Ongoing Improvement in Outcomes for Patients Diagnosed as Having Non-Hodgkin Lymphoma From the 1990s to the Early 21st Century

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Background: Non-Hodgkin lymphoma (NHL) is the most common hematologic malignant neoplasm in adults. We use the novel technique of period analysis to disclose the most recent trends in survival among adults diagnosed as having NHL on the population level with minimum delay.

Methods: We estimated trends in 5- and 10-year relative survival in patients 15 years or older diagnosed as having NHL in the United States between 1990 and 2004 using data from the Surveillance, Epidemiology, and End Results (SEER) program. We also estimated survival by age, location and histologic type of the tumor, sex, and race to further elucidate trends in survival in this disease.

Results: Overall, 5-year relative survival increased from 50.4% to 66.8%, and 10-year relative survival increased from 39.4% to 56.3% between 1990-1992 and 2002-2004. Improvements were most pronounced in patients younger than 45 years (+26.8 and +27.1 percentage points for 5- and 10-year survival, respectively), but improvements were seen in all age groups, in both sexes, in both nodal and extranodal disease, and in both low-grade and high-grade disease. Improvements in prognosis were less in black patients than in white patients, especially in younger black patients.

Conclusions: Our period analysis discloses a strongly improved outlook for patients diagnosed as having NHL in recent years. Changes in treatment of the disease and a decrease in the number of human immunodeficiency virus–related NHL cases attributable to highly active antiretroviral therapy are probably primarily responsible for these improvements.

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Non-Hodgkin lymphoma (NHL) is the most commonly occurring hematologic malignant neoplasm in adults in the United States. The incidence of NHL has risen over time, going from an age-adjusted rate of 11.1 per 100 000 in 1975 to 20.4 in 2004. However, NHL mortality rate peaked in 1997 at 8.9 and then began slowly decreasing, reaching a rate of 7.0 in 2004.[1] Treatment for NHL has evolved rapidly in recent years owing to the development of monoclonal antibody therapy directed against cell surface moieties expressed on most NHL cells[2] and improvements in the treatment of human immunodeficiency virus (HIV) that can both prevent the development of and improve the treatment of HIV-related lymphomas.[3,4] Existing estimates of long-term survival of patients with NHL from population-based cancer registries reflect the prognosis of patients diagnosed in the early and mid-1990s and thus do not capture the potential impact of recent advances in therapy. In this article, we use novel techniques of period analysis to provide the most up-to-date information on survival in this patient population.[5]

METHODS

All data presented in this article are derived from the 1973-2004 limited-use database of the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute issued April 2007.[6] Data included are from population-based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Georgia; Detroit, Michigan; Seattle–Puget Sound, Washington; and San Francisco–Oakland, California; which together cover a population of about 30 million people. Data are available from 1973 on for all these registries except for Seattle–Puget Sound and Atlanta, which joined in 1974 and 1975, respectively. The SEER population is comparable to the general US population with regard to measures of poverty and education, although it is more urban and has a higher proportion of foreign-born persons than the latter.[6]

For this analysis, we selected 86 955 patients 15 years or older with a first diagnosis

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Table 1. Numbers of Cases With Non-Hodgkin Lymphoma by Age Group, Site of Disease, Sex, Race, and Calendar Period

