ARTICLE

Differences in Non-Hodgkin Lymphoma Survival Between Young Adults and Children

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Objective: To examine differences in non-Hodgkin lymphoma (NHL) survival between young adults and children/adolescents.

Design: Survival analysis using 13 Surveillance, Epidemiology, and End Results registries.

Setting: Cancer survival information from population-based cancer registries from 1992 through 2001.

Participants: A total of 2442 cases of NHL among children/adolescents (aged 0-19 years) and young adults (aged 20-29 years).

Main Exposure: Differences in NHL survival between young adults and children.

Main Outcome Measures: Comparison of 5-year survival by constructing Kaplan-Meier survival curves and modeling 5-year survival with multivariate Cox proportional hazards.

Results: Young adults were more likely to die compared with children/adolescents (hazard ratio = 2.06; 95% confidence interval, 1.65-2.56) even after accounting for NHL subtype and stage at diagnosis. Persons diagnosed with stage III disease (hazard ratio = 1.71; 95% confidence interval, 1.20-2.46) and stage IV disease (hazard ratio = 3.19; 95% confidence interval, 2.47-4.13) were more likely to die compared with persons diagnosed with stage I disease.

Conclusions: Being a young adult at diagnosis and having a higher stage of disease at diagnosis were associated with higher risk of death from NHL. Increasing survival with NHL is dependent on receiving appropriate cancer therapy. Therefore, efforts to address survival should include improving enrollment in clinical trials as well as increasing access to care.

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SIGNIFICANT PROGRESS IN SURvival from cancer has been achieved in the United States in the past 30 years, especially in childhood cancer for which the 5-year relative survival rate has increased from around 60% in the 1970s to currently more than 80%.[1,2] For young adults, however, progress is more difficult to characterize because cancer rates for this population are often combined with overall adult cancer rates. Although cancer among young adults is rare, it is important to recognize that cancer remains the leading disease-specific cause of death and incidence rates have been increasing in the past quarter-century for this population subgroup.[1,3-5]

Lymphomas, one of the most common cancers among young adults, account for 22% and 16% of all cancers among persons aged 20 to 24 and 25 to 29 years, respectively.[6] Non-Hodgkin lymphoma (NHL) accounts for 6% of all malignancies among 20- to 29-year-olds.[7,8] Over the past 20 years, incidence rates of lymphoma among young adults aged 20 to 29 years have increased at a faster rate compared with those among persons younger than 20 years.[6] During this time, there has also been a lack of progress in survival improvement among young adults.[4] Survival rates from NHL have been shown to be lower among young adults compared with children.[4] However, these survival differences did not take into account the subtype of NHL and stage of disease. The objective of this study was to determine whether the 5-year survival from NHL differed between young adults aged 20 to 29 years and children aged 0 to 19 years by NHL characteristics.

METHODS

We used the 13 registries from the Surveillance, Epidemiology, and End Results (SEER) database, which includes cancer registry data from 13 areas (San Francisco–Oakland, Cali-

fornia; Connecticut; Atlanta [metropolitan], Georgia; Iowa; Utah; Seattle [Puget Sound], Washington; San Jose–Monterey, California; Hawaii; Detroit [metropolitan], Michigan; New Mexico; Los Angeles, California; Alaska natives; and rural Georgia), to identify persons diagnosed with NHL at ages 0 through 29 years from 1992 through 2001.[9] These population-based registries include nearly 14% of the United States population.[10] We included only malignant cases and excluded cases that were reported from death certificates or autopsy only (n=17), were not microscopically confirmed (n=93), had second or later primary malignancies (n=77), were alive with no survival time (n=16), and had no race information (n=38). Nine cases with unknown race information were alive with no survival time, and 2 cases with second primary malignancies were reported from death certificates or autopsy only. An additional 236 cases were excluded owing to unknown stage (n=163), unknown radiation treatment (n=48), mantle cell subtype (n=3), and death from a non-NHL cause with no survival time or survival shorter than 1 month (n=31). Compared with cases included in the analysis, a greater proportion of excluded cases were 20- to 29-year-olds (76% of excluded cases vs 60% of included cases). This age group was disproportionately excluded because second and later malignancies were more common in young adults. Of the 77 cases excluded because of second and later primary malignancies, 69 were aged 20 to 29 years. After these exclusions, 2442 cases remained for analysis.

