Recent trends in survival of adult patients with acute leukemia: overall improvements, but persistent and partly increasing disparity in survival of patients from minority groups

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ABSTRACT

The survival of younger patients with acute leukemia has improved in the early 21st century, but it is unknown whether people of all ethnic and racial backgrounds have benefited equally. Using cancer registry data from the Surveillance, Epidemiology and End Results Program, we assessed trends in 5-year relative survival for patients aged 15 years or more with acute lymphoblastic leukemia and acute myeloblastic leukemia divided by racial and ethnic group, including non-Hispanic whites, African-Americans, Hispanics, and Asian-Pacific Islanders in the 1990s and the early 21st century. Modeled period analysis was used to obtain the most up-to-date estimates of survival. Overall, the 5-year survival increased from 31.6% in 1997-2002 to 39.0% in 2003-2008 for patients with acute lymphoblastic leukemia and from 15.5% in 1991-1996 to 22.5% in 2003-2008 for those with acute myeloblastic leukemia. Nevertheless, among patients with acute lymphoblastic leukemia, age-adjusted 5-year relative survival rates remained lower for African-Americans and Hispanics than for non-Hispanic whites. Among patients with acute myeloblastic leukemia, the increase in survival was greatest (from 32.6% in 1991-1996 to 47.1% in 2003-2008) for younger patients (15-54 years), and was more pronounced for non-Hispanic whites (+16.4% units) than for other patients (+10.8% units). Increases in survival are observed in all ethnic or racial groups. Nevertheless, among patients with acute leukemias, disparities in survival persist between non-Hispanic white people and people of other ethnic or racial groups. Disparities are increasing in younger patients with acute myeloblastic leukemia. Improvements in access to treatment, especially for minority patients, may improve outcomes.

Introduction

The acute leukemias are a heterogeneous group of diseases characterized by the rapid expansion of a malignant clone derived from a very early hematopoietic progenitor, either in the lymphoid lineage in the case of acute lymphoblastic leukemia (ALL) or the myeloid lineage in acute myeloblastic leukemia (AML). Both conditions are rapidly fatal if not treated but are usually initially highly responsive to chemotherapy.

Progress in the treatment of both AML and ALL has been great in children, especially for ALL.[1-3] Lesser, but significant, improvements in survival on a population level have been seen for adults with AML[4-5] and ALL.[6] However, there is currently little information on whether the increases in survival observed have been equal in people of all races, especially in the adult population. In past work, we found that overall survival rates were lower in African-American and Hispanic patients with acute leukemia and that the discrepancy was increasing over time.[7] One recent study demonstrated improvements in survival in non-Hispanic whites (nHw), African-Americans (AA), and Hispanic children and adolescents with ALL who were treated on Children's Oncology Group protocols,[8] with similar magnitudes of improvement in each racial and ethnic group. However, not all patients are treated on protocol and adults are generally more likely to be treated off protocol than children. These results cannot, therefore, be automatically extended to adult patients. Another study found a higher 5-year survival rate among non-Hispanic patients than among Hispanic patients with ALL, as well as a higher incidence of ALL in the Hispanic population in California, but did not examine survival in other parts of the USA.[9] There is, therefore, a lack of population survival data for patients of different races and ethnic groups with specific acute leukemias especially with respect to whether increased 5-year survival is seen equally in all ethnic groups.

Here, we examine detailed survival rates by specific leukemia type, age, and race.

Design and Methods

All data presented in this paper were derived from the 1973-2008 database of the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute issued in April 2011 and updated May 12, 2011.[10] For AML, we used data

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included in the 1973-2008 SEER9 database which are from population-based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland and together cover a population of about 30 million people. Because ALL is a very rare condition in adults, the SEER9 database was not adequate for evaluating changes in survival in patients with ALL. The SEER13 database was, therefore, used for this population. The SEER13 database contains the data in the SEER9 database as well as data from four further cancer registries, Los Angeles, San Jose-Monterey, Alaska Native Registry, and rural Georgia, starting from 1992.

Geographical areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high-quality population-based cancer reporting system and for their epidemiologically significant population subgroups. The SEER population is similar to that of the general USA population in terms of racial and ethnic make-up, although it may be more affluent than average,[11] and oversamples some racial and ethnic minorities including Hispanics and Asian/Pacific Islanders.[12]

Data on rates of hematopoietic stem cell transplantation (HSCT) and survival after the transplant were obtained from the USA Department of Health and Human Services' Bone Marrow and Cord Blood Donation and Transplantation web site.[13] This web site provides survival data for patients undergoing transplantation, with the data divided by disease type, type of transplant, stage of disease (i.e. first remission, second remission, not in remission), and demographics. Data for specific minority groups are not available but the number of transplants and survival for the categories "white" and "non-white" can be compared. Data are available for 2003-2008 only.

Patients aged 15 or older with a first diagnosis of ALL or AML and no prior cancers and followed for vital status through the year 2008 were included in the data set for analysis. Because patients with one subtype of AML, acute promyelocytic leukemia (APL), have a higher survival rate that that of patients with other subtypes, an analysis excluding APL was performed, as well as the overall analysis.