Group, Age, y	Calendar Period, No. of Cases					Total No. of Cases
	1990-1992	1993-1995	1996-1998	1999-2001	2002-2004	
All						
15-44	2033	2250	1957	1831	1769	**9840**
45-54	1407	1707	1746	1896	2065	**8821**
55-64	1791	1845	2068	2179	2702	**10 585**
65-74	2594	2722	2841	2832	2720	**13 709**
≥75	2651	2975	3397	3690	3900	**16 613**
Total	**10 476**	**11 499**	**12 009**	**12 428**	**13 156**	**59 568**
Nodal						
15-44	1269	1394	1269	1226	1118	**6276**
45-54	985	1170	1193	1216	1369	**5933**
55-64	1293	1266	1420	1492	1840	**7311**
65-74	1811	1837	1929	1903	1856	**9336**
≥75	1866	2047	2326	2453	2573	**11 265**
Total	**7224**	**7714**	**8137**	**8290**	**8756**	**40 121**
Extranodal						
15-44	764	856	688	605	651	**3564**
45-54	422	537	553	680	696	**2888**
55-64	498	579	648	687	862	**3274**
65-74	783	885	912	929	864	**4373**
≥75	785	928	1071	1237	1327	**5348**
Total	**3252**	**3785**	**3872**	**4138**	**4400**	**19 447**
Men						
15-44	1461	1616	1307	1185	1080	**6649**
45-54	903	1105	1046	1151	1208	**5413**
55-64	1010	1053	1167	1265	1512	**6007**
65-74	1326	1413	1483	1521	1412	**7155**
≥75	1140	1292	1504	1655	1770	**7361**
Total	**5840**	**6479**	**6507**	**6777**	**6982**	**32 585**
Women						
15-44	572	634	650	646	689	**3191**
45-54	504	602	700	745	857	**3408**
55-64	781	792	901	914	1190	**4578**
65-74	1268	1309	1358	1311	1308	**6554**
≥75	1511	1683	1893	2035	2130	**9252**
Total	**4636**	**5020**	**5502**	**5651**	**6174**	**26 983**
White						
15-44	1626	1769	1483	1393	1307	**7578**
45-54	1215	1417	1434	1560	1670	**7296**
55-64	1572	1581	1801	1866	2243	**9063**
65-74	2300	2413	2506	2459	2339	**12 017**
≥75	2445	2683	3095	3286	3467	**14 976**
Total	**9158**	**9863**	**10 319**	**10 564**	**11 026**	**50 930**
Black						
15-44	285	317	317	267	300	**1486**
45-54	114	199	186	193	235	**927**
55-64	115	114	143	156	218	**746**
65-74	128	117	137	134	159	**675**
≥75	86	94	95	125	126	**526**
Total	**728**	**841**	**878**	**875**	**1038**	**4360**

Table 2. Distribution of Histologic Types of Non-Hodgkin Lymphoma (NHL) by Calendar Period

Histologic Type	Calendar Period, %					Total, % (n=59 568)
	1990-1992 (n=10 476)	1993-1995 (n=11 499)	1996-1998 (n=12 009)	1999-2001 (n=12 428)	2002-2004 (n=13 156)	
Low-grade NHL	18.2	18.6	23.4	25.0	28.0	22.9
High-grade NHL	44.5	42.8	40.0	39.9	38.9	41.1
T-cell/NK-cell NHL	4.7	6.4	7.9	8.3	8.9	7.4
Other/unspecified	32.5	32.3	28.6	26.9	24.2	28.7

Abbreviation: NK, natural killer.

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of NHL (61 012 with nodal disease and 25 943 with extranodal disease) and no prior cancer diagnosis between 1980 and 2004, who have been followed for vital status until the end of 2004. After the exclusion of 410 patients (0.5%) who were reported by autopsy findings and 652 patients (0.8%) who were reported by death certificate only, 85 893 patients (98.7%) remained for analysis.

Five- and 10-year survival was calculated for calendar periods 1990-1992, 1993-1995, 1996-1998, 1999-2001, and 2002-2004 using the period analysis method.[5] Furthermore, we tested for statistical significance of trends in 5- and 10-year survival from 1990-1992 compared with 2002-2004 using a recently described modeling approach.[7] Analyses were carried out separately on 5 major age groups: 15 to 44 years, 45 to 54 years, 55 to 64 years, 65 to 74 years, and 75 years or older, as well as by sex, location of disease (nodal vs extranodal), histologic subtype, and race. Analysis by race was limited to patients identified as white or black because the number of patients of other races was too small to examine survival with reasonable precision. Analysis by histologic subtype was limited to patients with "high-grade" vs "low-grade" NHL because of the small numbers of patients in other groups (mantle cell lymphoma and T-cell or natural killer [NK]–cell lymphomas).

With period analysis, first proposed by Brenner and Gefeller[8] in 1996, only survival experience during the period of interest is included in the analysis. This is achieved by left truncating observations at the beginning of the period in addition to right censoring at its end. For example, a period estimate of 10-year survival for the 2002-2004 period is obtained by combining survival in the first year following diagnosis derived from patients diagnosed in 2001-2004, conditional survival in the second year following diagnosis derived from patients diagnosed in 2000-2003, and so on, up to survival in the 10th year following diagnosis, which is obtained from patients diagnosed in 1992-1995. Period estimates of survival for the other periods are calculated analogously. Previous studies have demonstrated that period analysis provides more up-to-date, long-term survival estimates than traditional "cohort-based" or complete survival analysis and closely predicts the long-term survival expectations of patients with cancer diagnosed within the period of interest.[9,10]

According to standard practice in population-based cancer survival analysis, relative rather than absolute survival was calculated. Relative survival reflects survival of patients with cancer compared with survival in the general population. It is calculated as the ratio of absolute survival of patients with cancer divided by the expected survival of a group of the corresponding sex, age, and race in the general population.[11,12] Estimates of expected survival were derived according to the so-called Ederer II method[13] using US sex-, age-, and race-specific life tables.[14] All analyses were performed with the SAS software package (SAS Institute Inc, Cary, North Carolina) using adapted versions of previously described macros for period analysis.[5,7]

