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Childhood Cancer, Endocrine Disorders, and Cohort Studies

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In 1975, investigators convened the first international ‘late effects’ meeting at the National Cancer Institute (NCI) Conference on the Delayed Consequences of Cancer Therapy: Proven and Potential. Several of the topics focused on endocrine disorders, including growth hormone deficiency,¹ the consequences of gonadal irradiation,² and the ‘long-term effects of radiation on the pituitary and thyroid glands’.³ Since that momentous meeting, many studies have reported on endocrine outcomes, beginning with single institution studies and then more recently from large cohort studies. In this issue of *Lancet*, de Fine Licht and colleagues from the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) Study describe endocrine outcomes from a large population-based study consisting of 31 723 one-year childhood cancer survivors from five countries diagnosed from the 1940s and 1950s through 2008 and compare them to a matched cohort of 211 261 individuals without a childhood cancer.⁴ This study makes several significant and novel contributions to our understanding of the long-term and late effects of the curative therapy for childhood cancer and has important research and clinical implications.

Prior to discussing these contributions, it is essential to understand how the ALiCCS study design, a cohort data-linkage study, compares to other large cohort studies. There is not one ideal cohort study – each approach is based upon available resources and the idiosyncrasies of the country's health care infrastructure and thus has different strengths and limitations that must be taken into account when interpreting the findings or comparing outcomes from one study to another. That being said, it is truly remarkable that the data from different cohort studies continue to support the findings of others, thus increasing our confidence in the observations and broadening the generalizability of the results.

Twenty years ago, in 1994, the Childhood Cancer Survivor Study (CCSS) was launched, followed by the establishment of several other large cohort studies, including the British CCSS, the French-British Lymphoma and Solid Tumor Cohort Study, the Swiss CCSS, and now the Dutch LATE Effect Registry (LATER) Study and the ALiCCS Study. Key features of these six cohort studies are provided in the table.

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As highlighted by de Fine Licht, their study of endocrine outcomes had two important limitations: a lack of treatment information and a paucity of data on outcomes restricted to outpatient visits. However, despite the high likelihood of underestimating the risks, the authors found that cancer survivors had an almost 5-fold increased risk of having an endocrine disorder compared with individuals in the general population. While the relative risk was highest among the younger survivors, in part due to the uncommon nature of endocrine disorders in children and young adults, the absolute risk remain quite elevated into the sixth decade of life. Indeed, for survivors diagnosed from 1975 to 1989, the cumulative risk of an endocrine disorder was 42% by age 60. For survivors diagnosed from 1990 to 2008, the cumulative risk by age 40 was 38%, suggesting that the risk of endocrine dysfunction has not noticeably changed with more contemporary therapy. There were several other noteworthy findings. Perhaps most remarkable was the observation of an increased risk across all 22 categories of endocrine disorders. While pituitary hypofunction, hypothyroidism, and gonadal dysfunction accounted for 62% of endocrine disorders, the remaining outcomes encompassed a broad range of endocrine abnormalities. Interestingly, they observed a four-fold increased risk of hyperparathyroidism, an observation that has not, to our knowledge, been previously reported. Also hidden amongst the details, but a topic of recent discussion,⁵⁻⁷ was a 60% increased risk of diabetes. Similarly, it is notable that survivors from all 13 cancer groups had an overall elevated risk of developing an endocrinopathy.

The strengths of this study are many, thus increasing our confidence in the findings. As noted by the authors, the study design minimized selection bias by using a population-based approach with negligible loss to follow-up. The inclusion of all one-year childhood cancer survivors, including retinoblastoma and germ cell tumor survivors, from the five Nordic countries followed over a long period of time, including more recently treated individuals, provides a comprehensive picture. Moreover, the rigorous approach used to match individuals without a childhood cancer allows for an appropriate comparison and estimation of excess risk.

When the Dutch reported a similar cumulative incidence of chronic health conditions to that observed in the CCSS,⁸ we commented on the importance of external validation from differently designed cohort studies and settings and noted how studies are complementary.⁹ As noted by de Fine Licht et al, they found a remarkably similar risk for several key endocrine outcomes to those previously reported by CCSS investigators while also extending our observations across all childhood cancers treated over an extended period of time. We can convincingly conclude that endocrine disorders are common across all cancer types.