Throughout this paper, period estimates rather than traditional cohort-based estimates of survival are presented. Period analysis, first introduced in 1996,[14] described in detail elsewhere[15] and widely used in population-based survival analysis,[16] provides more up-to-date survival estimates than traditional cohort analysis by exclusively focusing on the survival experience of patients during some recent time period. Technically, this is achieved by left truncation of observations at the beginning of that period. It has been shown by extensive empirical evaluation that period analysis of 5-year relative survival for some recent period of time provides quite accurate predictions of the real 5-year relative survival later observed for cancer patients diagnosed in that period.[17]

According to standard practice in population-based cancer survival analysis, the relative survival was calculated. Relative survival reflects survival of cancer patients compared to survival of the general population. It is calculated as the ratio of absolute survival of cancer patients divided by the expected survival of a group of persons of the corresponding sex, age and race in the general population.[18,19] Because life tables are not available for people of Asian or Pacific Island descent, life tables for whites were used for this population as being the closest to the correct values. Life tables for people of Hispanic ethnicity are now available starting in 2006, but because older tables are not available, relative survival for people of Hispanic origin was calculated using life tables for the race listed for the individual without reference to their ethnicity (i.e. the life table for whites was used for a patient identified as ethnically Hispanic and racially white, whereas the table for AA was used for a patient identified as ethnically Hispanic and racially black). Estimates of expected survival were derived according to the Ederer II method,[20] using USA sex-, age- and race-specific life tables.[21]

In this study, we employed a model-based approach to estimate 5-year relative survival in 1991-1996, 1997-2002, and 2003-2008, the three most recent 6-year periods for which data were available for AML, and 1997-2002 and 2003-2008 for ALL and to test for trends in 5-year relative survival across those periods as described in detail elsewhere[22] and increasingly employed in recent years.[1,23] In model-based period analysis, numbers of patients at risk and of deaths by the year of follow-up were determined for each single period (i.e. 1991-1996, 1997-2002, and 2003-2008). A Poisson regression model for relative survival was fitted to the resulting data set, in which the logarithm of the excess number of deaths was modeled as a function of the year of follow-up (categorical variable) and calendar period (linear variable, coded 0 to 2), using the logarithm of the person-years at risk as the offset. Model-based estimates of 5-year relative survival for the first (1991-1996) and last (2003-2008) periods and a P value for the trend in relative survival between the three periods were derived. An α value of 0.05 was used as the level of significance for trend tests. Standard errors of the model-based 5-year relative survival estimates were calculated using the delta method.

Survival was examined based on age group for each type of leukemia, using the age groups 15-54, 55-74, and 75+ for AML and 15-44 *versus* 45+ for ALL. The cut-off of 55 years of age was used because few patients over the age of 55 are traditionally eligible for HSCT, one standard therapy in acute leukemia. However, within the last decade, transplantation of older individuals with less toxic conditioning regimens has become more accepted, so that patients in the intermediate age group, 55-74, may also be transplanted in some instances.[24] Transplant and even aggressive induction chemotherapy are still only rarely used in patients over the age of 75. For ALL, the cut-off of 45 years was used because after the age of 45, modified childhood regimens becomes less practical and patients are more likely to receive lower intensity treatment. An analysis with age adjustment according to the International Cancer Survival Standards using the age groups 15-44, 45-54, 55-64, 65-74 and over 75 was performed in order to evaluate the effects of variation in age on apparent overall changes in survival.[25]

Survival was calculated by racial or ethnic group as follows: patients identified racially as white and ethnically as not Hispanic were grouped as "non-Hispanic white". Patients who were categorized racially as black/African-American and ethnically as not Hispanic were categorized as "African-American". Patients identified ethnically as Hispanic were categorized as Hispanic, regardless of race. Patients identified in the SEER database as being of any east Asian, southeast Asian including Indian subcontinent, or Pacific Island racial group were categorized as Asian/Pacific Islander (API). Because each of the leukemias examined is rare and total case numbers for each minority group are small, a composite group of all non-white patients was examined as well as individual ethnic groups. This grouping of patients is of social, rather than biological significance: although the genetic and social backgrounds of various minority groups are highly diverse, they share the common experience of not being of the majority race and thus subject to socio-economic pressures and prejudice that the majority race is not subject to. Patients for whom ethnic or racial information was missing, patients identified as any other racial group, or for whom more than one race or ethnic group was listed were excluded from sub-group analysis but included in the overall analysis.

All calculations were carried out with SAS software (version 9.2), using macros developed for modeled period analysis.[22]

Results

As expected, the total number of adults diagnosed with ALL was small in both 1997-2002 and 2003-2008, with a total number of 1409 and 1739 cases, respectively. The median age at diagnosis was highest in API and nHw (46 and 45 years, respectively) in 2003-2008 and lowest in Hispanics (30 years) in 2003-2008. Interestingly, age at diagnosis increased for all ethnic groups except for nHw and Hispanics in 2003-2008, with the greatest increase in median age in AA patients, from 34 to 40 years of age (Table 1A).

The total number of AML cases was 3782 in 1991-1996 and 4366 in 2003-2008. Again, the majority of cases were nHw and the smallest number of cases occurred in Hispanics. Age at diagnosis was highest in nHw, being a median of 68 years in 1991-96, 70 in 1997-2002 and 69 years in 2003-2008 and lowest in Hispanics, being 50-51 years in each time period. Age at diagnosis was stable over the time period examined for this cancer (Table 1B). When APL was excluded from the analysis, the median age increased for all groups of patients, with the greatest increase among Hispanic patients (increasing by 2.5-5 years) and the smallest among nHw (0-1 years) (Table 1B).

Five-year relative survival increased substantially for patients with ALL, from 31.6% in 1997-2002 to 39% in 2003-2008 for all patients combined (Table 2). Statistically significant increases in survival were observed for all ethnic groups, although the statistical significance for Hispanics was marginal (P=0.05). The greatest increase was seen for API and AA, at +15.6 and +14.4 percentage units, respectively. The smallest increase was observed in the Hispanic population, at +6.1 percentage units. In 2003-2008, survival was still higher for nHw and API than for AA or Hispanics, although the disparity lessened for AA *versus* nHw.

