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Improved Survival for Children and Adolescents With Acute Lymphoblastic Leukemia Between 1990 and 2005: A Report From the Children's Oncology Group

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ABSTRACT

Purpose
To examine population-based improvements in survival and the impact of clinical covariates on outcome among children and adolescents with acute lymphoblastic leukemia (ALL) enrolled onto Children's Oncology Group (COG) clinical trials between 1990 and 2005.

Patients and Methods
In total, 21,626 persons age 0 to 22 years were enrolled onto COG ALL clinical trials from 1990 to 2005, representing 55.8% of ALL cases estimated to occur among US persons younger than age 20 years during this period. This period was divided into three eras (1990-1994, 1995-1999, and 2000-2005) that included similar patient numbers to examine changes in 5- and 10-year survival over time and the relationship of those changes in survival to clinical covariates, with additional analyses of cause of death.

Results
Five-year survival rates increased from 83.7% in 1990-1994 to 90.4% in 2000-2005 ($P < .001$). Survival improved significantly in all subgroups (except for infants age ≤ 1 year), including males and females; those age 1 to 9 years, 10+ years, or 15+ years; in whites, blacks, and other races; in Hispanics, non-Hispanics, and patients of unknown ethnicity; in those with B-cell or T-cell immunophenotype; and in those with National Cancer Institute (NCI) standard- or high-risk clinical features. Survival rates for infants changed little, but death following relapse/disease progression decreased and death related to toxicity increased.

Conclusion
This study documents ongoing survival improvements for children and adolescents with ALL. Thirty-six percent of deaths occurred among children with NCI standard-risk features emphasizing that efforts to further improve survival must be directed at both high-risk subsets and at those children predicted to have an excellent chance for cure.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, comprising 25% of cancers occurring before age 15 years and 19% among those younger than age 20 years.[1] The 5-year survival rate increased from less than 10% in the 1960s to 77% in 1985 to 1994.[1] Survival rate has continued to increase over the past 10 to 15 years.[2-11] The National Cancer Institute (NCI) SEER Program reported that 5-year survival for US patients younger than age 15 years with ALL increased from 80.2% to 87.5% between 1990-1994 and 2000-2004.[12] Five-year survival rates for adolescents age 15 to 19 years increased from 41.0% in 1980-1984 to 61.1% in 2000-2004.[13]

The Children's Oncology Group (COG) includes more than 200 member institutions in the United States, Canada, Australia, and New Zealand. Unlike the SEER system, which tracks outcome in five representative states and four metropolitan areas that include approximately 10% of the US population, COG data include patients from all areas of the United States and Canada and provide an opportunity to assess outcome for children with ALL throughout these countries and to examine the prognostic impact of covariates not included in registry data. We report changes in survival among children enrolled onto COG ALL clinical trials between 1990 and 2005 and the extent to which different clinical and biologically defined patient subgroups benefited from treatment improvements.

PATIENTS AND METHODS

Patients

In all, 21,626 eligible children and adolescents younger than age 22 years enrolled onto one of 36 COG ALL clinical trials (Appendix Table A1, online only) between January 1, 1990, and December 31, 2005. Patients were treated on clinical trials that tested treatment intensifications and the need for cranial irradiation, and they used clinical and biologic prognostic variables, including genetic subtype and early treatment response, to risk stratify patients and assign therapies of varying intensity.[18] We divided this period into three eras that included similar numbers of patients: 1990-1994 (7,304 patients; median follow-up, 9.13 years), 1995-1999 (7,169 patients; median follow-up, 8.02 years), and 2000-2005 (7,153 patients; median follow-up, 5.35 years). Most patients (92.2%) were treated in the United States, with 5.8% in Canada, and 2% elsewhere. Patients and/or a parent/guardian provided informed consent for clinical trial participation; trials were approved by institutional review boards at COG centers. We analyzed outcome on the basis of clinical features, including age and WBC count at diagnosis, sex, immunophenotype, race, and ethnicity as reported by the patient or parent.

Statistical Analyses

Overall survival estimates were obtained by using the Kaplan-Meier method,[19] with SEs calculated by using the method of Peto and Peto.[20] Survival time was calculated as the time from study entry to death or date of last contact. Comparisons of survival curves were performed by using the log-rank test.[21] Survival curves were truncated at year 15. The cumulative incidence of death due to various causes was determined after adjusting for competing risks.[22] Multivariate Cox regression analysis was used to identify prognostic factors affecting overall survival. Survival tree regression was used in both infant and non–infant subsets to identify prognostic factors and explore their association with overall survival.[23,24] Data were frozen in September 2009.

Incidence rates for ALL were determined by using published SEER data with additional information on rates obtained directly from the National Institutes of Health and Information Management Services. Total numbers of ALL cases expected to occur in the United States during specific time periods was determined by applying these incidence rates to population statistics derived from US census data.

RESULTS

Overall 5- and 10-year survival rates increased significantly over time (Fig 1; $P < .001$). Five-year survival increased from 83.7% (SE, 0.4%) in 1990-1994 to 87.7% (SE, 0.4%) in 1995-1999 and to 90.4% (SE, 0.5%) in 2000-2005 (Table 1). Similar increases were seen in 10-year survival between 1990-1994 (80.1%; SE, 0.8%) and 1995-1999 (83.9%; SE, 1.3%; $P < .001$). For the eras from 1990 to 1999, approximately 84% of deaths occurred within 5 years of diagnosis and only 1% occurred more than 10 years following diagnosis (Appendix Tables A2 to A6, online only). Because of these factors and the more limited follow-up for the 2000-2005 era, subsequent analyses focused on 5-year survival.

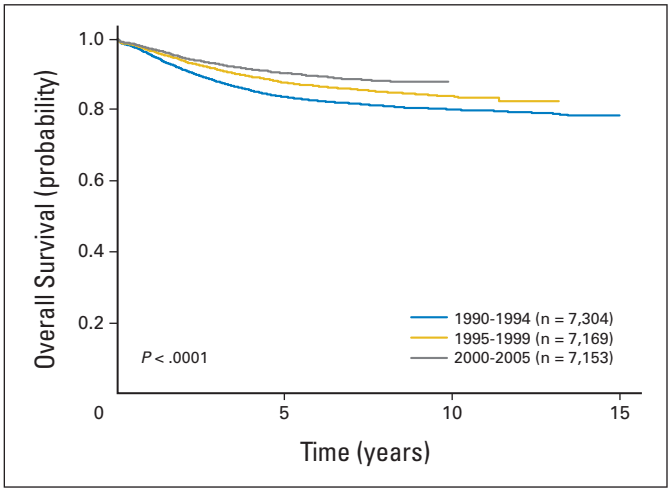

Fig 1. Overall survival probability by treatment era for patients enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

Survival improved significantly in all subgroups examined except for infants ≤ 1 year old (Table 1 and Appendix Figs A1 to A6, online only): ages 1 to 9 years, 10+ years, and 15+ years; males and females; self-reported whites, blacks, and other races; self-reported Hispanics, non-Hispanics, and persons of unknown ethnicity; those with B-cell and T-cell ALL; and those with standard-risk (age 1 to 9.99 years; initial WBC $< 50{,}000/\mu L$) or high-risk (age ≥ 10 years and/or initial WBC $\geq 50{,}000/\mu L$) features by using NCI/Rome[25] criteria. The relative reductions in 5-year risk of death between the 1990-1994 and 2000-2005 eras were similar in all non–infant subgroups examined, ranging from 30% to 50% (Table 1). Because the results for infants differed from those of older children, we also analyzed data separately for infants and non–infants (Appendix Tables A7 and A8, online only).

Deaths that occurred after induction failure or relapse were classified as leukemia related, and those that occurred without prior induction failure or relapse were deemed treatment related (Table 2 and Appendix Tables A9 and A10, online only). Among all patients, the 5-year cumulative incidence of death decreased from 16.35% in 1990-1994 to 9.6% in 2000-2005 ($P < .001$), and the 10-year cumulative incidence of death decreased from 19.86% in 1990-1994 to 16.07% in 1995-1999 ($P < .001$). This decrease was primarily due to reduction in the 5-year cumulative incidence of death following relapse/disease progression from 12.83% in 1990-1994 to 7.22% in 2000-2005 ($P < .001$), with similar reductions in 10-year rates between 1990-1994 and 1995-1999. Among infants (Appendix Table A9), the 5-year cumulative incidence of death changed little between 1990-1994 and 2000-2005 (52.1% *v* 50.3%; $P = .45$), but the causes of death changed considerably. The 5-year cumulative incidence of death following relapse/disease progression decreased from 43% in 1990-1994 to 27.2% in 2000-2005 ($P < .001$), and the cumulative incidence of treatment-related death increased from 3.9% in 1990-1994 to 13.9% in 2000-2005 ($P < .001$).

