Original Article

Enrollment of adolescent and young adult patients newly diagnosed with cancer in NCI CTEP-sponsored clinical trials before and after launch of the NCI National Clinical Trials Network

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BACKGROUND: Participation of adolescents and young adults (AYAs) in oncology clinical trials is important to ensure adequate opportunities for AYA patients to contribute to, and benefit from, advances in cancer treatment. **METHODS:** Accrual data for National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) cooperative group-led treatment trials were examined to assess enrollment of newly diagnosed AYA patients (15–39 years) during the period 2004–2019, with particular interest in comparing enrollment before launch of the NCI National Clinical Trials Network (NCTN) to after. All phase 2, 2/3, and 3 trials activated during the period between January 1, 2004, and December 31, 2019, were identified ($n = 1568$) and reduced to a set of 304 that met predetermined criteria to focus on cooperative group-led trials that involved therapy for newly diagnosed cancer and had age eligibility overlapping the AYA range. The proportion of AYA patients relative to total accrual, along with 95% bootstrapped CI was calculated for patients enrolled pre-NCTN and post-NCTN. **RESULTS:** AYA accrual comprised 9.5% (95% CI, 7.6–11.8) pre-NCTN compared with 14.0% (95% CI, 9.9–18.3) post-NCTN. The mean difference in proportions post-NCTN compared with pre-NCTN was 4.4% (0.7%–8.3%). **CONCLUSIONS:** These results indicate an increase in AYA participation in trials conducted within the NCTN relative to the pre- NCTN period. This suggests an awareness and utilization of NCTN trials for AYAs with cancer. ***Cancer* 2022;128:3843-3849**. Published 2022. This article is a U.S. Government work and is in the public domain in the USA. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution- NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: adolescent and young adult (AYA), cancer treatment clinical trial, clinical trial accrual, clinical trial participation, clinical trial trends, National Cancer Institute National Clinical Trials Network (NCTN), oncology clinical trial.

INTRODUCTION

More than 15 years ago, the National Cancer Institute (NCI) and Lance Armstrong Foundation focused attention on adolescent and young adults with cancer and the many issues associated with this population.[1] Although overall cancer survival among AYAs continues to exceed that of other age groups, numerous challenges remain for this population, which include differences in cancer biology and the host, impaired access to treatment centers experienced in treating AYAs with cancer, low participation and access to clinical trials, toxicity (acute and long term), survivorship care, and psychosocial support during therapy and after completion of therapy.[2–5] Cancer treatment trials in the United States are conducted by both the private sector through pharmaceutical companies, foundations, and academic institutions and the public sector with support from the NCI and other government entities. The clinical trials supported by the NCI generally address more complex clinical research questions related to treatment and are intended to be available to patients both in the academic setting as well as community.[6] The cooperative group system was initiated in the 1950s and evolved from researchers conducting studies for children and adults with acute leukemia to include most pediatric and adult cancers.[7] As a result of the Institute of Medicine recommendations in 2010, the NCI National Clinical Trials Network (NCTN) was formed and launched on March 1, 2014, comprising four medical oncology groups (Alliance for Clinical Trials in Oncology (Alliance), Eastern Cooperative Oncology Group-American College of Radiology Imaging Network, Southwest Oncology Group (SWOG), National Surgical Adjuvant Breast and Bowel Project, Radiation Oncology Group, Gynecologic Oncology Group, NRG), one pediatric group (Children's Oncology Group), and one international group (Canadian Cancer Trials Group).[6] One of

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several goals of the newly formed NCTN was to increase trial accrual particularly in rare cancers and from special populations including AYAs.[8,9]

The objective of this analysis is to compare the enrollment to NCI-sponsored cooperative group trials for newly diagnosed AYA oncology patients to enrollments after the formation of the NCTN. Our goal was to obtain a better understanding of whether features implemented in the NCTN including collaboration between the individual trials groups, allowing NCTN members access to trials across the entire network, and providing certain centralized services, were collectively having an impact on one of the challenges associated with AYAs with cancer, patient enrollment onto clinical trials.

