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Treatment Setting, Clinical Trial Enrollment, and Subsequent Outcomes Among Adolescents With Cancer: A Literature Review

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Abstract

BACKGROUND: There has been an overall improvement in survival rates for persons with cancer over the past 35 years. However, these gains are less prevalent among adolescents with cancer aged 15 to 19 years, which may be due to lower clinical trial enrollment among adolescents with cancer.

METHODS: We conducted a literature review to assess current research regarding clinical trial enrollment and subsequent outcomes among adolescents with cancer. The search included English-language publications that reported original data from January 1985 to October 2011.

RESULTS: The search identified 539 records. Of these 539 records, there were 30 relevant original research articles. Multiple studies reported that adolescents with cancer are enrolled in clinical trials at lower rates compared with younger children and older adults. Treatment setting, physician type, and institution type may all be factors in the low enrollment rate among adolescents. Few data focused solely on adolescents, with many studies combining adolescents with young adults. The number of available studies related to this topic was limited, with significant variability in study design, methods, and outcomes.

CONCLUSIONS: This literature review suggests that adolescents with cancer are not treated at optimal settings and are enrolled in clinical trials at low rates. This may lead to inferior treatment and poor subsequent medical and psychosocial outcomes. The scarcity in data further validates the need for additional research focusing on this population.

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Keywords

clinical trial enrollment; cancer; adolescents; oncology

Over the past 35 years, the number of cancer survivors in the United States has grown from <3 million to nearly 12 million.[1] Although there have been improvements in cancer survival, morbidity, and quality of life in the overall population of US cancer survivors, these gains are less prevalent among adolescents aged 15 to 19 years diagnosed with cancer.[2–4] This situation is especially true when compared with younger children aged 0 to 14 years and older adults,[2–4] for whom improved outcomes are correlated to enrollment in clinical trials.[5]

Adolescents with cancer are enrolled in clinical trials at much lower rates in the United States compared with younger children and older adults.[5–7] One reason adolescents are enrolled in clinical trials at low rates is because of referral patterns.[8–10] Unlike younger children or older adults, adolescents with cancer may be referred by pediatricians to either pediatric or adult oncologists.[11] Most adolescents are referred to adult oncology centers, and the referral of adolescents to pediatric oncology centers diminishes with age.[11–13] Adult cancer centers have lower rates of clinical trial enrollment and less access to clinical trials for adolescents compared with pediatric cancer centers. Additionally, there is evidence that adolescents diagnosed with certain types of cancer who are treated on pediatric protocols have better outcomes compared with those on adult protocols.[14–17] To address these and other issues related to clinical trial enrollment and health outcomes for adolescent survivorship, we examined the scientific literature regarding this topic. We performed a literature review to assess current research regarding treatment setting, clinical trial enrollment, and subsequent outcomes among adolescents with cancer.

METHODS

The literature review focused on treatment setting, enrollment in clinical trials, and subsequent medical and psychosocial outcomes among adolescents with cancer. To examine psychosocial outcomes, we examined adolescents who participated in randomized controlled trials targeting behavioral change and emotional symptoms related to cancer trajectory. With the use of the OVID, EBSCOhost, Medline, and Embase search platforms, we performed a keyword search of 5 databases: Medline, Embase, the Psychological Abstracts database (PsychINFO), Cochrane Library, and the Cumulative Index of Nursing and Allied Health Literature database. We reviewed reference lists of eligible articles found through the initial search to identify additional articles. We also identified additional articles not abstracted in the initial search in a cursory review from researchers and practitioners in the fields of oncology and health psychology. Figure 1 shows an example of a search syntax we used. We limited results to peer-reviewed original research studies from the United States, the United Kingdom, Australia, and Canada published in English between January 1, 1985, and October 31, 2011.

A 2-phase classification procedure was used to determine relevance. In phase I, a primary reviewer assessed all titles and abstracts and classified them as either potentially relevant, relevant, or not relevant. In phase II, the primary reviewer reviewed the full text of all

potentially relevant articles and classified them as either relevant or not relevant. A quality assurance procedure with 3 reviewers was used to verify the accuracy of relevance classifications. A first reviewer read a 25% random sample of articles and classified them as potentially relevant, relevant, or not relevant. A second reviewer repeated this process independently. Results from the 2 reviewers were sent to a third reviewer who identified and reconciled any discordance in classification.