RESULTS

Numbers of cases by age group, site of disease, sex, race, and calendar period are given in **Table 1**. The overall number of cases of NHL has increased over time, from 10 476 cases in 1990-1992 to 13 156 in 2002-2004. Increases were seen in both nodal and extranodal disease. The ratio of nodal to extranodal disease has fluctuated mildly over the period represented but has shown no clear trend. Increases were seen in both sexes; however, the increase was greater in female patients, with the ratio of male to female patients going from 1.26 in 1990-1992 to 1.13 in 2002-2004. However, the male to female ratio and its change over time strongly varied by age. In 1990-1992, more than 2.5-times as many men as women were diagnosed as having NHL at ages 15 to 44 years. After a transient increase in 1993-1995, the number of young men with NHL steadily declined, whereas the number of young women with NHL gradually increased, leading to a male to female ration of 1.57 in 2002-2004. The numbers of male patients exceeded the numbers of female patients in all periods at all ages, except for the 75-year-or-older age group, which consistently included more female than male patients. Increases in overall number of cases over time were seen for both black and white patients, except in the youngest age group in each race. The number of cases in each age group for a given calendar period increased with age for white patients but decreased for black patients, so that the ratio of white to black patients was 4.36 for the 15-to-44-year age group but 27.5 for patients 75 years or older in 2002-2004. Overall, case numbers have been stable or increased in each age group except for patients aged 15 to 44 years, for whom the case numbers decreased, from a peak of 2250 in 1993-1995 to 1769 in 2002-2004. The greatest increase was in patients 75 years or older, for whom overall case numbers went from 2651 in 1990-1992 to 3900 in 2002-2004.

Increases were observed over time in the percentage of NHL with low-grade and T-cell/NK-cell histologic subtypes compared with high-grade histologic subtypes (**Table 2**). The percentage of NHL for which no histologic subtype was specified decreased over time, from 32.5% in 1990-1992 to 24.2% in 2002-2004.

Prognosis for patients with NHL improved strongly and significantly between 1990-1992 and 2002-2004, both overall and for every age group, for patients with nodal or extranodal disease, for patients with low- or high-grade disease, for both sexes, and for both racial groups studied. Overall, 5- and 10-year survival improved from 50.4% and 39.4%, respectively, in 1990-1992 to 66.8% (+16.4 percentage points) and 56.3% (+16.9 percentage points), respectively, in 2002-2004 ($P < .001$ for both). The greatest gains were seen in patients aged 15 to 44 years, for whom 5-year relative survival increased by 26.8 percentage points, but large and statistically significant increases in survival were seen in all age groups (**Table 3** and **Figure 1**).

Survival in nodal NHL improved throughout the 1990s and early 21st century in all age groups (Table 3 and **Figure 2**). As with the overall results, the improvement was greatest in the younger age groups, with 10-year relative survival increasing to 67.0% (+22.2 percentage points; $P < .001$) for patients aged 15 to 44 years at diagnosis. Major improvements were also seen in older patients, with 10-year relative survival improving from 21.7% to 32.0% for patients 75 years or older at diagnosis ($P < .001$). However, a clear age gradient is still seen in this disease.

Survival in extranodal NHL has shown a less consistent course. Unusually, patients aged 15 to 44 years had the worst prognosis of any age group in 1990-1992, and survival for patients aged 45 to 54 years actually worsened between 1990-1992 and 1993-1995. However, survival for both these groups of patients, as well as all other age groups, improved rapidly in the late 1990s so that by the 2002-2004 calendar period, 10-year relative

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Table 3. Increase in 5- and 10-Year Relative Survival From 1990-1992 to 2002-2004 of Patients With Non-Hodgkin Lymphoma According to Age, Site of Disease, Sex, and Race