METHODS

All Cancer Therapy Evaluation Program (CTEP)-sponsored, phase 2, 2/3, and 3 trials activated between January 1, 2004, and December 31, 2019, were identified ($n = 1568$). To restrict to trials open to newly diagnosed AYA patients, trials were excluded if they were not led by a cooperative group ($n = 562$), were a nontreatment trial ($n = 119$), did not include the AYA age range or featured benign disease ($n = 76$), or enrolled patients with relapsed or refractory disease ($n = 507$). The number of trials remaining to be included in subsequent analyses was $n = 304$ (Fig. 1).

For each trial, variables extracted included protocol number, phase (2, 2/3, 3), lead disease name, AYA accrual, total accrual, date of activation, date of closure to accrual, date of closure to accrual, and treatment. Allowing for administrative ramp-up of the NCTN system, trials with activation date on or after January 1, 2015, were considered after NCTN trials, and others were considered before NCTN. To more broadly classify disease categories, lead disease names were matched to their respective CTEP category (e.g., breast neoplasm) and subcategory (e.g., invasive breast cancer) as defined by the CTEP Simplified Disease Classification v1.0 (MedDRA v10.0).

For each trial, the AYA proportion of total trial accrual (data pull September 11, 2019) was calculated and examined according to year of trial activation. Trials were categorized as pre-NCTN or post-NCTN based on activation date, and AYA accrual proportions along with a 95% bootstrapped CI were compared between time periods. The mean difference of these proportions was calculated along with a 95% bootstrapped CI. To examine the collection of trials available to AYA patients from 2004 to 2019, the date of activation and date of closure to accrual were recorded for each trial, and these accrual time intervals were plotted for all trials and for each CTEP disease category.

Patient level data ($n = 175,692$) were extracted for each eligible trial, including age at enrollment, sex, race, ethnicity, date of enrollment, and a ZIP code. To reduce confounding by health care system differences, patients without a US ZIP code were excluded ($n = 24,575$). Age groups were defined as pediatric (0–14 years), AYA (15–39 years), and adult (≥40). Race and ethnicity were combined into four categories (Hispanic, non-Hispanic White, non-Hispanic Black, and other). Descriptive statistics were computed, and cross-tabulations generated, for age groups by gender, race/ethnicity, and CTEP category. To analyze AYA accrual before and after the NCTN on a patient level, proportions of AYA accrual relative to total accrual along with 95% bootstrapped CI were calculated based on year of individual patient enrollment, grouping patients from 2004 to 2014 as pre-NCTN and 2015–2019 as post-NCTN. The mean difference of the bootstrapped estimates was also calculated. Pre- and post-NCTN proportions and mean differences by period were additionally calculated for the three disease categories with sufficient patient accrual (hematopoietic neoplasms, gastrointestinal neoplasms, breast cancer). For each year from 2004 to 2019, the total number of patients accrued and the proportion of those that were AYA were calculated. These proportions were plotted by year.

All analyses were conducted in RStudio version 1.4.1717 using tidyverse version 1.3.1.

RESULTS

A total of 304 trials that accrued patients during the period January 1, 2014–December 31, 2019 were included in the analyses. These trials involved 42 disease types (e.g., Ewing sarcoma) that were broadly categorized into 15 disease categories (e.g., bone neoplasm). Of the 304 trials, 254 (83.6%) were activated before the launch of the NCTN and 50 (16.4%) after the launch. The proportion of phase 3 trials (out of the total phase 2+2/3+3) launched after NCTN increased from 46.5% ($n = 118$) pre-NCTN to 60% ($n = 30$) ($p = .09$). Figure 2 displays the distribution of types of trials from 2004 to 2019 and is notable for an observed increase in the proportion of phase 2/3 trials before, compared with after, the launch of the NCTN (3.9% [$n = 10$] versus 20.0% [$n = 10$], respectively) and a peak in the number of available trials in 2010 with a nadir and subsequent rise in 2019. Figure S1 shows the available phase 2/3 and 3 trials in CTEP disease categories, highlighting