RESULTS

The combined database and reference list searches resulted in 66 relevant articles (Fig 2). Of these 66 articles, 36 were review articles or commentaries and 30 were original research articles. Of the 30 original research articles, there were 4 randomized controlled trials, 2 prospective cross-sectional studies, and 24 retrospective cross-sectional studies (Table 1). Although there was an emphasis on cancer types most commonly found in the adolescent population, the majority of articles examined all cancer types. Among all articles, there was variation in the definition of the adolescent and adolescent and young adult (AYA) population; age ranges were as low as 13 years for adolescents and up to 40 years for young adults. We present an overview of the relevant articles by the following topic areas: treatment setting, clinical trial enrollment, and subsequent outcomes.

Treatment Setting

Several studies focused primarily on the setting in which adolescents with cancer were treated. One study in Ohio found that of 169 adolescent patients aged 15 to 19 years, 47% were treated at pediatric institutions, 25% were treated at adult academic centers, and 29% were treated at community hospitals.[18] Treatment at pediatric centers decreased with increasing age. However, cancer type was found to be an important diagnostic factor independent of age: malignancies traditionally regarded as “pediatric,” such as acute lymphoblastic leukemia, central nervous system tumors, and osteosarcomas, were treated more often at pediatric hospitals regardless of age, whereas malignancies traditionally regarded as “adult,” such as melanoma and germ cell tumors, were more often treated at adult institutions regardless of age.[18] Another study in Canada found that ~30% of adolescents aged 15 to 19 years were treated at a pediatric institution.[19] Consistent with the study from Ohio, the likelihood of treatment at a pediatric institution decreased with increasing age, and adolescents treated at adult institutions were more likely to have a diagnosis of carcinoma or germ cell tumor and less likely to have lymphoma.[19] Another study found that only 14% of adolescents aged 16 to 19 years were treated at a pediatric institution.[20]

Clinical Trial Enrollment

A number of identified studies assessed clinical trial enrollment among adolescents with cancer. The range of adolescent patients enrolled in clinical trials ranged from 5% to 34%. A study of Children’s Oncology Group enrollment data showed that only 21% of patients aged 15 to 19 years of age were enrolled in clinical trials.[5] The Children’s Oncology Group accounted for >97% of all clinical trial participants <20 years of age, whereas adult cooperative groups collectively accounted for <3% of clinical trials for adolescents in the

15- to 19-year range.[21] A National Cancer Institute Patterns of Care study showed that 34% of adolescents aged 15 to 19 years were enrolled in a clinical trials.[22] The study showed that older patients and those treated by adult oncologists were less likely to be enrolled into clinical trials.[22] A decreasing rate of clinical trial enrollment with increasing age was also seen in the Los Angeles County Cancer Surveillance Program.[23] Adolescents aged 15 to 19 years, compared with children aged 14 and younger, were less commonly diagnosed at a Children's Oncology Group institution and were also enrolled in a clinical trial at lower rates.[23] In addition to lower clinical trial enrollment rates among adolescents, there were also fewer therapeutic trials available for this age group.[23] A comparison of clinical trial enrollment between adolescent and young adult oncology patients aged 15 to 22 years treated at affiliated adult and pediatric centers revealed that clinical trial enrollment was higher with treatment at a pediatric center. Of 91 cases with new cancer diagnoses treated at the pediatric center, 24 (26%) were enrolled, whereas only 5 of 121 (4%) cases with new cancer diagnoses treated at the adult center were enrolled in a clinical trial[24] A study in Australia showed that adolescents aged 10 to 19 years were more likely to be enrolled in a clinical trial if treated at a pediatric institution rather than at an adult institution (38% vs 3%).[20] Even if adolescents are seen at a pediatric institution, appropriate clinical trials may not be available. In a study in 640 patients with newly diagnosed cancer at a pediatric institution, 38% of patients under the age of 15 years were enrolled in a clinical trial and 27% of patients aged 15 to 22 years were enrolled in a clinical trial[25] More than half of the older patients were not enrolled because a trial was not available.[25] Clinical trial enrollment may be affected not only by differences in pediatric and adult institutions but by differences in academic compared with community institutions. Because most clinical trials are primarily conducted at academic institutions, most accrual into these trials is from academic centers. By reaching out to community oncologists and practices, physicians and researchers in academic settings may expand access to clinical trials.[18] Cooperative group protocols that could be implemented practically at community hospitals and outpatient offices could increase patient accrual.[18]