As the study of endocrine dysfunction continues, the next steps include case-control or case-cohort studies to investigate gene-environment interactions and to elucidate the mechanisms by which specific cancer therapies, or combinations of therapies, irreparably damage the various endocrine organs. The CCSS and other groups are currently developing such studies. The need for collaboration across cohorts will be critical to assess some of the more rare outcomes and to validate the findings.

While the authors provide an excellent summary of the clinical implications of this study, including the fact that endocrine disorders are very common across all cancer groups with an increasing risk that does not plateau with aging, it is essential for the clinician to remember that these disorders directly and indirectly lead to further non-endocrine morbidity. Thus, it is critical that while monitoring for and managing endocrine disorders in current survivors, we continue to investigate new curative cancer therapies that have less potential for endocrine and other serious late effects. Several national groups and the International Late Effects of Childhood Cancer Guideline Harmonization Group¹⁰ continue to systematically evaluate the evidence and develop clinical guidelines for screening asymptomatic childhood cancer survivors.

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Table Characteristics of six cohort studies of childhood cancer survivors

	CCSS	British CCSS	French-UK	Swiss CCSS	ALiCCS	Dutch LATER
Number	35,996 [*]	17 981	4 400	1 075	43 909	In process
Years of diagnosis	1970 - 1999	1940 - 1991	1942 - 1986	1976 - 2003	1943 - 2008	1960 - 2003
Age at diagnosis	< 21	< 15	< 17	< 15	< 21	< 18
All cancer types	No Exclude RB, GCT	Yes	No Exclude leukemia	Yes	Yes	Yes
Minority population	17.7% [*]	Not reported	Not reported	Not reported	Not reported	Not reported
Method of contact	Periodic surveys (N=4) ^{**}	One-time survey	Data-linkage	One-time survey	Data-linkage	Medical evaluation and survey
Identification	26 Hospitals	Population-based	11 Hospitals	Population-based	Population-based	Population-based
Loss to follow-up	23.2% [^]	29.4% [^]	Not reported	36.2% [^]	< 1%	In process
Comparison population	Siblings	None [‡]	None [‡]	None [‡]	Matched population-based	None [‡]
Treatment data	Yes > 90%	Yes < 20%	Yes > 95%	Not collected	Not collected	In process
Second cancer	Confirmed by pathology	Linkage with cancer registry	Linkage with cancer registry	Linkage with cancer registry	Linkage with cancer registry	Linkage with cancer registry
Long-term and late effects	Periodically self-reported	One-time self-reported	One-time self-reported	One-time self-reported	Hospital / outpatient data linkage	Planned, periodically
Lifestyle behaviors	Yes Periodically self-reported	One-time self-reported	One-time self-reported	One-time self-reported	Not collected	Self-reported to clinician at visit
Comorbidities	Periodically self-reported	One-time self-reported	One-time self-reported	One-time self-reported	Data-linkage	Medical evaluation
Banked samples	Yes (N=8646)	Yes (N=350)	No	No	No	Planned
Intervention trials	Yes	No	No	No	No	No
Open resource [‡]	Accessible	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Abbreviations: CCSS, Childhood Cancer Survivor Study; French-UK, French-United Kingdom Lymphoma and Solid Tumor Cohort; ALiCCS, Adult Life after Childhood Cancer in Scandinavia; Dutch LATER, Dutch Childhood Oncology Group Late Effect Registry (DCOG LATER) Study; RB, retinoblastoma; GCT, germ cell tumor

Footnotes: For each of the cohorts, additional data can potentially be collected for case-control studies

^{**}Second neoplasms, including meningiomas and non-melanoma skin cancer, are confirmed by pathology report

^{*} Original and expansion cohort

^{**} 4 surveys of the entire cohort; 17 surveys of a subpopulation of the cohort

[^] For analyses on all-cause and cause-specific mortality, can link to death registries; thus, no loss to follow-up with this type of analysis

[†] For analyses of mortality or second cancers, can link to population-based registries for comparison

[‡] Investigators from other institutions or countries can analyze data or use the cohort as a resource for additional studies