The highest relative risks of death occurred in known high-risk subgroups (Table 3). The relative risk of death was 2.3-fold (1990-1994) to 3.1-fold (2000-2005) higher for patients age 10+ years versus those age 1 to 9.99 years. The differences were even larger when those age 1 to 9.99 years were compared with infants age ≤ 1 year and adolescents age ≥ 15 years. We observed modest but statistically significant sex-based differences in survival, with males having a relative risk of death 1.2- to 1.3-fold higher than that of females. Self-described blacks had an increased relative risk of death compared with whites. Although information about ethnicity was not available for approximately 30% (6,509 of 21,626) of patients, self-described Hispanics (n = 2,589) had a higher relative risk of death than non-Hispanics. Leukemia immunophenotype was prognostic, with patients who had T-cell ALL having a higher relative risk of death than those with B-cell ALL. Patients with NCI high-risk ALL had a 2.4- to 3.6-fold higher relative risk of death than those with standard-risk

Table 1. Five-Year Overall Survival of Patient Subsets by Era

Patient Group	No.	5-Year Survival ± SE (%) 1990-1994	No. of Patients	1995-1999	No. of Patients	2000-2005	No. of Patients	% Reduction 2000-2005 *v* 1990-1994	*P**
All patients	21,626	83.7 ± 0.4	7,304	87.7 ± 0.4	7,169	90.4 ± 0.5	7,153	41	< .001
Age group, years									
< 1	461	47.9 ± 4.1	154	48.1 ± 4.3	148	53.2 ± 5.4	159	10	.4520
1-9.99	16,578	88.2 ± 0.4	5,599	91.7 ± 0.4	5,523	94.1 ± 0.4	5,456	50	< .001
≥ 10	4,587	70.8 ± 1.2	1,551	76.9 ± 1.2	1,498	81.6 ± 1.3	1,538	37	< .001
10-14.99	3,072	72.8 ± 1.4	1,094	78.9 ± 1.4	1,001	84.7 ± 1.5	977	44	< .001
≥ 15	1,515	66.1 ± 2.3	457	72.9 ± 2.2	497	75.9 ± 2.6	561	29	.0025
Sex									
Male	12,155	82.7 ± 0.6	4,117	86.3 ± 0.6	4,057	89.9 ± 0.6	3,981	42	< .001
Female	9,471	84.9 ± 0.7	3,187	89.5 ± 0.6	3,112	91.0 ± 0.7	3,172	40	< .001
Race									
White	15,759	86.3 ± 0.5	5,410	88.9 ± 0.5	4,890	91.1 ± 0.5	5,242	35	< .001
Black	1,474	75.3 ± 2.0	535	80.7 ± 1.9	472	87.8 ± 2.1	425	51	< .001
Other	4,393	77.0 ± 1.2	1,359	86.3 ± 0.9	1,807	88.1 ± 1.2	1,486	48	< .001
Ethnicity									
Hispanic	2,589	82.0 ± 1.8	547	86.2 ± 1.4	675	87.6 ± 1.2	1,367	31	.0076
Non-Hispanic	12,528	87.0 ± 0.6	3,626	88.5 ± 0.6	3,377	91.4 ± 0.5	5,525	34	< .001
Unknown	6,509	80.0 ± 0.7	3,131	87.1 ± 0.6	3,117	83.6 ± 3.0	261	18	< .001
Immunophenotype									
B cell	16,880	84.9 ± 0.5	5,068	88.3 ± 0.4	5,830	91.1 ± 0.5	5,982	41	< .001
T cell	1,831	70.7 ± 1.7	748	80.7 ± 1.7	624	81.6 ± 2.2	459	37	< .001
NCI risk group									
Standard risk	14,154	90.2 ± 0.5	4,624	92.7 ± 0.4	4,674	95.0 ± 0.4	4,856	49	< .001
High risk		73.8 + 0.9	2,680	79.8 ± 0.9	2,494	82.9 ± 1.1	2,286	32	< .001

Abbreviation: NCI, National Cancer Institute.
*The *P* values were computed by comparing the survival curves among all three eras.

ALL. However, because most patients have NCI standard-risk clinical features, a significant proportion of deaths occurred among the favorable prognosis subgroups (Table 4). Five-year survival of patients with NCI standard-risk ALL was 90% to 95% between 1990 and 2005 (Table 1 and Appendix Fig A6A), but approximately 36% of total deaths occurred among this subset.

For patients older than age 1 year, era, sex, race, immunophenotype, and NCI risk group were all significant prognostic factors in the multivariate Cox regression model (Table 5). To better understand the most important factors predicting risk of death, we performed survival tree regression modeling (Appendix Fig A7A, online only). This analysis showed that NCI risk group was the most significant overall prognostic factor. Among NCI standard-risk patients, era (2000-2005 *v* 1990-1999) was the most significant prognostic factor. For NCI high-risk patients, age (1 to 14.99 *v* ≥ 15 years) was the most prognostic factor. Among NCI high-risk patients younger than age 15 years, race was the most significant prognostic factor, with survival for black/other being inferior to that of whites. For adolescents age ≥ 15 years,

Table 2. Cumulative Incidence of Death After Relapse/Disease Progression *v* Death As a First Event in COG ALL Trials

Death As a First or Subsequent Event	Cumulative Incidence (%) 1990-1994	1995-1999	2000-2005	Overall	*P**
5-year					
Relapse/disease progression or secondary malignancies as first event	12.83	9.03	7.22	9.82	< .001
Treatment-related death prior to relapse/disease progression	2.16	1.92	1.57	1.89	.0335
Unknown or unrelated	1.37	1.36	0.81	1.19	.0013
Overall	16.35	12.31	9.60	12.90	< .001
10-year					
Relapse/disease progression or secondary malignancies as first event	15.80	12.45	—	12.98	< .001
Treatment-related death prior to relapse/disease progression	2.17	1.95	—	1.91	.3413
Unknown or unrelated	1.89	1.67	—	1.61	.7149
Overall	19.86	16.07		16.50	< .001

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group.
**P* values in the 5-year category were computed by comparing the corresponding cumulative incidence curves among all three eras; *P* values in the 10-year category were for comparison between the first two eras (1990-1994 *v* 1995-1999).

Table 3. Five-Year RR of Death by Era and Characteristic

Patient Group	Era					
	1990-1994		1995-1999		2000-2005	
	RR	*P*	RR	*P*	RR	*P*
Age, years						
1-9.99	1.0		1.0		1.0	
≥ 10	2.26	< .001	2.40	< .001	3.10	< .001
≥ 15	2.61	< .001	2.65	< .001	3.97	< .001
< 1	3.65	< .001	4.92	< .001	7.81	< .001
Sex						
Female	1.0		1.0		1.0	
Male	1.17	< .001	1.34	< .001	1.16	.0213
Race*						
White	1.0		1.0		1.0	
Black	1.73	< .001	1.60	< .001	1.37	.0119
Other	1.58	< .001	1.16	.0121	1.27	.0056
Ethnicity*						
Non-Hispanic	1.0		1.0		1.0	
Hispanic or Latino	1.31	.0024	1.16	.0645	1.47	< .001
Immunophenotype						
B cell	1.0		1.0		1.0	
T cell	1.75	< .001	1.46	< .001	2.04	< .001
NCI risk group†						
Standard risk	1.0		1.0		1.0	
High risk	2.42	< .001	2.52	< .001	3.59	< .001

NOTE. *P* values compare RR of the death to the baseline value defined as RR of 1.0 for each characteristic.
Abbreviations: NCI, National Cancer Institute; RR, relative risk.
*Self-reported race or ethnicity.
†Standard, age 1-9.99 years and initial WBC < 50,000/μL; high, age ≥ 10 years and/or initial WBC ≥ 50,000/μL.

era was the most significant prognostic factor, with better survival rates in 1995-2005 compared with 1990 to 1994.

For infants, age considered as a continuous variable was the most important prognostic factor (Appendix Fig A7B). The best age cutoff among infants was 92 days, with 5-year survival rates of 57.8% and 25.6% for age ≥ 92 days and less than 92 days, respectively ($P < .001$). Among infants ≥ 92 days old, WBC was the most significant predictor of survival, with higher WBC resulting in poorer outcome.

