Unique Challenges of Adult Congenital Heart Disease in CardioOncology

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KEYWORDS

• Adult congenital heart disease • Malignancy • Thymectomy • Anatomy variation

KEY POINTS

- Adults with congenital heart disease are at an increased risk of cancer related mortality and morbidity.
- Genetic predisposition, radiation, and timely access to preventative screening are some of the factors that play a role in increased risk of malignancy.
- A better understanding of these risk factors and how to mitigate them can help decrease the risk of malignancy.

INTRODUCTION

Congenital heart disease (CHD) has a prevalence of approximately 1% to 2% of live births, making it the most common congenital malformation in newborns.[1] The last few decades have seen unparalleled advancements in the medical, surgical, and interventional treatments and more than 97% of children with CHD are expected to reach adulthood.[2] As a result, adults with CHD represent a very heterogenous and growing population that currently comprises most patients with CHD.[3] Such increase in survival is associated with an increased risk of acquired diseases such as atherosclerotic disease and neoplastic disease. The incidence of cancer, in particular, has been shown in multiple large population-based studies to be approximately twice that of age and sex-matched controls.[4,5] This article aims to discuss some of the causes (**Fig. 1**) for this increased risk and explores the pathophysiologic underpinnings of malignancy in adult CHD.

SYNDROMES ASSOCIATED WITH CONGENITAL HEART DISEASE AND INCREASED RISK OF CANCER

There are certain syndromes strongly associated with CHD as well as malignancy. A recent population-based study from Sweden has demonstrated that these genetic syndromes appear to account for the increased mortality risk in CHD patients with cancer compared to patients without CHD who have cancer.[5] Among such syndromes, the most common are Down syndrome and 22q11.2 deletion syndrome.

Among individuals with intellectual disability, Down syndrome is the most common genetic abnormality, occurring in 1 out of every 800 to 1000 live births.[6] The vast majority of patients with Down syndrome have a full trisomy of chromosome 21 with subsequent overexpression of different genes that could explain the increased frequency of CHD.[7] Approximately 50% of the patients with Down syndrome have CHD.[8] The most

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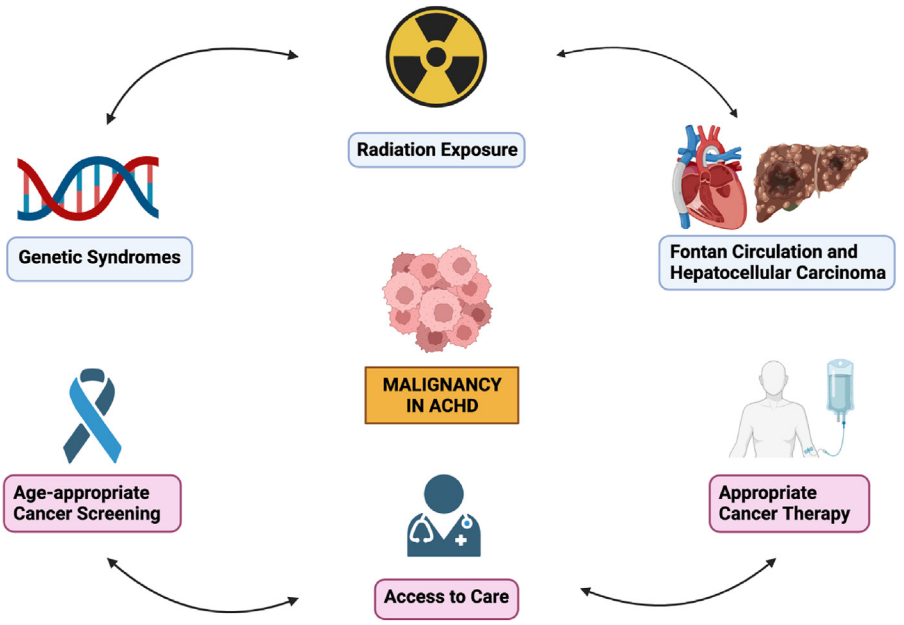

Fig. 1. Several factors play a role in the increased risk of cancer in adult patients with congenital heart disease.

