Sex and Gender Considerations After Surviving Acute Lymphoblastic Leukemia: An Exercise Oncology Context

Maxime Caru, PhD,¹⁻³ and Daniel Curnier, PhD^{1,2}

Childhood acute lymphoblastic leukemia (ALL) is the most common pediatric cancer in children worldwide. The distinction between sex (i.e., biological parameters) and gender (i.e., sociocultural and behavior) is not always taken into consideration in an exercise oncology context, despite its importance for the patient's care. A recent study showed that female survivors were more affected than males by low cardiorespiratory fitness several years after the end of their cancer treatments. This is all the more worrying considering that for a clinically equivalent level of moderate to vigorous physical activities, cardiorespiratory fitness is significantly lower in female survivors, compared with healthy females. Thus, the need for studies that help to better understand the physical deconditioning of female survivors after ALL is an essential aspect of exercise and oncology research. Because female survivors' cardiorespiratory fitness is directly impacted for many years, this article aims at discussing these aspects in an exercise and oncology context with sex and gender consideration.

Keywords: acute lymphoblastic leukemia, sex and gender, exercise oncology, pediatric cancer survivorship, female's cardiorespiratory fitness

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) is the most common pediatric cancer in children worldwide. Over the past 4 decades, the progress in ALL treatments has considerably improved the survival rate to more than 80%.¹ Unfortunately, about 65% of survivors who were exposed to chemotherapeutic agents during treatment with doxorubicin suffer from multiple late adverse effects after the end of their treatments.²⁻⁴ Among these long-term adverse effects, cardiovascular issues and cardiotoxicity are the most common problems encountered, as well as physical deconditioning in ALL survivors.^{5,6} However, even though both males and females were treated with chemotherapy during their cancer, female survivors are at higher risk than males to have an impairment in their cardiorespiratory fitness.⁷

The distinction between sex (i.e., biological parameters) and gender (i.e., sociocultural and behavior) is not always taken into consideration in an exercise oncology context, despite its importance for the patient's care. A recent study showed that female survivors were more affected than males by low cardiorespiratory fitness several years after the end of their cancer treatments.⁷ Moreover, the female survivors' physical deconditioning, represented by a low cardiorespiratory fitness measured during an exercise stress test, also seems to increase with

age.^{5,7} This is all the more worrying considering that for a clinically equivalent level of moderate to vigorous physical activities, cardiorespiratory fitness is significantly lower in female survivors, compared with healthy females.⁷

Thus, the need for studies that help to better understand the physical deconditioning of female survivors after ALL is an essential aspect of exercise and oncology research. Because female survivors' cardiorespiratory fitness is directly impacted for many years,⁴ this article aims at discussing these aspects in an exercise and oncology context with sex and gender consideration.

Female Survivors' Accessibility to Physical Activity

Female survivors' cardiorespiratory fitness should not be neglected in the follow-up of cancer patients. This is all the more important considering that ensuring a good cardiorespiratory fitness is an essential component to the care of female survivors.^{8,9} A recent systemic review published by Clarke et al. in the *Journal of Adolescent and Young Adult Oncology* reported a gap in the understanding of cancer in lesbian, gay, bisexual, transgender, and intersex adolescents and young adults and discussed the unique disparities in their

¹Laboratory of Pathophysiology of Exercise (LPEX), School of Kinesiology and Physical Activity Sciences, Faculty of Medicine, University of Montreal, Montreal, Canada.

²Sainte-Justine University Health Center, Research Center, Montreal, Canada.

³Laboratoire EA 4430–Clinique Psychanalyse Développement (CliPsyD), University of Paris Nanterre, Nanterre, France.

access to health care.¹⁰ In the exercise and oncology domain, it is clearly shown that it is females who suffer from disparities in access to physical activity.

Indeed, it has been found that Canadian female youth are systematically less active than boys.¹¹ Females face barriers (i.e., intrapersonal, social, and environmental factors as barriers) to maintain a good level of physical activity, particularly during their adolescence.¹² This is especially reinforced by the familial environment where parents overprotect their children.¹³ This has the effect of parents abstaining from encouraging their children to be physically active, especially for females.¹⁴

Indeed, it has been shown that for parents, it is more acceptable for a female to adopt a sedentary lifestyle after cancer than a male.¹⁴ Combined with lack of knowledge about the importance of physical activity in pediatric oncology, overprotection can have harmful consequences for children with cancer. Coupled with the anxiety and social isolation experienced by children with cancer, overprotection can increase their exposure to physical inactivity, resulting in a reduction in their autonomy and cardiorespiratory fitness. Thus, the familial environment increases females' exposure to low cardiorespiratory fitness during and after their cancer treatments.