DISCUSSION

This study, which includes the largest childhood ALL cohort ever reported, documents progressive improvements in survival for children with ALL enrolled onto COG clinical trials between 1990-1994 and 2000-2005. Five-year survival increased from 83.7% to 90.4% during this time. The improved survival was explained primarily by an approximately 44% decrease in the risk of death following relapse/disease progression. Although we examined overall and not event-free survival (EFS) and cannot comment directly on changes in the incidence of relapse, a study of almost 10,000 children treated on COG ALL trials between 1988 and 2002, including 1,961 who relapsed, showed no significant improvements in survival after relapse over time.[26] Taken together with results of COG ALL clinical trials showing significant improvements in EFS during this period, we believe that the major reason for improved survival was decreased risk of relapse.[14,15,17]

Our cohort includes 18,501 (55.8%) of 33,139 US ALL cases in persons age 0 to 14.99 years predicted to occur between 1990 and 2005. Thus, our results are representative of survival following contemporary therapy in the United States and are consistent with previous reports of outcomes for children younger than age 15 years diagnosed with cancer between 1990 and 1994 enrolled onto COG trials.[27,28] In contrast, only approximately 25% of adolescents age 15 to 19 years diagnosed with cancer were enrolled onto COG trials between 1990 and 1994.[27] Our data are similar, with 33.5% (1,392 of 4,159) of US adolescents age 15 to 19.99 years predicted to develop ALL between 1990 and 2005 enrolling onto COG trials. There are a variety of reasons that children and adolescents with ALL might not be included in COG ALL trials, including participation in trials conducted by other centers,[6,8] lack of an open study at the time of diagnosis, having the patient/parent decline participation, or failure to meet eligibility criteria. Most US children with ALL still enroll onto COG trials. In 2009, 1,951 (68%) of 2,869 US children and adolescents age 0 to 19.99 years predicted to develop ALL enrolled onto a COG trial, including 1,758 (69%) of 2,540 of those age 0 to 14.99 years and 168 (51%) of 329 of those age 15 to 19.99 years. The number of older adolescents with ALL enrolling onto COG trials has increased over time, which is an important trend, given the higher survival rates obtained with pediatric versus adult ALL trials for this age group.[29-31]

Pulte et al[12,13] reported survival for US children and adults diagnosed with ALL between 1990 and 2004 by using the SEER 9 Registries database, which includes about 30 million people. Our results show higher survival rates than the SEER-estimated 5-year survival of 87.5% from 2000-2004 for children younger than age 15 years and 61.1% for those age 15 to 19 years. We found 5-year survival rates of 91.4% for US children younger than age 15 years and 74.5% for those age 15 to 19 years in 2000-2005. It is unlikely that the slight difference in time period analyzed (SEER: 2000-2004 *v* COG: 2000-2005) accounts for these differences. There may be differences based on clinical trial enrollment because the SEER data include all patients reported to tumor registries in the specified areas, although the COG data are based on patients who met eligibility criteria and were offered and accepted clinical trial enrollment. The SEER 9 population is more urban and includes a higher percentage of foreign-born persons than the overall US population; these differences might contribute to observed differences in survival. There was a 13% absolute survival advantage for older adolescents in this COG cohort compared with the SEER estimates, consistent with the significant survival advantages for older adolescents with ALL treated on COG versus adult cooperative group trials.[29] These data emphasize that optimal treatment for an older adolescent with ALL is referral to a pediatric center and enrollment onto a pediatric cooperative group trial.

In our analyses, survival improvements occurred in every subgroup analyzed with the exception of infants age ≤ 1 year (Table 1 and Appendix Figs A1 to A6). The magnitude of the decrease in risk of death between 1990-1994 and 2000-2005 was generally similar among non–infant subgroups and ranged from approximately 30% to 50%.

There were no survival improvements for infants enrolled onto COG ALL trials between 1990 and 2005 (Appendix Fig A1A). Infants contributed disproportionately to deaths because they accounted for only 2.1% (461 of 21,626) of patients but 8.0% (231 of 2,878) of deaths ($P < .001$). During this period, the COG pursued several strategies to attempt to increase survival for infants with ALL. Chemotherapy treatment was intensified significantly in the Children's Cancer Group

Table 4. Number of Deaths by Era and Presenting Characteristics

Patient Group	Total No. of Patients	Projected No. of Deaths in 5 Years							
		1990-1994		1995-1999		2000-2005		1990-2005	
		No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
All patients	21,626	1,194	100	882	100	687	100	2,763	100
Age group, years									
≤ 1	461	80	6.7	77	8.7	74	10.8	231	8.4
1-9.99	16,578	662	55.5	461	52.0	324	46.9	1,447	52.2
≥ 10	4,587	453	37.9	346	39.2	283	41.3	1,082	39.1
10-14.99	3,072	298	24.9	211	24.0	150	21.8	659	23.8
≥ 15	1,515	155	13.0	135	15.3	135	19.7	425	15.4
Sex									
Male	12,155	714	59.8	557	63.0	402	58.6	1,673	60.5
Female	9,471	480	40.2	326	37.1	285	41.6	1,091	39.6
Race									
White	15,759	727	60.9	547	61.9	493	71.8	1,767	63.9
Black	1,474	129	10.8	101	11.4	53	7.7	283	10.2
Other	4,393	341	28.6	235	26.7	141	20.6	717	26.0
Ethnicity									
Hispanic	2,589	98	8.2	93	10.5	170	24.7	361	13.1
Non-Hispanic	12,528	470	39.4	388	43.9	473	69.0	1,331	48.2
Unknown	6,509	626	52.4	402	45.6	43	6.3	1,071	38.7
Immunophenotype									
B cell	16,895	768	64.3	684	77.5	537	78.1	1,989	72.0
T cell		1,831		121	13.7	84	12.3	424	15.3
NCI risk group									
Standard	14,002	438	36.7	323	36.6	233	34.0	994	36.0
High	7,154	677	56.7	484	54.9	366	53.3	1,527	55.3

Abbreviation: NCI, National Cancer Institute.

(CCG) 1953 and COG P9407 trials, and the use of stem-cell transplantation in first remission was explored for those with *MLL* gene rearrangements. Stem-cell transplantation was not beneficial for infants in these COG ALL trials,[16] and treatment intensification shifted the causes of death, with a significant decrease in death following relapse/disease progression but a parallel increase in death related to toxicity, with no net improvement in survival (Appendix Table A9). The Interfant99 infant ALL trial (1999-2005) obtained results similar to those of the COG trials, with 4-year EFS of only 48%.[32] Although Interfant99 showed a benefit for stem-cell transplantation among a select high-risk subgroup of infants, survival was still poor for these patients.[33] Infant ALL is a unique high-risk subset that requires new therapeutic strategies.

Table 5. Multivariate Cox Regression Analysis for Patients Older Than Age 1 Year

Variable	HR	95% CI	*P*
Sex			
Female *v* male	0.83	0.77 to 0.90	< .001
Race			
White *v* black	0.84	0.73 to 0.97	.0208
White *v* other	0.64	0.56 to 0.72	< .001
Age, years			
1-9 *v* 15+	0.53	0.46 to 0.60	< .001
10-14 *v* 15+	0.71	0.63 to 0.81	< .001
NCI risk group			
Standard *v* high	0.48	0.42 to 0.53	< .001
Immunophenotype			
B cell *v* T cell	0.76	0.68 to 0.84	< .001
Era			
1995-1999 *v* 1990-1994	0.73	0.67 to 0.80	< .001
2000-2005 *v* 1990-1995	0.56	0.50 to 0.62	< .001

Abbreviation: HR, hazard ratio; NCI, National Cancer Institute.

Survival for self-reported blacks with ALL improved significantly during the eras examined. The absolute difference in 5-year survival between blacks and whites decreased from 11.0% in 1990-1994 to 3.3% in 2000-2005. There are race-based differences in ALL biology, with blacks having a higher incidence of T-cell ALL and other high-risk features.[34] Among the COG patients, 17.7% of blacks versus 9.5% of whites had T-cell ALL ($P < .001$) and 44.5% of blacks had NCI high-risk features versus 32.9% of whites ($P < .001$). Thus, black children and adolescents with ALL are predicted to have an inferior survival compared with whites because of the different percentages of ALL subtypes in the two racial groups. However, within these ALL subtypes, although patient numbers are small, our results show decreases in the racial outcome gap between 1990-1994 and 2000-2005. The absolute difference in 5-year survival for blacks versus whites with T-cell ALL decreased from 5.0% in 1990-1994 (94 blacks) to 0.02% in 2000-2005 (57 blacks). Similarly, for children with NCI high-risk B-cell ALL, the gap decreased from 11.1% in 1990-1994 (129 blacks) to 6.6% in 2000-2005 (53 blacks).