common types of CHD anomalous in Down syndrome patients are endocardial cushion defects, such as atrioventricular canal defects, atrial septal defects (ASD), ventricular septal defects , and Tetralogy of Fallot (TOF). [9] Additionally, it is also well known that the risk of malignancy, specifically hematologic malignancies, such as acute myeloid leukemia and germ cell tumors is significantly increased in individuals with Down syndrome. Overexpression of chromosome 21 genes, such as RUNX1 could account for this increased risk.[10,11] In animal studies, some chromosome 21 genes have been found to play a role on DNA stability, mutations, and immune alterations of all the factors that contribute to malignancy development.[12] While genetic predisposition as well as environmental factors play a role in the risk of malignancy development, it is important for providers caring for patients with Down syndrome to be aware regarding the risk of cancer and the sites of cancer and pursue aggressive preventative strategies as well as early detection and treatment.

Another genetic syndrome associated with cardiac congenital defects as well as increased risk of malignancies is the chromosome 22q11.2 deletion syndrome. This deletion occurs in approximately 1 of 4000 to 10000 children.[13] It is manifested in a multisystem fashion with a broad variety of phenotypical syndromes, the most common one being DiGeorge syndrome. Among the most common cardiac abnormalities are truncus arteriosus, TOF as well as interrupted aortic arch and hematologic disorders.[14] It should be noted that in addition to alterations in genes for proper cardiac hematologic development, patients with 22q11.2 deletion have thymic hypoplasia, which results in immunodeficiency and subsequent risk of malignancy. While large prospective studies evaluating long-term malignancy risk in these patients are lacking, several case reports of premature malignancy in patients with 22q11.2 deletion syndrome suggest increased malignancy risk with this condition.[15]

Given that the patients with these genetic syndromes are reaching adult age, it is extremely important to remain vigilant regarding the appropriate screening and diagnosis of cancer among this special population.

PATIENTS WITH COMPLEX SINGLE VENTRICLE PHYSIOLOGY AND RISK OF HEPATOCELLULAR CARCINOMA

Patients with Fontan circulation are at particularly high risk for developing hepatocellular carcinoma (HCC). The Fontan operation was first described in the early 1970s for patients with tricuspid valve atresia.[16] It has undergone several modifications since its initial description and it is being applied as a third surgical step for pediatric patients with univentricular cardiac physiology where a biventricular repair is not feasible.[17] Before such surgical advancements, children born with univentricular physiology faced an early death during infancy. Following a three-step surgical approach, and preceded by the Glenn procedure where a superior cavopulmonary connection is created, the Fontan

procedure involves the creation of a surgical shunt where the blood from the inferior vena cava is diverted to the pulmonary arteries. As a result, blood from the superior vena cava and inferior vena cava bypasses a subpulmonary ventricle, and drains directly into the pulmonary arteries.

A major characteristic of the Fontan circulation is the absence of a subpulmonary ventricle, which leads to an obligatory high central venous pressure, to allow for the forward flow of the blood into the pulmonary circulation. Diminished cardiac preload for the systemic ventricle leads to a chronic low cardiac output state. These hemodynamic factors as well as mildly decreased arterial blood oxygen saturations lead to chronic multiorgan dysfunction, including chronic liver dysfunction. In the United States, there are more than 900 patients who undergo Fontan operation every year with excellent greater than 97% early survival.[18] The Fontan palliation is usually completed before the age of 5 year; however, the long-term effects of Fontan physiology are noted throughout adult life.[19]