Children were defined as those aged 0 to 19 years at diagnosis and young adults were defined as those aged 20 to 29 at diagnosis. We examined 9 independent variables: sex, race/ethnicity, stage of cancer, year of diagnosis, histology, radiation treatment, poverty level, household income, and migration. All variables were chosen a priori. Race and Hispanic ethnicity variables were combined to form the following categories: non-Hispanic white, Hispanic, non-Hispanic black, and other. The stages of cancer at diagnosis were based on criteria from *SEER Extent of Disease, 1988*.[11] We grouped year of diagnosis as 1992 to 1994, 1995 to 1998, and 1999 to 2001. Cases were classified as aggressive, indolent, or unspecified.[12] Aggressive subtypes included diffuse large B-cell lymphoma, Burkitt lymphoma, peripheral T-cell/other T-cell/natural killer cell lymphoma, and lymphoblastic lymphoma. Cases were identified using *International Classification of Diseases for Oncology, Version 2* or *International Classification of Diseases for Oncology, Version 3* morphology codes (eTable, http://www.archpediatrics.com). A dichotomous variable for radiation treatment was formed for cases receiving any type of radiation vs those who received none or refused treatment. We did not examine data on chemotherapy treatment because it is not included in the SEER data set. To explore any differences in the social environment of cases, we applied 1990 US census county attributes of the cases' county of residence at the time of diagnosis; this included the percentage of persons below the federal poverty level in 1989 (grouped as percentage of those in the 0-74th percentile and ≥75th percentile), the median household income level in 1989 grouped into quartiles, and the percentage of the population migrating out of state grouped into quartiles.

Cases were followed through December 2005 for vital status through linkages with death indices and active follow-up with the patient, hospitals, or clinicians. We examined overall cause-specific survival. We were unable to examine event-free or relapse-free survival because the SEER data set does not include information on recurrences or relapses of cancer. Survival time was calculated as the number of months from the date of diagnosis to the date of death or the end of the follow-up period. We censored cases that died of causes other than NHL at their last follow-up time. Cases alive at 5 or more years after their diagnosis were censored at 60 months following their date of diagnosis.

We used SAS version 9.1 statistical software (SAS Institute, Inc, Cary, North Carolina) for all analyses. For the descriptive analysis, *P* values for categorical variables were obtained from χ^2 tests. We examined 5-year survival with each variable of interest by first constructing Kaplan-Meier survival curves. We modeled 5-year survival with multivariate Cox proportional hazards to obtain hazard ratios and 95% confidence intervals adjusted for selected clinical and demographic variables. Only variables significant at $P < .05$ from log-rank tests of homogeneity of the product-limit survivor functions were included in the model. County median household income level was excluded because there was little variability in the distribution of this variable. The Cox proportional hazards assumption was assessed by graphical examination of Kaplan-Meier survival curves, time-dependent covariates in the Cox proportional hazards model, and the Schoenfeld residual correlation test. Variables for both diagnosis period and histologic subtype were found to violate the Cox proportional hazards assumption. Thus, the final model was stratified on diagnosis period and histologic subtype and included age group, race/ethnicity, and stage. Five-year survival by age group, histologic subtype, and diagnosis period was estimated from the model while holding the other covariates at their mean values.

RESULTS

Among the 2442 persons younger than 30 years diagnosed with NHL from 1992 to 2001, 40% were children aged 0 to 19 years and 60% were young adults (aged 20-29 years) (**Table 1**). More males than females were diagnosed with NHL (66% vs 34%, respectively; $P=.02$). For all cases, 12% were non-Hispanic black and 21% were Hispanic; there were no differences in race/ethnicity distribution by age group. Thirty-three percent of all persons were diagnosed with stage I disease, 20% with stage II, 11% with stage III, and 36% with stage IV. There were modest differences in stage distribution by age group ($P=.02$). A higher proportion of young adults were diagnosed at stage I (35%) and a lower percentage were diagnosed at stage IV (34%) compared with childhood NHL cases (30% and 38%, respectively). Among all persons, 75% had aggressive subtypes of NHL, 11% had indolent subtypes of NHL, and 14% had unspecified subtypes of NHL. There were clear differences between children and young adults by histologic subtype of NHL ($P \leq .001$). Nearly half (49%) of young adults were diagnosed with diffuse large B-cell lymphoma, compared with 28% of children. After diffuse large B-cell lymphoma, the other most common histologic subtypes of NHL diagnosed in young adults were the indolent subtype (16%) and not otherwise specified (16%); among children, the other common subtypes were lymphoblastic (24%) and Burkitt (22%) lymphomas. The proxy indicators for income (county poverty level and median household income) were slightly higher for young adults ($P=.02$ and .03, respectively), and there was no difference between age groups and the percentages of county residents who migrated out of state.