Age-standardized analysis of survival for patients with ALL showed statistically significant improvement overall and for each ethnic group except for Hispanics (Table 2). Point estimates of the increase in survival for each ethnic group were less after adjustment for age, with the exception of API, for which the age-adjusted increase in survival was slightly higher (16.5 percent units after age adjustment *versus* 15.6 percent units before). As with the non-adjusted estimates, the greatest increase was observed for API, the smallest for Hispanics. Five-year relative survival after age adjustment was highest for API at 49.2% and lowest for AA and Hispanics (30.6% and 31.5%, respectively).

Because age is an important factor for survival in patients with ALL, survival by major age groups was evaluated. For patients aged 15-44, survival increased significantly for all patients, all non-white patients, AA, and Hispanics, but the increase for API or nHw did not reach statistical significance (Table 3). The greatest magnitude of increase was seen for AA at 19.3 percent units. The point estimate for increase in survival for API was large, but not statistically significant, possibly because of the small numbers. The point estimate for survival in 2003-2008 was highest for nHw (56.4%) and API (57.7%). Despite having the greatest increase in relative survival, younger AA patients still experienced the lowest survival in the more recent time period (43.4%).

For patients aged over 45 years old, the overall survival was markedly lower than for younger patients. There was a significant improvement in survival in the overall population and for nHw, all non-whites, and in particular API (+19.8 percent units), and also a strong but only marginally statistically significant improvement for AA (Table 3). Interestingly, in 2003-2008 survival was much higher for API than for other ethnic groups. In this age group, survival was lowest in Hispanics, for whom there was no hint of improvement between the earlier and later time periods.

Five-year relative survival likewise improved substantially overall for patients with AML and in nHw and API. Trends towards improvement were also observed for patients of other racial or ethnic backgrounds, but did not reach significance for AA or Hispanics (Table 4A). After adjustment for age, the highest survival in 2003-2008 was observed in nHw (18.4%) and API (19.1%). The change in survival was significant for nHw, all non-whites, AA, and API. Survival for patients diagnosed in the years 1998-2002 was intermediate between the first and final time

Table 1A. Numbers of patients and median age at diagnosis of ALL by ethnicity and calendar period.

Ethnicity	Number of cases		Median age	
	1997-2002	2003-2008	1997-2002	2003-2008
All patients	1409	1739	39	38
Non-Hispanic white	770	827	47.5	46
All non-white	241	317	38	40
African-American	89	120	34	40
Hispanic	398	593	31	30
Asian/Pacific Islander	134	163	41.5	45

Table 1B. Number of patients and median age at diagnosis of AML by ethnicity and calendar period, with and without inclusion of APL cases.

Ethnicity	AML						AML without APL					
	Number of patients			Median age			Number of patients			Median age		
	1991-1996	1997-2002	2003-2008	1991-1996	1997-2002	2003-2008	1991-1996	1997-2002	2003-2008	1991-96	1997-2002	2003-2008
All patients	3782	4450	4366	67	68	67	3591	4167	3977	68	69	69
nHw	3010	3474	3257	68	70	69	2882	3266	3001	69	70	70
All non-white	589	719	815	61	61	62	546	672	735	62	63	63
AA	275	331	350	60	61	60	258	309	311	61	63	63
Hispanic	174	283	283	51	50	50	154	222	232	53.5	55	54
API	296	350	418	62.5	62	63	273	327	383	63	63	65

nHw: non-Hispanic whites; AA: African-American; API: Asian/Pacific Islandor.

periods examined in all cases. When cases of APL were removed, survival decreased for all groups of patients. Additionally, the increase in survival was significant only for nHw and all non-whites in the unadjusted analysis, although a significant increase in survival was seen for nHw, AA, and API after age adjustment (Table 4B). The largest numerical difference in survival was observed for nHw and API at +4.8 and +5.4 percentage units, respectively, after age adjustment (Table 4B).

For patients aged 15-54, there was a large improvement for nHw (+18.2 percentage units) and a smaller, but marginally significant increase in survival for API (+11.9 percentage points) (Table 5A). Notably, the point estimates of survival for 2003-2008 were lower for each minority group examined than for nHw, in contrast to 1991-1996 in which period survival was actually lower for nHw than for Hispanics or API. For patients aged 55-74, a significant improvement was seen for all racial groups except for Hispanics. The magnitude of the improvement was greatest for API, at +13.1 percentage units and similar for AA and nHw at +7.7 and +8.4 percentage units, respectively. No significant improvement in survival was seen overall or for any ethnic group for patients over 75 years old and in this age cohort 5-year relative survival rates were less than 10% for all racial and ethnic groups (Table 5A). When patients with APL were removed from the analysis, all survival estimates were lower, smaller increases were seen, and survival increased significantly only for nHw patients aged 15-54 years (Table 5B).

