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Review

Cancer Risk in Congenital Heart Disease—What Is the Evidence?

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ABSTRACT

As life expectancy in patients with congenital heart disease (CHD) has improved, the risk for developing noncardiac morbidities is increasing in adult patients with CHD (ACHD). Among these noncardiac complications, malignancies significantly contribute to the disease burden of ACHD patients. Epidemiologic studies of cancer risk in CHD patients are challenging because they require large numbers of patients, extended follow-up, detailed and validated clinical data, and appropriate reference populations. However, several observational studies suggest that cancer risks are significantly elevated in patients with CHD compared with the general population. CHD and cancer share genetic and environmental risk factors. An association with exposure to low-dose ionizing radiation secondary to medical therapeutic or diagnostic procedures has been reported. Patients with Down syndrome, as well as, to a lesser extent, deletion of 22q11.2 and

RÉSUMÉ

Comme l'espérance de vie des patients atteints d'une cardiopathie congénitale augmente, le risque d'apparition de maladies non cardiaques est aussi en hausse chez les adultes qui sont atteints de ce type de cardiopathie. Parmi les complications non cardiaques, les affections malignes contribuent fortement au fardeau de la maladie dans cette population. La réalisation d'études épidémiologies sur le risque de cancer chez les patients atteints d'une cardiopathie congénitale présente des défis, car de telles études exigent un grand nombre de sujets qu'il faut suivre sur une longue période, des données cliniques détaillées et validées et des populations de référence appropriées. Malgré tout, plusieurs études observationnelles semblent indiquer que le risque de cancer est considérablement élevé chez les patients atteints d'une cardiopathie congénitale comparativement à la population générale. De fait, les facteurs de risque génétiques et

As survival in patients with congenital heart disease (CHD) has improved,[1-3] a new generation of adult patients with CHD (ACHD) is at risk for noncardiovascular morbidities. We have shown that this population has poor outcomes centring around life-long comorbidities with mortality shifting away from children and toward adults.[4] Moreover, we have shown that cancer is a strong predictor of death in this population.[5] These findings emphasize the impact of age-related noncardiac morbidities, including malignancies, on mortality in ACHD patients.[5]

In the present review we turn our attention to cancer as a specific concern due to radiation exposure from medical procedures and to the genetic associations between CHD and cancer.[6,7] A few specific malignancies have been reported in some specific CHD conditions. As this population ages, practitioners who care for ACHD patients need to be aware of this new issue. Our aim is to provide a comprehensive review of evidence and recommendations based on current available literature in the field. Figure 1 gives an overview of all the risk variables that may affect cancer outcomes in patients with CHD, highlighting the challenge of robust measurement that accounts for confounders and effect modifiers in CHD patients.

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renin-angiotensin system pathologies, may manifest both CHD and a predisposition to cancer. Such observations suggest that carcinogenesis and CHD may share a common basis in some cases. Finally, specific conditions, such as Fontan circulation and cyanotic CHD, may lead to multisystem consequences and subsequently to cancer. Nonetheless, there is currently no clear consensus regarding appropriate screening for cancer and surveillance modalities in CHD patients. Physicians caring for patients with CHD should be aware of this potential predisposition and meet screening recommendations for the general population fastidiously. An interdisciplinary and global approach is required to bridge the knowledge gap in this field.

environnementaux sont les mêmes pour la cardiopathie congénitale et pour le cancer. Une association avec l'exposition à de faibles doses de rayonnements ionisants secondaire aux démarches thérapeutiques ou diagnostiques a été rapportée. Les patients atteints du syndrome de Down ainsi que, dans une moindre mesure, ceux qui présentent une délétion 22q11.2 ou dont le système rénine-angiotensine est atteint, sont susceptibles d'avoir à la fois une cardiopathie congénitale et une prédisposition au cancer. De telles observations semblent indiquer que la carcinogenèse et la cardiopathie congénitale pourraient dans certains cas avoir des causes communes. Enfin, certaines conditions, comme la présence d'un circuit de Fontan et une cardiopathie congénitale cyanogène, pourraient avoir des effets sur plusieurs organes et finir par provoquer l'apparition d'un cancer. Il n'en demeure pas moins qu'il n'existe à l'heure actuelle aucun consensus clair quant aux stratégies appropriées de dépistage du cancer et aux modalités de surveillance des patients atteints de cardiopathie congénitale. Les médecins qui traitent des patients atteints de cardiopathie congénitale doivent être au fait de cette prédisposition potentielle et suivre à la lettre les recommandations en matière de dépistage s'appliquant à la population générale. Une approche interdisciplinaire et globale s'impose afin de combler les lacunes des connaissances dans ce domaine.

