

The need for long-term follow-up of childhood cancer survivors in British Columbia

Initiating a prospective surveillance system and follow-up registry would contribute to the health and well-being of British Columbians who have received cancer treatment as children or adolescents.

ABSTRACT: Many survivors of childhood cancer have incomplete knowledge of their past treatment and are unaware of the risks they may face, including long-term negative health consequences such as second cancers, cardiovascular disease, and infertility. These late effects are predominantly the result of radiation, anthracycline therapy, and alkylator therapy. Currently there is no formal program for long-term care of British Columbians who have survived cancer in childhood or adolescence. A program is needed to provide life-long health surveillance, counseling, and a registry for this population. Such a program would also provide GPs with current and relevant recommendations for follow-up care and support the shared goals of the federally funded Canadian Partnership Against Cancer and the BC Cancer Agency.

In British Columbia there are approximately 3000 patients aged 17 years or older who are survivors of childhood cancer (diagnosed before the age of 17 years). Each year an additional 120 or more patients “graduate” to become adult survivors of childhood cancer. There is increasing evidence that although children, adolescents, and young adults diagnosed with cancer have an improved survival rate, many survivors face long-term negative health, educational, and social consequences of their cancer experience.¹⁻⁵ Many of these survivors are unaware of the specific cancer therapy they received earlier in life and do not know that they may face significant long-term risks to their health and well-being.^{2,6-8} These “late effects” may not become apparent until many years after treatment. The most serious health risks are late recurrence of disease, as well as second cancers, cardiovascular disease, and endocrinological and neuropsychological abnormalities. In 2003 the American Institute of Medicine identified the need for a systems approach to the health care needs of survivors of childhood cancer and made specific recommendations.⁹ The National Cancer Institute’s Office of Cancer Survivorship identified programs in

existence in 2006 for long-term follow-up for pediatric cancer.¹⁰ Unfortunately, only one such program was identified in Canada, the Provincial Pediatric Oncology AfterCare Program through the Pediatric Oncology Group of Ontario.

Late effects

Long-term sequelae in survivors of childhood cancer are predominantly secondary to radiation, anthracycline therapy, and alkylator therapy. Late effects of cancer treatment are not unique to survivors of childhood cancer, but they are usually more severe than those experienced by survivors of adult cancer, as the cancer treatment is received during periods of growth and development. Knowledge of health risks has resulted in changes in therapy to obviate untoward effects.

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This article has been peer reviewed.

For example, radiation therapy is now rarely used in the treatment of Hodgkin disease in children, and the recommended maximum total dose of anthracyclines has been significantly reduced. However, it is not yet known how increasing the intensity of therapy currently used and new or innovative cancer treatments may affect the observed late effects. This lack of knowledge of future long-term side effects provides further rationale for lifelong surveillance of survivors at risk. It is important to emphasize that not all childhood cancer survivors are at risk for late effects and therefore surveillance recommendations should be risk-based. Surveillance also provides an opportunity to undertake research into host factors such as genetic polymorphisms that may make an individual more susceptible to late sequelae.¹¹

Surveillance practice in BC

In BC most adult survivors of childhood cancer have been discharged from cancer care programs and are not followed by physicians knowledgeable about their health risks. They are no longer being cared for by a pediatrician and the majority do not require the specialist care of an oncologist. While pediatric and radiation oncologists are the most knowledgeable health care providers concerning the late sequelae of cancer therapy in children, it is inappropriate for them to provide life-long surveillance.

In our health care system, the general practitioner is in the best position to carry out surveillance of late health problems and comorbid conditions, promote follow-up care, and counsel patients on lifestyle issues. Given the complexity of diagnosis and treatment-specific late effects, GPs need to be provided with current and relevant information on the risks and recom-

mendations for follow-up care and new knowledge about late effects of cancer therapy as it becomes available. In order to ensure quality life-long care, it is also essential to obtain feedback and maintain a database regarding late health problems as they develop in order to assess longer-term risks and new problems as they arise among the survivor population. A

obstetrical problems, and posttraumatic stress disorder.

Second tumors

Studies show that survivors of childhood malignancy have a three to ten times increased risk of developing a second malignancy compared with the general population.^{12,13} Radiation exposure increases the risk for brain

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systematic follow-up program is needed to link pediatricians, oncologists, and GPs through surveillance clinics to ensure successful transition of childhood cancer survivors from treatment and recovery to survivor care.¹⁰ Currently in BC there is no separate funding available to support such a program, nor is there appropriate reimbursement for GPs to undertake surveillance and prevention. This considerable deficiency must be addressed given that the unique needs of childhood cancer survivors in BC require an effective province-wide survivor follow-up program and post-cancer care from GPs.