Possible contributors to decreased survival in patients with AML from minority groups are lower rates of HSCT and worse outcomes after HSCT. Data for 2003-2008 showed no differences in 100-day, 1-year, or 3-year survival for non-white *versus* white patients undergoing autologous, related, or unrelated transplant in first remission, second remission, or relapse (*data not shown*). However, a smaller percentage of non-white patients underwent transplantation for each category of stem cell transplant. In 2003-2008, approximately 81% of cases of AML occurred in whites (Hispanics are included in this estimate since ethnic group is not given in the transplant database). Additionally, in patients aged 15-74, the percentage of cases occurring in whites was 79% and in patients <55 years old it was 76%. Thus, in the age range for which transplantation is widely accepted (15-54 years) and reasonable for selected patients (55-74 years), the percentage of patients who are classified racially as "white" is even lower than overall. In contrast, over 80% of HSCT were performed in whites in all categories except "other related" transplants in first remission. Rates of transplantation were particularly low for non-white patients in the non-related category, with rates of 10-12%, which are at least 10% less than might be expected assuming equality of all other variables (Table 6).

Discussion

Five-year relative survival of adult patients with ALL and AML in USA has improved substantially in the 1990s and first decade of the 21st century. However, the changes in survival are not evenly distributed between different

Table 2. Survival of patients with ALL by ethnicity and calendar period.

Ethnicity	Unadjusted				Age-adjusted			
	5-year relative survival (SE) [%]		Change [% units]	*P* value	5-year relative survival (SE) [%]		Change [% units]	*P* value
	1997-2002	2003-2008			1997-2002	2003-2008		
All patients	31.6 (1.3)	39.0 (1.2)	+7.4	0.00002	31.8 (1.1)	38.1 (1.1)	+6.3	<.0001
Non-Hispanic white	33.2 (1.7)	39.9 (1.8)	+6.7	0.005	37.0 (1.6)	42.3 (1.6)	+5.3	0.007
All non-white	26.6 (2.9)	37.5 (2.9)	+10.9	0.006	25.8 (2.6)	37.1 (2.7)	+11.3	0.001
African-American	18.1 (4.0)	32.5 (4.5)	+14.4	0.01	18.0 (3.4)	30.6 (4.0)	+12.6	0.008
Hispanic	31.2 (2.4)	37.3 (2.2)	+6.1	0.05	26.9 (2.0)	31.5 (1.8)	+4.6	0.07
Asian/Pacific Islander	32.7 (4.1)	48.3 (4.2)	+15.6	0.007	32.7 (3.8)	49.2 (3.9)	+16.5	0.001

SE:standard error; change: change from 1997-2002 to 2003-2008.

Table 3. Survival of patients with ALL by age.

Ethnicity	15-44				45+			
	5-year relative survival rates (SE) [%]		Change [%] [units]	*P* value	5-year relative survival rates (SE) [%]		Change [%] [units]	*P* value
	1997-2002	2003-2008			1997-2002	2003-2008		
All patients	43.7 (1.8)	50.8 (1.7)	+7.1	0.003	15.8 (1.5)	22.7 (1.7)	+6.9	0.0007
Non-Hispanic white	51.6 (2.6)	56.4 (2.6)	+4.8	0.2	16.4 (1.9)	23.6 (2.2)	+7.2	0.006
All non-white	34.6 (4.1)	45.7 (4.0)	+11.1	0.05	15.2 (3.5)	28.3 (4.1)	+13.1	0.009
African-American	24.1 (5.7)	43.4 (6.2)	+19.3	0.02	5.8 (3.4)	17.1 (6.1)	+11.3	0.05
Hispanic	36.6 (3)	46.3 (2.6)	+9.7	0.01	13.8 (3.3)	13.9 (3.0)	+0.1	0.98
Asian-Pacific Islander	44.6 (6)	57.7 (5.8)	+13.1	0.1	19.5 (5.1)	39.3 (6.0)	+19.8	0.01

SE: standard error; change: change from 1997-2002 to 2003-2008.

Table 4A. Survival of patients of all ages with AML, divided by ethnicity and calendar period.

Ethnicity	Unadjusted 5-year relative survival rates (SE) [%]			Change [% units]	*P* value	Age-adjusted 5-year relative survival rates (SE) [%]			Change [% units]	*P* value
	1991-1996	1997-2002	2003-2008			1991-1996	1997-2002	2003-2008		
All patients	15.5 (0.5)	18.8 (0.4)	22.5 (0.6)	7.0	<0.0001	12.4 (0.4)	15.1 (0.4)	18.1 (0.5)	+5.7	<0.0001
NHw	14.5 (0.6)	17.8 (0.4)	21.3 (0.7)	6.8	<0.0001	12.6 (0.5)	15.3 (0.4)	18.4 (0.6)	+5.8	<0.0001
All non-white	17.7 (1.4)	20.8 (1)	24 (1.4)	6.3	0.003	10.9 (1)	13.6 (0.8)	16.8 (1.2)	+5.9	<0.0001
AA	15.5 (2)	18.1 (1.4)	20.8 (2)	5.3	0.06	9.3 (1.4)	11.6 (1.1)	14.2 (1.6)	+4.9	0.02
Hispanic	25.6 (3)	28.8 (1.9)	32 (2.7)	6.4	0.13	14 (2.1)	15.7 (1.6)	17.4 (2.2)	+3.4	0.23
API	19 (2.1)	22.5 (1.4)	26.2 (2.1)	7.2	0.02	12 (1.6)	15.3 (1.3)	19.1 (1.8)	+7.1	0.001

SE and change should be defined as in Table 4b. nHw: non-Hispanic whites; AA: African-American; API: Asian/Pacific Islander.

Table 4B. Survival of patients of all ages with AML, excluding APL, divided by ethnicity and calendar period.

