 (30.0)	41 (52.6)	211 (61.7)	178 (54.9)	
<14	442 (33.2)	58 (29.4)	163 (41.8)	22 (28.2)	88 (25.7)	111 (34.3)	
14-28	117 (8.8)	16 (8.1)	54 (13.9)	9 (11.5)	22 (6.4)	16 (4.9)	
>28	117 (8.8)	15 (7.6)	56 (14.4)	6 (7.7)	21 (6.2)	19 (5.9)	<0.0001
NHL type, n (%)							
DLBCL	390 (29.3)	46 (23.3)	88 (22.6)	26 (33.3)	111 (32.4)	119 (36.7)	
FL	214 (16.1)	23 (11.7)	65 (16.7)	9 (11.6)	64 (18.7)	53 (16.4)	
MZL	105 (7.9)	19 (9.6)	24 (6.2)	3 (3.9)	31 (9.1)	28 (8.6)	
CLL/SLL	287 (21.6)	61 (31.0)	127 (32.6)	20 (25.6)	32 (9.4)	47 (14.5)	
T-cell	91 (6.8)	21 (10.7)	19 (4.9)	5 (6.4)	33 (9.6)	13 (4.0)	
Others	244 (18.3)	27 (13.7)	67 (17.2)	15 (19.2)	71 (20.8)	64 (19.8)	<0.0001
SEER stage, n (%)							
Local	287 (21.6)	28 (14.2)	82 (21.0)	22 (28.2)	92 (26.9)	63 (19.4)	
Regional	148 (11.1)	15 (7.6)	43 (11.0)	4 (5.1)	43 (12.6)	43 (13.3)	
Distant	805 (60.5)	136 (69.0)	249 (63.9)	49 (62.8)	191 (55.9)	180 (55.6)	
Unstaged/unknown	91 (6.8)	18 (9.1)	16 (4.1)	3 (3.9)	16 (4.7)	38 (11.7)	<0.0001
Chemotherapy, n (%)	708 (53.2)	108 (54.8)	193 (49.5)	43 (55.1)	186 (54.4)	178 (54.9)	0.55
Immunotherapy, n (%)	58 (4.4)	0	19 (4.9)	10 (12.8)	28 (8.2)	1 (0.3)	<0.0001
Steroid treatment, n (%)	388 (29.1)	47 (23.9)	107 (27.4)	29 (37.2)	123 (36.0)	82 (25.3)	0.004
Radiotherapy, n (%)	203 (15.3)	17 (8.6)	51 (13.1)	18 (23.1)	75 (21.9)	42 (13.0)	<0.0001

^a Unless specified, means (standard deviation) presented; percentages may not add to 100 because of rounding.

^b P value based on ANOVA for continuous variables, χ^2 test for categorical variables, and χ^2 for log-rank test for estimated 5-year survival.

^c P Includes heart attack/angina, hypertension and diabetes.

Table 2

All-cause and NHL-specific mortality for NHL cases in the Multiethnic Cohort study, 1993–2007^a

Characteristic ^c	Cases	All-cause mortality			NHL-specific mortality		
		Deaths	HR (95% CI)	P ^b	Deaths	HR (95% CI)	P ^b
Sex							
Male	729	392	1.00		254	1.00	
Female	602	275	0.74 (0.62–0.88)	0.0008	196	0.83 (0.67–1.03)	0.08
Ethnicity							
African American	197	115	0.98 (0.76–1.26)		76	1.02 (0.74–1.39)	
Caucasian	390	171	1.00		110	1.00	
Native Hawaiian	78	43	1.28 (0.90–1.82)		27	1.21 (0.78–1.88)	
Japanese American	342	171	0.94 (0.74–1.19)		127	1.15 (0.86–1.52)	
Latino	324	167	1.08 (0.85–1.36)	0.46	110	1.06 (0.79–1.42)	0.83
BMI, kg/m ²							
<22.5	220	109	1.45 (1.13–1.85)	0.004	70	1.40 (1.03–1.91)	0.03
22.5–24.9	337	152	1.00		96	1.00	
25.0–29.9	530	275	1.21 (0.99–1.49)	0.06	191	1.36 (1.06–1.75)	0.02
30	244	131	1.46 (1.13–1.87)	0.004	93	1.77 (1.30–2.41)	0.0003
Comorbidity ^d							
None	661	279	1.00		200	1.00	
1	494	275	1.23 (1.03–1.47)		182	1.09 (0.89–1.35)	
2	176	113	1.54 (1.22–1.94)	0.0008	68	1.31 (0.98–1.75)	0.19
Education, years							
12	595	331	1.00		224	1.00	
>12	736	336	0.90 (0.76–1.07)	0.23	226	0.91 (0.75–1.12)	0.38
SEER stage							
Local	287	112	1.00		65	1.00	
Regional	148	71	1.17 (0.86–1.59)		49	1.27 (0.86–1.86)	
Distant	805	438	2.02 (1.59–2.56)	<0.0001	307	2.44 (1.81–3.30)	<0.0001
NHL type							
DLBCL	390	230	1.00		167	1.00	