Health risks

Survivors of childhood cancer face a number of health risks, including a second malignancy, recurrence of their original disease, fertility and

tumors, breast cancer, thyroid cancer, bone tumors, and soft tissue sarcoma. Exposure to alkylating agents and the topoisomerase II inhibitors increases the risk for myeloid malignancy and myelodysplastic syndromes.¹⁴

Basu and colleagues reported the cumulative incidence of breast cancer among female survivors of Hodgkin disease who received radiation to the chest region in their teenage years was 19% by 25 years after diagnosis, rising to 24% by 30 years and to 35% by 40 years after diagnosis.¹⁵ The expected cumulative incidence of breast cancer in the matched general population is 10%. This gives a risk of treatment-related breast cancer developing in one in four female survivors of Hodgkin disease treated with chest irradiation within 40 years of initial diagnosis. Goshen and colleagues reported that survivors of childhood leukemia who

received low-dose cranial irradiation have a 15% risk of developing benign meningiomas within 20 years of initial diagnosis, while Strojjan and colleagues reported an 8% cumulative incidence at 25 years following high-dose cranial irradiation.^{16,17} These tumors are often asymptomatic—a concern because surgical cure can only be achieved with early diagnosis.

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The Childhood, Adolescent, Young Adult Cancer Survivorship Research Program (CAYACS) is a population-based study utilizing BC Cancer Agency and BC Children's Hospital data linked to provincial databases for the examination of long-term outcomes of cancer survivors diagnosed before age 25.¹⁸ CAYACS reported 55 second malignant neoplasms among a population-based cohort of 2322 5-year survivors diagnosed in BC before 20 years of age; 15 of these neoplasms were found in males and 40 in females.¹⁹ The mean age at diagnosis of a second malignant neoplasm was 27 years and the mean time from the original diagnosis was 15 years. The increased cumulative prevalence of second malignant neoplasms over the normal population was 1.3% at 15 years, 2.5% at 20 years, and 4% at 25

years. The most common second malignancies were breast cancers (18%), thyroid cancers (18%), and central nervous system tumors (15%). This is consistent with the experience from other countries.^{12,13}

Premature death

Survivors of childhood cancer have a reduced life expectancy when compared with the general population.²⁰ CAYACS data reveal that the standardized mortality rate is nine times that observed for age- and sex-matched controls in the general BC population.²¹ However, 77% of the observed deaths (139/181) were due to recurrence of the subjects' original disease, 8% were related to second malignancies, and only 12% were not cancer related, with cardiovascular causes being the most common. The cause of death was unknown in 3% of cases.²¹ The CAYACS data confirm what other childhood cancer survivor study data show—that, after cancer, cardiovascular disease, most likely related to radiation or chemotherapy, is the principal cause of death in survivors of childhood cancer.²² Total anthracycline dose tolerated by adults can be associated with cardiac failure when given to children.²³⁻²⁵ Furthermore, there is accumulating evidence that progressive cardiac dysfunction may manifest itself up to 22 years after treatment.²⁶ Radiation to the heart and great vessels can also result in premature coronary disease or vascular damage, increasing the risk of cerebrovascular accidents.²⁷

Gonadal and fertility effects

Male and female fertility can be impaired by exposure to radiation and high doses of chemotherapy, particularly alkylating agents.²⁸

Females. The ovaries may be damaged if in or adjacent to the radiation field. High doses of radiation or alkylator

exposure in the prepubertal child may result in primary ovarian failure, while lower doses may result in normal development of puberty and menstruation but premature menopause, which can occur at any age from mid-teens onwards.^{28,29} Methods for preservation of female fertility are limited but include ovarian shielding or transposing (repositioning the ovaries out of the radiation field) during radiation; ovarian suppression with GnRH analogs during chemotherapy (this is experimental and not currently accepted practice);³⁰ oocyte cryopreservation for postpubertal females only (requires ovarian stimulation over at least 2 weeks prior to starting chemotherapy or radiation, so it is not usually possible for acute malignancies in adolescents); cryopreservation of ovarian tissue (this is experimental and so far unsuccessful); and embryo cryopreservation (requires ovarian stimulation and a partner and has both moral and ethical implications).

Males. Testicular function is also extremely sensitive to radiation and high-dose alkylating agents. Radiation doses greater than 600 cGy in boys can cause permanent azospermia.²⁸ The doses of alkylating agents often used for Hodgkin disease may also permanently impair spermatogenesis. Methods for fertility preservation in males include shielding of the testes during radiation, which is done whenever possible; sperm banking for patients with Tanner stage 4 or higher; surgical sperm retrieval if patient is Tanner stage 4 but unable to produce a semen sample; and testicular tissue preservation for prepubertal boys (this is experimental and so far unsuccessful).

Other late effects

Every organ system can be affected by radiation and chemotherapy, especially during early developmental years.

The endocrine system is susceptible to a number of late effects. Adrenocorticotropic hormone deficiency secondary to pituitary lesions or cranial radiation may occur and can result in death from a simple upper respiratory infection.³¹ Irradiation to the thyroid gland results in a very high incidence of hypothyroidism.³² Cranial radiation and chemotherapy have been linked to an increased incidence of obesity in survivors of childhood leukemia.³³

An increased incidence of miscarriages, complications during delivery, and low birth weight infants are related to pelvic radiation.^{34,35}

Late deafness, poor educational outcomes, psychological effects such as posttraumatic stress disorder, and impaired quality of life have all been reported.³⁶⁻³⁸

Health care utilization

Not surprisingly, CAYACS data show these late morbidities result in increased health care utilization with respect to physician visits, hospitalizations, and outpatient procedures.^{39,40} Among survivors, 24% had at least one subsequent hospitalization compared with 13% of age- and gender-matched controls. Overall, demand for physician visits, hospitalizations, and outpatient services were greatest among survivors of a brain tumor, female survivors, and older survivors.