Ethnicity	Unadjusted 5-year relative survival rates (SE) [%]			Change [% units]	*P* value	Age-adjusted 5-year relative survival rates (SE) [%]			Change [% units]	*P* value
	1991-1996	1997-2002	2003-2008			1991-1996	1997-2002	2003-2008		
All patients	13.9 (0.5)	16.3 (0.4)	18.8 (0.6)	+4.9	<0.0001	11.3 (0.4)	13.5 (0.4)	15.9 (0.5)	+4.6	<0.0001
nHw	13.2 (0.6)	15.5 (0.4)	18.0 (0.6)	+4.8	<0.0001	11.6 (0.5)	13.8 (0.4)	16.4 (0.6)	+4.8	<0.0001
All non-white	15.9 (1.4)	17.9 (1)	20.1 (1.4)	+4.2	0.04	9.9 (1.0)	12.1 (0.8)	14.6 (1.1)	+4.7	0.001
AA	13.0 (1.9)	14.7 (1.3)	16.5 (1.9)	+3.5	0.20	8.0 (1.3)	9.9 (1.1)	12.1 (1.5)	+4.1	0.03
Hispanic	21.9 (3.0)	23.1 (1.9)	24.4 (2.7)	+2.5	0.56	12.5 (2.1)	13.1 (1.6)	13.8 (2.0)	+1.3	0.64
API	17.8 (2.1)	20.1 (1.4)	22.6 (2.0)	+4.8	0.11	11.3 (1.6)	13.8 (1.2)	16.7 (1.7)	+5.4	0.01

SE: standard error; change: change from 1991-96 to 2003-08. nHw: non-Hispanic whites; AA: African-American; API: Asian/Pacific Islander.

ethnic and racial groups. In the case of ALL, survival has improved more for people of minority races or ethnic groups than for nHw, such that non-adjusted survival is nearly equal between different racial and ethnic groups in 2003-2008. However, after age standardization, a large gap in survival is still present and little decrease in the discrepancies could be seen between patients with ALL.

Although improvement in survival was observed for nHw aged 15-54 with AML, the survival improvement for minority patients in the same age group was much smaller and not statistically significant after cases with APL were removed. The pattern was slightly more equitable for patients aged 55-74 years among whom small but significant increases in survival were observed for nHw, API, and AA, but still not for Hispanics.

The finding that patients of minority racial or ethnic backgrounds present at an earlier age was unexpected. Several previous publications have noted a younger age at onset in AA,[26,27] but little information was found for Hispanic patients. The reasons for this age difference are not clear from the available data, but given that younger age is generally a good prognostic indicator in AML, the finding makes the lack of improvement for patients of minority racial and ethnic background especially troubling. Additionally, the lack of major change in median age at presentation between the earlier and later time periods rules out differences in change of median age at presentation as an explanation for the differences observed.

Therapy for both AML and ALL relies on intensive chemotherapeutic regimens that require multiple agents and several courses of therapy to achieve a lasting remission.[28,29] Allogeneic HSCT is often used for poor prognosis disease or relapse for both AML and ALL.[28,29]

Recently, more intensive regimens based on pediatric protocols have come into favor for treating adult ALL,[30] with preliminary data suggesting that these regimens can be used in patients up to at least 40 to 45 years old.[31,32] However, the use of pediatric protocols in adult ALL is a new phenomenon and relatively few patients over 25 years old would have been likely to have been treated on pediatric protocols during the periods examined. Thus, the effects of the introduction of pediatric protocols would be much stronger in populations with a younger median age at diagnosis. Furthermore, the addition of tyrosine kinase inhibitors to chemotherapeutic regimens has improved survival in patients with Philadelphia chromosome-positive ALL, a group of patients with a previously very poor prognosis.[33] However, the optimal use of these medications in ALL has not yet been established and, as with the use of more intensive chemotherapy, the full effects of the use of tyrosine kinase inhibitors in ALL have yet to be seen.

The larger increase in survival in ALL initially observed in patients from minority groups was unexpected given the relative lack of increase in survival for minority patients with acute leukemia overall.[7] Additionally, several recent publications described poorer survival among AA and Hispanic children with ALL as compared to white or API children.[34,35] As the age-standardized results demonstrate, much of the apparent relative increase in survival for non-API minorities compared to nHw could be attributed to lower age at diagnosis. A decrease in the survival disparity between nHw and other races was observed for younger patients, but was less for older patients; the disparity worsened for older Hispanics, in whom, in contrast to all other racial and ethnic groups, no increase in survival was observed.

In contrast to ALL, few changes have been made in the

Table 5A. Survival of patients with AML by ethnicity, calendar period and age.

Ethnicity	15-54					55-74					75+				
	5-year relative survival rates (SE) [%]			Change [% units]	*P* value	5-year relative survival rates (SE) [%]			Change [% units]	*P* value	5-year relative survival rates (SE) [%]			Change [% units]	*P* value
	1991-96	1997-2002	2003-08			1991-96	1997-2002	2003-08			1991-96	1997-2002	2003-08		
All patients	32.6 (1.3)	39.9 (0.8)	47.1 (1.3)	+14.5	<0.0001	8.9 (0.6)	12.8 (0.6)	17.4 (0.9)	+8.5	<0.0001	3.2 (0.5)	3.6 (0.5)	3.9 (0.6)	+0.7	0.15
nHw	32.9 (1.5)	41.2 (1.0)	49.3 (1.6)	+16.4	<0.0001	9.0 (0.7)	12.8 (0.6)	17.4 (1.0)	+8.4	<0.0001	2.6 (0.5)	3.0 (0.5)	3.4 (0.6)	+0.8	0.12
All non-white	30.4 (2.7)	35.8 (1.8)	41.2 (2.6)	+10.8	0.008	7.4 (1.6)	11.7 (1.4)	17.1 (2.1)	+9.7	<0.0001	6.6 (2.1)	6.7 (1.7)	6.9 (1.9)	+0.3	0.90
AA	26.8 (3.8)	30.7 (2.4)	34.7 (3.7)	+7.9	0.17	5.9 (2.0)	9.3 (1.9)	13.6 (2.9)	+7.7	0.01	4.7 (2.8)	4.9 (2.3)	5.1 (2.6)	+0.4	0.90
Hispanic	37.1 (4.6)	41.9 (2.8)	46.5 (3.8)	+9.4	0.14	13.0 (4.0)	14.9 (3.0)	16.9 (4.1)	+3.9	0.49	5.4 (4.1)	4.4 (2.7)	3.5 (2.7)	-1.9	0.61
API	33.3 (4.0)	39.3 (2.6)	45.2 (3.8)	+11.9	0.05	8.4 (2.4)	14.2 (2.2)	21.5 (3.3)	+13.1	0.001	8.0 (3.1)	8.2 (2.4)	8.5 (2.8)	+0.5	0.89