Cancer Prevalence

Cancer risk in CHD patients

Congenital anomaly and cancer share genetic and environmental risk factors. Congenital cardiovascular anomaly is the most common congenital anomaly and is the most frequent type of birth defect associated with a subsequent cancer diagnosis.[8] Associations between CHD and cancer risk have been inconsistently reported in children (Table 1).[8-12] Such studies are challenging, requiring large sample size, extended follow-up, detailed and validated clinical data, and appropriate reference populations.

In Norway and Sweden, a population-based cohort study of 5.2 million children showed an increased overall cancer risk in individuals with all types of birth defects combined with a standardized incidence ratio (SIR) of 1.7 (95% confidence interval [CI] 1.6-1.9).[9] However, the SIR of cancer occurrence in patients with CHD was not significantly increased relative to the general population.[9] An excess risk of cancer was identified in children with malformations in the nervous system, Down syndrome, and multiple defects.[9]

Using the Danish National Hospital Registry and the Danish Cancer Registry, Sun et al.[10] estimated the cancer risk among children with a nonchromosomal birth defect in the nervous or circulatory system. Out of more than 1,709,456 live births identified from 1977 to 2007, 1.44% of the children were diagnosed with CHD. Compared with children without any congenital malformation, they had a 2.64-fold (95% CI 2.21-3.16) higher overall risk of cancer, including cancer in the lymphatic and hematopoietic tissues (hazard ratio [HR] 3.22, 95% CI 2.43-4.27) and cancer in the central nervous system (HR 2.40, 95% CI 1.43-4.02).[10] In an alternate analysis, some of these associations were weaker depending on the subtypes of CHD.[10]

Using the Texas Birth Defects and Texas Cancer Registries,[8] a cohort study among children born from 1996 to 2000 was conducted. More than 3 million children records were included, and 115,686 (3.6%) had birth defects, of whom 2,351 (2.0%) had cancer. The authors showed a 3-fold increased risk of developing cancer relative to children without birth defects (incidence rate ratio [IRR] 3.05, 95% CI 2.65-3.50). More specifically, children with CHD had a 3.5-fold higher risk for overall cancer.[8]

More recently, a population-based cohort study was conducted in 3 US states to compare 11,211 children aged $\leq$ 14 years who were monitored for 82,890 person-years and had nonchromosomal CHD with a cohort of 147,940 children without birth defects who were matched by year of birth and monitored for 1,380,235 person-years.[11] Cancer incidence was 2.9-fold higher in patients with CHD relative to the reference cohort (IRR 2.9, 95% CI 1.9-4.3).

A nationwide population-based cohort study from Taiwan evaluated 31,961 patients with a recent CHD diagnosis from 1998 to 2006. Over a follow-up of 163,430 person-years, they showed an increased risk of cancer compared with the general population (SIR 1.45, 95% CI 1.25-1.67). More specifically, CHD patients presented significantly elevated risks of hematologic malignancies (SIR 4.04, 95% CI 2.76-5.70), solid tumours, such as central nervous system cancers (SIR 3.51, 95% CI 1.92-5.89), and head and neck malignancies (SIR 1.81, 95% CI 1.03-2.94).[12] Patients with chromosomal anomalies (n = 734 [2.3%]) were included without any specification, but surprisingly such anomalies were not a risk factor of cancer.