Group, Age, y	5-Year Relative Survival				10-Year Relative Survival			
	1990-1992 PE (SE), %	2002-2004 PE (SE), %	Diff[a]	*P* Value	1990-1992 PE (SE), %	2002-2004 PE (SE), %	Diff[a]	*P* Value
All								
15-44	47.4 (1.1)	74.2 (1.1)	+26.8	<.001	41.5 (1.2)	68.6 (1.2)	+27.1	<.001
45-54	59.3 (1.4)	77.9 (1.0)	+18.6	<.001	48.2 (1.6)	67.2 (1.3)	+19.0	<.001
55-64	58.5 (1.3)	72.8 (1.0)	+14.3	<.001	44.8 (1.4)	61.5 (1.3)	+16.7	<.001
65-74	52.8 (1.2)	66.8 (1.1)	+14.0	<.001	38.2 (1.5)	54.7 (1.4)	+16.5	<.001
≥75	38.9 (1.4)	52.2 (1.2)	+13.3	<.001	26.4 (2.0)	36.5 (1.8)	+10.1	<.001
Total	50.4 (0.6)	66.8 (0.5)	+16.4	<.001	39.4 (0.7)	56.3 (0.6)	+16.9	<.001
Nodal								
15-44	52.5 (1.4)	72.8 (1.4)	+20.3	<.001	44.8 (1.5)	67.0 (1.5)	+22.2	<.001
45-54	58.1 (1.7)	75.5 (1.3)	+17.4	<.001	44.8 (1.9)	64.7 (1.6)	+19.9	<.001
55-64	56.6 (1.5)	70.2 (1.3)	+13.6	<.001	40.7 (1.6)	56.7 (1.6)	+16.0	<.001
65-74	50.5 (1.4)	62.2 (1.4)	+11.7	<.001	34.9 (1.7)	47.5 (1.7)	+12.6	<.001
≥75	33.6 (1.6)	47.5 (1.5)	+13.9	<.001	21.7 (2.1)	32.0 (2.1)	+10.3	<.001
Total	49.2 (0.7)	63.4 (0.6)	+14.2	<.001	36.7 (0.8)	52.0 (0.8)	+15.3	<.001
Extranodal								
15-44	38.8 (1.9)	76.9 (1.7)	+38.1	<.001	36.6 (1.9)	71.5 (2.0)	+34.9	<.001
45-54	62.9 (2.6)	82.3 (1.6)	+19.4	<.001	59.1 (3.0)	72.0 (2.2)	+12.9	<.001
55-64	64.1 (2.5)	78.4 (1.8)	+14.3	<.001	57.9 (2.9)	71.8 (2.3)	+13.9	<.001
65-74	59.2 (2.3)	76.5 (1.9)	+17.3	<.001	47.9 (3.1)	69.5 (2.6)	+21.9	<.001
≥75	53.1 (2.9)	61.4 (2.2)	+8.3	<.001	39.7 (5.0)	45.3 (3.4)	+5.6	<.001
Total	53.9 (1.1)	73.7 (0.9)	+19.8	<.001	47.4 (1.4)	65.1 (1.2)	+17.7	<.001
Low grade								
15-44	83.5 (2.4)	92.6 (1.5)	+9.1	<.001	64.0 (3.3)	84.1 (2.3)	+20.1	<.001
45-54	77.4 (2.7)	90.6 (1.4)	+13.2	<.001	59.0 (3.4)	81.2 (2.1)	+22.2	<.001
55-64	69.7 (2.5)	87.2 (1.6)	+17.5	<.001	53.5 (2.9)	73.2 (2.5)	+19.7	<.001
65-74	70.9 (2.7)	84.1 (1.9)	+13.2	<.001	48.8 (3.5)	70.0 (3.1)	+21.2	<.001
≥75	54.1 (4.0)	74.2 (2.8)	+20.1	<.001	30.9 (5.5)	48.6 (4.8)	+17.7	<.001
Total	70.7 (1.3)	84.9 (0.9)	+14.2	<.001	52.2 (1.6)	71.5 (1.4)	+19.3	<.001
High grade								
15-44	41.9 (1.6)	68.8 (1.6)	+26.9	<.001	39.1 (1.6)	64.6 (1.7)	+25.5	<.001
45-54	53.0 (2.2)	69.1 (1.8)	+16.1	<.001	44.9 (2.6)	61.1 (2.2)	+16.2	<.001
55-64	48.1 (2.0)	63.3 (1.9)	+15.2	<.001	39.8 (2.2)	54.5 (2.2)	+14.7	<.001
65-74	43.2 (1.7)	56.6 (1.9)	+13.4	<.001	32.7 (2.2)	48.0 (2.3)	+15.3	<.001
≥75	32.4 (1.9)	43.6 (1.8)	+11.2	<.001	24.4 (2.9)	28.6 (2.6)	+4.2	<.001
Total	42.1 (0.8)	57.8 (0.8)	+15.7	<.001	35.2 (1.0)	49.9 (1.0)	+14.7	<.001
Men								
15-44	39.2 (1.3)	71.1 (1.4)	+31.9	<.001	33.9 (1.3)	64.6 (1.5)	+30.7	<.001
45-54	54.0 (1.8)	74.6 (1.4)	+20.6	<.001	42.1 (2.1)	62.5 (1.7)	+20.4	<.001
55-64	54.1 (1.7)	69.5 (1.4)	+15.4	<.001	39.3 (1.9)	58.9 (1.8)	+19.6	<.001
65-74	48.3 (1.7)	63.7 (1.6)	+15.4	<.001	34.2 (2.1)	51.8 (2.1)	+17.6	<.001
≥75	40.5 (2.4)	49.7 (1.9)	+9.2	<.001	26.3 (3.8)	36.5 (3.0)	+10.2	<.001
Total	46.4 (0.8)	64.9 (0.7)	+18.5	<.001	35.6 (0.9)	54.8 (0.9)	+19.2	<.001
Women								
15-44	68.7 (2.0)	79.3 (1.6)	+10.6	<.001	61.5 (2.2)	75.2 (1.8)	+13.7	<.001
45-54	69.0 (2.3)	82.6 (1.5)	+13.6	<.001	59.1 (2.6)	74.2 (1.9)	+15.1	<.001
55-64	64.0 (1.8)	77.1 (1.5)	+13.1	<.001	51.6 (2.1)	65.1 (1.9)	+13.5	<.001
65-74	57.6 (1.7)	70.1 (1.5)	+12.5	<.001	42.3 (2.1)	57.7 (2.0)	+15.4	<.001
≥75	37.9 (1.7)	54.1 (1.6)	+16.2	<.001	26.2 (2.4)	36.9 (2.3)	+10.7	<.001
Total	55.3 (0.9)	69.0 (0.8)	+13.7	<.001	44.1 (1.0)	58.0 (1.0)	+13.9	<.001
White								
15-44	48.1 (1.3)	77.0 (1.2)	+28.9	<.001	42.0 (1.3)	70.4 (1.3)	+28.4	<.001
45-54	59.9 (1.5)	80.1 (1.1)	+20.2	<.001	48.5 (1.3)	69.8 (1.4)	+21.3	<.001
55-64	59.6 (1.3)	73.3 (1.1)	+13.7	<.001	45.5 (1.5)	61.1 (1.4)	+15.6	<.001
65-74	53.5 (1.3)	67.8 (1.2)	+14.3	<.001	38.2 (1.5)	55.4 (1.5)	+17.2	<.001
≥75	39.1 (1.5)	52.4 (1.3)	+13.3	<.001	26.4 (2.1	35.8 (1.9)	+9.4	<.001
Total	50.9 (0.6)	67.5 (0.6)	+16.6	<.001	39.6 (0.7)	56.4 (0.7)	+16.8	<.001
Black								
15-44	41.1 (3.2)	59.9 (3.1)	+18.8	<.001	38.0 (3.4)	55.8 (3.3)	+17.8	<.001
45-54	48.9 (5.4)	60.6 (3.7)	+11.7	.002	40.1 (6.1)	47.6 (4.1)	+7.5	.003
55-64	53.7 (5.4)	65.0 (4.3)	+11.3	.19	39.6 (6.2)	57.6 (5.2)	+18.0	.11
65-74	44.9 (5.7)	60.2 (5.2)	+15.3	.03	34.4 (6.9)	40.2 (6.7)	+5.8	.05
≥75	38.5 (7.9)	50.2 (7.0)	+11.7	.23	21.9 (9.1)	32.0 (8.8)	+10.1	.18
Total	44.6 (2.2)	60.0 (1.9)	+15.4	<.001	36.8 (2.6)	50.7 (2.2)	+13.9	<.001