Self-described ethnicity is another important risk factor in childhood ALL. Hispanics have inferior outcomes to non-Hispanics.[35] Our

study confirms this observation, with some differences in the magnitude of differences in the three eras (Tables 1 and 3). Importantly, there was much greater capture of information regarding self-described ethnicity in 2000-2005, with only 3.6% (261 of 7,153) of unknown ethnic group compared with 43.2% (6,284 of 14,473) in 1990-1999. We observed a 1.5-fold higher risk of death for Hispanics versus non-Hispanics in 2000-2005. A variety of reasons might account for the inferior outcome of Hispanics. For example, recent investigations have shown a much higher incidence of certain high-risk leukemia cell genomic alterations in Hispanics enrolled onto COG ALL trials.[36]

Simple demographic and clinical prognostic factors can identify patient subsets with significantly increased risk of death: infants, adolescents age ≥ 10 or ≥ 15 years, T-cell ALL, and NCI high-risk ALL. The relative risks of death for these subsets ranged from about two- to eight-fold higher than for lower-risk subsets (Table 3). However, 36% of total deaths occurred among patients with NCI standard-risk ALL. Thus, efforts to decrease ALL deaths must focus both on high-risk patient subsets and on the large subset of patients with favorable clinical characteristics. Detailed biologic characterization of lymphoblasts and host germline variability and sophisticated measurements of early treatment response can improve identification of ultra-low-risk patient subsets and identify patients at high risk of treatment failure.[18,36-47]

We analyzed whether death occurred as a first event or after relapse/induction failure to investigate whether observed survival improvements were due to better front-line antileukemia therapy, better supportive care leading to a decrease in non–leukemia-related death, or both. Five to six times as many deaths occurred following relapse/disease progression compared with toxicity (Table 2). Although the cumulative incidence of deaths related to toxicity is relatively low at approximately 2%, it accounted for a higher percentage of overall deaths as the rate of death from leukemia decreases and was a particular problem among infants. Prevention of treatment-related deaths must be a critical component of efforts to improve childhood ALL survival.

Ten-year survival was 3% to 4% lower than 5-year survival in 1990-1999, when 84% of deaths occurred within 5 years, and only 1% occurred more than 10 years following diagnosis (Appendix Tables A2 to A4). Given this lower 10-year survival rate, the death rates observed in the 2000-2005 era (Appendix Tables A5 and A6), and the shape of the survival curves (Fig 1), we believe that it is extremely unlikely that there will be a significant increase in deaths beyond 5 years for patients diagnosed in 2000-2005, and we anticipate significant improvements in 10-year survival. We anticipate that the 10-year survival rate for children treated on COG ALL trials in 2006-2010 will approach or exceed 90%. The trend from 1990 to 2005 predicts an absolute 2% to 3% increment in survival during each 5-year era. More importantly, randomized COG ALL clinical trials conducted between 1995 and 2005 established superior treatment regimens that then became the baseline therapy for COG trials conducted in 2006 to 2010.[4,5,14,15]

This report underscores the remarkable improvements in the outcomes for childhood ALL since Farber et al[48] first described temporary remissions in 1948. The ongoing discovery of important biologic subsets of ALL[36,38-40,46] will further refine risk stratification and facilitate the combination of molecularly targeted therapies with chemotherapy. As proof of principle, addition of imatinib to chemotherapy resulted in a dramatic increase in survival for pediatric Philadelphia chromosome–positive ALL.[49] As these changes occur, it will remain essential to closely assess the survival for the majority of US children, adolescents, and young adults with ALL who are treated on COG clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Clinical Trials Included in Present Report

Trial No.	Trial Name	NCT ID	Accrual Closed	Reference
CCG 1881	Treatment of Newly Diagnosed ALL in Children Aged 2-9 Inclusive With WBC $< 10{,}000/\mu L$		December 15, 1992	Hutchinson RJ, et al: J Clin Oncol 21:1790-1797, 2003
CCG 1882	Treatment of Newly Diagnosed ALL in Children With a Poor Prognosis Excluding Infants and Patients With Lymphoma-Leukemia or FAB L3 Blasts		June 23, 1995	Nachman JB, et al: N Engl J Med 338:1663-1671, 1998; Nachman J, et al: J Clin Oncol 16:920-930, 1998
CCG 1883	Treatment of Newly Diagnosed ALL in Infants Less Than 12 Months of Age		August 25, 1993	Reaman GH, et al: J Clin Oncol 17:445-455, 1999
CCG 1891	Treatment of Newly Diagnosed ALL in Children With an Intermediate Prognosis		July 20, 1990	Lange BJ, et al: Blood 99: 825-833, 2002
CCG 1901	Phase III Protocol for the Treatment of Newly Diagnosed Childhood Acute Lymphoblastic Leukemia with Multiple Poor-Risk Factors Exclusive of FAB L3 Leukemia		September 9, 1994	Heath JA, et al: J Clin Oncol 21:1612-1617, 2003
CCG 1922	Phase III Randomized Comparison of Intravenous vs Oral Mercaptopurine During Consolidation and of Prednisone vs Dexamethasone during Induction, Consolidation, and Maintenance in Children with Good-Prognosis and Intermediate-Prognosis ALL Receiving Standard Chemotherapy		August 1, 1995	Bostrom BC, et al: Blood 101:3809-3817, 2003
CCG-1952	Randomized Comparisons of Oral Mercaptopurine vs. Oral Thioguanine and Intrathecal Methotrexate vs. Intrathecal Methotrexate/Cytarabine/ Hydrocortisone for Standard Acute Lymphoblastic Leukemia	NCT00002744	February 1, 2000	Stork LC, et al: Blood 115: 2740-2748, 2010
CCG 1953	Treatment of Newly Diagnosed ALL in Infants < 1 Year of Age		August 31, 2000	Hilden JM, et al: Blood 108:441-451, 2006
CCG-1961	Treatment of Patients With Acute Lymphoblastic Leukemia With Unfavorable Features: A Phase III Group-Wide Study	NCT00002812	May 1, 2002	Seibel NL et al[14]
CCG 1962	A Randomized Comparison of PEG and Native *E. coli* Asparaginases in the Standard Arm of CCG-1952 for Standard Risk ALL		November 10, 1998	Avramis VI, et al: Blood 99:1986-94, 2002
CCG-1991	Escalating Dose Intravenous Methotrexate Without Leucovorin Rescue Versus Oral Methotrexate and Single Versus Double Delayed Intensification for Children With Standard Risk Acute Lymphoblastic Leukemia	NCT00005945	January 31, 2005	Matloub Y et al[15]
POG 8602	Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (ALinC #14)		January 7, 1991	Harris MB, et al: Leukemia 14:1570-6, 2000
POG 8698	Up Front Alternating Chemotherapy vs Up Front Intensive 6-Mercaptopurine/ Methotrexate for Acute Lymphocytic Leukemia In Childhood - A Pediatric Oncology Group Pilot Study		January 7, 1991	Camitta B, et al: J Clin Oncol 12:1383-9, 1994
POG 8699	Intensive Intravenous Treatment for Acute Lymphocytic Leukemia in Childhood - A Pediatric Oncology Group Pilot Study		January 7, 1991	Mahoney DH Jr, et al: Cancer 75:2623-31, 1995
POG 8704	T-Cell #3 Protocol - A Pediatric Oncology Group Phase III Study		January 9, 1992	Amylon MD, et al: Leukemia 13:335-42, 1999

(continued on following page)

Table A1. Clinical Trials Included in Present Report (continued)

Trial No.	Trial Name	NCT ID	Accrual Closed	Reference
POG 9005	Phase III Comparison of Intensification with Intravenous Mercaptopurine plus Intermediate-Dose Intravenous Methotrexate vs Low-Dose Oral Methotrexate Following Induction with Prednisone/Vincristine/Asparaginase in Children with Low-Risk ALL		September 1, 1994	Mahoney DH Jr, et al: J Clin Oncol 16:246-54, 1998
POG 9006	Up-Front Intensive 6-Mercaptopurine/ Methotrexate vs. Up-Front Alternating Chemotherapy for Acute Lymphocytic Leukemia in Childhood - A Randomized Pediatric Oncology Group Phase III Study		November 1, 1994	Lauer SJ, et al: Leukemia 15:1038-45, 2001
POG 9086	Phase I Pilot Study of Therapy for T-cell ALL or NHL		April 24, 1992	
POG 9107	Infant Leukemia Protocol - A Pediatric Oncology Groupwide Pilot Study		June 15, 1993	Maloney KW, et al: Leukemia 14:2276-85, 2000
POG 9201	ALinC #16 Treatment for Patients With Lesser Risk Acute Lymphoblastic Leukemia—A Pediatric Oncology Group Phase III Study		November 15, 1999	Chauvenet AR, et al: Blood 110:1105-11, 2007
POG 9202	ALinC #16: Protocol for Patients with Standard Risk Acute Lymphoblastic Leukemia - A Pediatric Oncology Group Limited-Institution Pilot Study		October 1, 1994	
POG 9203	ALinC #16: Pilot Study for Patients with High-Risk ALL - A Pediatric Oncology Group Limited-Institution Pilot Study		April 28, 1994	Salzer WL, et al: J Pediatr Hematol Oncol 29:369-75, 2007
POG 9295	T-Cell #4 "A" Pilot (With PEG-L-Asparaginase) - A Pediatric Oncology Group Limited-Institution Pilot Study		December 1, 1993	
POG 9296	T-Cell #4 Pilot "B" (With Intravenous Methotrexate/Intravenous 6-Mercaptopurine) - A Pediatric Oncology Group Limited-Institution Pilot Study		June 15, 1993	
POG 9297	T-Cell #4 Pilot "C" (With Intermediate Dose Methotrexate/Intravenous 6-Mercaptopurine and High-Dose Cytosine Arabinoside) - A Pediatric Oncology Group Pilot Study		June 15, 1993	
POG 9398	Efficacy of recombinant human granulocyte-colony stimulating factor in an Intensive Treatment for T-Cell Leukemia and Advanced-Stage Lymphoblastic Lymphoma of Childhood - A Pediatric Oncology Group-Wide Pilot Study		December 15, 1994	
POG-9404	Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced Stage Lymphoblastic Non-Hodgkin's Lymphoma: A Pediatric Oncology Group Phase III Study	NCT01230983	September 10, 2001	Asselin B, et al: Blood 118: 874-883, 2011
POG 9405	ALinC 16: Protocol for Patients with Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL)		December 26, 1995	