SE: standard error; change: change from 1991-96 to 2003-08.

Table 5B. Survival of patients with AML by ethnicity, calendar period and age, excluding patients with APL.

Ethnicity	15-54					55-74					75+				
	5-year relative survival rates (SE) [%]			Change [% units]	*P* value	5-year relative survival rates (SE) [%]			Change [% units]	*P* value	5-year relative survival rates (SE) [%]			Change [% units]	*P* value
	1991-96	1997-2002	2003-2008			1991-96	1997-2002	2003-2008			1991-96	1997-2002	2003-2008		
All patients	30.8 (1.3)	36.1 (0.9)	41.3 (1.4)	+10.5	<0.0001	8.2 (0.6)	11.4 (0.5)	15.1 (0.8)	+6.9	<0.0001	2.7 (0.5)	3.0 (0.5)	3.4 (0.5)	+0.7	0.10
nHw	31.1 (1.6)	37.5 (1.1)	43.9 (1.7)	+12.8	<0.0001	8.4 (0.7)	11.5 (0.6)	15.2 (0.9)	+6.8	<0.0001	2.2 (0.5)	2.6 (0.5)	3.0 (0.6)	+0.8	0.08
All non-white	29.1 (2.8)	32.5 (1.8)	35.9 (2.8)	+6.8	0.11	6.1 (1.4)	9.8 (1.4)	14.6 (2.1)	+8.5	0.0002	6 (2.0)	6.2 (1.6)	6.4 (1.9)	+0.4	0.86
AA	24.2 (3.9)	26.3 (2.5)	28.5 (3.9)	+4.3	0.47	4.7 (1.8)	7.5 (1.8)	11.3 (2.8)	+6.6	0.02	3.3 (2.3)	3.9 (2.1)	4.5 (2.6)	+1.2	0.63
Hispanic	33.4 (4.9)	35.6 (3.0)	37.7 (4.2)	+4.3	0.54	11.8 (3.8)	13.1 (2.9)	14.5 (4.0)	+2.7	0.61	*	*	*	*	*
API	33.0 (4.3)	36.6 (2.7)	40.1 (4.0)	+7.1	0.26	7.3 (2.2)	12.2 (2.1)	18.4 (3.3)	+11.1	0.003	8.0 (3.1)	7.8 (2.4)	7.6 (2.7)	-0.4	0.90

SE: standard error; change: difference between 1991-96 and 2003-08.

treatment of AML, for which the use of cytarabine and an anthracycline has been the standard of care for induction treatment since the mid-20th century, when AML became one of the first diseases for which there was effective chemotherapy.[36] However, improvements in supportive care, more intensive chemotherapeutic regimens, and HSCT have led to improved survival in AML, also at a population level.[26] One subtype of AML, APL, can be treated with several specific agents including all trans retinoic acid[37] and arsenic trioxide,[38] treatments introduced in the late 1990s and early 21st century. APL has a much better prognosis than other forms of AML. However, it is a rare malignancy and thus has only a minor effect on overall survival in patients with AML. However, even when cases of APL were excluded from the analysis, no qualitative difference in the previously described pattern was observed, although survival was lower within each subgroup (Tables 4B and 5B).

As for multiple myeloma, in cases of AML survival was better for most patients of minority ethnic or racial background in the 1990s but worse in the 2000s. This suggests that biology is not a major factor, i.e. that the differences are not simply due to a more resistant disease state in people of minority ethnic groups. A relative lack of matched donors and, therefore, fewer opportunities for allogeneic HSCT may account for some of the differences observed. However, HSCT has been used for the treatment of AML since the 1980s and the first effects of this difference should, therefore, be observable in the earlier time period.

Outcomes of patients with leukemia may vary depending on the volume of care at the center at which the patient is treated.[39] Recent work has suggested that people of lower socio-economic status, who include a larger than average number of minorities, may be seen more often at low volume and non-teaching centers, possibly compromising their care.[40] Additionally, lack of insurance and other socio-economic factors may increase the risk of treatment delays or lead to sub-optimal treatment,[41] especially in the consolidation phase of treatment. Our results show that the majority of the worsening disparity for AML can be attributed to lack of progress or even worsening in survival of younger patients (15-54 years old) with AML. This is also the group of patients most likely to be uninsured, especially patients in early adulthood.[42] Previous work has demonstrated relatively low survival for patients aged 15-24 with AML.[43] This supports the hypothesis that lack of health insurance and thus access to timely and expert care may be a major contributor to the disparity observed. Notably, people of minority ethnic or racial background, especially AA and Hispanics, are less likely to have private insurance and more likely to be completely uninsured compared to nHw.[44] Additionally, rates of insurance of non-US born people who are not US citizens have dropped significantly since 1999.[45] This difference may partially explain why survival has not improved in patients of AA or Hispanic ethnic background, especial-

ly among the Hispanic population.