There is also evidence that clinical trial enrollment is improved when adolescent patients are seen at a dedicated AYA oncology program.[26] In the 3 years before the establishment of an AYA program at the University of Pittsburgh, clinical trial enrollment at the adult center was 4%. In the 4 years after the creation of the AYA program, clinical trial enrollment at the pediatric center and adult center increased to 33%.[26] Thus, the development of AYA programs may be a strategy to increase clinical trial enrollment for adolescent patients with cancer.[26] Another potential strategy to increase clinical trial enrollment is expanding national clinical trials accessibility to patients treated at both pediatric and medical oncology tertiary care centers through collaboration between pediatric and adult oncologists.[24–26] This collaboration could be facilitated through improved communication between pediatric and adult oncologists, such as the establishment of an AYA cancer resource network that provides current information about currently available clinical trials.[20,22]

Survival

Several studies reported on survival trends among adolescents with cancer.[27–37] A number of studies showed that increasing age was a poor prognostic factor for certain cancers,

including acute myeloid leukemia, non-Hodgkin's lymphoma, Burkitt's and Burkitt-Iike lymphoma, and rhabdomyosarcoma.[29–32] Two studies reported that adolescents with acute lymphoblastic leukemia were shown to have superior outcomes when treated on pediatric protocols compared with adult protocols.[27,28] Despite limitations in the comparison of clinical trials due to differences in methodology, comparative studies indicate that adolescents with cancer may have a survival advantage when treated on pediatric protocols compared with adult protocols.[27,28] However, this finding may not hold true for all patients, cancers, and therapies. Ultimately, improved survival may be best achieved by risk-directed selection of therapies based on the biology and response to therapy.[27] The age limits for recruitment into clinical trials may need to be reconsidered.[27,28]

Psychosocial Outcomes

Several studies have identified that adolescent cancer survivors and their families may struggle with posttraumatic stress disorder, depression, and other clinical emotional and behavioral concerns as a result of their cancer diagnosis, treatment, and long-term trajectory.[38] However, the onset, frequency, and duration of adverse emotional or behavioral symptoms and diagnosed psychosocial disorders among adolescent cancer survivors are vastly underexplored. Psychosocial interventions and their effect on psychosocial outcomes of adolescent cancer survivors have been examined in randomized controlled trials.[39] Two randomized controlled trials showed that an integrated cognitive-behavioral and family therapy approach as well as a telephone-delivered coping skills training intervention may be effective components in the reduction in posttraumatic stress symptoms and other symptoms among adolescent cancer survivors.[40–42] Efforts to decrease posttraumatic stress symptoms are especially important in this population because stress may increase risk behaviors such as physical inactivity, smoking, and nonadherence to sun protection among adolescent cancer survivors.[43] One study examined the effect of a multicomponent educational intervention to decrease risk behaviors and health-protective behaviors among adolescent cancer survivors[44] Results indicated that age and gender may have a strong influence on the impact of interventions targeting health behaviors in this population, and future trials should consider more factors including an improved understanding of patient-clinician interactions, patient motivations, and more specific outcome measures.[44]

DISCUSSION

This literature review suggests that adolescents with cancer are not treated at optimal settings and are enrolled in clinical trials at low rates. This situation may lead to inferior treatment and poor subsequent medical and psychosocial outcomes. Barriers that prevent adolescents from enrolling in clinical trials include the treatment setting, treating physician, and institution type. Adolescents with cancer are often referred to nonpediatric centers and community hospitals. Access to clinical trials is more limited for adolescents in these settings compared with pediatric tertiary care institutions, thereby reducing the possibility of clinical trial enrollment for a majority of adolescents with cancer.

Increasing referral to pediatric centers, when appropriate, is needed to increase enrollment of adolescents in clinical trials. Because it may be more appropriate for adolescents with

certain types of cancer, such as melanoma and germ cell tumors, to be treated at adult institutions for medical reasons, it is also important to increase enrollment for adolescents with cancer who are seen in adult and community settings. This increase may be achieved through collaboration between pediatric and adult institutions and oncologists. There is also a need for unified clinical trial protocols for adolescents that can be followed by both pediatric and adult oncologists in national cooperative groups. Increased collaboration may also be facilitated through dedicated AYA oncology programs, which have been shown to increase clinical trials enrollment for both adolescents and young adults.

The number of available studies related to this topic was limited. The identified studies had significant variability in study design, methods, populations, and outcomes. Therefore, conclusions based on these studies may not be generalizable to all populations. The lack of a standardized age category may also lead to misclassification and bias among the studies reviewed.