Abbreviations: Diff, difference; PE, period estimate.
[a] Increase from 1990-1992 to 2002-2004.

survival rates for patients aged 15 to 74 years were very similar, with survival rates ranging from 69.5% for the 65-to-74-year age group to 72.0% for the 45-to-54-year age group (Table 3 and Figure 2). Only the oldest age group showed less impressive increases, although even in this group, the 10-year relative survival rate im-

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Figure 1. Ten-year relative survival estimates by age group and calendar period. All patients had non-Hodgkin lymphoma.

proved from 39.7% in 1990-1992 to 45.3% in 2002-2004 ($P<.001$; Table 3). The trend in this age group appeared to be not monotonic, but the relatively large standard errors of the survival estimates have to be taken into account.

Because survival in NHL differs according to histologic subtype, we analyzed trends in NHL by histologic grade. We found that 5- and 10-year relative survival improved significantly in both low- and high-grade NHL between 1990-1992 and 2002-2004 in all age groups. Overall, 5-year relative survival improved from 70.7% to 84.9% in low-grade NHL and 42.1% to 57.8% in high-grade NHL ($P<.001$ for both) between 1990-1992 and 2002-2004. Ten-year relative survival improved from 52.2% to 71.5% in low-grade NHL and 35.2% to 49.9% in high-grade NHL during the same periods ($P<.001$; Table 3).