Fontan-associated liver disease (FALD) is an example of one such effect of the physiology, particularly in adulthood. FALD encompasses the development of congestive hepatopathy, liver fibrosis, and even cirrhosis over time. Liver neoplasia is found at relatively high rates in patients after the Fontan operation, ranging from 3% to 15% in patients who have had Fontan physiology for 22 years.[20] A regenerative liver nodules are fairly common with a prevalence of 20% to 30%, any hepatic lesion warrants a detailed evaluation for HCC.[21] Although there is a paucity of robust data on the relationship of Fontan hemodynamics and risk of HCC, there are several single-center studies that suggest a relationship of Fontan pressures by cardiac catheterization and progression of FALD.[22,23] In addition, surveillance cardiac catheterization and transjugular liver biopsy studies show a strong correlation of FALD severity and time since Fontan completion.[24,25] In general, the American Association for the Study of Liver disease guidelines for HCC surveillance recommend ultrasound and alpha-fetoprotein levels every 6 months in patients at high risk of developing HCC.[26] Such guidelines can reasonably be applied to FALD patients until a more specific approach for this patient population is validated.[27] Suspicious lesions should be evaluated with advanced imaging, such as contrast magnetic resonance. As such, patients with Fontan circulation should be cared by a multidisciplinary team approach including adult congenital cardiologists, hepatologists, and other subspecialists. Any liver surveillance strategy should be implemented starting 10 to 15 years after Fontan surgery as the time since Fontan completion remains the most important predictor of advanced FALD.

RISK OF THYMECTOMY AND CANCER

Several studies have attempted to delineate the potential risk factors for malignancy in patients with CHD. One such possible risk factor is thymectomy at a young age.[28] For infants with CHD undergoing surgical repair, thymectomy is routinely performed to optimize surgical access. However early thymectomy has been associated with several immunologic changes including T-cell lymphopenia, with a less robust T-cell receptor profile and a skewed autoantibody repertoire.[29,30] These immunologic alterations could lead to a suboptimal immune surveillance and subsequent increased risk for infections, cancers, and autoimmune diseases. When compared with the general population, the thymectomy group from a major Swedish national registry study, showed an overall risk of cancer significantly increased with a Hazard Ratio of 1.61.[28] Because of the observational nature of this study, a causal mechanism cannot be assumed. Nevertheless, it is reasonable that during early cardiac surgery, total thymectomy be avoided if possible.

RADIATION EXPOSURE AND CANCER

A significant number of patients with adult congenital heart disease (ACHD) have undergone cardiac catheterization procedures, either diagnostic or interventional. For some of these patients, such procedure has occurred more than once, including during childhood years. Interventional ACHD cardiac procedures have forever changed the landscape in the care of this patient population. However such procedures are performed using X-rays, which is associated with an increased lifetime risk for cancer (the United Nations Scientific Committee on Atomic Radiation. Sources, effects, and risks of ionizing radiation. Volume II, Annex B: Effects of radiation exposure of children. New York: United Nations, 2013). An understanding of the potential long-term risks of X-ray exposure is critical in optimizing exposure reduction as well as communicating with patients and their families when describing such procedures and obtaining consent. Cancers attributed to X-ray exposure typically can take decades to develop, including cancers of organs receiving the largest dose of radiation, such as the lungs, the esophagus, the breast, the stomach, and the liver. In the general population, many risk projections assume a normal

life expectancy and while the study of risk of cancer due to X-ray exposure is inherently challenging when controlling many confounding factors, such study is particularly challenging in the ACHD population because of the wide variability of survival in such patient population. For many conditions such as pulmonary valve stenosis or ASD, survival approaches that of the general population.[31] However, for patients with much more complex congenital heart defects (for example, hypoplastic left heart syndrome), survival is significantly reduced despite optimal medical, surgical, and interventional therapies.[32] Harbron and colleagues concluded that the adjusted cancer risk of radiation exposure from cardiac catheterizations in children is relatively low and the risk of breast cancer following pulmonary artery angioplasty and valve replacement is of greatest concern.[33] A landmark study from Cohen and colleagues concluded that patients with higher radiation exposure (defined as 6 or more cardiac catheterization procedures) had a 2.4-fold greater risk of developing cancer than the low-exposure group.[34] It should be noted that while cardiac catheterization is a source of X-ray exposure, it is not the only source. Patient with CHD undergo different types of diagnostic imaging tests, including computed tomography, which could be another source of radiation exposure. This exposure is heightened particularly in those with complex CHD who often have undergone several surgeries, fluoroscopic procedures, and advanced imaging studies, all of which would increase cumulative lifetime radiation exposure. A unique group of patients, includes patients with complex CHD who have undergone several surgeries and interventions during their lifetime (such as Fontan circulation patients as described above), and despite this, ultimately they will require heart (or heart and liver) transplant evaluation. Although overall transplant patients are at an increased risk of malignancy, this applies also specifically to CHD patients who have undergone transplants.[35]