The limited number and scope of articles identified through this literature review is reflective of the small but emerging view of adolescents with cancer as a distinct and unique entity. Results from this literature review indicate that few data focused solely on adolescents are available, with many studies combining adolescents with young adults. This scarcity in data further validates the need for additional research focusing on this population. The experience and needs of adolescent patients with cancer are different from those of other age groups in many respects. Continued focus on the biology of AYA tumors, therapies to improve survival and decrease toxicity, and the long-term impacts of cancer treatment is needed. Increased attention is needed on initial engagement with the health care system after a cancer diagnosis, including referral and choosing optimal treatment settings and physicians. As the cancer survivor population continues to increase, it is of public health importance that adolescents are not excluded from improvements seen in other age groups and receive the highest standard of care.

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ABBREVIATION

AYA	adolescent and young adult

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((clinical trial [tw] OR clinical trial [kw] OR clinical research [tw]) AND (adolescen* [tw] OR teen* [tw] OR young adul* [tw]) AND (neoplasm* [tw]) AND (neoplasm* [tw] OR cancer [tw]) AND (participat* [tw] OR enroll* [tw] OR accru* [tw] OR recruit* [tw])) NOT clinical trial [pt]

FIGURE 1.
Sample search syntax for Medline, Embase, PsychINFO, and Cochrane databases.