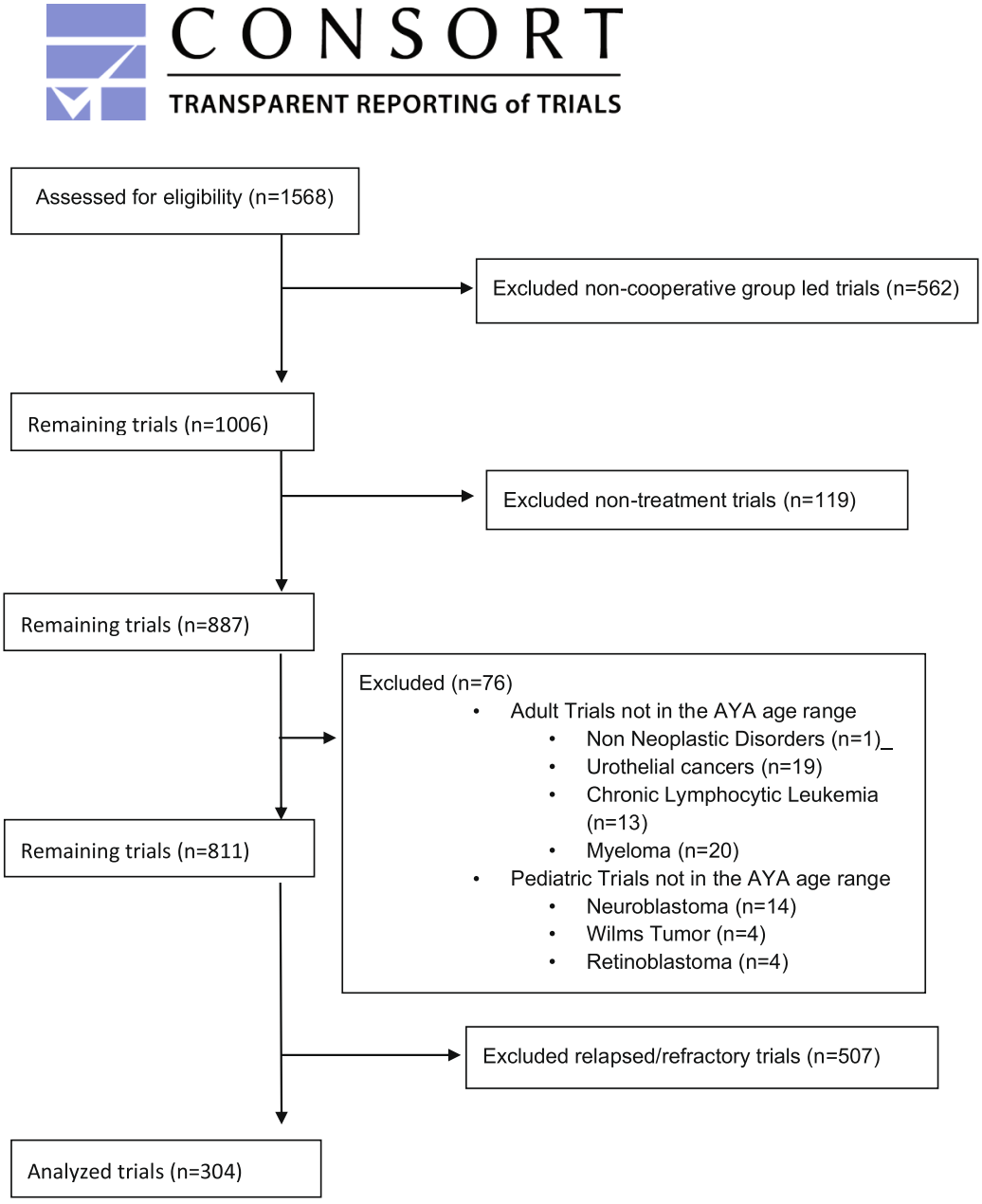

Figure 1. CONSORT 2010 flow diagram.[a]
[a]Although the objective of this study is to provide a summary of data across many clinical trials rather than reporting a single trial, this diagram indicating criteria for inclusion and inclusion of individual trials has been patterned after the CONSORT flow diagram.

the uniform availability of clinical trials in some disease types (e.g., breast cancer) and variable coverage in other disease types (e.g., liver and hepatobiliary cancer). For trials with activation date before the NCTN, the observed proportion of AYA patients relative to total accrued was 10.0% (95% CI, 7.9–12.3) and for trials with activation date after the NCTN was 16.6% (95% CI, 10.0–26.0).