(continued on following page)

Table A1. Clinical Trials Included in Present Report (continued)

Trial No.	Trial Name	NCT ID	Accrual Closed	Reference
POG 9406	ALinC 16: Protocol for Patients With Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL)		November 15, 1999	
POG 9407	Induction Intensification and Allogeneic Bone Marrow Transplant In Infant ALL: A Children's Oncology Group Pilot Study	NCT00002756	October 29, 2006	Dreyer ZE et al[16]
POG 9605	ALinC 16: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL)		November 15, 1999	
POG 9904	ALinC #17 Treatment for Patients With Low Risk Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Phase III Study	NCT00005585	April 15, 2005	Martin PL, et al: Pediatr Blood Cancer 51:58, 2008
POG 9905	ALinC 17: Protocol for Patients With Newly Diagnosed Standard Risk Acute Lymphoblastic Leukemia (ALL): A Phase III Study	NCT00005596	April 15, 2005	Winick N et al[17]
POG 9906	ALinC 17: Protocol for Patients With Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL) - Evaluation of the Augmented BFM Regimen: A Phase III Study	NCT00005603	April 25, 2003	Bowman WP, et al: Pediatr Blood Cancer 57:569-577, 2011
COG-AALL00P2	The Use Of Modified BFM +/− Compound 506U78) (NSC# 686673) In an Intensive Chemotherapy Regimen For The Treatment Of T-Cell Leukemia	NCT00016302	October 4, 2005	Dunsmore KP, et al: J Clin Oncol 26:539s, 2008 (suppl; abstr 10002)
COG-AALL0232	High Risk B-Precursor Acute Lymphoblastic Leukemia	NCT00075725	January 21, 2011	Larsen EC, et al: J Clin Oncol 29:6s, 2011 (suppl; abstr 3)

Abbreviations: ALinC, acute leukemia in children; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; CCG, Children's Cancer Group; COG, Children's Oncology Group; FAB, French-American-British [leukemia classification system]; ID, identification; NCT, numbered clinical trial; NHL, non-Hodgkin's lymphoma; PEG, polyethylene glycol; POG, Pediatric Oncology Group.

Table A2. Number of Patients Who Died Within 0-4.99, 5-9.99, and ≥ 10 Years of Diagnosis for Patients Enrolled in 1990-1999

	Time to Death (years)						
	0-4.99		5-9.99		≥ 10		
Patient Group	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total No. of Deaths
All patients	2,041	83.85	367	15.08	26	1.07	2,434
Age group, years							
≤ 1	156	98.73	2	1.27	0	0	158
1-9.99	1,103	79.3	270	19.41	18	1.29	1,391
≥ 10	782	88.36	95	10.73	8	0.9	885
10-14.99	500	87.11	69	12.02	5	0.87	574
≥ 15	282	90.68	26	8.36	3	0.96	311
Sex							
Male	1,248	83.26	232	15.48	19	1.27	1,499
Female	793	84.81	135	14.44	7	0.75	935
Race							
White	1,257	82.48	244	16.01	23	1.51	1,524
Black	224	86.49	34	13.13	1	0.39	259
Other	560	86.02	89	13.67	2	0.31	651
Ethnicity							
Hispanic	184	84.79	32	14.75	1	0.46	217
Non-Hispanic	841	82.78	169	16.63	6	0.59	1,016
Unknown	1,016	84.6	166	13.82	19	1.58	1,201
Immunophenotype							
B cell	1,426	81.86	298	17.11	18	1.03	1,742
T cell	335	91.78	25	6.85	5	1.37	365
Risk group							
Standard	746	76.75	214	22.02	12	1.23	972
High	1,139	87.35	151	11.58	14	1.07	1,304

Table A3. Number of Patients Age ≤ 1 Year Who Died Within 0-4.99, 5-9.99, and ≥ 10 Years of Diagnosis for Patients Enrolled in 1990-1999

	Time to Death (years)						
	0-4.99		5-9.99		≥ 10		
Patient Group	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total No. of Deaths
Age, years							
≤ 1	156	98.73	2	1.27	0	0	158
Sex							
Male	78	97.5	2	2.5	0	0	80
Female	78	100	0	0	0	0	78
Race							
White	103	98.1	2	1.9	0	0	105
Black	9	100	0	0	0	0	9
Other	44	100	0	0	0	0	44
Ethnicity							
Hispanic	18	100	0	0	0	0	18
Non-Hispanic	73	100	0	0	0	0	73
Unknown	65	97.01	2	2.99	0	0	67
Immunophenotype							
B cell	123	98.4	2	1.6	0	0	125
T cell	2	100	0	0	0	0	2

Table A4. Number of Patients Older Than Age 1 Year Who Died Within 0-4.99, 5-9.99, or ≥ 10 Years of Diagnosis for Patients Enrolled in 1990-1999

	Time to Death (years)						
	0-4.99		5-9.99		≥ 10		
Patient Group	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total
All patients	1,885	82.82	365	16.04	26	1.14	2,276
Sex							
Male	1,170	82.45	230	16.21	19	1.34	1,419
Female	715	83.43	135	15.75	7	0.82	857
Race							
White	1,154	81.32	242	17.05	23	1.62	1,419
Black	215	86	34	13.6	1	0.4	250
Other	516	85.01	89	14.66	2	0.33	607
Ethnicity							
Hispanic	166	83.42	32	16.08	1	0.5	199
Non-Hispanic	768	81.44	169	17.92	6	0.64	943
Unknown	951	83.86	164	14.46	19	1.68	1,134
Immunophenotype							
B cell	1,303	80.58	296	18.31	18	1.11	1,617
T cell	333	91.74	25	6.89	5	1.38	363

Table A5. Number of Patients Who Died Within 0-4.99 or 5-9.99 Years of Diagnosis for Patients Enrolled In 2000-2005

	Time to Death (years)				
	0-4.99		5-9.99		
Patient Group	No. of Patients	%	No. of Patients	%	Total No. of Deaths
All patients	618	91.56	57	8.44	675
Age group, years					
≤ 1	73	100	0	0	73
1-9.99	285	88.79	36	11.21	321
≥ 10	260	92.53	21	7.47	281
10-14.99	140	93.33	10	6.67	150
≥ 15	120	91.6	11	8.4	131
Sex					
Male	363	90.75	37	9.25	400
Female	255	92.73	20	7.27	275
Race					
White	445	90.82	45	9.18	490
Black	48	92.31	4	7.69	52
Other	125	93.98	8	6.02	133
Ethnicity					
Hispanic	154	91.12	15	8.88	169
Non-Hispanic	425	91.4	40	8.6	465
Unknown	39	95.12	2	4.88	41
Immunophenotype					
B cell	482	90.6	50	9.4	532
T cell	81	97.59	2	2.41	83
Risk group					
Standard	203	88.65	26	11.35	229
High	341	91.67	31	8.33	372

Table A6. Number of Patients Who Died Within 0-4.99 or 5-9.99 Years of Diagnosis for Patients Older Than Age 1 Year Enrolled in 2000-2005*

	Time to Death (years)				
	0-4.99		5-9.99		
Patient Group	No. of Patients	%	No. of Patients	%	Total No. of Deaths
All patients	545	90.53	57	9.47	602
Sex					
Male	318	89.58	37	10.42	355
Female	227	91.9	20	8.1	247
Race					
White	390	89.66	45	10.34	435
Black	45	91.84	4	8.16	49
Other	110	93.22	8	6.78	118
Ethnicity					
Hispanic	142	90.45	15	9.55	157
Non-Hispanic	373	90.31	40	9.69	413
Unknown	30	93.75	2	6.25	32
Immunophenotype					
B cell	416	89.27	50	10.73	466
T cell	81	97.59	2	2.41	83

*All the deaths that occurred in infants age ≤ 1 year who were enrolled in 2000-2005 occurred within 5 years of initial diagnosis.