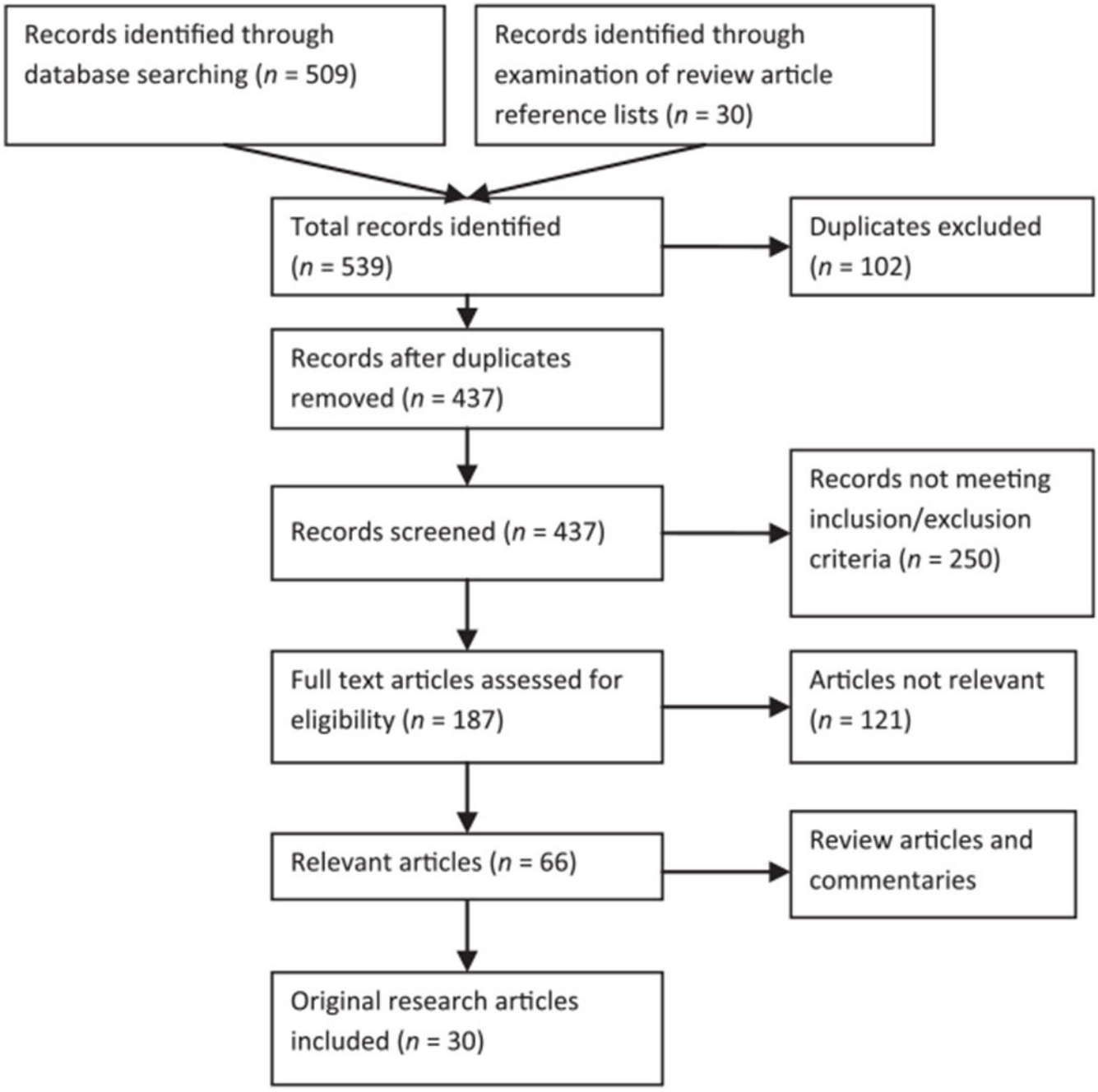

FIGURE 2.
Flowchart of article screening, assessment, and inclusion.

TABLE 1

Studies on Patterns of Referral, Clinical Trial Enrollment, and Subsequent Outcomes Among Adolescents With Cancer

First Author	Year	Sample Size	Age of Study Population	Study Design	Type of Cancer	Primary Outcome
Alderfer[39]	2009	144	11–19 y	Prospective, cross-sectional	All	Family functioning
Baider[45]	1989	8	15–25 y	Prospective, cross-sectional	All	Psychological distress
Bleyer[5]	1997	29 859	0–20 y	Retrospective, cross-sectional	All	Clinical trial enrollment
Burkhardt[30]	2011	378	15–18 y	Retrospective, cross-sectional	Non-Hodgkin's lymphoma	Survival
Cairo[29]	2003	470	0–21 y	Retrospective, cross-sectional	Burkitt's lymphoma	Survival
Cox[44]	2005	272	12–18 y	Randomized controlled trial	All	Behavior change
Creutzig[31]	2007	1181	0–30 y	Retrospective, cross-sectional	Acute myeloid leukemia	Survival
Downs-Canner[24]	2009	91	15–22 y	Retrospective, cross-sectional	All	Clinical trial enrollment
Hill[46]	2007	77	7–19 y	Retrospective, cross-sectional	Colorectal	Clinical and pathologic features
Joshi[32]	2004	2343	0–21 y	Retrospective, cross-sectional	Rhabdomyosarcoma	Survival
Judge Santacroce[41]	2009	21	15–25 y	Randomized controlled trial	All	Coping skills
Kazak[40]	2004	150	11–19 y	Randomized controlled trial	All	Posttraumatic stress symptoms
Klein-Geltink[19]	2005	204	15–19 y	Retrospective, cross-sectional	All	Provider type
Krailo[23]	1993	2788	0–19 y	Retrospective, cross-sectional	All	Clinical trial enrollment
Millot[34]	2011	44	10 mo–17 y	Retrospective, cross-sectional	Chronic myelogenous leukemia	Survival
Mitchell[20]	2004	576	10–24 y	Retrospective, cross-sectional	All	Clinical trial enrollment
Moreno[33]	2009	16	14–24 y	Retrospective, cross-sectional	Ependymoma	Survival
Pao[47]	2006	347	1–21 y	Retrospective, cross-sectional	All	Psychotropic medication use
Parsons[22]	2011	1358	15–39 y	Retrospective, cross-sectional	All	Factors associated with clinical trial enrollment
Pinkerton[36]	2010	11 915	0–29 y	Retrospective, cross-sectional	Hematologic malignancies	Survival
Polishchuk[35]	2011	39	≥10 y	Retrospective, cross-sectional	Neuroblastoma	Survival
Portteus[48]	2006	216	—	Retrospective, cross-sectional	All	Antidepressant medication use
Ramanujachar[27]	2007	128	15–17 y	Retrospective, cross-sectional	Acute lymphoblastic leukemia	Provider type
Ramanujachar[28]	2006	48	15–21 y	Retrospective, cross-sectional	Acute lymphoblastic leukemia	Provider type
Shaw[25]	2007	640	0–22 y	Retrospective, cross-sectional	All	Clinical trial enrollment
Shaw[26]	2010	57	15–22 y	Retrospective, cross-sectional	All	Clinical trial enrollment
Silverman[37]	2010	1457	0–18 y	Retrospective, cross-sectional	Acute lymphoblastic leukemia	Survival
Sultan[49]	2010	159	4–20 y	Retrospective, cross-sectional	Colorectal	Clinical and pathologic features
Tercyak[43]	2006	75	11–21 y	Randomized controlled trial	All	Behavioral risk factors
Yeager[18]	2006	169	15–19 y	Retrospective, cross-sectional	All	Provider type