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Adolescents and young adults with cancer and the risk of subsequent primary neoplasms: not just big children

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Improved outcomes in childhood cancer have led to an increased focus on the cost of long-term survival: long-term physical, psychological, and financial morbidities that arise as a consequence of cancer therapy or the cancer itself. Several landmark childhood cancer survivor cohorts have informed our ability to describe, predict, and minimise these late effects.[1,2] About 80% of adolescents and young adults (AYAs) with cancer will also achieve long-term cure.[3] Consequently, late effects are also highly relevant to this population, but very few AYA-specific data exist, forcing clinicians to extrapolate from the literature on childhood cancer survivors. Subsequent primary neoplasms (also known as second malignant neoplasms) are one of the most feared late effects, and are associated with substantial morbidity and mortality. Previous work has shown that survivors of AYA cancer have a higher absolute risk of subsequent primary neoplasms than do younger or older populations, which in turn has a substantial impact on overall survival.[4,5]

In *The Lancet Oncology*, Chloe Bright and colleagues[6] describe the risk of subsequent primary neoplasms in a population-based cohort of more than 200 000 survivors of AYA cancer. The large sample size and more than 2·6 million person-years of follow-up allow the investigators to describe, comprehensively for the first time and in great detail, the risk of specific subsequent primary neoplasms after specific primary cancers. The cumulative incidence of any subsequent primary neoplasm at 35 years from diagnosis ranged from 11·9% in survivors of breast cancer to 26·6% in female survivors of Hodgkin lymphoma. The level of granularity provided in the risk estimates (eg, by primary cancer, type of subsequent primary neoplasm, and years from diagnosis) should assist clinicians and policy makers in determining what type of interventions would be of greatest benefit for specific populations of AYA cancer survivors.

Beyond improving risk prediction, several implications of the data are worth highlighting. The results illustrate the dangers of applying findings from childhood cancer survivors to the AYA population. For example, the surprising burden of subsequent lung cancers stands in contrast to the childhood cancer literature.[7] In male survivors of Hodgkin lymphoma, lung cancer accounted for approximately 40% of the total number of excess subsequent primary neoplasms, with a cumulative incidence of lung neoplasms of 5·1% at 35 years from diagnosis. Substantial incidences were also seen in other survivor groups. It is unclear whether this difference compared with childhood cancer survivors is caused by several primary AYA cancers being themselves related to smoking history (eg, cervical cancer), a higher probability of smoking after diagnosis,[8] increased use of treatments such as lung radiotherapy, greater attained age, or a combination of these factors. Irrespective of the mechanism, Bright and colleagues' results support smoking cessation interventions for survivors and raise the intriguing question of whether lung cancer screening guidelines developed for other high-risk populations may be appropriate.[9]

A second difference concerns temporal trends. The risk of subsequent primary neoplasms in childhood cancer survivors has decreased over consecutive cohorts, largely associated with reductions in radiotherapy doses.[2,10] In this study, treatment decade was not significantly associated with subsequent primary neoplasm risk, suggesting that no such decline has occurred in the AYA survivor population. The reasons for this finding are unclear. AYA treatment intensity

might not have decreased as it has in childhood cancer. Alternatively, reducing the incidence of subsequent primary neoplasms in survivors of AYA cancer might require a stronger focus on lifestyle factors.

Although this study represents a substantial contribution, several limitations merit note. Late effects are most closely associated with the types and doses of therapy received. Unfortunately, the investigators did not have access to treatment data, relying instead on diagnosis as proxy. However, a patient with Hodgkin lymphoma might receive only two cycles of chemotherapy or might undergo six cycles and radiotherapy, with consequently vastly different risks for subsequent primary neoplasm. Without treatment data, the clinician is still left uncertain on how to counsel an individual patient on his or her personalised risk, or what screening to recommend. AYA-specific risk prediction models that include treatment exposure are urgently needed.

Finally, description of risk is only a first step towards the ultimate goal of improving the quantity and quality of life for survivors of AYA cancer. Studies that identify effective interventions for this population, whether in the prevention, screening, or treatment of late effects, are crucial. Determining what health-care delivery models maximise uptake of such interventions in a population known to face substantial barriers to access will also be necessary.

For decades, paediatricians have insisted that children are "not just little adults". We must now be equally emphatic in declaring that when it comes to the late effects of cancer and cancer therapy, AYAs are "not just big children", but instead deserve recognition as their own unique group.

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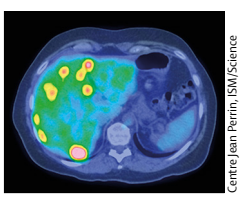
PET oestrogen receptor imaging: ready for the clinic?

Oestrogen signalling is a key component of normal mammary gland physiology and mediates breast cancer pathogenesis in most breast cancers.[1] Drugs targeting oestrogen-mediated growth in breast cancer, termed endocrine therapy, provide a key therapeutic strategy. The presence or absence of oestrogen receptors is a predictor of breast cancer response to endocrine therapy; documenting oestrogen receptor expression from a biopsy sample before initiating therapy is a well established clinical standard.[1] Although primary breast tumour biopsy is well developed, safe, and effective, tissue sampling and assays pose challenges in the metastatic setting. These challenges spurred investigators to develop non-invasive approaches for oestrogen receptor assay, including PET molecular imaging methods,[2,3] investigated by Sun Young Chae and colleagues in this issue of *The Lancet Oncology*.[4]

Among several early candidates for PET oestrogen receptor imaging probes, 16α-[^{18}F]fluoro-17β-oestradiol (^{18}F-FES) emerged as the most successful agent.[2,3,5] ^{18}F-FES is a synthetic oestrogen labelled with the positron-emitting isotope ^{18}F and closely mimics oestradiol's binding affinities for oestrogen receptors and sex hormone-binding globulin.[2] ^{18}F-FES PET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