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Editorial

What's Missing in the Assessment of Adolescent and Young Adult (AYA) Cancer Outcomes?

Brad H. Pollock, PhD, MPH [1,2,*]

[1]Department of Public Health Sciences, School of Medicine, University of California Davis, Medical Sciences 1C, Room 104, One Shields Avenue, Davis CA 95616, USA and [2]UC Davis Comprehensive Cancer Center, Department of Epidemiology, University of California Davis, Sacramento, CA, USA

*Correspondence to: Brad H. Pollock, PhD, MPH, Department of Public Health Sciences, Medical Sciences 1C, Room 104, University of California, Davis One Shields Avenue, Davis, CA 95616, USA (e-mail: BPollock@ucdavis.edu).

Outcome disparities for US adolescents and young adults (AYAs) with cancer were first identified by analysis of Surveillance, Epidemiology, and End Results (SEER) Program data from the National Cancer Institute (1). The descriptive epidemiology of AYA cancers in the United States was reported in a SEER monograph (2), and a partnership between the National Cancer Institute and the Lance Armstrong Foundation convened a Progress Review Group (PRG) to begin to address the unique needs of AYAs with cancer (3). Since then, there has been heightened interest in tracking incidence patterns and survival trends for AYAs with cancer (4,5). Analyses using population-based cancer registry (PBCR) data have generally shown poorer survival of AYAs compared with children and older adults. They have also shown secular decreases in mortality for all AYAs combined with notable differences by malignancy type (4–6).

In this issue of the Journal, Anderson and Nichols (7) report the results of an updated comprehensive analysis of changes in AYA mortality over time. They observed a striking decrease in late mortality for AYAs. Five-year all-cause conditional mortality, measured starting 5 years after initial diagnosis, decreased from 8.3% for AYAs diagnosed in 1975–1984 to 5.4% for AYAs diagnosed in 2005–2011. However, this improvement was not uniformly exhibited across all malignancies. Anderson and Nichols describe the lack of full treatment and disease relapse information from SEER data as a limitation—the same limitation that has afflicted other studies that relied solely on PBCR data.

Identification of the AYA outcomes gap (1) using PBCR data has prompted efforts to expand the availability of clinical trials and lower barriers for trial participation for AYAs, the development of more effective treatment regimens and evidence-based secondary prevention surveillance strategies, and identification of the broad range of needed clinical services for AYAs (8). Studies using PBCRs have compared AYA mortality patterns across countries (6), determined the prognostic significance of location of care (9), assessed the impact of sociodemographic characteristics and health-care insurance on AYA outcome disparities (10), and determined the prognostic significance of second primary malignant neoplasms (11). SEER data were used to evaluate the impact of the HIV/AIDS epidemic on AYA mortality trends (12), but discordant analytic approaches and the exclusion of selected malignancy diagnoses clouded interpretation of these findings (13,14). Without individual patient HIV exposure information, inferences about the impact of the HIV/AIDS epidemic on changes in AYA mortality cannot overcome an ecological fallacy—when inferences about individuals are deduced from inferences about the group to which these individuals belong. The absence of detailed patient clinical and treatment data, treatment-related toxicities, nonlethal treatment failures, and use of salvage therapies limit the utility of PBCRs, which are not sensitive enough to detect safety signals related to therapy. For example, clinical data from treating institutions made possible the observation that epipodophyllotoxin treatment was associated with an increased risk of secondary childhood leukemias (15). PBCRs do not include lifestyle factors, comorbidities that develop in survivorship, or patient-reported outcome measures, also limiting their utility.

Important findings have been gleaned by linkage of PBCR data to public administrative databases including statewide hospital discharge datasets (9) and the SEER–Medicare Linked Database. But these linked databases still do not incorporate complete clinical or biological information nor do they necessarily include nonlethal treatment failures, incident comorbidities and treatment-related sequelae, or patient-reported outcomes. These data are needed to advance AYA oncology research.

Clinical cohort studies overcome many of the limitations of PBCR studies. For example, the Childhood Cancer Survival Study (CCSS), established in 1994, includes detailed regimen-specific treatment information and a full complement of outcome measures (16). The CCSS has provided a wealth of information about the prognostic role of treatment-related medical exposures in long-term survivorship. It includes a comprehensive set of long-term outcomes including nonlethal treatment failures, acute toxicities, long-term sequelae, and patient-reported outcomes. However, the CCSS is limited to a relatively

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small number of treating institutions and thus covers only a small proportion of the North American population. It does not include all malignancy diagnoses or patients aged 21 years and older at the time of diagnosis limiting its utility for AYA oncology research. The Children's Oncology Group (COG) has also successfully conducted ad hoc pooled analyses of AYA outcomes for patients treated on COG clinical trials (17), but outcome assessments are limited to trial-enrolled patients only.

We are well beyond the point where large prospective AYA cancer cohorts that combine clinical data with population-based data should be established. Currently underway, the COG, the US Centers for Disease Control and Prevention, and the Kentucky Cancer Registry are conducting a feasibility study linking COG AYA records to state cancer registry records. Ultimately, such efforts are a first step in establishing AYA cancer cohorts that include detailed diagnostic information (including biologic characteristics and other important prognostic factors); detailed treatment information; acute toxicities and long-term adverse events; treatment failures including refractory response to therapy, release, and progression of disease; and cause-specific mortality. Whereas creating such a cohort study on a national level may be impractical, starting on a more limited geographic scale such as within a single state may be more feasible.

Substantial investment is needed to develop a comprehensive prospective AYA cohort study. Now that we are in the era of big data, the extremely fast-evolving health information technology infrastructure would contribute to success in building a cohort. Capabilities of capturing, storing, curating, and accessing large stores of clinical data, most often in electronic health record systems, are growing exponentially. Cancer researchers interested in AYA oncology are currently limited to using relatively small institution-based cohorts, clinical trials data, or PBCRs. Incremental resources are needed to collect new AYA-relevant data elements; structure, curate, and link in electronic health record clinical data; incorporate external administrative data (eg, hospital discharge and insurance claims); and implement policies and develop data governance structures to promote large-scale AYA oncology research while maintaining confidentiality and ensuring privacy. Integrated clinical- and population-based data are required for the development of prevention, screening, and treatment strategies to improve AYA cancer outcomes. Without large, representative, detailed, and accessible cohort data sources, research efforts to substantially improve therapy and long-term outcomes for AYAs with cancer will remain hampered.

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