When survival was considered by sex, overall survival was higher among women than among men. In particular, the most striking differences were seen in the younger age groups in 1990-1992, with a sex difference of almost 30 percentage points between women and men for both 5- and 10-year relative survival in the 15-to-44-year age group. By contrast, survival was essentially the same in men and women 75 years or older. In the most recent periods, improvement was seen for both men and women, but greater improvement was generally seen for men. In this way, the age-dependent sex gap in survival diminished but was not entirely overcome. Overall, 5- and 10-year relative survival went from 46.4% and 35.6%, respectively, to 64.9% and 54.8%, respectively, for men diagnosed in 1990-1992 compared with those diagnosed in 2002-2004 ($P<.001$ for both; Table 3 and **Figure 3**). Five-year survival for men aged 15 to 44 years almost doubled, going from 39.2% in 1990-1992 to 71.1% in 2002-2004 (+31.9 percentage points; $P<.001$). The smallest, but still substantial, gains were seen in patients 75 or older, with 10-year relative survival increasing from 26.3% to 36.5% ($P<.001$). Prognosis improved for women as well, though most of the changes were somewhat less pronounced. Ten-year relative survival improved from 44.1% in 1990-1992 to 58.0% ($P<.001$; Table 3 and Figure 3) overall. In the 15-to-44- and 45-to-54-year age groups, 5-year relative survival close to or above 80% and 10-year relative survival close to 75% were achieved in 2002-2004. Interestingly, the single greatest improvement in survival was for 5-year relative survival in patients 75 years or older, with an improvement of 16.2 percentage points seen between 1990-1992 and 2002-2004 (Table 3). Unfortunately, this improvement was not entirely sustained for 10-year survival, for which only a 10.7–percentage point improvement was seen ($P<.001$ for both).

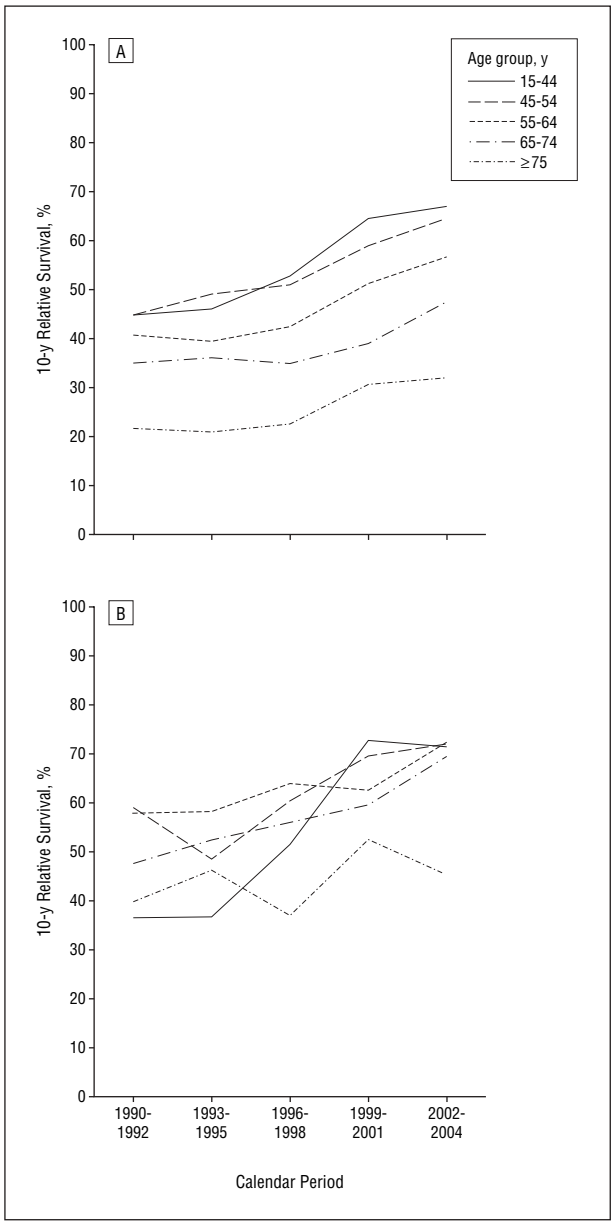

Figure 2. Ten-year relative survival estimates by type of non-Hodgkin lymphoma (A, nodal; B, extranodal), age group, and calendar period.