Unadjusted survival rates for NHL by age group, diagnostic period, and histologic subtype are presented in **Figures 1**, **2**, and **3**, respectively. Figure 1 displays the Kaplan-Meier curve of NHL 5-year survival by age group. Persons aged 20 to 29 years had lower unadjusted sur-

Table 1. Selected Characteristics of Persons With Non-Hodgkin Lymphoma, From 13 Surveillance, Epidemiology, and End Results Registries for 1992 to 2001

Characteristic	Total No. (N=2442)	No. (%)[a] Aged 0-19 y at Diagnosis (n=987)	No. (%)[a] Aged 20-29 y at Diagnosis (n=1455)	*P* Value[b]
Sex				.02
Male	1603	674 (68)	929 (64)	
Female	839	313 (32)	526 (36)	
Race/ethnicity				.13
Non-Hispanic white	1380	577 (59)	803 (55)	
Hispanic	510	197 (20)	313 (22)	
Non-Hispanic black	288	101 (10)	187 (13)	
Non-Hispanic other	264	112 (11)	152 (11)	
Stage of disease				.02
I	806	294 (30)	512 (35)	
II	493	210 (21)	283 (20)	
III	275	107 (11)	168 (12)	
IV	868	376 (38)	492 (34)	
Diagnosis period				.03
1992-1994	734	271 (28)	463 (32)	.
1995-1998	969	394 (40)	575 (40)	
1999-2001	739	322 (33)	417 (29)	
Histologic subtype				<.001
Aggressive				
Diffuse large B-cell lymphoma	987	275 (28)	712 (49)	
Burkitt lymphoma	301	216 (22)	85 (6)	
Peripheral T-cell/other T-cell/natural killer cell lymphoma	206	108 (11)	98 (7)	
Lymphoblastic lymphoma	330	232 (24)	98 (7)	
Indolent	274	44 (5)	230 (16)	
Lymphoma not otherwise specified	344	112 (11)	232 (16)	
Radiation treatment				<.001
No	1751	818 (83)	933 (64)	
Yes	691	169 (17)	522 (36)	
County poverty level in 1990				.02
0-74th percentile	1536	648 (66)	888 (61)	
≥75th percentile	906	339 (34)	567 (39)	
County median household income level in 1990 by quartile, $				.03
<31 220	614	271 (28)	343 (24)	
31 220-34 969	168	55 (6)	113 (8)	
34 970-38 829	1007	392 (40)	615 (42)	
≥38 830	653	269 (27)	384 (26)	
Out-of-state migration, county level percentage in 1990				.35
<5.1	235	103 (10)	132 (9)	
5.1-7.42	928	364 (37)	564 (39)	
7.43-12.47	652	254 (26)	398 (27)	
≥12.48	627	266 (27)	361 (25)	

[a] Due to rounding, percentages may not total 100.0%.
[b] Using χ^2 test.

vival from NHL compared with persons aged 0 to 19 years. At 24 months, 87% of children diagnosed with NHL were alive compared with 79% of young adults. The 5-year survival rates were 85% for children and 75% for young adults. Figure 2 and Figure 3 display the Kaplan-Meier curves of NHL 5-year survival of children and young adults by diagnosis period and histologic subtype, respectively. The NHL 5-year survival has improved from 73% for cases diagnosed in 1992 to 1994 to 85% for cases diagnosed in 1999 to 2001. The histologic subtypes with the poorest survival were peripheral T-cell/other T-cell/natural killer cell lymphoma, lymphoma not otherwise specified, and lymphoblastic lymphoma (5-year survival rates were 76%, 78%, and 78%, respectively). The highest 5-year survival was among persons with indolent NHL (90%).

