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Socioeconomics, Race, and Ethnicity in Childhood Cancer Survival: Accessing and Addressing Root Causes of Disparities

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In this issue of *Cancer*, Kehm et al[1] report on racial and ethnic differences in childhood cancer survival and quantify how socioeconomic status (SES) mediates these disparities. They show that SES accounts for 28% to 73% of racial and ethnic disparities for several childhood cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), neuroblastoma, and non-Hodgkin lymphoma. In addition, the authors note that there are still statistically significant racial and ethnic disparities in survival independent of SES, the sources of which remain unclear. Both of these statements represent important steps in the understanding of childhood cancer disparities; they are at once calls for further work to improve our understanding of inequalities as well as opportunities to address them. In this editorial, we explore the epidemiologic challenges of understanding social determinants of childhood cancer survival, specifically those concerning racial and ethnic disparities, and we discuss future directions for increasing health equity for childhood cancer patients.

There is resounding evidence that social factors, including race, ethnicity, and SES, are associated with disparities in cancer survival.[2,3] The current study makes important progress in deconvoluting these different factors while also highlighting the challenges of these efforts. Large databases such as the Surveillance, Epidemiology, and End Results (SEER) database provide powerful evidence that is widely generalizable and not prone to selection and survival biases.[4,5] Compared with clinical trials, this population-based study provides a better opportunity for understanding possible differences in racial and ethnic populations, which are often underrepresented in clinical trials.[4,6] However, there are some distinct limitations to consider with the SES classification in the SEER database. Because it is an ecological variable rather than an individual-level determination, there may be significant measurement error or misclassification of individuals, which may bias the socioeconomic effect toward the null[7,8]; therefore, its contribution to disparities may be underestimated. Because individuals are uniformly labeled, variations in education, income, and occupation

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within the area-based grouping will not be detectable. The individuals who are worst off and in turn may have the worst survival outcomes will not be identified. Previous research has shown large variability between area-based and household incomes.[9] Consortium trials may provide a balance between collecting individual data and being widely generalizable, but requiring access to advanced centers may limit the generalizability to geographically or economically isolated populations.

Furthermore, with the adjustment of the SES status, there is the risk of residual confounding stemming from the broadness of the SES grouping parameters and errors in the classification of SES grouping.[10] A more comprehensive analysis of health insurance status, rather than the crude measure used in this study, could provide an opportunity to further explore the role that SES and insurance play in racial/ethnic disparities in survival. A recent California Cancer Registry study found that compared with privately insured patients, both uninsured patients and patients with public insurance had significantly higher cancer-specific mortality.[11] In conjunction with SES, a more in-depth analysis of insurance coverage may further highlight factors affecting survival, such as access to care and adherence to treatment.

There is also concern about misclassification of race in large databases such as SEER. Although SEER has streamlined methods for identifying 4 key races and discriminating between race and ethnicity, there are still no clear guidelines for how institutions and providers should initially classify patients. Several bodies have evaluated the correlation between self-reported and documented race and found significant misclassification of American Indians/Alaska Natives as well as milder misclassification of Hispanic and Asian/Pacific Islander populations.[12] The NAACCR Hispanic Identification Algorithm (version 2) has greatly improved correlation, but some degree of misclassification will continue to persist. These discordances also highlight the importance of defining whether the study question addresses perceived or selfidentified race, the former perhaps focusing on societal discrimination and the latter more precisely defining lived experiences and ancestry. Because race is ultimately a social construct without strict taxonomic rules, any study of racial disparity faces the challenge of uniform definitions and applications of this term. Importantly, SES is also a social construct, but combined with race, these 2 variables are the most robust predictors of health around the world. Their ubiquity imports a moral obligation to understand the mechanisms that drive these disparities.

In addition, there are limitations in interpreting observational studies such as the current one when we do not have streamlined methods of reporting. For example, the relative magnitude of mediation (as reported in the current study) may portray more exaggerated results than the absolute magnitude of mediation. Although there was a large relative percent reduction from the total effect to the direct effect of race and ethnicity on mortality risk (see Tables 2 and 3, respectively, in Kehm et al[1]), the absolute differences were fairly small. For instance, the percent reduction for ethnicity in AML was 73%, whereas the absolute difference was only a hazard ratio of 1.19 versus a hazard ratio of 1.05, with overlapping confidence intervals. In addition, the application of the inverse odds weighting to test for mediation holds the assumption that the mediator is measured without error.[13] With the previously mentioned limitations of an area-based SES variable, mediation effects should be cautiously considered.