Recommendations

A program providing lifelong health surveillance, counseling, and an ongoing registry for adult survivors of childhood and adolescent cancer is greatly needed in BC in accordance with the Institute of Medicine recommendations.⁹ Currently there is no formal program for long-term care of this population. Many adult survivors have incomplete knowledge regarding their past diagnoses, treatment, and risks for significant future health

problems.⁸ This fact, together with the extensive evidence for late effects of childhood cancer, and the observed excess health services utilization, indicates an increased need for a comprehensive follow-up care strategy. It is important to impart knowledge to primary health care providers and autonomy to cancer survivors by using BC-specific data to develop risk-based follow-up guidelines that address the special needs of these patients.

Initiation of a prospective surveillance system and follow-up registry would contribute to the health and well-being of adult survivors by preventing or ameliorating late effects. The recommendations for surveillance monitoring of cancer survivors varies slightly with country and resources, making it important to generate a set of uniform, evidence-based guidelines appropriate to the situation in BC. This will not only provide standards of follow-up care, but enable ongoing evaluation of the guidelines and effectiveness of any interventional health action. This will also assist in identifying late-onset health issues related to newer therapies. Such a surveillance system should be lifelong and based on the latest evidence available. This type of program will provide a positive reinforcement mechanism through annual contact, and empower the patient to make any recommended changes in lifestyle.

Lifelong surveillance should be supported by an ongoing registry for adult survivors of childhood cancer to provide vital facts regarding diagnosis, treatment, and risk category for late effects, while providing the means for quantifying the extent and severity of any subsequent health problems in a longitudinal population-based fashion.

Health care providers and institutions have professional, ethical, and legal responsibilities to inform patients, not only of the known risks

associated with therapy at the time of diagnosis, but also the risks revealed as new information becomes available.

Surveillance monitoring

All adult survivors of childhood cancer in BC, together with their primary health care providers, should be given a medical summary including details of their diagnosis and therapy. They should also be counseled regarding anticipated health risks by nurse practitioners or physicians knowledgeable about late sequelae.⁹ Survivors should be asked to consent to annual contact (directly, via their primary health care provider, or both) for follow-up of their health. Risk-based guidelines should be made available to patients and health care professionals. In the interim, the following general recommendations are provided to address the most important potential late sequelae in survivors of childhood cancer:

- All survivors should receive education on healthy lifestyle to minimize the added effects of obesity on cardiovascular disease and the risk of malignancy associated with obesity.
- Survivors who received anthracyclines should have echocardiograms to measure ejection fraction and fractional shortening, and ECG monitoring every 5 years, and be advised regarding the latest “healthy heart” recommendations.^{25,41}
- Females who received radiation to the chest region should have mammography or MRI breast screening starting at age 25.⁴²⁻⁴⁵
- Survivors who received radiation to the brain should be screened for benign meningiomas by MRI starting at 10 years posttreatment.
- Survivors who received radiation to the brain or thyroid should be screened for thyroid nodules with ultrasounds of the neck starting at 5 years posttreatment, and monitored for thyroid function with T4 and TSH.

Fertility counseling and obstetric monitoring

Female survivors should be counseled regarding their risk for infertility and premature menopause. Monitoring for ovarian reserve to predict early menopause is important but is not easy. Although changes in menstrual history and an increase in follicle-stimulating hormone are easily monitored, the abnormalities indicating impending ovarian failure occur late. Serial antral follicle count by ultrasound is more accurate but time-consuming and not readily available. Measurement of anti-müllerian hormone (AMH) reflects the primordial follicle number and is a more reliable method to monitor ovarian reserve; however, testing for AMH is only available at private laboratories in BC and is expensive.²⁸ Males should also be counseled regarding risk for infertility. Fortunately, assessment of male fertility is more easily achieved by measuring the number and quality of sperm in a semen sample.

Females who received anthracyclines need close cardiac monitoring during pregnancy as they are at risk for anthracycline-induced cardiac failure. Those who received pelvic radiation are at risk for early pregnancy loss and premature delivery due to uterine insufficiency and also require close obstetric monitoring.^{34,35}

Conclusions

A program that provides survivors of childhood cancer with lifelong health surveillance, counseling, and a follow-up registry is needed in BC. If adequately funded, such a program would improve the knowledge, health, and well-being of survivors of childhood cancer, and provide GPs with current and relevant recommendations for follow-up care. Such a program would also support the shared goals of the federally funded Canadian Partnership Against Cancer and the

BC Cancer Agency: to reduce the incidence of cancer and the number of cancer-related deaths, and to improve the quality of life for those living with cancer.

Acknowledgments

Grants for this project were provided by the Canadian Institute for Health Research, the Canadian Cancer Society Research Institute, and the Canadian Cancer Society BC and Yukon Division.

Competing interests

None declared.

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