In the multivariate analysis, which accounted for diagnostic year and histologic subtype of NHL, 3 factors were independently associated with death from NHL: age at the time of diagnosis, stage of disease, and race classified as non-Hispanic other (**Table 2**). Persons aged 20 to 29 years were more likely to have died of NHL (hazard ratio=2.06; 95% confidence interval, 1.65-2.56) compared with persons aged 0 to 19 years. As expected, persons diagnosed with stage III disease (hazard ratio=1.71; 95% confidence interval, 1.20-2.46) and stage IV disease (hazard ratio=3.19; 95% confidence interval, 2.47-4.13) were more likely to die compared with persons diagnosed with stage I disease.

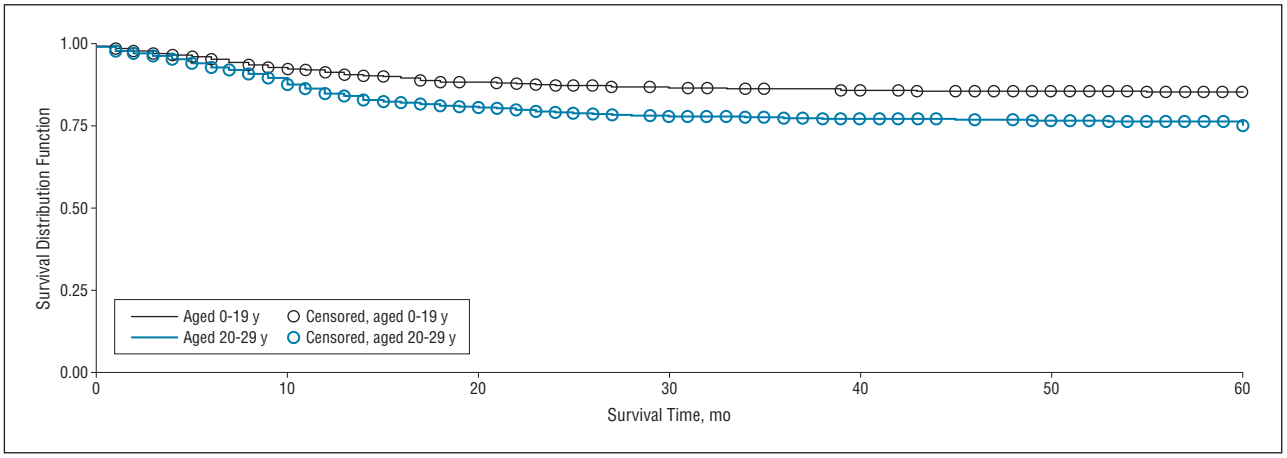

Figure 1. Non-Hodgkin lymphoma 5-year survival by age group, from 13 Surveillance, Epidemiology, and End Results registries for 1992 to 2001.

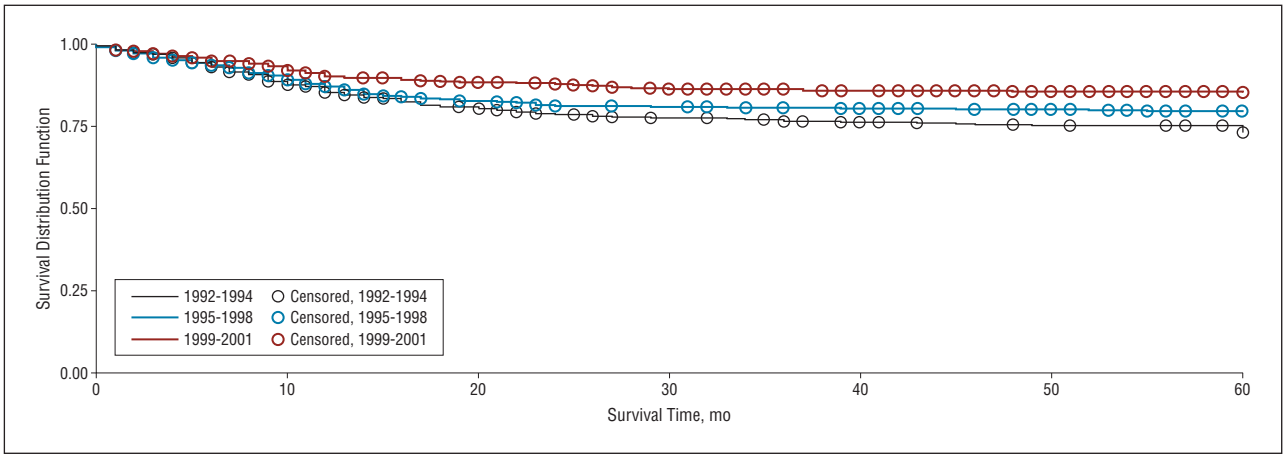

Figure 2. Non-Hodgkin lymphoma 5-year survival by diagnosis period, from 13 Surveillance, Epidemiology, and End Results registries for 1992 to 2001.

