To the editor:

Rising rates of acute lymphoblastic leukemia in Hispanic children: trends in incidence from 1992 to 2011

Leukemia is the most common type of cancer in children younger than 20 years, with an age-adjusted incidence rate (AAIR) of 4.9 cases per 100 000 children for all leukemia types diagnosed between 2007 and 2011 in the United States.[1] The highest rates of childhood leukemia have been reported for children of Hispanic ethnicity,[1] but whether the higher incidence rate in this ethnic group is a result of environmental or genetic factors or both, or other factors related to surveillance, is unclear. Acute lymphoblastic leukemia (ALL) is the most common cancer type in children. ALL incidence rates in all races/ethnicities have increased by approximately 1% per year since 1973, suggesting a change in risk-modulating environmental or lifestyle factors.[2]

In this analysis of Surveillance, Epidemiology and End Results (SEER) registry data, we evaluated trends in the incidence of childhood leukemia in the United States from 1992 to 2011 and examined differences by race/ethnicity. AAIRs and trends in incidence rates (annual percentage change [APC]) were calculated using the 2000 US Standard Population for age standardization. Analyses used a 2-sided level of significance of 0.05.

From 2007 to 2011, 5412 children younger than 20 years were diagnosed with childhood leukemia, including 2071 Hispanic children and 3341 non-Hispanic children. The AAIR for all leukemia subtypes was 5.68 per 100 000 persons for Hispanic children (95% confidence interval [CI], 5.44-5.94) compared with 4.08 per 100 000 persons for non-Hispanic children (95% CI, 3.94-4.22). From 1992 to 2011, the incidence rate for all leukemias increased significantly among both Hispanic children (APC = 1.03; 95% CI, 0.47-1.58) and non-Hispanic children (APC = 0.63; 95% CI, 0.15-1.11).

When restricting analyses to children diagnosed with the ALL subtype, Hispanic children experienced statistically significantly higher AAIRs than non-Hispanic children from 2007 to 2011 for all demographic groups (by race, gender, and age, except in children younger than 1 year; $P < .05$). The difference in ALL incidence rates between Hispanic and non-Hispanic children was greatest among older children: Hispanic children aged 15 to 19 years were 1.71 times as likely to be diagnosed with ALL as non-Hispanic children (95% CI, 1.49-1.96). There was a statistically significant increase in the incidence of ALL for Hispanic children (APC = 1.19; 95% CI, 0.60-1.78) and a lesser increase among non-Hispanic children (APC = 0.72; 95% CI, 0.06-1.39; Figure 1).

The overall increase in childhood leukemia incidence rates from 1992 to 2011 appears largely to have been driven by increasing rates of ALL among Hispanic children. Although the incidence of childhood ALL was highest in younger children (1-4 years of age), the largest increase in incidence rates during the period occurred in Hispanic children aged 10 to 19 years at diagnosis. The APC for Hispanic children diagnosed at 10 to 19 years of age from 1992 to 2011 (APC = 2.95; 95% CI, 1.74-4.18) was more than 6.5 times higher than the APC observed in Hispanic children diagnosed from 1 to 4 years of age (APC = 0.45; 95% CI, −0.57 to 1.47). Incidence rates also increased significantly among all Hispanic adolescents and young adults aged 15 to 39 years (APC = 2.75; 95% CI, 1.31-4.22), but not among non-Hispanics of the same age (APC = 0.58; 95% CI, −0.35 to 1.51).

Factors that may explain the observed increase in rates of childhood leukemia, such as changes in diagnostics, classification, and environmental or lifestyle factors, would need to differentially increase in Hispanic children compared with other ethnic groups to explain these patterns. Although histologic classification of leukemia has improved in recent years, improvements in diagnostic practices

