 Advances in cancer therapy have led to increased survival; there are more than 9 million 5-year survivors of cancer in the United States. As this number continues to grow, focus on improved health and quality of life becomes a priority. It is especially important in survivors of childhood, adolescent, and young adult cancer who have 5-year survival rates exceeding 80%1 and who are expected to live many decades after diagnosis and treatment. Because of their young age at treatment, this population is the most vulnerable to long-term detrimental effects of cancer therapy. Many studies have shown that childhood and adolescent cancer survivors are at increased risk for chronic medical problems and emotional late effects as they age.2-5 These late effects influence overall health and quality of life.

While the impact of cancer and its treatment on children is an area of increasing research, there is a paucity of late-effects data for young adults. The risk of developing treatment-related sequelae and the type of surveillance screening necessary for this population are often extrapolated from studies of children or middle-aged adults. However, adolescents and young adults (AYAs) have a unique pattern of cancer development with distinct biological findings6 and different psychosocial stressors associated with the transition to adulthood. This distinctive biology and psychosocial environment suggest that the late-effects burden in AYAs may differ greatly from that of other survivors. Studies are needed in this age group to describe the breadth of late effects to guide screening and treatment.

In this issue of JAMA Oncology, Rugbjerg and Olsen7 provide a glimpse into the late-effects burden among AYA survivors through the use of national Danish registries. The authors compare the long-term risk of hospitalization in 33 555 5-year survivors of AYA cancer (diagnosed at age 15-39 years) with that of 228 447 age- and sex-matched population controls. They identified 53 032 hospitalizations among survivors compared with 38 423 expected, based on the control population, leading to a standardized hospitalization rate ratio (RR) of 1.38 (95% CI, 1.37-1.39) and absolute excess risk (AER) of 2803 (95% CI, 2712-2893) hospitalizations per 100 000 person-years. The highest AERs were found for malignant neoplasms, diseases of the digestive system, and cardiovascular disorders. Those with the highest risk of hospitalization included survivors of leukemia (RR, 2.21; 95% CI, 2.02-2.42), brain tumors (RR, 1.93; 95% CI, 1.86-2.00), and Hodgkin lymphoma (RR, 1.87; 95% CI, 1.80-1.94), which are malignant conditions known to have increased late effects in pediatric survivors. More than 50% of the cancer-specific AER for survivors of brain cancer was due to neurologic or endocrine disorders, while approximately 50% of the AER for survivors of Hodgkin lymphoma was attributed to malignant neoplasms and cardiovascular disease. Of interest, the AER for leukemia survivors was attributed mostly to infectious and parasitic diseases (20%) and respiratory conditions (28%), especially influenza and pneumonia.

The large sample size and low attrition rate of this study7 allow for a comprehensive view of the inpatient treatment of AYA survivors and offer early insight into their overall disease burden. However, the full range of treatment sequelae cannot be evaluated using these data, since many late effects of cancer therapy are treated in the outpatient setting. For example, in contrast to infectious or respiratory complications seen in the Rugbjerg and Olsen study,7 the preponderance of treatment-related sequelae in previously published reports of survivors of childhood leukemia are musculoskeletal, cardiac, endocrine, or neurologic in origin8,9; these are often treated in outpatient clinics. Because leukemia treatment is often longer than treatment for other malignant conditions, and many patients who have relapsed are treated more than 5 years after the original diagnosis, it is difficult to determine if the infectious and respiratory complications observed in this study are owing to long-term immunocompromise in these survivors, which requires further surveillance, or acute sequelae in patients who have experienced a relapse requiring hospitalization.

Importantly, the subsequent malignant neoplasms described in this study7 differ greatly from those previously observed in survivors of childhood and adolescent cancers. The most common malignant conditions leading to hospitalization in AYA survivors were nonmelanoma skin cancer, neoplasms of the digestive organs, and cancers of the respiratory system. It is surprising that breast and thyroid cancer, 2 of the most commonly reported subsequent malignant neoplasms in survivors of childhood and adolescent cancer,10 were not as prevalent in this study. However, this variation in types of subsequent cancers may be owing to the difference in primary cancer location and treatment. In this study,7 survivors of cervical, testicular, and primary breast cancer made up nearly 50% of the study population. These cancers are often treated with irradiation to the pelvis or chest, which increases the risk of gastrointestinal and lung cancer.