When survival by racial group was considered, survival was higher among white than among black pa-

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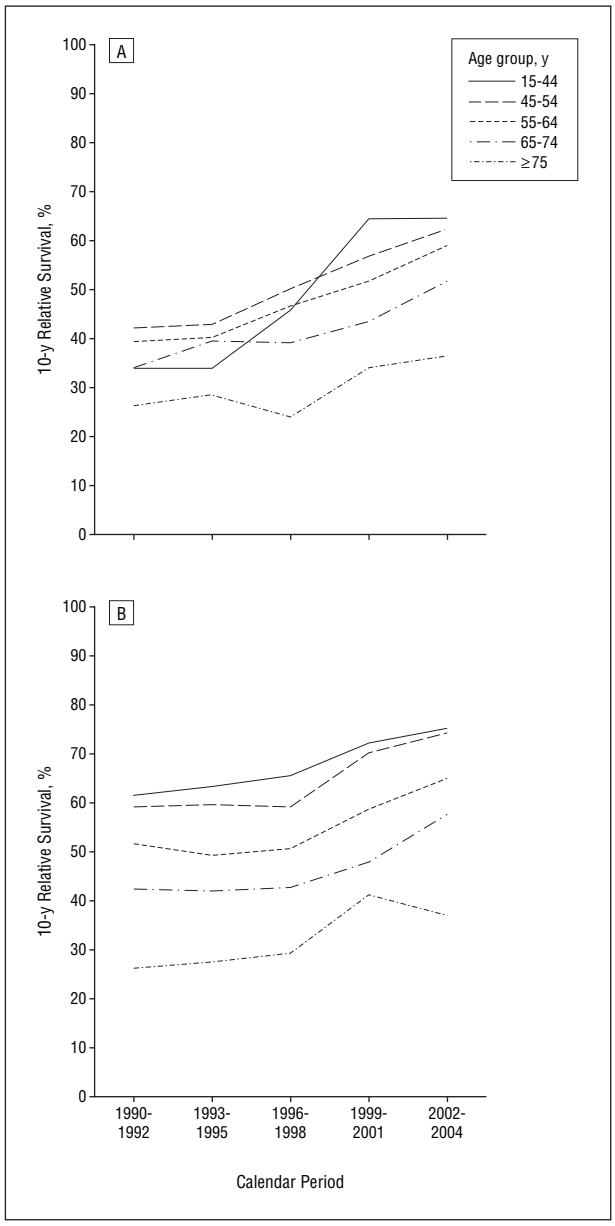

Figure 3. Ten-year relative survival estimates by sex (A, male; B, female), age group, and calendar period.

tients in all age groups in 1990-1992. Since then, improvements in survival were seen in both black and white patients, but improvements were greater for white patients in most age categories (Table 3). In particular, improvements in 5- and 10-year relative survival in the 15-to-44- and 45-to-54-year age groups were much more pronounced among white than among black patients. In 2002-2004, 5-year relative survival was close to 80% among white patients in these age groups compared with approximately 60% among black patients, and a similar race gradient was seen for 10-year relative survival.

COMMENT

The prognosis of patients with NHL strongly improved during the 1990s and early 21st century for all age groups, both sexes, both low- and high-grade histologic subtypes, and both nodal and extranodal disease. The most dramatic increases were seen in men and patients with extranodal disease aged 15 to 44 years, with 5- and 10-year relative survival almost doubling in each of these groups. Ten-year survival in patients with extranodal disease reached levels around 70% in all age groups younger than 75 and appears to be improving further. Despite somewhat less pronounced improvement, 10-year survival was reached in approximately two-thirds of patients with nodal disease younger than 55 years. Survival was better in low-grade NHL than in high-grade NHL, but improvement was seen in both histologic subtypes, with 10-year relative survival over 70% for low-grade NHL and almost 50% for high-grade NHL in 2002-2004. In general, survival remains lower in men than in women, but the tremendous gender gap among younger patients was reduced over time owing to very strong improvements in relative survival among men in the younger age groups. Survival is lower in blacks patients than in white patients, especially in the younger age groups, and the race gradient increased over time owing to less pronounced improvements among black compared with white patients.

In general, improvements in 5- and 10-year relative survival were of similar magnitude. However, a large gap between 5- and 10-year relative survival continues to exist, indicating that a number of the 5-year survivors are not cured but have relapsed or will relapse. Although we did not examine cause of death in this study, our data suggest that a significant proportion of 5-year survivors eventually die of their disease. However, the improvement in 10-year relative survival gives rise to the hope that the proportion of cured patients may have increased as well.