Patient-level analyses revealed that from January 1, 2004, to December 31, 2019, there were 175,692 total patients accrued to the 304 included trials, of which 18,008 were AYA patients and 157,684 were non-AYA patients. After filtering to retain only patients with a US ZIP code, 151,117 patients were analyzable, of which 15,983 were AYA patients and 135,134 were non-AYA

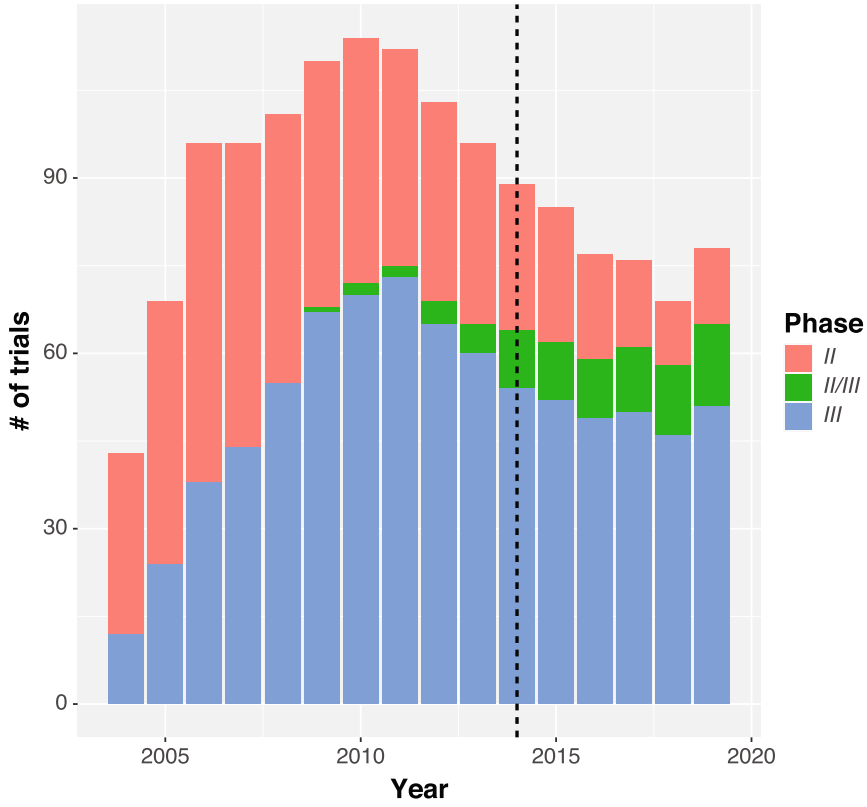

Figure 2. Distribution of trial types by year. For each calendar year, the number of actively accruing trials for which adolescent and young adult patients were eligible is represented as a stacked bar plot. For example, if a trial was activated in 2014 and closed to accrual in 2018, that trial contributes to calendar years 2014–2018. The vertical black bar represents the year of the National Clinical Trials Network launch.

patients. The demographic characteristics of the AYA and non-AYA population are described in Table 1. The observed proportion of AYA patients accrued pre-NCTN was 9.5% (95% CI, 7.6–11.8) compared with 14.0% (95% CI, 9.9–18.3) for post-NCTN. The mean difference in proportions post-NCTN compared to pre-NCTN was 4.5% (0.7%–8.3%). In a sensitivity analysis done using a post-NCTN cutoff of March 1, 2014, the observed proportion of AYA patients accrued pre-NCTN was 9.5% (95% CI, 7.6–11.7) compared with 14.0% (95% CI, 9.8–18.4) for post-NCTN and a mean difference in proportions post-NCTN compared with pre-NCTN was 4.5% (0.7%–8.5%). Two additional sensitivity analyses restricting the pre-NCTN time period to 2010–2014 and including non-US resident patients yielded results similar to the analysis including pre-NCTN patient accrual from 2004 to 2014 and restricting to only US patients.