Cancer prevalence in ACHD patients

To further elucidate the cancer risk in ACHD patients, Gurvitz et al.[7] determined and compared the ACHD cancer prevalence rates with those of the general population. They performed detailed population-based analyses using the Québec CHD database[2] by age, sex, and type of cancer. Of the 34,965 adults alive on January 1, 2005, an estimated 1,156 ACHD patients had cancer (3.31%). Two-, 5-, and 10-year cancer prevalences were higher in both men and women with CHD compared with the Canadian

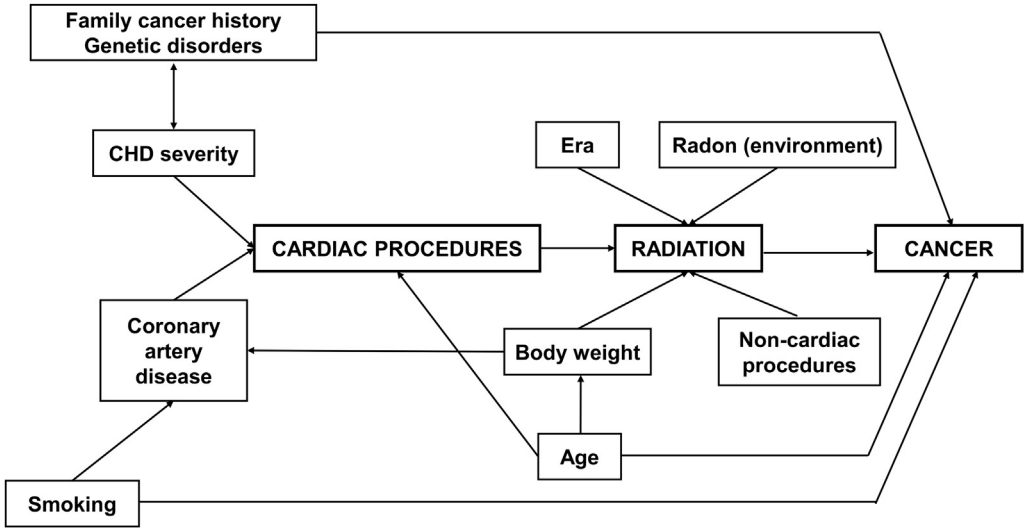

Figure 1. Graphical representation of risk variables that may affect cancer outcomes in patients with congenital heart disease (CHD).

population. Overall age-standardized cancer prevalence rates compared with the general population were 2.00 (95% CI 1.79-2.24) at 2 years, 1.74 (95% CI 1.60-1.89) at 5 years, and 1.65 (95% CI 1.55-1.77) at 10 years. The 3 most common sites of cancers in men and women with CHD were the same as the general population (breast, colorectal, and uterine in women and prostate, colorectal, and bladder in men). However, the differed in the fourth most common cancer, which was leukemia for both male and female ACHD patients and lung cancer for both sexes in the general population.[7]

Deaths from cancer

The annual incidence of age-related malignancy is increasing among ACHD patients, with cancer identified as the fourth main cause of mortality after heart failure, pneumonia, and sudden cardiac death.[13] A large Finnish study included 10,964 patients who underwent pediatric cardiac surgery from 1953 to 2009. The study showed that death caused by cancer was more frequent in patients with CHD compared with the general population, particularly among women who underwent surgery from 1990 to 2009.[14] Furthermore, in an analysis of ACHD patients > 65 years of age in Québec, cancer was a predictor of increased all-cause mortality with an HR of 1.43 (95% CI 1.17-1.76).[5]

Risk Factors Associated with Cancer in the CHD Population

Exposure to medical low-dose ionizing radiation and malignancy in ACHD

Over the past years, most research on malignancy issues in CHD patients focused on the possible association with radiation exposure, especially related to children and cancer. To address this issue, decades of follow-up in a large sample size with precise dosimetry data are required owing to the low incidence of cancer.[15]

Increasing use of low-dose ionizing radiation procedures in CHD. Improved diagnosis and therapy are achieved with increasing numbers of cardiac imaging modalities using low-dose ionizing radiation (LDIR). These modalities lead to an overall increase in LDIR exposure for patients with acquired[16] and congenital[17] heart disease. In a previous longitudinal population-based study from our group, we showed that children and adults with CHD were exposed to an increasing number of LDIR-emitting cardiac procedures. These surged from 18.5 to 51.9 per 1,000 CHD patients per year from 1990 to 2005 ($P < 0.0001$). Age at the time of first LDIR exposure in children decreased from 5 years to 9.6 months during the study period, indicating an increasing accessibility and perceived value of these types of procedures.[17] Notably, as