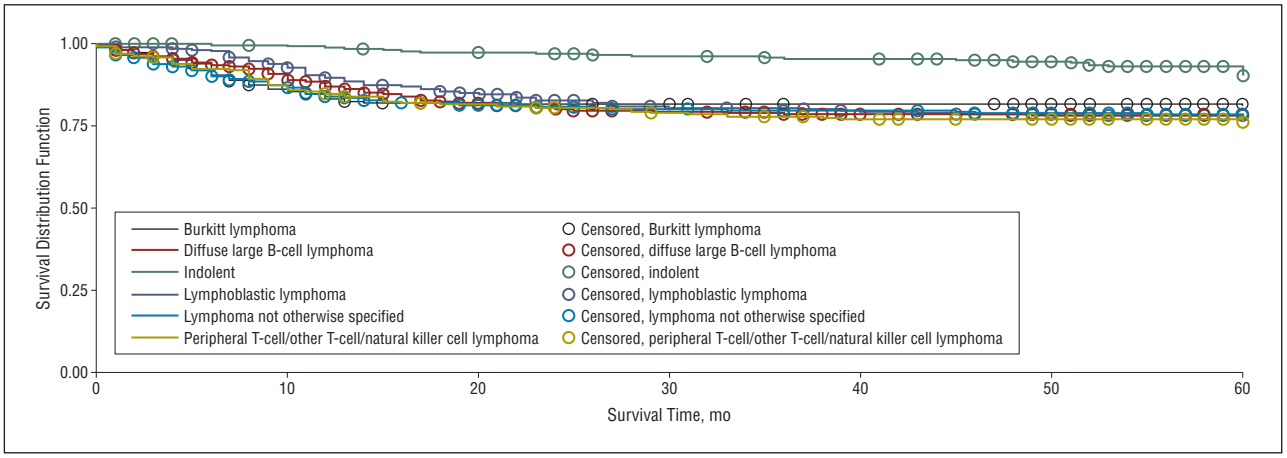

Figure 3. Non-Hodgkin lymphoma 5-year survival by histologic subtype, from 13 Surveillance, Epidemiology, and End Results registries for 1992 to 2001.

Table 3 presents trends in NHL 5-year survival estimates during 3 specific diagnosis periods from 1992 to 2001 by age group and histologic subtype, accounting for diagnosis year, histologic subtype, race/ethnicity, stage, and age group. Among both children and young adults, the diffuse large B-cell lymphomas had the most significant increases in survival from the 1992 to 1994 diagnosis period to the 1999 to 2001 diagnosis period: the 5-year survival estimates increased from 82% to 92% among children and from 66% to 85% among young adults. Among young adults, the absolute increases in 5-year survival estimates from the earliest to the latest periods for the same histologic subtypes were higher than for children (for young adults, from 85% to 96% for indolent NHL subtypes and from 66% to 85% for diffuse large B-cell lymphoma). Notably, despite the increase in survival among young adults,

Table 2. Multivariate Cox Proportional Hazard Ratios and 95% Confidence Intervals for Death From Non-Hodgkin Lymphoma, From 13 Surveillance, Epidemiology, and End Results Registries for 1992 to 2001[a]

Characteristic	Proportional HR (95% CI)	*P* Value
Age group, y		
0-19	1 [Reference]	
20-29	2.06 (1.65-2.56)	<.001
Race/ethnicity		
Non-Hispanic white	1 [Reference]	
Hispanic	1.21 (0.95-1.54)	.12
Non-Hispanic black	1.24 (0.92-1.67)	.17
Non-Hispanic other	1.46 (1.10-1.94	.006
Stage of disease		
I	1 [Reference]	
II	1.35 (0.98-1.85)	.07
III	1.71 (1.20-2.46)	.002
IV	3.19 (2.47-4.13)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]The HRs are stratified by diagnosis period (1992 to 1994, 1995 to 1998, 1999 to 2001) and histologic subtype (Burkitt lymphoma, diffuse large B-cell lymphoma, indolent, lymphoblastic lymphoma, lymphoma not otherwise specified, peripheral T-cell/other T-cell/natural killer cell lymphoma).

the adjusted 5-year survival estimates for young adults lagged behind those for children.