Figure 3A displays the overall accrual of AYA and non-AYA patients and the proportion of AYA accrual (Fig. 3B) for the included trials from 2004 to 2019. These figures display gradual increase in the proportion of AYA patients enrolled in relevant clinical trials for newly diagnosed disease. Similar figures show the proportion of patients by race/ethnicity enrolled in relevant clinical trials for newly diagnosed disease (Fig. S2A and 2B).

Results for breast cancer were comparable to results for the overall comparison of pre- and post-NCTN proportions of AYA enrollment and mean difference (pre-NCTN 7.6%, post-NCTN 12.9%, difference 5.3% [95% CI, 1.6–8.9]). Gastrointestinal neoplasms had a numerically higher proportion post-NCTN, but the difference was not statistically significant (pre-NCTN 4.9%, post-NCTN 5.8%, difference 0.8% [95% CI, −1.3 to 3.6]). In hematologic neoplasms, pre- and post-NCTN proportions were comparable (pre-NCTN 2.2%, post-NCTN 2.1%, difference − 0.1% [95% CI, −1.0 to 7.3]).

DISCUSSION

One of the goals of the formation of the NCTN was to increase clinical trial access to subpopulations of patients that have had low enrollment, such as AYA patients.

TABLE 1. Patient Demographics

		Before the NCTN (2004–2014) n = 113,847			After the NCTN (2015–2019) n = 37,270		
		Adult (n = 90,346) (≥40 y)	AYA (n = 10,786) (15–39 y)	Pediatrics (n = 12,715) (<15 y)	Adult (n = 23,465) (≥40 y)	AYA (n = 5197) (15–39 y)	Pediatrics (n = 8608) (<15 y)
Sex	Female	67,554 (74.8%)	6807 (63.1%)	5630 (44.3%)	16,305 (69.5%)	3106 (59.8%)	3869 (44.9%)
	Male	22,789 (25.2%)	3978 (36.9%)	7085 (55.7%)	7159 (30.5%)	2090 (40.2%)	4739 (55.1%)
	Unknown	3 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.0%)	0 (0.0%)
Race/ethnicity	Hispanic	4777 (5.3%)	1364 (12.6%)	2921 (23.0%)	1902 (8.1%)	1018 (19.6%)	2245 (26.1%)
	Non-Hispanic Black	7674 (8.5%)	1271 (11.8%)	1268 (10.0%)	2230 (9.5%)	459 (8.8%)	635 (7.4%)
	Non-Hispanic White	73,699 (81.6%)	7296 (67.6%)	7304 (57.4%)	17,583 (74.9%)	3190 (61.4%)	4669 (54.2%)
	Other	4196 (4.6%)	855 (7.9%)	1222 (9.6%)	1750 (7.5%)	530 (10.2%)	1059 (12.3%)
CTEP category	Bone neoplasm	13 (0.0%)	669 (6.2%)	808 (6.4%)	0 (0.0%)	199 (3.8%)	205 (2.4%)
	Breast neoplasm	44,775 (49.6%)	3647 (33.8%)	0 (0.0%)	10,453 (44.5%)	1560 (30.0%)	0 (0.0%)
	CNS neoplasm (primary tumor)	2049 (2.3%)	517 (4.8%)	1135 (8.9%)	2034 (8.7%)	307 (5.9%)	391 (4.5%)
	Endocrine neoplasm	0 (0.0%)	5 (0.0%)	38 (0.3%)	2349 (10.0%)	152 (2.9%)	158 (1.8%)
	Gastrointestinal neoplasm	17,285 (19.1%)	914 (8.5%)	192 (1.5%)	1 (0.0%)	171 (3.3%)	126 (1.5%)
	Head and neck neoplasm	2539 (2.8%)	140 (1.3%)	52 (0.4%)	1541 (6.6%)	102 (2.0%)	0 (0.0%)
	Hematopoietic neoplasm/leukemia	1709 (1.9%)	2376 (22.0%)	8841 (69.5%)	742 (3.2%)	1658 (31.9%)	7263 (84.4%)
	Hematopoietic neoplasm/lymphoma	2030 (2.2%)	919 (8.5%)	305 (2.4%)	516 (2.2%)	466 (9.0%)	309 (3.6%)
	Kidney neoplasm	2732 (3.0%)	192 (1.8%)	237 (1.9%)	993 (4.2%)	41 (0.8%)	0 (0.0%)
	Lung, mediastinal, and pleural neoplasm	7576 (8.4%)	85 (0.8%)	0 (0.0%)	2703 (11.5%)	19 (0.4%)	0 (0.0%)
	Miscellaneous neoplasm	73 (0.1%)	4 (0.0%)	0 (0.0%)	96 (0.4%)	12 (0.2%)	0 (0.0%)
	Reproductive system neoplasm, female	7559 (8.4%)	507 (4.7%)	0 (0.0%)	973 (4.1%)	236 (4.5%)	0 (0.0%)
	Skin neoplasm	1980 (2.2%)	353 (3.3%)	0 (0.0%)	1014 (4.3%)	206 (4.0%)	0 (0.0%)
	Soft-tissue neoplasm	26 (0.0%)	458 (4.2%)	1107 (8.7%)	50 (0.2%)	68 (1.3%)	156 (1.8%)