Table 1. Reported cancer risks in children with congenital heart disease

Location	Study period	CHD population	Risk of cancer (95% CI)
Norway and Sweden[9]	Norway: 1967-2004; Sweden: 1973-2004	29,313	Norway: SIR 1.2 (0.7-2.0); Sweden: SIR 1.2 (1.0-1.6)
Denmark[10]	1977-2007	24,643	HR 2.64 (2.21-3.16)
Texas[8]	1996-2005	Data not available	IRR 3.50 (2.81-4.31)
Utah, Arizona, and Iowa[11]	Arizona: 1986-2004; Iowa: 1983-2004; Utah: 1994-2006	11,211	IRR 2.9 (1.9-4.3)
Taiwan	1998-2006	31,961	SIR 1.45 (1.25-1.67)

CHD, congenital heart disease; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; SIR standardized incidence ratio.

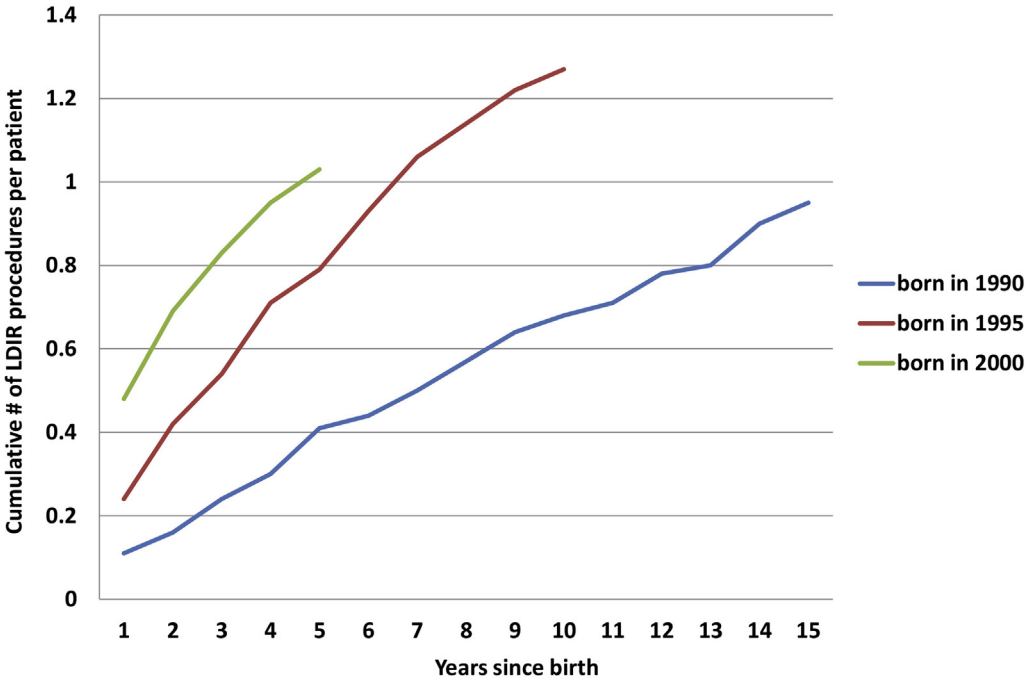

Figure 2. Cumulative number of low-dose ionizing radiation (LDIR)—related cardiac procedures in severe congenital heart disease by birth cohort.[17]

shown in Figure 2, for patients born in 2000 exposure occurs not only in higher doses but also at an earlier age.[17] The results were driven primarily by a greater use of diagnostic catheterizations. Structural heart interventions contributed increasingly to radiation exposure. Although conventional radiographs account for most of these examinations, higher-exposure imaging modalities, such as cardiac catheterization and chest computed tomography (CT) are the main source of cumulative radiation exposure, representing 81%-95% of total radiation exposure.[18,19]

Glatz et al. demonstrated that most children with CHD undergoing cardiac surgery received a low level of overall cumulative LDIR exposure (< 3 mSv/y), although 5.3% of them were exposed to > 20 mSv/y.[20] Similarly, Johnson et al. collected dosimetry data from 337 children with CHD undergoing various heart surgeries. Overall median cumulative effective dose was relatively low (2.7 mSv) although the range was very broad, from 0.1 to 76.9 mSv.[19] Populations at risk for higher exposure levels are children with complex CHD and those with genetic syndromes.[17,20,21]

