blood

To the editor:

Increased risk of leukemia among sickle cell disease patients in California

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Due to improvements in treatment and care, the life expectancy of patients with sickle cell disease (SCD) has improved over the last 50 years[1] such that many patients now survive to an age where they are at an increased risk for cancer.[2] Previously reported small case series[3-6] or surveys[7] have suggested an increased cancer risk in patients with SCD. In addition, an increased cancer incidence of hematologic cancers and some solid tumors was recently observed among 7512 SCD patients in England compared with patients hospitalized with minor medical and surgical conditions.[8] However, cancer incidence rates of SCD patients were not compared with the general population of England. There is limited understanding as to whether the risk of certain cancers among those with SCD differs from the general population. Therefore, we used 27 years of population-based data from California to determine cancer incidence in SCD patients compared with the general population.

As previously described, the SCD study cohort was identified using serial records from the California Patient Discharge Data and the Emergency Department Utilization databases from the Office of Statewide Health Planning and Development.[9,10] SCD patients were identified using a search algorithm informed by the Registry and Surveillance System for Hemoglobinopathies project[11] and validated by the Public Health Research, Epidemiology, and Surveillance for Hemoglobinopathies study.[2] Although genotype is available by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, 69% had multiple genotypes coded across different admissions; therefore, genotype was deemed unreliable.[12] Patients with an average of ≥3 visits per year (across all study years in the cohort) were defined as having severe SCD; all other patients were defined as having less severe SCD.[9,10]

Cancer occurrence among SCD patients was obtained through a linkage with the population-based California Cancer Registry (1988-2014).[13] Cancer-specific data, including date of diagnosis, primary site, and histology, and patient demographics are collected for all malignant and selected in situ cancers in California.

Standardized incidence ratios (SIRs) are commonly used to compare specific cohorts' cancer incidence to the general population and are adjusted for demographic differences in the population distributions. Additionally, SIRs are designed to handle smaller sample sizes.[14] SIRs with 95% confidence intervals (CIs) were calculated as observed cancers in SCD patients to expected cancers using California cancer rates for all cancers combined and specific cancers with ≥5 observed cases in all SCD patients. Additional SIR stratifications by sex, age, and time period of diagnosis were calculated for leukemia because of the fear of association with hyroxyurea,[15,16] which was approved for use in 1998. This study was approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects and the University of California, Davis Institutional Review Boards. Additional details on methods are presented in supplemental Methods (available on the *Blood* Web site).

There were 6423 SCD patients identified from 1991 to 2014 (supplemental Table 1). SCD patients were observed for a total of 141 752 person-years, with a median length of follow-up of 22.2 person-years. A total of 115 SCD patients were diagnosed with first primary cancers at a median age of 46 years.

Compared with the California population, SCD patients had a 72% increased risk of hematologic malignancies and a 38% reduced risk of solid tumors (Table 1). SCD patients were not at increased risk for most cancer types, with the exception of leukemia where SCD patients had over a twofold increased risk. Among subtypes of leukemia, the risk was higher for acute myeloid leukemia (SIR, 3.59; 95% CI, 1.32-7.82) and borderline increased for chronic lymphocytic leukemia (SIR, 4.83; 95% CI, 1.00-14.11). We also observed lower risk of breast cancer and male genital cancers (prostate, testis, penis, and other male genital organs).

Female SCD patients and adolescent and young adults patients (15-39 years of age) had a threefold increased risk for leukemia (Table 2). Patients with severe SCD had a fourfold increased risk of leukemia. There were no differences in cancer risk by decade.

To our knowledge, this is one of the first studies to determine cancer incidence among SCD patients compared with a general population. A recent study using hospitalization data in England reported a threefold to 10-fold higher cancer incidence among SCD patients for hematologic cancers, and an increased risk for colon cancer,

Table 1. Age, sex, race/ethnicity, and time-adjusted SIRs for selected cancers among patients with SCD, California, 1988-2014

	Observed cases	Expected cases	SIR	95% CI
All cancers	115	143.70	0.80	(0.66-0.96)
Solid tumor	76	123.25	0.62	(0.49-0.77)
Breast	16	29.73	0.54	(0.31-0.87)
Respiratory	16	13.13	1.22	(0.70-1.98)
Digestive system	16	22.18	0.72	(0.41-1.17)
Urinary system	8	6.06	1.32	(0.57-2.60)
Female genital	5	11.63	0.43	(0.14-1.00)
Male genital	6	16.71	0.36	(0.13-0.78)
Hematologic tumors	31	18.03	1.72	(1.17-2.44)
Lymphoma	15	10.38	1.45	(0.81-2.38)
Leukemia	12	5.17	2.32	(1.20-4.05)
ALL	3	1.64	1.83	(0.38-5.35)
CLL	3	0.62	4.83	(1.00-14.11)
AML	6	1.67	3.59	(1.32-7.82)

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia.