Note: Because trials that were eligible for newly diagnosed AYA patients only were included, the number of pediatric and adult patients does not reflect enrollment of the NCTN overall.
Abbreviations: AYA, adolescent and young adult; CNS, central nervous system; CTEP, Cancer Therapy Evaluation Program; NCTN, National Clinical Trials Network

Measures implemented to increase trial access and accrual included requiring all NCTN members to use NCI-supported central services such as the Clinical Trials Support Unit and NCI Central Institutional Review Board, early collaboration on trial development, and designated "study champions" for each cooperative group for a specific trial to garner support for the trial within the group. To assess whether progress has been made in access and accrual for AYA patients in particular, the number of cooperative group trials available for AYA oncology patients and the number of AYA patients enrolling onto these clinical trials before and after the formation of the NCTN were examined. The proportion of phase 3 trials activated post-NCTN was observed to be higher in comparison to the proportion of phase 3 trials open pre-NCTN. This proportional increase in phase 3 trials post-NCTN could reflect a higher priority by the groups and NCI on getting phase 3 trials activated in the NCTN.

Examining the proportion of newly diagnosed AYA patients enrolling onto a clinical trial, the percentage of AYA patients has increased significantly with the formation of the NCTN (9.5% vs 14.0%). All NCTN (Alliance, Eastern Cooperative Oncology Group-American College of Radiology Imaging Network, NRG Oncology, SWOG, and COG) trials for relevant newly diagnosed AYA cancers were included in the analyses presented here. The patient population examined in this study was intentionally limited to newly diagnosed patients in relevant AYA cancers to achieve a better understanding of the availability of trials in certain disease categories.

SWOG Cancer Research Network (one of the NCTN 5 cooperative groups) published their AYA patient accrual over a 25-year period (1996–2020) and reported that 8.4% of the enrolled patients were AYAs. They included patients enrolled in phase 1 to 3 therapeutic trials although for patients enrolled on multiple trials, only the first enrollment was included. They also only included trials in their analysis for which SWOG enrolled 100 or more patients during the specified period.[10] These results