Table A7. Five-Year Overall Survival of Infants (age ≤ 1 year) by Era

Patient Group	No.	5-Year Survival ± SE (%) 1990-1994 %	1990-1994 No. of Patients	1995-1999 %	1995-1999 No. of Patients	2000-2005 %	2000-2005 No. of Patients	% Reduction 2000-2005 *v* 1990-1994	*P*
Age, years									
≤ 1	461	47.9 ± 4.1	154	48.1 ± 4.3	148	53.2 ± 5.4	159	10	.4520
Sex									
Male	233	46.2 ± 5.6	82	46.9 ± 6.5	65	45.8 ± 7.0	86	−1	.9299
Female	228	49.9 ± 6.1	72	49.0 ± 5.7	83	61.6 ± 8.0	73	23	.2754
Race									
White	322	46.4 ± 5.1	101	50.1 ± 5.3	99	54.3 ± 6.0	122	15	.5909
Black	25	—	12	—	6	—	7	—	—
Other	114	48.5 ± 8.2	41	45.7 ± 7.7	43	48.3 ± 12.3	30	0	.8509
Ethnicity									
Hispanic	63	64.3 ± 13.6	14	38.5 ± 10.7	22	54.0 ± 13.0	27	−29	.4606
Non-Hispanic	274	52.9 ± 5.5	83	54.8 ± 6.0	76	53.8 ± 6.5	115	2	.9982
Unknown	124	36.7 ± 6.7	57	52.0 ± 7.2	50	47.1 ± 14.0	17	16	.8070
Immunophenotype									
B cell	382	45.9 ± 4.8	115	48.7 ± 4.8	120	54.3 ± 5.6	147	16	.2434
T cell	6	—	2	—	2	—	2	—	—

Table A8. Five-Year Overall Survival of Non-Infants (older than age 1 year) by Era

Patient Group	Total No. of Patients	5-Year Survival ± SE (%) 1990-1994 %	1990-1994 No. of Patients	1995-1999 %	1995-1999 No. of Patients	2000-2005 %	2000-2005 No. of Patients	% Reduction 2000-2005 *v* 1990-1994	*P*
All patients	21,165	84.4 ± 0.4	7,150	88.5 ± 0.4	7,021	91.3 ± 0.4	6,994	44	< .001
Sex									
Male	11,922	83.4 ± 0.6	4,035	86.9 ± 0.6	3,992	90.9 ± 0.6	3,895	45	< .001
Female	9,243	85.8 ± 0.6	3,115	90.6 ± 0.6	3,029	91.8 ± 0.7	3,099	42	< .001
Race									
White	15,437	87.0 ± 0.5	5,196	89.7 ± 0.5	4,289	92.0 ± 0.5	5,412	38	< .001
Black	1,449	75.7 ± 2.0	509	81.3 ± 1.8	517	88.4 ± 2.1	423	52	< .001
Other	4,279	77.8 ± 1.2	1,445	87.3 ± 0.9	1,675	89.2 ± 1.2	1,159	51	< .001
Ethnicity									
Hispanic	2,526	82.5 ± 1.8	533	87.8 ± 1.4	653	88.3 ± 1.1	1,340	33	.0036
Non-Hispanic	12,254	87.9 ± 0.6	3,543	89.3 ± 0.6	3,301	92.3 ± 0.5	5,410	36	< .001
Unknown	6,385	80.8 ± 0.7	3,074	87.9 ± 0.6	3,067	86.3 ± 2.9	244	28	< .001
Immunophenotype									
B cell	16,518	85.8 ± 0.5	4,957	89.1 ± 0.4	5,716	92.0 ± 0.5	5,845	44	< .001
T cell	1,825	70.8 ± 1.7	746	80.8 ± 1.7	622	81.5 ± 2.2	457	37	< .001

Table A9. Cumulative Incidence of Death After Relapse/Disease Progression *v* Death As a First Event for Infants Age ≤ 1 Year by Cause in COG ALL Trials

Death As a First or Subsequent Event	Cumulative Incidence (%)				*P*
	1990-1994	1995-1999	2000-2005	Overall	
5-year					
Relapse/disease progression or secondary malignancies as first event	43.03	15.89	27.21	28.92	< .001
Treatment-related death prior to relapse/disease progression	3.90	27.17	13.87	14.79	< .001
Unknown or unrelated	5.21	8.88	5.72	6.56	.2774
Overall	52.14	51.94	46.80	50.27	.4503
10-year					
Relapse/disease progression or secondary malignancies as first event	43.73	15.89	—	29.20	< .001
Treatment-related death prior to relapse/disease progression	3.90	27.17	—	14.79	< .001
Unknown or unrelated	5.21	9.86	—	6.95	.1454
Overall	52.83	52.92		50.93	.6231

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group.

Table A10. Cumulative Incidence of Death After Relapse/Disease Progression *v* Death As a First Event for Patients Older Than Age 1 Year by Cause in COG ALL Trials

Death As a First or Subsequent Event	Cumulative Incidence (%)				*P*
	1990-1994	1995-1999	2000-2005	Overall	
5-year					
Relapse/disease progression or secondary malignancies as first event	12.18	8.89	6.74	9.40	< .001
Treatment-related death prior to relapse/disease progression	2.12	1.39	1.28	1.60	< .001
Unknown or unrelated	1.29	1.20	0.70	1.08	< .001
Overall	15.58	11.48	8.72	12.07	< .001
10-year					
Relapse/disease progression or secondary malignancies as first event	15.20	12.38	—	12.62	< .001
Treatment-related death prior to relapse/disease progression	2.13	1.42	—	1.62	.0012
Unknown or unrelated	1.82	1.50	—	1.49	.4130
Overall	19.15	15.31		15.74	< .001

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group.

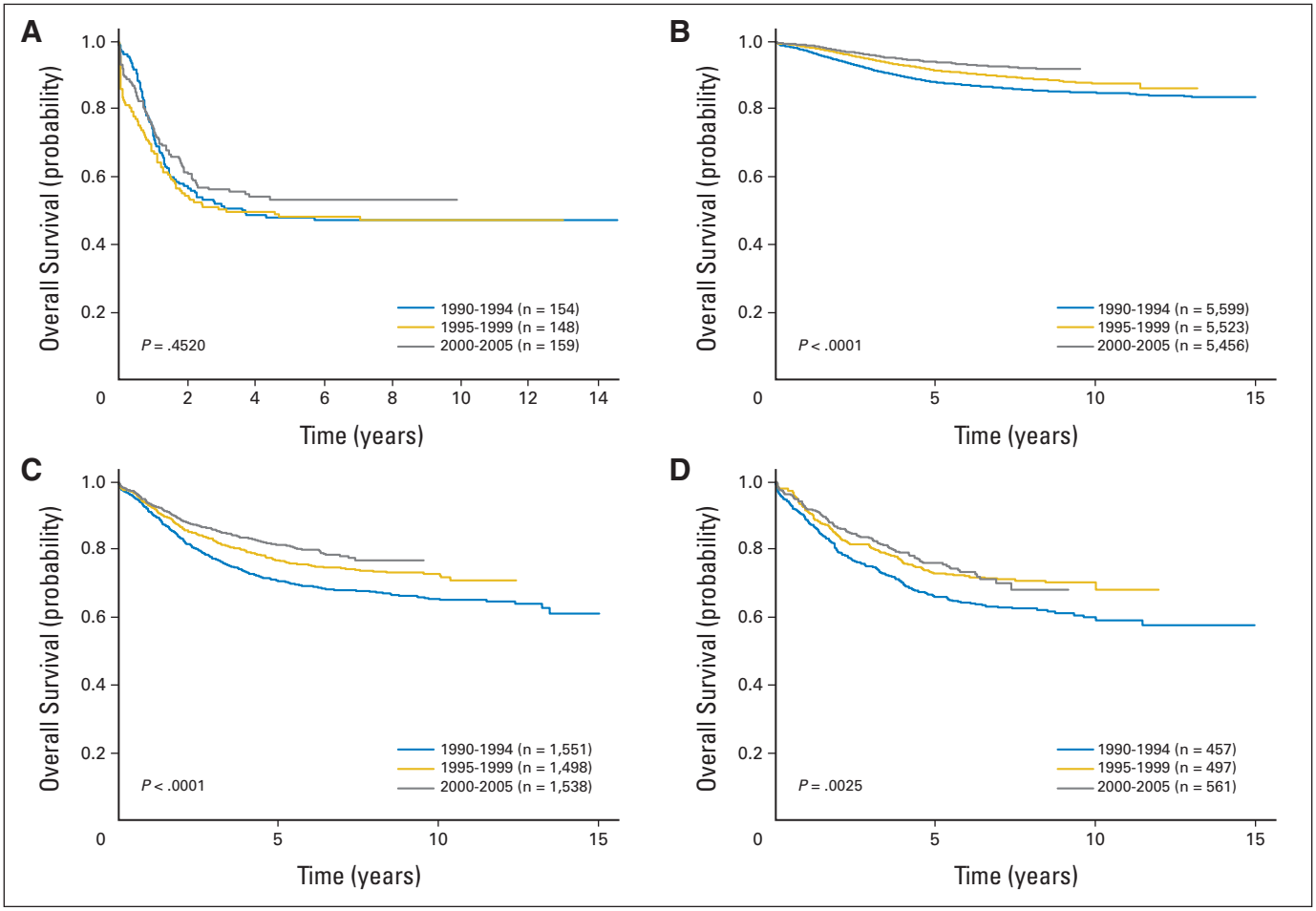

Fig A1. Overall survival probability for patients with acute lymphoblastic leukemia of different ages enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005; (A) infants age ≤ 1 year, and persons age (B) 1 to 9.99 years, (C) 10 years or older, and (D) 15 years or older.