INADEQUATE CANCER SCREENING IN ADULT CONGENITAL HEART DISEASE PATIENTS

Cardiac complications including heart failure, valve disease, and arrhythmias can overshadow the need for primary care and preventative screening measures. Among many factors affecting preventative screening, lack of a primary care provider is a major one.[36] Many patients with complex chronic conditions rely heavily on subspecialists for their medical care, thus reducing the likelihood to seek and access general preventative care. Not only does this hold particularly true for ACHD patients, but there are also additional challenges that ACHD patients face— inadequate understanding by patients and their parents, of the importance of life-long medical care, and the challenges in proper transition from pediatric to adult care.[37,38] Christman and colleagues showed the importance of cancer screening in ACHD patients and emphasize the need for collaboration of ACHD providers and primary care physicians, which not only can save lives but also could transfer the approach to overall care of ACHD patients.[39] The median age of cancer diagnosis in ACHD patients at 43.5 years when compared with the general US population at 66 years limits some of the health benefits of age-appropriate screening.[40] Hence additional research is needed to develop appropriate screening protocols for ACHD patients in general. As ACHD patients are less likely to participate in cancer screening, it leads to the cancer being diagnosed at later stages, which affects their survival rate.[40] Appropriately so, the importance of increased access to primary care and appropriate transition from pediatric to adult care for ACHD patients have been incorporated in the 2018 American College of Cardiology/American Heart Association ACHD Guidelines.[41]

CANCER TREATMENT IN ADULT CONGENITAL HEART DISEASE PATIENTS

Whereas ACHD patients face such additional challenges in proper cancer screening and diagnosis, they can face equally daunting concerns with regard to treatment. It is well established that cancer treatments can lead to various cardiac adverse events, among which heart failure, arrhythmias, blood pressure abnormalities, are not uncommon. Patients with CHD have a higher risk of heart failure and arrhythmias when compared to aged-matched controls.[42] Not surprisingly, a single-center cohort study of ACHD patients with malignancy found a markedly high rate of major adverse cardiovascular and cerebrovascular events of 59% over a 5-year follow-up period.[40] This could affect cancer treatments and it requires a close collaboration of hematology–oncology and ACHD providers for proper monitoring and treatment of adverse cardiovascular events. Among those undergoing cancer therapy, a reassuringly low rate of suspected cancer therapy related cardiac effects of 14% was observed in the aforementioned single-center study—only a single patient required temporary cessation of cancer therapy—followed by resumption at the original therapeutic dosing.[40] Additional data regarding safety and tolerability of cancer therapy in ACHD patients are required.

SUMMARY

With the exponentially increasing number of ACHD patients and concurrent uptrend in cancer diagnosis in these patients, it is only proper to speculate that the new exciting area of ACHD–oncology is taking shape. Among many factors that can affect the risk of cancer in ACHD, some can be modified and some are intrinsic to this patient population; but when it comes to treatment, we can make a difference in helping these patients by ensuring that they benefit from the full range of treatment options. Additional long-term outcome studies are required to further enhance our understanding of pathophysiology and influence treatment decision in this complex patient population.

CLINICS CARE POINTS

- Adult patients with congenital heart disease undergo diagnostic imaging as well as invasive procedures, which can increase lifetime radiation exposure. Such exposure could play a role in the observed increased risk of malignancy that is seen in the adults with congenital heart disease (CHD).
- Patients with single ventricle physiology who have undergone Fontan palliation are at an increased risk of hepatocellular carcinoma. Aggressive periodic screening can lead to early detection and better outcomes in the treatment of hepatocellular carcinoma.
- Certain genetic mutations such as Trisomy 21 and chromosome 22q11.2 deletion are commonly associated with CHD as well as increased risk of malignancy.
- Although increased risk of malignancy is multifactorial, access to preventative care and timely age-appropriate screening should be emphasized by all providers caring for these patients.

DISCLOSURE

The authors have nothing to disclose.

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