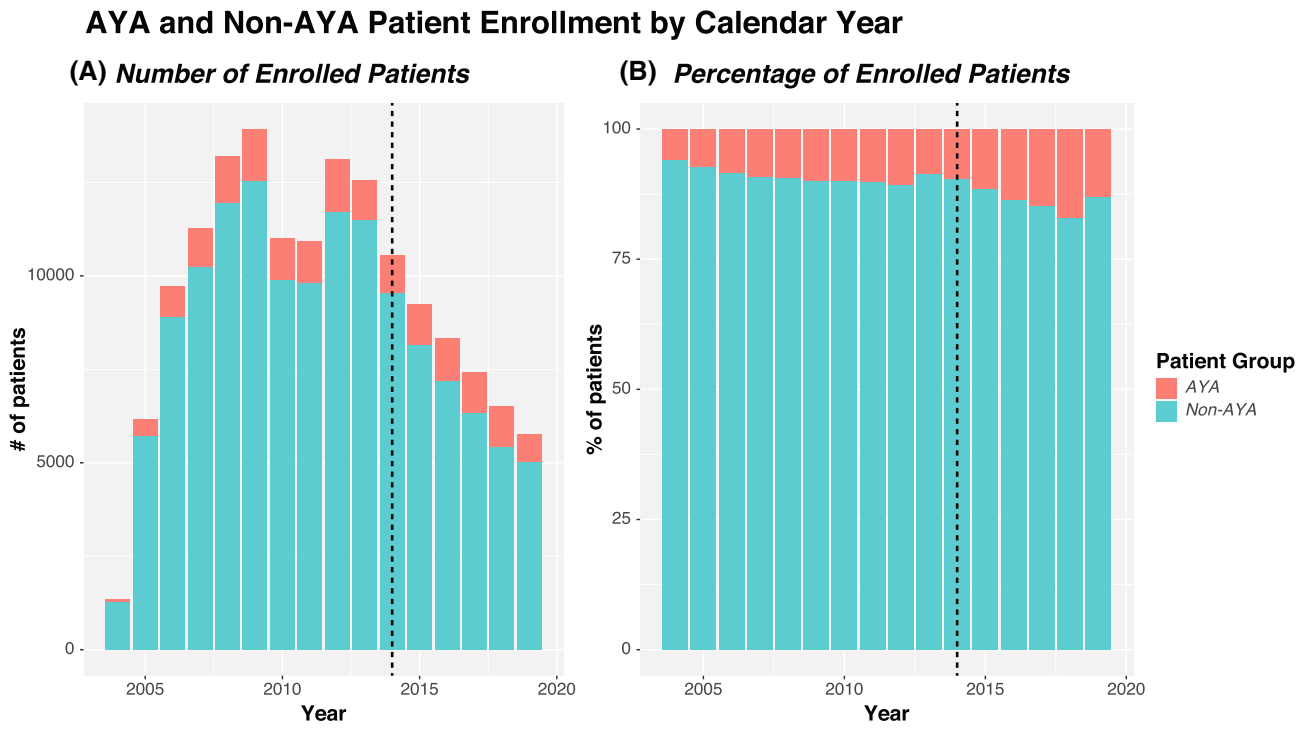

Figure 3. Proportion of AYA patients relative to total accrual enrolled by year. (A) Total number of newly diagnosed patients enrolled from 2004 to 2019 for included trials. (B) Percentage of AYA patients for each calendar year, which was calculated using the number of AYA patients accrued on all included trials for that calendar year divided by the total accrual for those trials in that calendar year. Because only trials activated after January 1, 2004, are included, the first few years in the bar graph may not be representative of the patients accrued those respective years because patients enrolled on a trial that activated before 2004 would not be included. The vertical black bar represents the year of the NCTN launch. AYA indicates adolescent and young adult; NCTN, National Clinical Trials Network.

are similar to the 10.6% observed in this study for newly diagnosed patients. After the launch of the NCTN, the proportion of newly diagnosed AYA patients accrued onto eligible clinical trials has increased. Though it is not possible to directly attribute this to the launch of the NCTN, similar findings regarding increased AYA accrual were noted in the SWOG publication.

Notably, there was an observed increase in phase 2/3 and phase 3 trials for newly diagnosed AYA patients after NCTN. This programmatic change highlights a shift from traditional phase 2 trials to adaptive 2/3 trial designs that prospectively incorporate planned modification to one or more aspects of the trial. The benefit of this approach is that trials can be completed in a shorter period and with fewer total number of patients.[11] Changes in AYA enrollment proportions after the launch of NCTN differed across major disease categories and might reflect programmatic differences for those disease groups. For example, the majority of included trials for hematopoietic neoplasms were run by the Children's Oncology Group both pre- and post-NCTN, which may contribute to consistency between the two time periods.