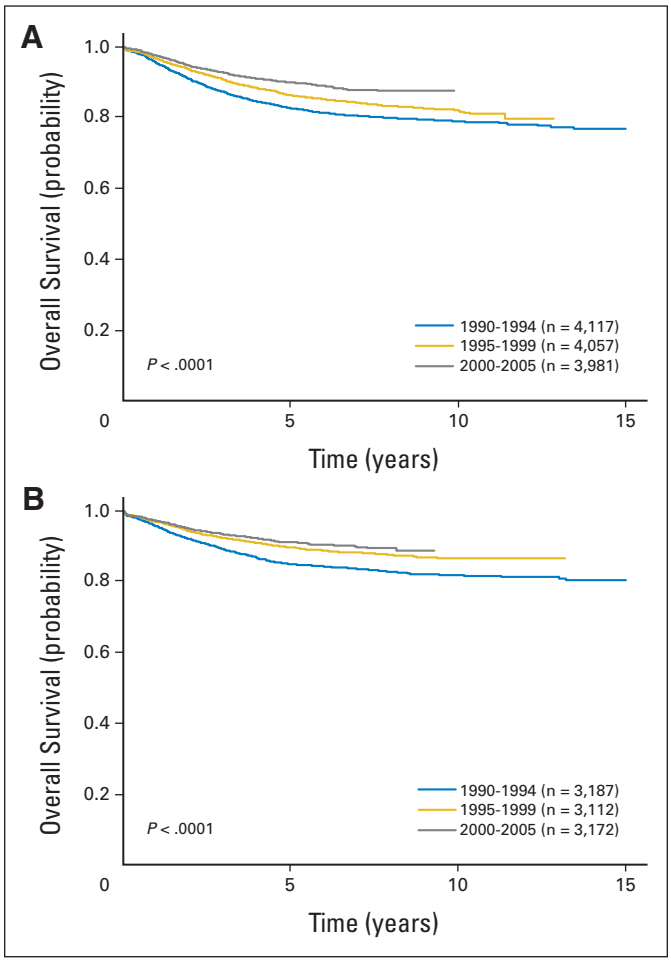

Fig A2. Overall survival probability for (A) males and (B) females enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

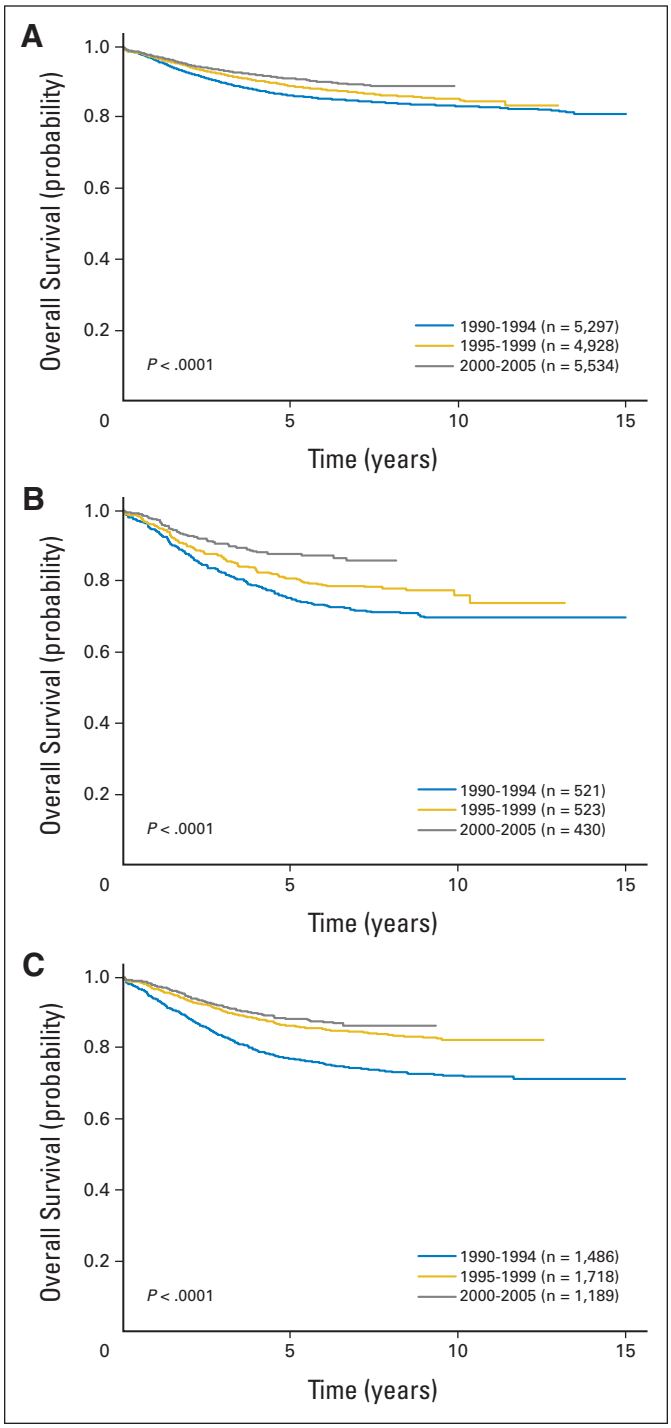

Fig A3. Overall survival probability for (A) whites, (B) blacks, and (C) persons of other ethnicities enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

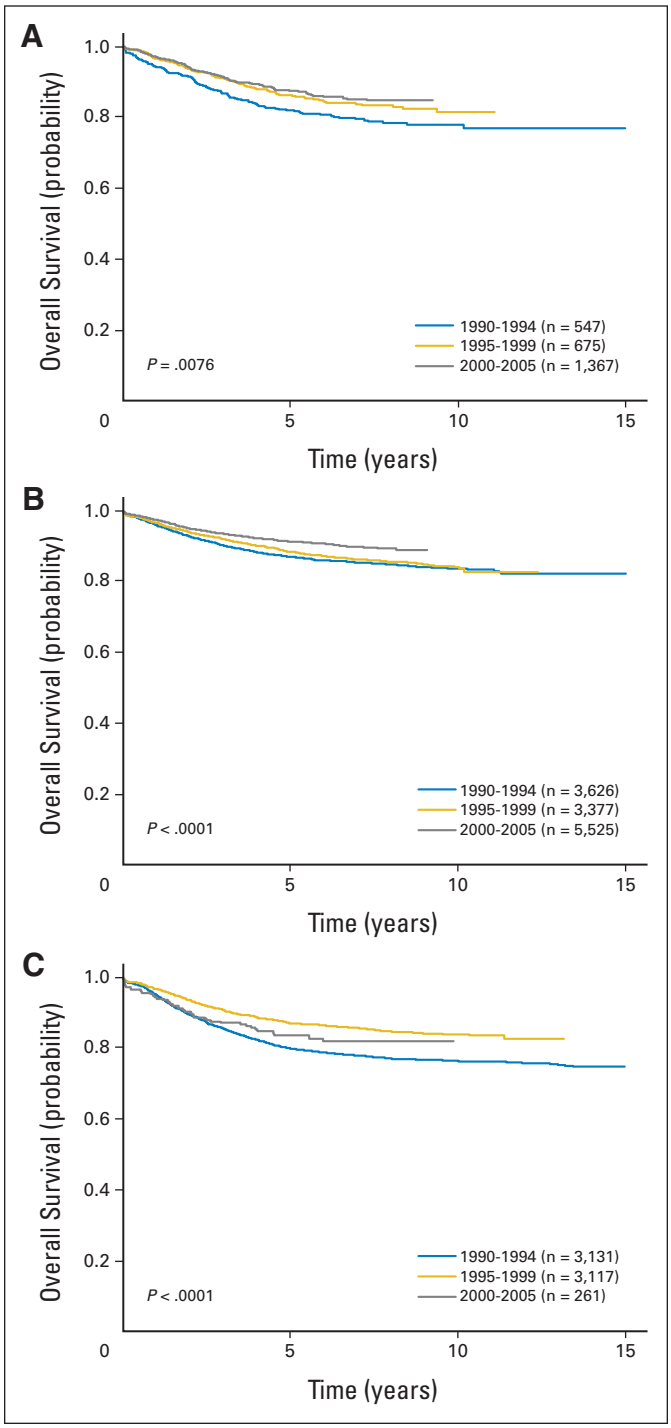

Fig A4. Overall survival probability for persons who reported themselves as (A) Hispanic, (B) non-Hispanic, or (C) unknown ethnicity enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