As evidenced by Rugbjerg and Olsen,7 treatment sequelae in AYA cancer survivors, including subsequent malignant neoplasms, differ from those in survivors of childhood cancer. Prevention and management of late effects necessitate early detection and intervention, which require a comprehensive view of the treatment-related sequelae that can-
not be garnered solely from inpatient data. To fully understand the risks faced by AYA cancer survivors, large cohorts are needed to evaluate inpatient and outpatient disease processes as well as their psychosocial implications.

Although research in the late effects of pediatric cancers is better established than that in AYAs, there remain areas that require increased attention. Of particular importance is neurocognitive development, which affects education, employment, and quality of life. Initial studies of neurocognitive late effects in pediatric survivors have focused on the harmful effects of cranial irradiation on the developing brain, but more recent studies have examined the impact of chemotherapy alone in survivors of acute lymphoblastic leukemia (ALL). A recent meta-analysis of 10 studies included 509 survivors of ALL treated with chemotherapy alone and 555 controls. The study showed significant moderate impairments in full scale intelligence quotient (IQ), verbal IQ, performance IQ, working memory, information processing speed, and fine motor domains. However, while the neurocognitive impairments in patients with ALL have been well-established, there is a paucity of information about these outcomes in survivors of pediatric solid tumors.

Edelmann and colleagues address this in their study published in the current issue of JAMA Oncology. They compare the neurocognitive outcomes in 80 adult survivors of pediatric osteosarcoma nearly 25 years after diagnosis with 39 community controls and with national norms. Due to their exposure to high doses of intravenous methotrexate, these survivors were thought to be at increased risk of neurocognitive sequelae. The cross-sectional study assessed intelligence, academic skills, attention, memory, processing speed, and executive function using licensed examiners as well as patient-reported neurobehavioral symptoms, emotional symptoms, and health-related quality of life. Compared with controls and population normative data, respectively, survivors of pediatric osteosarcoma demonstrated poorer performance in reading (P = .01 and P < .001), attention (P = .002 and P = .006), short-term recall (P = .01 and P = .05), reaction time (P = .03 and P = .02), motor processing speed (P < .001 and P < .001), and cognitive fluency (P = .006 and P = .003). In addition, the survivors reported worse working memory compared with controls (P < .001) and national norms (P = .004). In survivors, neurocognitive sequelae were related to low educational and employment attainment as well as decreased income.

One of the major strengths of the study by Edelmann et al is the authors’ ability to examine the association among neurocognitive findings, the pharmacokinetic indices of methotrexate exposure, and the presence of chronic health conditions. The authors found no association between poor neurocognitive functioning and the number of high-dose methotrexate courses, cumulative dose, median peak concentration, median systemic clearance, or median or cumulative exposure. However, compared with survivors without a grade 3 (severe/disabling) or 4 (life-threatening) chronic medical condition, survivors with a grade 3 or 4 chronic cardiac, pulmonary, or endocrine condition demonstrated worse memory (P = .006) and motor processing speed (P = .002). Based on these findings, the authors conclude that the risk for neurocognitive impairment in long-term survivors of pediatric osteosarcoma is related to the development of chronic health conditions and not to high-dose methotrexate exposure per se. However, the authors also state that the extended time since diagnosis may lessen the association between methotrexate exposure and neurocognitive impairment as more chronic conditions emerge. Without a longitudinal study, it is impossible to determine if neurocognitive deficits were present prior to the development of chronic health conditions and linked to chemotherapy exposure. Furthermore, a genetic predisposition that increases sensitivity to chemotherapy may influence neurocognitive outcomes and the development of chronic conditions. In fact, this same research group previously published data demonstrating an association between neurocognitive outcomes and various genetic polymorphisms in survivors of pediatric ALL.

This study highlights the need for further longitudinal neurocognitive testing of cancer survivors to identify deficits, determine possible modifying factors, and evaluate the trajectory of change. Since neurocognitive outcomes have a significant impact on daily functioning, it is imperative that we develop interventions to improve the long-term outcomes of survivors.

Going forward, we must apply our knowledge of late effects to improve monitoring and interventions for patients. While the progress made in the management of cancer in children and young adults has been gratifying, we must remember the words of Giulio D’Angio, who reminds us that “cure is not enough.”

**REFERENCES**