By demonstrating that SES is a significant but not sole contributor to racial and ethnic survival disparities in childhood cancer, Kehm et al[1] have also added to the body of evidence suggesting that there are contributing factors independent of SES. The question here is what these other causes are and how they interact with SES factors. The authors posit that several factors, including tumor biology, mediate the racial/ethnic differences in survival. There is still debate on how biology might drive racial disparities in health. Most clinicians agree that race is a poor marker of genomics because of the greater amount of genetic heterogeneity within races than between races.[14] However, new evidence on racial/ethnic susceptibility loci (eg, the IL-1B-1464G/−511C/−31T haplotype and increased risk of gastric cancer among Asians[15] and the diverse loci associated with poor survival in prostate cancer among black men[16]) continues to emerge. Recently, Lim et al[17] illustrated that the newly implicated Philadelphia chromosome–positive ALL with CRLF2 lesions was overrepresented in self-reported Hispanic children in comparison with non-Hispanic children, and this could help explain why Hispanic children with ALL have higher rates of relapse and worse survival. However, genome-wide association studies can only highlight associations and are still susceptible to confounding by environmental or social exposures. Notably, they found no racial distribution of other prognosis-associated alleles (ETV6-RUNX1, TCF3-PBX1, BCR-ABL1, or MLL).

Recent genomic work has greatly increased the sophistication of our understanding of the role of biology by shifting the discussion from perceived or self-reported race to a focus on ancestry. The use of ancestry-informative markers helps to illustrate that self-reported racial groups are ancestrally diverse and that self-reported racial disparities in ALL could be explained, in part, by the genomic variation associated with Native American ancestry. In their novel study, Yang et al[18] showed that the percentage of Native American ancestry predicts the risk of relapse and, independently of initial prognostic factors, could help to determine which children would benefit from additional chemotherapy. Although new genomic data may offer insight into the biologic underpinnings of survival disparities, the reliability of these findings is still questionable because of the significant underrepresentation of minorities in genomic studies. In 2009, 96% of genome-wide association study participants were of white ancestry, with only 0.57% and 0.06% of African and Hispanic ancestry, respectively.[19] Seven years later, nonwhite participants reached close to 20% of samples, but African and Hispanic participants still represented only 3% and 0.54%, respectively.[20]

Kehm et al[1] do highlight a unique biological driver of racial disparities in leukemia survival. Black children are less likely to have a matched family donor for hematopoietic stem cell transplantation (HSCT) in comparison with white or Hispanic children,[21] and further studies show that it is more difficult for black children to find unmatched donors.[22] There may also be systemic reasons for this disparity; however, we now understand that it is more difficult to find unmatched donors for black patients because of the increased frequency of rare human leukocyte antigen alleles and overall heterogeneity within the human leukocyte antigen gene complex among US black populations.[22,23] This sociobiological issue may help to explain why both SES and non-SES factors contribute to the racial and ethnic disparities seen in ALL and AML, for which allogeneic HSCT is such an important treatment modality. The complexity of treatment overall appears to differentiate cancer types with a major SES

contribution to disparities in comparison with those without one: Treating leukemia, neuroblastoma, and non-Hodgkin lymphoma requires multimodality approaches and/or lengthy inpatient stays and overall treatment, whereas the treatment of Hodgkin lymphoma, germ cell tumors, and Wilms tumors is usually shorter and more straightforward. These differences may determine the impact of low SES through related factors such as parental work interruption, insurance status, clinical trial availability, access to care, and quality of treatment.

Any of these sources of SES-driven disparities can be addressed. Several groups have suggested that patientlevel interventions, such as improved treatment education, improved insurance enrollment and coverage,[11] and patient navigators,[24] can improve patient outcomes. Specific hospital-level actions to address these inequalities include providing access to financial aid assistance programs and nonemergency medical transportation as well as increasing access to social workers. Pui et al[25] evaluated survival disparities in SEER and at St. Jude Children's Research Hospital between 1992 and 2007 and found that advances in survival during this time were not experienced for black children in SEER. However, this disparity was not seen at St. Jude Children's Research Hospital, where patients are accepted without regard for their insurance status or ability to pay, and psychosocial services and transportation are greatly subsidized. We note that it is still not clear which of these interventions would have the greatest impact on reducing survival disparities. There is still a need for studies examining where in the diagnostic and treatment process low-SES patients face barriers. To highlight areas of potential intervention, future studies should dissect the individual components of the SEER SES index to identify the strongest SES drivers.