COMMENT

We found that being a young adult and having a later clinical stage of disease at diagnosis of NHL were factors associated with a greater risk of death from NHL. Young adults remained at higher risk for dying of NHL compared with children even when we accounted for NHL histology and stage of disease at diagnosis regardless of diagnosis period. Our study also showed the remarkable improvements over time in survival after NHL diagnosis for both children and young adults. The increase in 5-year survival among persons aged 20 to 29 years was greater than the increase among persons aged 0 to 19 years from the 1992 to 1994 diagnostic period to the 1999 to 2001 diagnostic period; however, young adults still had lower adjusted survival rates than children for all subtypes of NHL.

Many factors may underlie these observed improvements in NHL survival. A major milestone in treating NHL was the introduction of rituximab, a monoclonal antibody, that when combined with the mainstay of NHL therapy, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, increased remission rates and survival from NHL.[13,14] Despite these advances in treatment, it is not clear why young adults have lower survival rates than children. The many different clinical manifestations, morphologic variants, and molecular characteristics of NHL make comparisons in survival rates challenging because it is a heterogeneous disease.[15] Factors to consider, however, are differences in underlying conditions known to increase the incidence of NHL, differences in treatment, lack of participation in clinical trials, potential long-term or late effects on mortality, and lack of optimal follow-up.

Immunodeficiency, whether acquired (eg, human immunodeficiency virus or posttransplant suppression), inherited, or rheumatologic, and specific viruses are associated with NHL.[16] Our study did not explore whether young adults are more likely than children to have these predisposing factors; however, it may affect prognosis of NHL. Some of the failure to improve treatment outcome in young adults with cancer may also be due to referral patterns.[8] Fewer than 10% of young adults between ages 20 and 30 years are managed at academic medical institutions or settings that are members of oncology cooperative groups.[8] More than 90% of young adults are managed by community physicians.[8] Thus, young adults as a group may not be treated at medical centers optimized for cancer care. This may lead to delays in triage, diagnosis, and treatment. Additionally, because clinical trials are primarily available through academic medical settings and not community practices, few young adults have the opportunity to enroll in clinical trials even if trials are available to treat their cancers.[17,18] Lack of participation in clinical trials of therapies may contribute to higher mortality among young adults as well as limited knowledge of late effects of cancer in this population.[17] Less than an estimated 2% of young adults with cancer between ages 20 and 30 years had participated in clinical trials between 1997 and 2000. This rate is far lower than the 60% clinical trial participation rate for children with cancer and less than half the rate in adults between ages 40 and 65 years.[8,17,18]

Radiation therapy is used less as a treatment modality for children with NHL than for adults. In our study, 36% of young adults received radiation compared with 17% of children. Late effects related to radiation therapy include cardiovascular and pulmonary toxicities, myelodysplasia, and secondary malignancies.[19,20] Thus, differences in survival may be related to late effects impacting morbidity and mortality.

Young adults are one of the largest and fastest growing segments of the US population without health insurance.[21] In 2006, 13.7 million young adults were uninsured. Even though young adults account for only 17% of the US population, they account for 29% of the nonelderly uninsured.[22] Young adults may not be covered by their parents' health insurance plans and may have jobs without health insurance coverage.[21] Public programs such as Medicaid and State Children's Health Insurance Programs also reclassify teenagers as adults when they turn 19 years of age. As a result of the impact of these public and private insurance policies, uninsured rates jump sharply after age 19 years.[21] Lack of health insurance may put young adults at risk for delayed cancer diagnosis and treatment because lag times from symptoms to diagnosis are longer among patients with inadequate health care insurance.[23] A number of other factors may also contribute to a higher risk of delayed diagnosis of cancer among young adults, including a lack of routine medical care and a lack of recognition among many clinicians of cancer signs and symptoms in this age group.[24,25]

There are many additional challenges to appropriate follow-up during the years following active treatment. In addition to the increased likelihood of being uninsured, other social factors can potentially impact young