Table 2. Leukemia-specific SIRs among patients with SCD, California, 1988-2014

	Observed cases	Expected cases	SIR	95% CI
Leukemia	12	5.17	2.32	(1.20-4.05)
Sex				
Male	5	2.71	1.85	(0.60-4.31)
Female	7	2.47	2.84	(1.14-5.84)
Age at diagnosis, y				
Pediatric, <15	1	1.47	0.68	(0.02-3.79)
AYA, 15-39	6	1.78	3.37	(1.24-7.33)
Adult, ≥40	5	1.92	2.60	(0.84-6.07)
SCD severity*				
Less severe	4	2.59	1.54	(0.42-3.95)
Severe	8	1.81	4.41	(1.91-8.70)
Treatment era†				
1988-1999	5	1.92	2.61	(0.85-6.08)
2000-2014	7	3.26	2.15	(0.86-4.43)

AYA, adolescent and young adult.

*Patients with an average of ≥3 visits per year were defined as severe SCD; patients with an average <3 visits per year were defined as less severe SCD.[17]

†Hydroxyurea was approved by the FDA in February 1998.

nonmelanoma skin cancer, kidney cancer, and thyroid cancer.[8] Our findings may have differed from this study due to the differing comparison populations and more stringent criteria used to define cases with SCD in our cohort. We also used highly validated cancer registry data and did not rely on hospital coding for the diagnosis of malignancies. The prior study[8] may have underestimated cancer incidence in the control group if controls were more likely than SCD patients to be treated in the outpatient setting and were never identified as cancer patients in hospital records.

Hydroxyurea was the only US Food and Drug Administration (FDA)-approved drug for SCD during the study period. One of the barriers to hydroxyurea use is the perceived increased risk of cancer, especially leukemia.[16,17] Although we did not have pharmaceutical drug use in this database, we did not observe a higher risk of leukemia after hydroxyurea was approved in 1998, suggesting that the increased risk of leukemia is not related to hydroxyurea use. However, future studies with hydroxyurea data will need to confirm these findings.

SCD is accompanied by chronic inflammation, increased iron from frequent transfusions, increased infectious risk, and increased red cell proliferation and cellular turnover in the bone marrow.[18] Previous reports have shown that these risk factors play a multifaceted role in cancer development.[19-23] These common complications may explain the increased risk of leukemia. A possible explanation for the 38% reduced risk of solid tumors may be the sickling of the red blood cells.[24] Terman et al used sickle-shaped red blood cells to target oxygen-deprived breast cancer in infected mice and found that sickled red blood cells blocked the blood vessels surrounding the tumor.[24] Sickled red blood cells may be acting as antiangiogenic agents and inhibiting solid tumor formation.

Because we relied on hospital admission and emergency department data, a limitation of our study is that healthier SCD patients, particularly children, may have been excluded. However, we believe most patients would have hospitalizations and/or emergency department visits over the long person-years of observation. Additionally, we did not have population data for some important covariates, including socioeconomic status, which could impact cancer incidence rates. Despite these limitations, this is the largest known population-based SCD cohort linked to cancer registry data.

Compared with the general California population, SCD patients in our study were at an increased risk of leukemia and a reduced risk of female breast cancer and male genital cancers after standardizing demographic differences in the populations. The increased incidence of leukemia suggests a role of high cellular turnover (bone marrow in this instance) and chronic inflammation in leukemic pathogenesis, and implies that mutations commonly seen in acute leukemia and myelodysplasia[25] might be seen with greater frequency in patients with SCD. Despite the lower incidence of solid tumors, recommendations for routine screening for the common cancers, such as breast and colon, should continue to be followed for this population. However, health care providers should be aware of the possibility of an increased risk of leukemia among SCD patients. Further studies are needed to confirm our findings in a larger population and to identify risk factors for developing cancer among SCD patients and the impact on survival.

The online version of this article contains a data supplement.

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