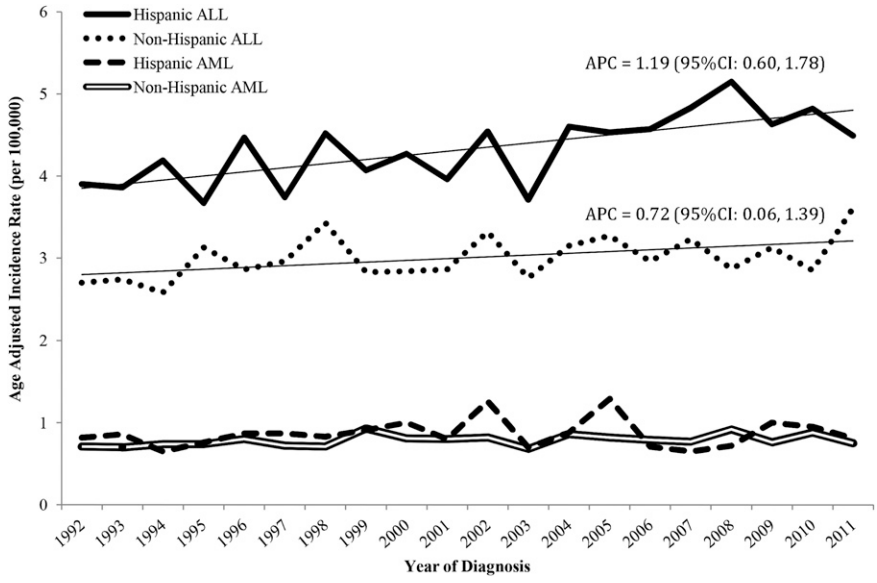

Figure 1. Age-adjusted incidence rates of childhood acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) by ethnicity and subtype, SEER 13, 1992-2011.

are unlikely to have differentially identified new cases that previously would have been missed. Further, ethnic differences in incidence trends have only been observed in childhood ALL and are not present in other childhood cancers (eg, childhood brain tumors), suggesting that changes in ethnic classification are unlikely to be solely responsible for trend differences. In utero exposure to factors such as tobacco are likely to have remained stable or decreased in prevalence during this period.[3,4] Other suspected risk factors for childhood leukemia that may explain the increase in incidence in Hispanic children, such as childhood atopic conditions, pesticide exposure, and maternal and child weight, have increased during this period, but may not be specific to Hispanic children and require further evaluation. Large, well-designed epidemiologic studies of childhood leukemia with diverse ethnic backgrounds, such as the California Childhood Leukemia Study, seek to further elucidate the reasons for the observed increases in incidence rates among Hispanic children in the last 2 decades.

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To the editor:

Platelet dense granule secretion defects may obscure α-granule secretion mechanisms: evidence from Munc13-4–deficient platelets

We were very interested to read in *Blood* the recent papers by Meng et al, "Defective release of α granule and lysosome content from platelets in mouse Hermansky-Pudlak syndrome models" and by Sharda et al, "Defective PDI release from platelets and endothelial cells impairs thrombus formation in Hermansky-Pudlak syndrome."[1,2] In these papers, the authors show that platelet adenosine diphosphate (ADP) secretion from dense granules is an important autocrine regulator of α-granule secretion. We have reached essentially the same conclusion, however, from a different perspective. We believe that, together, our data show that experimental manipulations or conditions that disrupt dense granule secretion may indirectly affect α-granule secretion and should be taken into account when investigating the mechanisms of α-granule secretion.

We are interested in the molecular machinery that controls platelet granule secretion. The SNARE regulator, Munc13-4, was shown to be an essential factor for dense granule secretion.[3] Consistent with this, *Unc13d*^{Jinx} mice (which lack Munc13-4) have prolonged tail bleeding and are protected from arterial thrombosis and cerebral infarct progression.[3-5] It has also been previously shown that *Unc13d*^{Jinx} platelets have a substantial, but incomplete, suppression of α-granule secretion,[3] an effect that we also observe. Washed platelets were stimulated with PAR4-activating peptide (PAR4-AP) (300 μM) and surface expression of CD62P was used as a marker of α-granule secretion. PAR4-AP–induced CD62P expression was significantly less in *Unc13d*^{Jinx} platelets compared with wild-type (WT) platelets (Figure 1A). This suggests that almost all α-granule secretion is dependent on Munc13-4. However, the block to α-granule secretion in the absence of functional Munc13-4 was substantially rescued by the addition of ADP (Figure 1A-B). Therefore, there must also be a Munc13-4–independent pathway that is capable of inducing substantial α-granule secretion.

ADP alone was not able to induce detectable CD62P expression under these conditions, suggesting that ADP acts synergistically to enhance PAR4-AP–induced α-granule secretion. In the presence of the $P2Y_{12}$ antagonist AR-C69931MX, there was a marked suppression of CD62P surface expression in both WT and *Unc13d*^{Jinx} platelets, and the ADP-mediated rescue of secretion was ablated (Figure 1B). The $P2Y_1$ antagonist, MRS2279, had no effect. In addition, we found that 5-HT was not able to induce α-granule secretion, and