Characteristic ^c	Cases	All-cause mortality		<i>P</i> ^b	NHL-specific mortality		<i>P</i> ^b
		Deaths	HR (95% CI)		Deaths	HR (95% CI)	
FL	214	86	0.50 (0.38–0.64)		61	0.49 (0.36–0.68)	
CLL/SLL	287	127	0.41 (0.31–0.53)		71	0.32 (0.23–0.45)	
MZL	105	36	0.53 (0.37–0.77)		13	0.30 (0.17–0.53)	
T-cell	91	52	0.98 (0.71–1.35)	<0.0001	39	1.04 (0.72–1.51)	<0.0001
Treatment							
Chemotherapy	708	405	1.26 (1.04–1.54)	0.02	297	1.48 (1.16–1.88)	0.001
Immunotherapy	58	23	0.65 (0.42–1.00)	0.05	16	0.59 (0.35–1.00)	0.05
Steroid treatment	388	225	1.00 (0.82–1.22)	0.98	162	0.92 (0.73–1.16)	0.47
Radiotherapy	203	93	0.81 (0.63–1.03)	0.09	69	0.86 (0.65–1.15)	0.30
Smoking status							
None	560	264	1.00		183	1.00	
Former	578	288	1.04 (0.87–1.24)		190	0.99 (0.79–1.23)	
Current	193	115	1.67 (1.31–2.12)	<0.0001	77	1.47 (1.10–1.97)	0.01
Alcohol intake, g/day							
None	655	359	1.00		240	1.00	
<14	442	191	0.72 (0.60–0.87)		130	0.78 (0.62–0.98)	
14–28	117	58	0.79 (0.59–1.07)		38	0.83 (0.57–1.21)	
>28	117	59	0.73 (0.54–0.99)	0.006	42	0.88 (0.61–1.25)	0.19

BMI body mass index, *HR* hazard ratio, *CI* confidence interval

^a HR and 95% CI from Cox proportional hazards models adjusted for all covariates in table plus age at diagnosis

^b *P* value based on Wald χ^2 test.

^c Adjusted for all covariates in table plus age as a categorical variable (age as continuous variable not included in this model only)

^d Includes heart attack/angina, diabetes and hypertension

Table 3

All-cause and NHL-specific mortality for major NHL subtypes in the Multiethnic Cohort Study, 1993–2007^a