Table 3. Trends in 5-Year Survival Estimates for Non-Hodgkin Lymphoma by Age Group, Histologic Subtype, and Diagnosis Period, From 13 Surveillance, Epidemiology, and End Results Registries for 1992 to 2001

Age at Diagnosis, y[a]	Histologic Subtype	Estimate of Survival, % (95% CI)[b]			
		1992-1994	1995-1998	1999-2001	Difference[c]
0-19	Indolent	92.4 (87.2-97.9)	96.9 (94.4-99.5)	97.8 (95.7-100.0)	+5.4
	Burkitt lymphoma	84.1 (77.2-91.6)	85.6 (80.0-91.6)	91.6 (87.4-96.0)	+7.5
	Diffuse large B-cell lymphoma	81.5 (76.9-86.3)	86.7 (83.2-90.4)	92.2 (89.3-95.2)	+10.7[d]
	Lymphoblastic lymphoma	85.4 (79.8-91.4)	83.3 (77.7-89.2)	91.1 (86.7-95.8)	+5.7
	Peripheral T-cell/other T-cell/natural killer cell lymphoma	87.6 (79.3-96.8)	87.3 (81.4-93.6)	81.4 (74.5-88.9)	–6.2
	Lymphoma not otherwise specified	88.1 (82.8-93.6)	88.5 (84.1-93.1)	86.1 (79.3-93.6)	–2.0
20-29	Indolent	84.9 (75.7-95.2)	93.7 (89.0-98.7)	95.5 (91.4-99.9)	+10.6
	Burkitt lymphoma	70.0 (58.4-84.1)	72.5 (62.8-83.8)	83.5 (75.7-92.1)	+13.5
	Diffuse large B-cell lymphoma	65.6 (59.7-72.1)	74.6 (69.7-79.8)	84.7 (79.8-89.8)	+19.1[d]
	Lymphoblastic lymphoma	72.3 (63.1-83.0)	68.6 (59.3-79.4)	82.6 (74.4-91.8)	+10.3
	Peripheral T-cell/other T-cell/natural killer cell lymphoma	76.2 (62.2-93.4)	75.6 (65.6-87.1)	65.4 (54.8-78.1)	–10.8
	Lymphoma not otherwise specified	77.0 (68.3-86.7)	77.7 (70.6-85.7)	73.6 (62.8-86.2)	–3.4

Abbreviation: CI, confidence interval.
[a] Adjusted for race/ethnicity and stage of disease.
[b] Survival estimates are from a Cox proportional hazards model stratified by diagnosis period and histologic subtype and included race/ethnicity, stage of disease, and age group.
[c] Difference in survival from the first to the last period.
[d] Statistically significant difference from the first to the last period, $P < .05$.

adults.[26] Young adults may not have the advantage of a parent advocate who ensures they are receiving follow-up care. Young adults may be receiving fragmented health care owing to job or geographic instability. Compared with young adults, children with cancer are more likely to be treated in institutions associated with the Children's Oncology Group, and parents of children with cancer may be more likely than young adults to be aware of institutional follow-up clinics specializing in survivorship and to be aware of online resources such as the long-term follow-up guidelines from the Children's Oncology Group.[27] In contrast, young adults may be receiving care from providers who are unaware of the appropriate follow-up and potential late effects related to NHL and its treatment. Because the SEER data set does not include whether the treating institution was a pediatric one, we could not determine where patients were treated.

Our study has several limitations. The data were limited to 13 SEER registries covering approximately 14% of the US population. Therefore, our results may not be generalizable to the entire US population.[28] In addition, we were unable to assess the effects and complications of treatment of NHL, treatment center type, research trial participation, and health insurance coverage because this information is not available in the SEER database. We also did not include information on chemotherapy treatment because it is not included in the data set.

The distribution of different types of cancer among young adults is unique compared with other age groups. Lymphomas, melanomas, testicular cancer, female genital tract malignancies, thyroid cancer, leukemias, and central nervous system tumors account for most cancers in this age group.[4] Overall, there has been a lack of progress in improving survival rates among young adults compared with children and older adults.[4] In contrast, our study showed that NHL survival has increased over time, with smaller gains made by young adults compared with children and adolescents. Increased survival among patients with NHL is dependent on timely and appropriate cancer therapy. Therefore, efforts to address survival should include increasing the number of clinical trials for young adults, encouraging them to enroll in these trials, and promoting improved access to care for this population.

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