There are 2 major advances that might explain the improvement in survival seen in NHL in the late 1990s and early 21st century. One is advances in therapy that have occurred between 1990 and 2004, particularly the introduction of antibody therapy for NHL. Treatment with antibody therapy and chemotherapy has extended life expectancy in many cases, but whether and how often this extension represents a true cure is still unknown.[15] The second component is improvements in the treatment of HIV that have led to both decreases in the incidence and improvements in the treatability of HIV-related NHL. Other advances, including the use of stem cell transplantation, antibiotic therapy for selected cases of marginal zone lymphoma, and improvements in supportive care, may also have contributed to the improvements in outcomes observed to some extent.

Rituximab, a chimeric monoclonal antibody directed against the B-lymphocyte marker CD20, was first approved for use in NHL in the United States in 1997. In both high- and low-grade NHL, rituximab has been shown to produce higher response rates when combined with chemotherapy compared with chemotherapy alone.[15-19] Rituximab has been shown to be safe and effective in older patients.[18,20] Our data suggest that these improved results from clinical trials have translated into better survival on the population level.

Human immunodeficiency virus–related NHL was first observed in the early 1980s. Non-Hodgkin lymphoma in

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the setting of HIV infection is an AIDS-defining illness and generally occurs when CD4 lymphocyte counts are very low. Human immunodeficiency virus–related NHL is more likely to be high grade and extranodal, responds poorly to treatment, and occurs most frequently in men and younger patients. These characteristics may largely explain the unusual finding that in 1990-1992, younger patients with extranodal NHL did much worse than older patients. The decrease in case numbers of younger men and the very strong improvements in survival in younger patients with extranodal NHL and in young men observed throughout the 1990s correspond well with the development of highly effective antiretroviral therapy (HAART) in the mid-1990s. Human immunodeficiency virus that is well controlled with HAART rarely leads to lymphomas, and the rate of NHL associated with HIV fell in the late 1990s.[3,21] Human immunodeficiency virus–related lymphoma responds better to treatment if HAART is given along with the specific chemotherapy for NHL.[4,22]

While improvements in survival for patients with NHL were impressive overall, several areas of concern remain. Most notably, racial differences in survival were large and the gap was increasing over time, except for patients 75 years or older. There are several possible, nonmutually exclusive reasons for this finding. First, less treatable histologic subtypes may occur more frequently in blacks patients than in white patients, with black patients being more likely to be diagnosed as having T-cell lymphoma.[23,24] This and other differences in the biological features of the disease may affect prognosis in some patients. However, non–B-cell lymphomas are rare in either racial group, suggesting that this difference plays only a minor role. Differences in care are likely to be a larger contributing factor. One study in elderly patients demonstrated that black patients were significantly less likely to receive chemotherapy after being diagnosed as having NHL.[25] In addition, blacks are more commonly incarcerated than whites in the United States, and a higher rate of death due to cancers, including NHL, has been documented in the incarcerated population.[26] Other socioeconomic problems including lack of health insurance may play a role as well.

Unlike in many hematologic malignant neoplasms, survival in older patients with NHL also improved substantially between 1990-1992 and 2002-2004. Because rituximab plus chemotherapy has been demonstrated to be safe and effective in older patients,[18,20] clinicians may have a higher comfort level with prescribing this combination for elderly patients than they would for some of the more aggressive treatments needed to produce remissions in other hematologic malignant neoplasms. Nonetheless, approximately 42% of patients with NHL diagnosed between 1992 and 1999 who were 75 years or older did not receive any specific treatment for their disease,[25] suggesting that there is room for improvement in the treatment of this age group.

In the interpretation of our results, a number of limitations demand careful discussion. Although period analysis method provides more up-to-date estimates of long-term survival than conventional "cohort-based" analysis, even the period estimates tend to be too pessimistic in situations of ongoing improvement in prognosis, such as observed for NHL. Also, further progress is likely to have occurred since 2004, which cannot be reflected in our survival figures, and further improvements in survival may occur as new therapeutic options become available. Owing to the lack of data on medication in the SEER database, the role of various therapeutic regimens in the improvement in survival could not be assessed directly. Finally, the SEER database pertains to the US population and results may not be generalizable to other populations.

In conclusion, our population-based period analysis disclosed marked improvements in the prognosis of patients with NHL between 1990-1992 and 2002-2004. This improvement was observed in all age groups, both sexes, and both races studied as well as in both nodal and extranodal disease. Greater progress occurred in the treatment of men, white patients, and younger patients, but clear improvements were seen in other groups as well. Our estimates of long-term survival in patients with NHL obtained by the period analysis method for the 2002-2004 period are much higher than previously available survival estimates, which mostly pertain to patients diagnosed in the 1990s.[1,27] Timely disclosure of the improvements in survival achieved in patients, clinicians, researchers, and the public is essential.

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