In terms of contributing causes to racial and ethnic disparities outside SES, evidence suggests that these go beyond tumor biology, including historical mistrust in the medical system, barriers to communication and follow-up, implicit racial bias, and poor access to advanced clinical trials.[2,6,26] The National Marrow Donor Program has drastically improved its recruitment of and participation by racial/ethnic minorities, including African Americans, in a concerted effort over the last decade.[27] To do so, it first conducted surveys to identify barriers to participation and found modifiable factors such as a lack of awareness of the potential benefits of HSCT, the cost of donation, and a lack of opportunities. It also found cost-effective interventions such as providing educational programs before conducting marrow drives. Tertiary centers conducting clinical trials might learn from this example by increasing the education around availability and costs associated with clinical trial participation. Many of these sources of disparities also provide opportunities for changing health practices to meet the needs of vulnerable populations, including educating providers on issues of race and racism.[28] Tumor biology, on the other hand, is not currently modifiable. Although cytogenetic information may one day will continue to help us risk-stratify patients, the methods for understanding the role of ancestry and genomics are rapidly evolving, and we still have much to learn about racial and ethnic tumor biology differences. Until these differences are shown to be a more significant contributor to disparities, we believe that greater gains can be made by addressing modifiable causes of disparities, challenging as they may be.

Ultimately, the more we can zero in on the specific contributors to disparities, the more effective and efficient our efforts will be, given limited resources. This means performing further studies and improving our research tools. There is a need to integrate information that will allow researchers to better identify the drivers of racial and ethnic disparities in health, including individual-level data on SES, into comprehensive cancer registries such as SEER. Studies of SES in SEER often use a well-validated composite of 7 area-based SES indicators, including the proportion employed in working-class occupations, the proportion aged 16 years or older and unemployed, the education index, the median household income, the proportion below the 200% poverty level, the median rent, and the median house value.[29] Integrating individual-level information will require adaptations to personal variables and thoughtful privacy protections. In a field that already has advanced methods to protect patient confidentiality, privacy concerns should not pose a barrier to collecting important SES information.

Tumor biology data could also eventually be incorporated into large databases to better understand its contribution. The field of oncology is rapidly changing, and it is important for minority populations to be actively recruited for clinical trials so that the results of novel treatments are as generalizable as possible. This is difficult because of the medical system's historical mistreatment of nonwhite populations. Nevertheless, the progress that has been made in increasing the diversity of hematopoietic stem cell donors, a modifiable biological cause of disparities, is evidence that this is possible.[30]

In summary, Kehm et al[1] have capably distilled the issue of racial and ethnic disparities in childhood cancer survival facing our field. Despite the challenges with measuring SES and defining race inherent to our current research tools, they provide compelling evidence that SES independently contributes meaningfully to these inequalities in specific cancers requiring complex treatment. They have also clarified key remaining questions: What accounts for the portion of disparities not explained by SES, and how do we address both SES-related and non–SES-related sources? We should take action now to address causes with broad impacts on our health system as a whole. Improving and carefully planning future studies of childhood cancer disparities, however, will allow targeted interventions likeliest to improve survival for our most vulnerable patients.

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REFERENCES

1. Kehm RD, Spector LG, Poynter JN, Vock DV, Altekruse SF, Osypuk TL. Does socioeconomic status account for racial and ethnic disparities in childhood cancer survival? Cancer. 2018;124. [PubMed: 29394923]
2. Bhatia S Disparities in cancer outcomes: lessons learned from children with cancer. Pediatr Blood Cancer. 2011;56:994–1002. [PubMed: 21328525]
3. Kahn JM, Keegan TH, Tao L, Abrahao R, Bleyer A, Viny AD. Racial disparities in the survival of American children, adolescents, and young adults with acute lymphoblastic leukemia, acute

myelogenous leukemia, and Hodgkin lymphoma. Cancer. 2016;122:2723–2730. [PubMed: 27286322]

4. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer. 2014;110:551–555. [PubMed: 24495873]
5. Kukull WA, Ganguli M. Generalizability: the trees, the forest, and the low-hanging fruit. Neurology. 2012;78:1886–1891. [PubMed: 22665145]
6. Nooka AK, Behera M, Lonial S, Dixon MD, Ramalingam SS, Pentz RD. Access to Children's Oncology Group and Pediatric Brain Tumor Consortium phase 1 clinical trials: racial/ethnic dissimilarities in participation. Cancer. 2016;122:3207–3214. [PubMed: 27404488]
7. Mooney SJ, Richards CA, Rundle AG. There goes the neighborhood effect: bias owing to nondifferential measurement error in the construction of neighborhood contextual measures. Epidemiology. 2014; 25:528–535. [PubMed: 24815303]
8. Greenland S The effect of misclassification in the presence of covariates. Am J Epidemiol. 1980;112:564–569. [PubMed: 7424903]
9. Hanley GE, Morgan S. On the validity of area-based income measures to proxy household income. BMC Health Serv Res. 2008;8:79. [PubMed: 18402681]
10. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. Am J Epidemiol. 2007;166:646–655. [PubMed: 17615092]
11. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Trends in cancer survival by health insurance status in California from 1997 to 2014. JAMA Oncol. 2018;4:317–323. [PubMed: 29192307]
12. Clegg LX, Reichman ME, Hankey BF, 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;18:177–187. [PubMed: 17219013]
13. Tchetgen Tchetgen EJ. Inverse odds ratio–weighted estimation for causal mediation analysis. Stat Med. 2013;32:4567–4580. [PubMed: 23744517]
14. Lewontin RC. The apportionment of human diversity In: Dobzhansky T, Hecht MK, Steere WC, eds Evolutionary Biology. Vol 6 Boston, MA: Springer US; 1995:381–398.
15. Kim J, Kim Y, Lee KA. Ethnic differences in gastric cancer genetic susceptibility: allele flips of interleukin gene. World J Gastroenterol. 2014;20:4558–4565. [PubMed: 24782608]
16. Lachance J, Berens AJ, Hansen MEB, Teng AK, Tishkoff SA, Rebbeck TR. Genetic hitchhiking and population bottlenecks contribute to prostate cancer disparities in men of African descent. Cancer Res. 2018;78:2432–2443. [PubMed: 29438991]
17. Lim JY, Bhatia S, Robison LL, Yang JJ. Genomics of racial and ethnic disparities in childhood acute lymphoblastic leukemia. Cancer. 2014;120:955–962. [PubMed: 24382716]
18. Yang JJ, Cheng C, Devidas M, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. Nat Genet. 2011; 43:237–241. [PubMed: 21297632]
19. Need AC, Goldstein DB. Next generation disparities in human genomics: concerns and remedies. Trends Genet. 2009;25:489–494. [PubMed: 19836853]
20. Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016;538:161–164. [PubMed: 27734877]
21. Aplenc R, Alonzo TA, Gerbing RB, et al. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2006;108:74–80. [PubMed: 16537811]
22. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371:339–348. [PubMed: 25054717]
23. Beatty PG, Mori M, Milford E. Impact of racial genetic polymorphism on the probability of finding an HLA-matched donor. Transplantation. 1995;60:778–783. [PubMed: 7482734]
24. Natale-Pereira A, Enard KR, Nevarez L, Jones LA. The role of patient navigators in eliminating health disparities. Cancer. 2011; 117:3543–3552. [PubMed: 21780089]

25. Pui CH, Pei D, Pappo AS, et al. Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. J Clin Oncol. 2012;30:2005–2012. [PubMed: 22547602]

26. Penner LA, Dovidio JF, Gonzalez R, et al. The effects of oncologist implicit racial bias in racially discordant oncology interactions. J Clin Oncol. 2016;34:2874–2880. [PubMed: 27325865]

27. Laver JH, Hulsey TC, Jones JP, Gautreaux M, Barredo JC, Abboud MR. Assessment of barriers to bone marrow donation by unrelated African-American potential donors. Biol Blood Marrow Transplant. 2001;7:45–48. [PubMed: 11215698]

28. Nelson SC, Prasad S, Hackman HW. Training providers on issues of race and racism improve health care equity. Pediatr Blood Cancer. 2015;62:915–917. [PubMed: 25683782]

29. Yu M, Tatalovich Z, Gibson JT, Cronin KA. Using a composite index of socioeconomic status to investigate health disparities while protecting the confidentiality of cancer registry data. Cancer Causes Control. 2014;25:81–92. [PubMed: 24178398]

30. Dehn J, Arora M, Spellman S, et al. Unrelated donor hematopoietic cell transplantation: factors associated with a better HLA match. Biol Blood Marrow Transplant. 2008;14:1334–1340. [PubMed: 19041054]