These secular trends, which reflect an increasing use of medical procedures conferring secondary LDIR exposure, parallel those observed in adults with acquired heart disease.[16,22] However, cardiac procedures in CHD patients are heterogeneous and less standardized than in non-CHD patients. In congenital cardiology, and particularly in catheterization, exact dose exposure may vary widely according to the procedure type and complexity.[19,23,24] Bacher et al. described differences in effective doses for diagnostic (median 4.6 mSv, range 0.6-23.2 mSv) and therapeutic (6.0 mSv, range 1.0-37.0 mSv) procedures, with variation in the duration of the procedures as well.[24] Therefore, although lessons may be learned from studies of patients with acquired heart disease, dedicated research efforts within the CHD population are needed.

Radiation-induced chromosomal DNA damage. There is a concern that such exposure may contribute to the risk of malignancy.[25] Exposure to ionizing radiation, even at low doses, can cause numerous types of DNA damage in cells that might result in radiation-induced cancer in later years. Ait-Ali et al. assayed micronucleus as a biomarker of DNA damage before and 2 hours after catheterization procedures in a subset of 18 patients (age 5.2 ± 5.7 years).[18] Short-term DNA damage was shown, with median micronucleus values increasing significantly after the procedure.[18] An excess number of γ-H2AX foci (representing DNA double-strand breaks, which are considered to be one of the most dangerous chromosomal alterations from exposure to radiation) have been shown after pediatric cardiac catheterization.[26] More recently, leukocyte telomere length was measured in 50 ACHD patients and 50 healthy age- and sex-matched subjects.[27] Leukocyte telomere length, a biomarker of genomic instability, is associated with increased risk of malignancy. Adults with CHD had significantly shorter leukocyte telomere length compared with control subjects, suggesting evidence of early biologic aging.[27]

Association between exposure to LDIR from cardiac procedures and malignancy. The association between radiation and cancer arises from studies conducted among atomic bomb survivors.[28,29] In medical imaging, the magnitude of this risk has been difficult to assess. The LifeSpan Study observed a relative risk of 1.0005 per mSv.[30] In a Québec cohort of adults with coronary artery disease, the authors found a hazard ratio of 1.003 per mSv.[31] Currently, the "linear no-threshold" model has become accepted as the standard in radiation protection practice. This implies that any amount of radiation is potentially associated with an increased risk of cancer.[15]

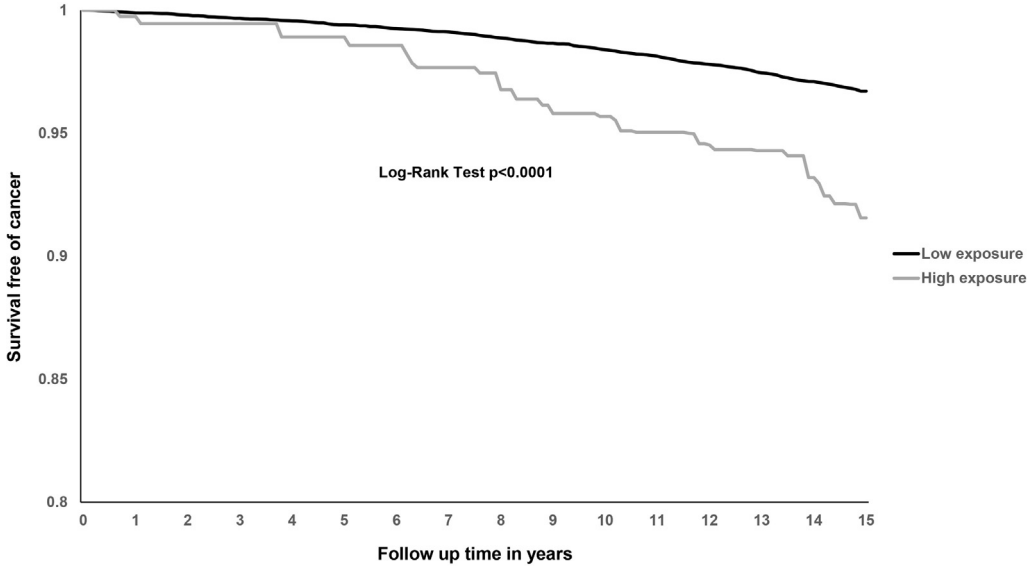

Figure 3. Adjusted Kaplan-Meier curve for cancer-free survival probability for patients with high exposure from low-dose ionizing radiation—related cardiac procedures (≥ 6 procedures, **grey line**) in comparison with low exposure (≤ 1 procedure, **black line**).