Characteristics	DLBCL			Follicular Lymphoma			CLL/SLL	
	All-causes	NHL-specific	All-causes	All-causes	NHL-specific	All-causes	All-causes	NHL-specific
Number of cases	390			214			287	
Number of deaths	230	167	86	61		127	71	
Sex								
Male	1.00	1.00	1.00	1.00		1.00	1.00	
Female	0.61 (0.45–0.83)	0.74 (0.52–1.07)	0.79 (0.44–1.42)	0.61 (0.30–1.23)		0.70 (0.44–1.07)	0.59 (0.32–1.10)	
Ethnicity								
African American	0.79 (0.47–1.32)	0.73 (0.40–1.33)	1.10 (0.47–2.62)	1.53 (0.57–4.15)		1.17 (0.70–1.94)	1.53 (0.75–3.13)	
Caucasian	1.00	1.00	1.00	1.00		1.00	1.00	
Native Hawaiian	1.26 (0.68–2.34)	1.35 (0.64–2.83)	0.94 (0.27–3.26)	1.23 (0.32–4.71)		1.51 (0.66–3.46)	1.32 (0.39–4.51)	
Japanese American	0.74 (0.48–1.41)	0.79 (0.48–1.30)	1.11 (0.57–2.17)	1.12 (0.50–2.55)		1.21 (0.64–2.30)	3.12 (1.39–6.97)	
Latino	0.95 (0.63–1.43)	0.91 (0.56–1.47)	1.00 (0.48–2.08)	0.92 (0.37–2.25)		0.73 (0.40–1.33)	0.71 (0.30–1.72)	
BMI, kg/m ²								
<22.5	1.42 (0.91–2.24)	1.44 (0.84–2.47)	1.11 (0.57–2.17)	0.80 (0.33–1.98)		2.50 (1.35–4.63)	3.89 (1.54–9.81)	
22.5–24.9	1.00	1.00	1.00	1.00		1.00	1.00	
25.0–29.9	1.36 (0.96–1.94)	1.70 (1.12–2.61)	0.72 (0.38–1.34)	0.63 (0.31–1.29)		1.58 (0.92–2.71)	2.42 (1.05–5.58)	
>30.0	1.21 (0.78–1.89)	1.34 (0.79–2.29)	1.96 (0.87–4.42)	1.67 (0.64–4.35)		2.54 (1.36–4.72)	4.99 (1.98–12.6)	
Education								
12	1.00	1.00	1.00	1.00		1.00	1.00	
>12	0.97 (0.72–1.31)	0.96 (0.68–1.36)	1.38 (0.80–2.39)	1.18 (0.62–2.25)		0.61 (0.41–0.92)	0.57 (0.32–1.01)	
Comorbidity								
None	1.00	1.00	1.00	1.00		1.00	1.00	
1	1.09 (0.79–1.49)	0.97 (0.67–1.40)	1.19 (0.71–1.99)	1.44 (0.77–2.69)		1.74 (1.12–2.71)	1.63 (0.89–3.00)	
2	1.55 (1.05–2.29)	1.23 (0.77–1.97)	1.17 (0.47–2.91)	1.21 (0.41–3.64)		1.58 (0.92–2.72)	1.31 (0.60–2.85)	
SEER stage								
Local	1.00	1.00	1.00	1.00		1.00	1.00	
Regional	1.09 (0.70–1.70)	1.12 (0.66–1.95)	1.27 (0.55–2.96)	1.68 (0.57–5.01)		1.48 (0.22–10.1)	0.95 (0.12–7.85)	
Distant	2.01 (1.41–2.86)	2.24 (1.47–3.42)	2.25 (1.02–4.95)	3.90 (1.42–10.76)		1.73 (0.50–5.93)	0.86 (0.22–3.34)	

Characteristics	DLBCL			Follicular Lymphoma			CLL/SLL	
	All-causes	NHL-specific		All-causes	NHL-specific		All-causes	NHL-specific
Unstaged/unknown	1.65 (0.87–3.11)	1.94 (0.93–4.04)		2.17 (0.79–5.97)	2.69 (0.73–9.89)		1.41 (0.27–7.43)	0.36 (0.04–2.93)
Treatment								
Chemotherapy	0.63 (0.43–0.92)	0.65 (0.42–1.02)		1.38 (0.77–2.46)	1.27 (0.63–2.56)		1.79 (1.17–2.74)	3.70 (2.09–6.53)
Radiotherapy	0.82 (0.57–1.18)	0.83 (0.55–1.26)		1.28 (0.59–2.81)	2.00 (0.80–5.01)		-	-
Immunotherapy	0.67 (0.36–1.24)	0.65 (0.31–1.35)		-	-		1.10 (0.31–3.90)	1.32 (0.27–6.53)
Steroid treatment	1.23 (0.87–1.74)	1.17 (0.78–1.75)		0.71 (0.37–1.36)	0.66 (0.30–1.46)		0.93 (0.48–1.79)	0.76 (0.32–1.83)
Smoking status								
Never	1.00	1.00		1.00	1.00		1.00	1.00
Former	1.03 (0.75–1.42)	0.84 (0.58–1.23)		0.59 (0.33–1.07)	0.41 (0.20–0.85)		1.22 (0.79–1.88)	1.54 (0.84–2.84)
Current	1.53 (1.01–2.32)	1.11 (0.67–1.82)		1.00 (0.48–2.10)	0.77 (0.31–1.90)		2.49 (1.27–4.86)	2.88 (1.12–7.44)
Alcohol								
None	1.00	1.00		1.00	1.00		1.00	1.00
<14	0.84 (0.60–1.17)	0.91 (0.61–1.36)		0.57 (0.32–1.00)	0.57 (0.29–1.12)		0.58 (0.36–0.94)	0.76 (0.39–1.49)
14–28	0.57 (0.28–1.19)	0.64 (0.27–1.53)		0.82 (0.36–1.86)	0.66 (0.24–1.81)		0.93 (0.48–1.82)	1.29 (0.52–3.18)
>28	0.58 (0.33–1.03)	0.83 (0.43–1.59)		1.47 (0.60–3.61)	1.49 (0.52–4.27)		0.64 (0.33–1.25)	0.64 (0.24–1.71)

^aHR and 95% CI from Cox proportional hazards models adjusted for all covariates in table plus age at diagnosis