It is notable that survival did not improve for patients of Hispanic ethnicity in any age category. This finding is particularly notable for patients in the 55-74 age group with AML and in those over 45 years old with ALL, since the survival of such patients improved in every other racial and ethnic group. Several factors may account for this finding. Reporting of race and ethnicity in SEER has been verified as highly reliable with respect to race and moderately to highly reliable with respect to ethnicity.[46] Hispanic patients are more likely to be misclassified as non-Hispanic than *vice versa* so that the total number of patients classified as Hispanic may be lower than the true value, resulting in larger standard errors for this group of patients. Additionally, people of Hispanic origin are relatively likely to be immigrants to the United States compared to people of other ethnic backgrounds.[47] Recent changes in immigration law have increased the barriers for immigrants needing health care for acute illness[48] and the increase in barriers may have negated improvement in standards of care, resulting in no net change in survival for this group.

When considering our results, some limitations must be kept in mind. First, life tables were not available for Hispanic ethnicity or API race (or any subpopulation within the general category of API). Thus, relative survival could be slightly biased. In particular, API, especially API women, may have a slightly longer life expectancy than whites, leading to a slight overestimate of relative survival in this population. Because the SEER database does not contain information on chemotherapy or HSCT, we cannot directly assess the effects of differences in treatment on survival in the various ethnic groups. Furthermore, because the bone marrow registry does not have data prior to 2003,we cannot be certain that the rate of transplantation among minorities relative to that of whites has changed between the earlier and later time periods. Similarly, there are relatively few data available concerning socio-economic status in the SEER database, so that it is not possible to make definitive statements with respect to the influence of lower socio-economic status on outcome. Finally, the data from the bone marrow registry do not perfectly match those in the SEER database, i.e. the data are collected from the general US population rather than only the SEER population, and data for specific minority groups are not available.

Table 6. Percentage of patients undergoing HSCT for AML.

	Autologous	HLA matched sibling	Other related	Non-related
White-1st remission	87%	86%	78%	88%
Non-white-1st remission	13%	14%	22%	12%
White-2nd remission	80%	87.5%	82.5%	88.5%
Non-white-2nd remission	20%	12.5%	17.5%	11.5%
White-not in remission	*	88%	83%	90%
Non-white-not in remission	*	12%	17%	10%

*Too few patients to calculate reliably.

In summary, our results demonstrate a decrease in the discrepancy in survival of patients with ALL between nHw and other racial or ethnic groups due to greater improvements in the latter groups. Nevertheless, substantial disparity persists in age-adjusted 5-year relative survival. Survival has substantially increased for younger patients with AML, but the increase was much less pronounced for patients in minority groups. These results demonstrate an urgent need to improve access to treatment and improve care for patients of minority ethnic and racial background in order to avoid unnecessary loss of life due to potentially curable leukemias.

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References

1. Pulte D, Gondos A, Brenner H. Trends in 5- and 10-year survival after diagnosis with childhood hematologic malignancies in the United States 1990-2004. J Natl Cancer Inst. 2008;100(18):1301-9.
2. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008; 371 (9617):1030-43.
3. Rubnitz JE, Gibson B, Smith FO. Acute myeloid leukemia. Hematol. Oncol Clin North Am. 2010;24(1):35-63.
4. Pulte D, Gondos A, Brenner H. Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century. Haematologica. 2008;93(4):594-600.
5. Pulte D, Gondos A, Brenner H. Expected long-term survival of patients diagnosed with acute myeloblastic leukemia during 2006-2010. Ann Oncol. 2010;21(2):335-41.
6. Pulte D, Gondos A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. Blood. 2009;113(7):1408-11
7. Pulte D, Redaniel MT, Brenner H, Jeffreys M. Changes in survival by ethnicity of patients with cancer between 1992-96 and 2002-06: is the discrepancy decreasing? Ann Oncol. 2012;23(9):2428-34.
8. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. J Clin Oncol. 2012;30 (14):1663-9.
9. Pullarkat ST, Danley K, Bernstein L, Bryans RK, Cozen W. High lifetime incidence of adult acute lymphoblastic leukemia among Hispanics in California. Cancer Epidemiology Biomarkers Prev. 2009;18(2): 611-5.
10. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2008), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010 submission.
11. Mariotto A, Capocaccia R, Verdecchia A, Micheli A, Feuer EJ, Pickle L, Clegg LX. Projecting SEER cancer survival rates to the US: an ecological regression approach. Cancer Causes Control. 2002;13(2):101-11.
12. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.gov), National Cancer Institute.
13. Bone Marrow and Cord Blood Donation and Transplantation. http://bloodcell.transplant.hrsa.gov/index.htm. Last Updated: May 18, 2011.
14. .Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer. 1996;78(9):2004-10.
15. Brenner H, Gefeller O, Hakulinen T. Period