Although not a primary aim of the study, descriptive analyses of enrollments by race/ethnicity were also conducted. Within the AYA group, the observed percentage of Hispanic and non-Hispanic Black patients enrolled was 12.6% and 11.8% pre-NCTN and 19.6% and 8.8% post-NCTN. Our observations regarding the increase in Hispanic ethnicity enrollment in the AYA population and lack of increase in the non-Hispanic Black population are comparable to those reported by SWOG for patients accrued 1996–2020.[10]

Results of this study should be interpreted in the context of its strengths and limitations. Trials included in this study were restricted to those that were phase 2, 2/3, and 3, and accrued only newly diagnosed patients. Trials for cancers with age distribution mainly in older adult or pediatric range, and trials that primarily enrolled relapsed patients but may have included some newly diagnosed patients, were also excluded. A comprehensive evaluation of relapsed/refractory AYA patient accrual was beyond the scope of this study. These restrictions may have led to underestimation of AYA enrollments overall. Additionally, this analysis highlights the difficulties of assessing the trend

in accrual by disease category because accrual requires an available disease-specific, and in some cases stage-specific, trial in any given year. For example, Figure S1 shows that since the closure of AOST0331, there has not been an open trial for newly diagnosed localized osteosarcoma in the NCTN. For the four most common cancer types causing death among AYA patients (breast, brain, leukemia, and colorectal),[12] at least one trial for newly diagnosed patients in each respective category was available in any given calendar year from 2004 to 2019 (Figs. 3A–D). Because trials activated before January 1, 2004, were excluded, some trials (e.g., AEWS0331 for newly diagnosed localized Ewing sarcoma) were not included in this analysis, which may underrepresent the availability of trials in some disease categories (i.e., Ewing sarcoma) as well as AYA enrollments.

This study is the most comprehensive study examining how AYA accrual changed with the formation of the NCTN for newly diagnosed cancers. Although it is beyond the scope of this study to conduct a detailed examination of factors potentially responsible for increased AYA enrollment, possible explanations for increased AYA enrollment are broader investigator (both through the NCTN and NCI Community Oncology Research Program) and patient education to look for trial availability for newly diagnosed AYA patients, broadening eligibility criteria to make sure that AYA patients are eligible to enroll if appropriate, ease of activating a NCTN trial at the local site when an AYA patient is diagnosed with a cancer eligible for NCTN clinical trial (e.g., Central Institutional Review Board, Clinical Trials Support Unit) and consideration of AYA subpopulation early in the development of a concept for a clinical trial. As noted recently from Surveillance, Epidemiology, and End Results data, despite significant improvements in outcome for some AYA cancer types (such as brain and other nervous system tumors, colon and rectum, lung and bronchus, acute myeloid leukemia, and non-Hodgkin lymphoma) there have been limited to no improvements in AYA survival for female breast cancer, cervical cancer, ovarian, and bone and joint sarcomas.[13] To confront one of the challenges for AYA patients diagnosed with these cancers, it will be imperative that they have access to the newest and best treatments available for their cancer type at the time of diagnosis. Availability of treatment trials for AYA patients through the NCTN must remain a priority.

In conclusion, after the launch of the NCTN, the proportion of AYA patients from a total enrollment in NCI CTEP-sponsored clinical trials for newly diagnosed cancers has increased.

AUTHOR CONTRIBUTIONS

Hari Sankaran: Data curation, formal analysis, writing-original draft preparation, and visualization. **Shanda R. Finnigan:** Data curation, visualization. **Lisa M. McShane:** Formal analysis, visualization. **Ana F. Best:** Formal analysis, visualization, and supervision. **Nita L. Seibel:** Data curation, formal analysis. All authors assisted with writing – review and editing, conceptualization, and methodology.

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CONFLICTS OF INTEREST

The authors made no disclosures.

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