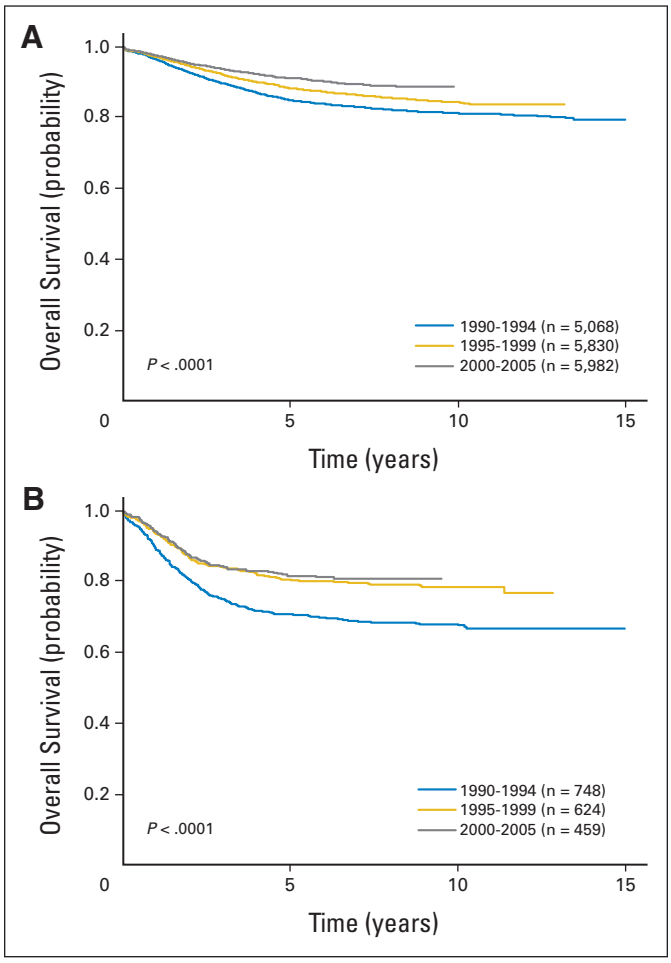

Fig A5. Overall survival probability by leukemia immunophenotype for patients with (A) B-cell and (B) T-cell acute lymphoblastic leukemia enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

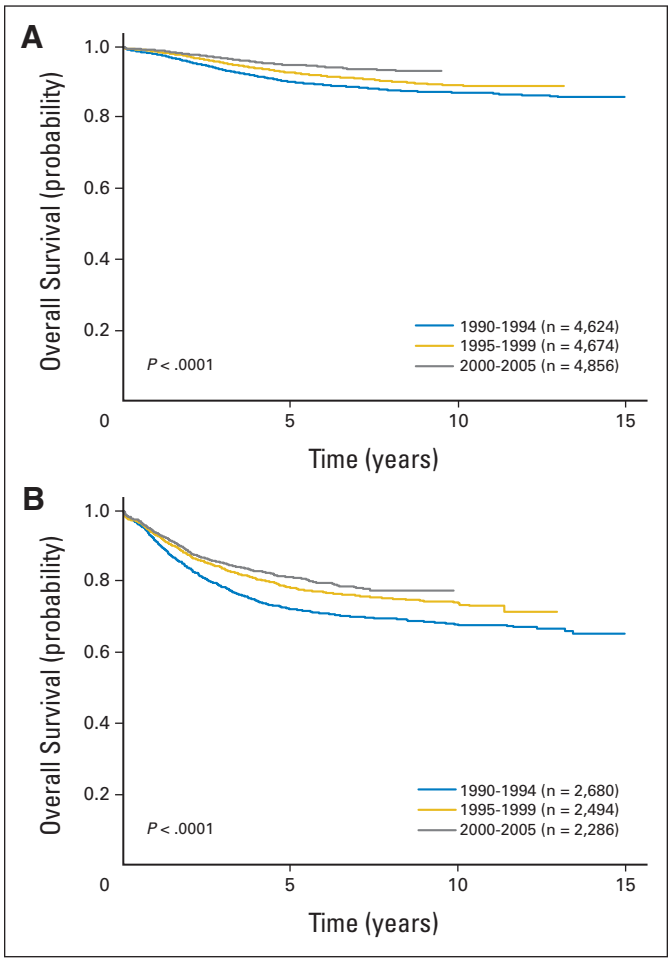

Fig A6. Overall survival probability by National Cancer Institute risk group for patients with (A) standard-risk (age 1-9.99 years and initial WBC count $< 50{,}000/\mu L$) and (B) high-risk (age 10 years or older and/or initial WBC count $> 50{,}000/\mu L$) acute lymphoblastic leukemia enrolled onto Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005.

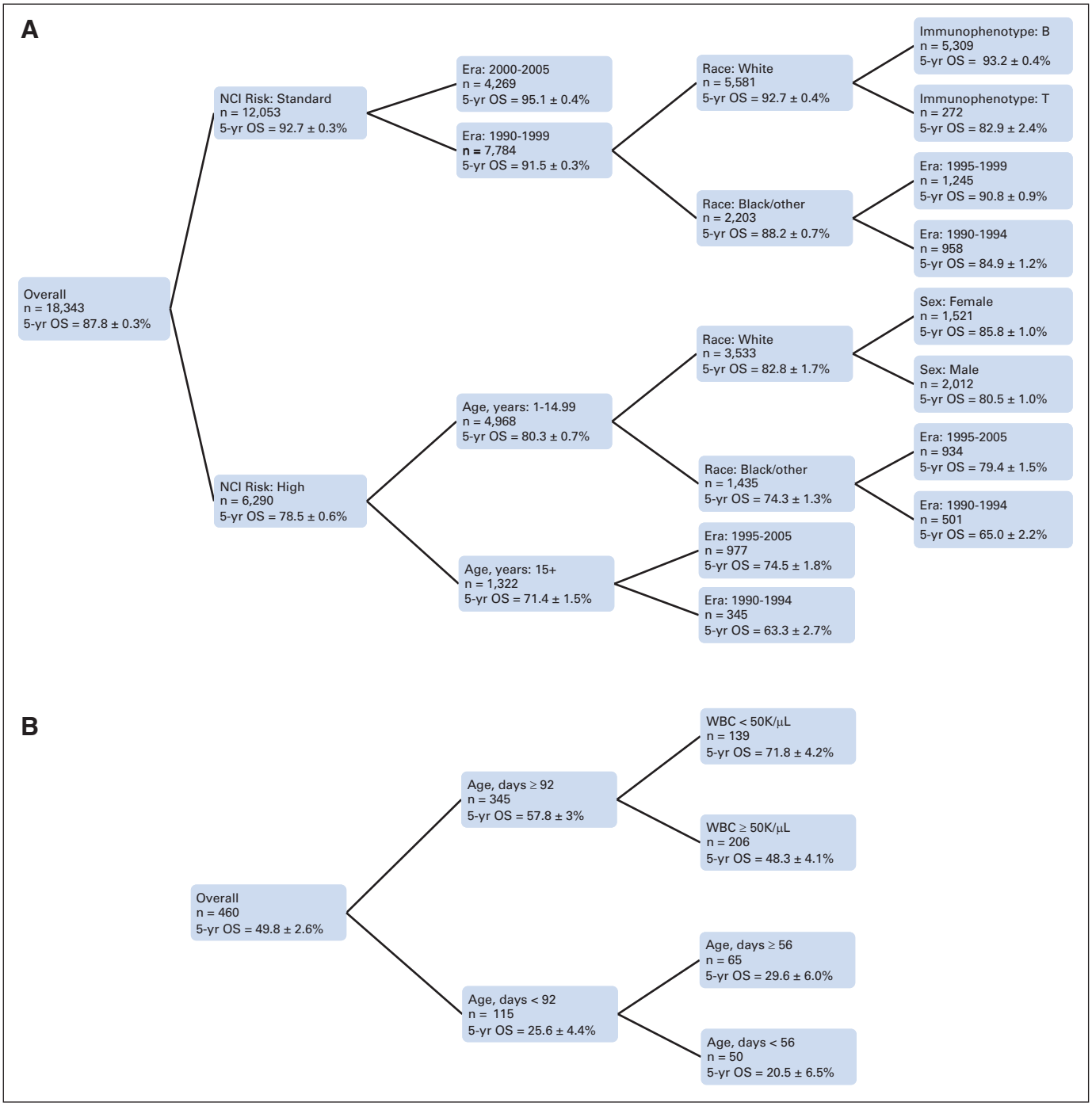

Fig A7. Survival tree regression analysis was performed by using complete data for (A) patients older than age 1 year (yr); and (B) infants age ≤ 1 year. NCI, National Cancer Institute; OS, overall survival.