analysis for 'up-to-date' cancer survival data: empirical evaluation, computational realisation and applications. Eur J Cancer. 2004;40(3):326-35.
16. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet. 2011;377(9760):127-38.
17. Brenner H, Hakulinen T. Up-to-date long-term survival curves of patients with cancer by period analysis. J Clin Oncol. 2002;20 (3):826-32.
18. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr. 1961;6:101-21.
19. Henson DE, Ries LA. The relative survival rate. Cancer. 1995;76(10):1687-8.
20. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note No. 10. Bethesda, MD.: National Cancer Institute; 1959.
21. Arias E. United States life tables, 2000. Vol. 51: Natl Vit Stat Rep. 2002:1-39
22. Brenner H, Hakulinen T. Up-to-date and precise estimates of cancer patient survival: model-based period analysis. Am J Epidemiol. 2006;164(7):689-96.
23. van de Schans SA, Gondos A, van Spronsen DJ, Rachtan J, Holleczek B, Zanetti R, et al. Improving relative survival, but remaining differences in survival for non-Hodgkin's lymphoma across Europe and the United States from 1990 to 2004. J Clin Oncol. 2011;29(2):192-9.
24. Malladi RK, Peniket AJ, Norton AE, Campbell AJ, Collins GP, Samol J, et al. Favourable outcome for patients with myeloid disorders treated with fludarabine-melphalan reduced-intensity conditioning and allogeneic bone marrow stem cell transplantation without the use of T-lymphocyte-depleting antibodies Eur J Haem. 2004;73(2):85-92.
25. Corazziari I, Quinn M, Capocacci R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer. 2004;40(15):2307-16.
26. Bierenbaum J, Davidoff AJ, Ning Y, Tidwell ML, Gojo I, Baer MR. Racial differences in presentation, referral and treatment patterns and survival in adult patients with acute myeloid leukemia: a single-institution experience. Leuk Res. 2012;36(2):140-5.
27. Sekeres MA, Peterson B, Dodge RK, Mayer RJ, Moore JO, Lee EJ, et al. Differences in prognostic factors and outcomes in African Americans an whites with acute myeloid leukemia. Blood. 2004;103(11):4036-42.
28. Cortes JE, Kantarjian HM. Acute lymphoblastic leukemia. A comprehensive review with emphasis on biology and therapy. Cancer. 1995 76(12):2393-417.
29. Stone RM, O'Donnell MR, Sekeres MA. Acute myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2004:98-117.
30. Stock W. Adolescents and young adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2010:21-9.
31. Haïat S, Marjanovic Z, Lapusan S, Vekhoff A, Rio B, Corre E, et al. Outcome of 40 adults aged from 18 to 55 years with acute lymphoblastic leukemia treated with double-delayed intensification pediatric protocol. Leuk Res. 2011;35(1):66-72.
32. Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAAL-2003 study. J Clin Oncol. 2009;27(6):911-8.
33. Yanada M, Takeuchi J, Sugiura I, Akiyama H, Usui N, Yagasaki F, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Group. J Clin Oncol. 2006;24(3):460-6.
34. Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JC. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA. 2003;290(15):2008-14.
35. Yang JJ, Cheng C, Devidas M, Cao X, Fan Y, Campana D, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. Nat Genetics. 2011;43(3):237-41.
36. Atkinson K, Wells DG, Clink HM, Kay HE, Powles R, McElwain TJ. Adult acute leukaemia. Br J Cancer. 1974;30(3):272-8.
37. Sanz MA, Martín G, Rayón C, Esteve J, González M, Díaz-Mediavilla J, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly developed PML/RAR-positive acute promyelocytic leukemia. Blood. 1999;94(9):3015-21.
38. Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol. 2001;19(18):3852-60.
39. Horowitz MM, Przepiorka D, Champlin RE, Gale RP, Gratwohl A, Herzig RH, et al. Should HLA-identical sibling bone marrow transplant for leukemia be restricted to large centers? Blood. 1992;79(10):2771-4.
40. Wong SL, Gu N, Banerjee M, Birkmeyer JD, Berkmeyer NJ. The impact of socioeconomic status on cancer care and survival. J Clin Oncol. 2011; 29 (suppl; abstr 6004)
41. Hadley J. Sicker and poorer-the consequences of being uninsured: a review of research on the relationship between health insurance, medical care use, health, work, and income. Med Care Res Rev. 2003;60(2 Suppl):3S-75S; discussion 76S-112S.
42. Martin S, Ulrich C, Munsell M, Taylor S, Lange G, Bleyer A. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist. 2007;12(7): 816-24.
43. Pulte D, Gondos A, Brenner H. Trends in survival after diagnosis with hematologic malignancy in adolescence or young adulthood in the United States, 1981-2005. Cancer. 2009;115(21):4973-9.
44. DeNavas-Walt C, Proctor BD, Smith JC, US Census Bureau, Current Population Reports, P60-238. Income, poverty, and health insurance coverage in the United States:2009. US Government Printing Office, Washington DC, 2010.
45. U.S. Census Bureau Health Insurance Historical Tables HIB-7 Health Insurance Coverage Status and Type of Coverage by Nativity: 1999 to 2010. Retrieved from http://www.census.gov/hhes/www/hlthins/data/historical/HIB_tables.html April, 2012.
46. Clegg LX, Reichman MF, Hankey BF, Miller BA, Lin YD, Johnson NJ, et al. Quality of race, Hispanic ethnicity, and immigrant status in population-based cancer registry data: implications for health disparity studies. Cancer Causes Control. 2007;18(2): 177-87.
47. US Census Bureau Migration by race and Hispanic origin: 1995 to 2000 Census 2000 Special Reports Issued 0ctober, 2003.
48. Hacker K, Chu J, Leung C, Marra R, Pirie A, Brahimi M, et al. The impact of immigration and customs enforcement on immigrant health: perceptions of immigrants in Everett, Massachusetts, USA. Soc Sci Med. 2011;73(4):586-94.