Female Survivors' Genetic Dispositions to a Low Cardiorespiratory Fitness

The literature shows that blaming environmental factors only partially addresses these disturbing observations since genetic factors may have a positive effect on the association between health-related fitness and regular exercise.^{15–17} Female survivors represent an at-risk patient population in regard to genetic dispositions to low cardiorespiratory fitness. A recent study, the first in its domain, has provided evidence of genetic predispositions to the low cardiorespiratory fitness level in childhood ALL survivors.¹⁸ This phenomenon is particularly significant in female survivors. Indeed, many years after the end of their cancer treatments, female survivors have significant genetic associations between their cardiorespiratory fitness and their trainability genes that play an important role in the functioning of their skeletal and cardiac muscles, as well as muscle development and regeneration.¹⁸

These results suggest an adaptation of female survivors' trainability capacity to their low cardiorespiratory fitness to counter the late adverse effects. This is consistent with the existing literature that reported genetic variations between healthy participants¹⁹ and inter-individual variability in responses to regular exercise in regard to their capacity to improve their cardiac profile.²⁰ In childhood ALL survivors, genetic associations have also been reported between skeletal muscle function deficits and genes involved in muscle and bone metabolism.²¹ These findings have an important influence on the female survivors' trainability and their capacity to improve their cardiorespiratory fitness levels, especially in those who received high doxorubicin doses.

To the best of our knowledge, every study of genetic associations in ALL survivors who were interested in health conditions (i.e., cardiorespiratory fitness and skeletal muscle function) and health-related fitness genes^{18,21} reported that survivors exposed to a highly aggressive treatment regimen were most affected than survivors exposed to low treatment doses. Moreover, this is reinforced by anticancer drugs that

can modify gene expression²² and induce an impairment of cardiac function.²³ These recent findings seem to be the missing piece to better understand the physical deconditioning in female ALL survivors.

Physical Activity in Oncology Needs to Be Strengthened in Female Survivors

It seems well established that the exercise supports care in pediatric oncology plays an important role in the care of females with cancer. However, the findings are very clear: Females with cancer are not equal to their male counterparts, because they are more affected by a lower cardiorespiratory fitness.⁷ There are genetic, epidemiological, and sociocultural disparities in both populations and physical activity inaccessibility for females with cancer, especially in pediatrics. In this sense, female survivors respond less well than their counterparts to physical activity.⁷ Another explanation could be their exposure to long-term adverse effects due to their cancer treatments. Cardiotoxicity is one of the most common problems encountered by childhood ALL survivors.³

Many years after the end of the treatments, survivors suffer from an alteration of their cardiac system²⁴ and a dysfunction of their cardiac autonomic nervous system.²⁵ Female childhood cancer survivors are at four times as greater risk for developing anthracycline-induced clinical heart failure than their male childhood cancer survivors.^{26,27} A slight deterioration in their ejection fraction,²⁵ and a high proportion of left ventricular dysfunction in survivors exposed them to high doses of cancer drugs.²⁸ This aspect is reinforced by the fact that the left ventricular contractility of female childhood survivors is significantly worse than males' contractility.²

Thus, female survivors represent a patient population that is at risk of developing premature cardiovascular diseases such as congestive heart failure.²⁹ This suggests an inappropriate remodeling of the myocardium and a deterioration in cardiac function,³⁰ which could limit their cardiorespiratory fitness. This can be prevented by exercise training in survivors, as suggested in chronic heart failure patients.^{31,32} These findings constitute a hope for female survivors to regain good cardiorespiratory fitness. However, it is the responsibility of health care professionals and parents to consider the importance of physical activity in the care of children with cancer.

Responsibility of Health Care Professionals in Regard to Female Survivors' Accessibility to Physical Activity

The absence of favorable conditions (family, environmental, social, economic, medical, etc.), despite strong behavior intentions, reduces the possibility of physical activity practice.³³ This aspect is reinforced in the oncology field where health care professionals play an important role in encouraging patients' regular practice of physical activity. The relationship between the oncologist and their patient is central to patient care and the promotion of physical activity and a healthy lifestyle.³⁴ It has been shown that oncologists who discuss the benefits of physical activity with their patients help them to achieve a good level of physical activity during treatments.³⁵

In light of these findings, females with cancer deserve to receive advice from their oncologist and health care professionals in regard to the benefits of physical activity, which contributes to their good cardiorespiratory fitness. However,

vigilance is required by oncologists in this process to equally advise males and females to be physically active with special attention to females' physical activity support by their oncologist. Thus, the promotion of physical activity needs to be encouraged through the care system with the involvement of oncologists, health care professionals, and exercise physiologists. It is the exercise physiologist's role to propose a physical activity program that is in accordance with the patient's aims. This exercise program should be adapted, progressive, and individualized to improve its functional capacities.

The evidence-based medicine approach is essential to help females improve their cardiorespiratory fitness through physical activity. As health care professionals, we need to focus on these aspects.

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Address correspondence to:

Daniel Curnier, PhD

Laboratoire de Physiopathologie de l'Exercice (LPEX)

Département de Kinésiologie

Université de Montréal

CEPSUM, 2100, Boulevard Édouard Montpetit

Montréal H3C 3J7

Canada

E-mail: daniel.curnier@umontreal.ca