Retrospective studies suggested that general pediatric populations exposed to radiation from medical imaging, particularly from CT, have an increased risk of cancer.[32,33] Pearce et al. identified 178,604 patients < 22 years of age who were first examined with the use of CT from 1985 to 2002, focusing on the risks of leukemia and brain tumours. They observed a 3-fold increased risk of leukemia after cumulative doses of ∼ 50 mGy from CT scans in children (relative risk [RR] 3.18, 95% CI 1.46-6.94), and the RR for brain cancer in those who received a cumulative mean dose of 60 mGy was 2.82 (95% CI 1.33-6.03).[33] In Australian Medicare records, 60,674 cancers were recorded in a population-based cohort of 10.9 million people 0-19 years of age from 1985 to 2005. Among them, 3,150 cancers occurred in 680,211 people exposed to CT. After stratification for age, sex, and year of birth, cancer incidence was 24% greater in the exposed group than in the nonexposed group (IRR 1.24 (95% CI 1.20-1.29), with a dose-response relationship (IRR increasing by 0.16 [0.13-0.19]) with each additional CT scan.[32]

Lifetime attributable risks of cancer from cardiac procedures have been projected,[18,19,34,35] but epidemiologic data on the risk of cancer in CHD patients are limited. A Canadian single-center study showed no increase in cancer incidence among 3,915 children exposed to at least 1 catheterization before the age of 18 from 1950 to 1965.[36] In contrast, an Israeli study examined records of 674 children who had undergone catheterization from 1950 to 1970 and found an excess risk of solid cancers and lymphomas.[37] Small sample sizes, with limited power and possible selection bias, may account for these controversial results.

Using the Québec CHD Database, we included 24,833 ACHD patients aged 18-64 years from 1995 to 2009 and measured the cumulative exposure from LDIR-related cardiac procedures for each patient.[6] In more than 250,791 person-years of follow-up, 602 cancer cases were observed (median age 55.4 years). After adjusting for age, sex, year of birth, CHD severity, and comorbidities, we reported an association between increase in exposure to LDIR-related cardiac procedures and incident cancer risk (odds ratios 1.08 per procedure [95% CI 1.04-1.13] and 1.10 per 10 mSv [95% CI 1.05-1.15]), possibly with a dose-related response. Figure 3 shows that survival free of cancer was significantly lower in patients with high exposure from LDIR-related cardiac procedures (≥ 6 procedures: 91.5% [95% CI 90.9%-92.2%]) in comparison with patients with low exposure (≤ 1 procedure: 96.7% [95% CI 96.4%-97%]). Figure 4 shows that high LDIR exposure was associated with high risk of cancer, whether the exposure was defined as a cumulative number of procedures or with the use of dose estimates. Several sensitivity analyses were performed to compensate the limitations of the data such as lack of data on smoking status, and the association was persistent.[6] Our data supported the "linear no-threshold" model, which states that cancer incidence increases with dose in linear fashion with no lower threshold.[38]

Cancer risk from radiation may be dependent not only on dose but also on nonmodifiable person-specific factors, such as sex, and it is typically higher in women.[38] Non-CHD studies have suggested that cancer may be more likely in women than in men after similar levels of exposure.[38-40] This difference may be attributable to the relatively smaller body sizes for the same amount of LDIR as well as to the breasts' increased exposure in the radiation field.

Genetic disorders

Another potential association between CHD and cancer may be genetic. Some patients with genetic disorders manifest both CHD and a tumour predisposition.

The most common example occurs in patients with Down syndrome, who have a known high risk of CHD and a 10- to 20-fold higher risk of leukemia compared with the general population, mostly in childhood.[41-45] A predisposition for testicular germ cell tumours in young men, only partly attributable to cryptorchidism and testicular microlithiasis, has been observed as well.[42-44] To a lesser extent, liver and

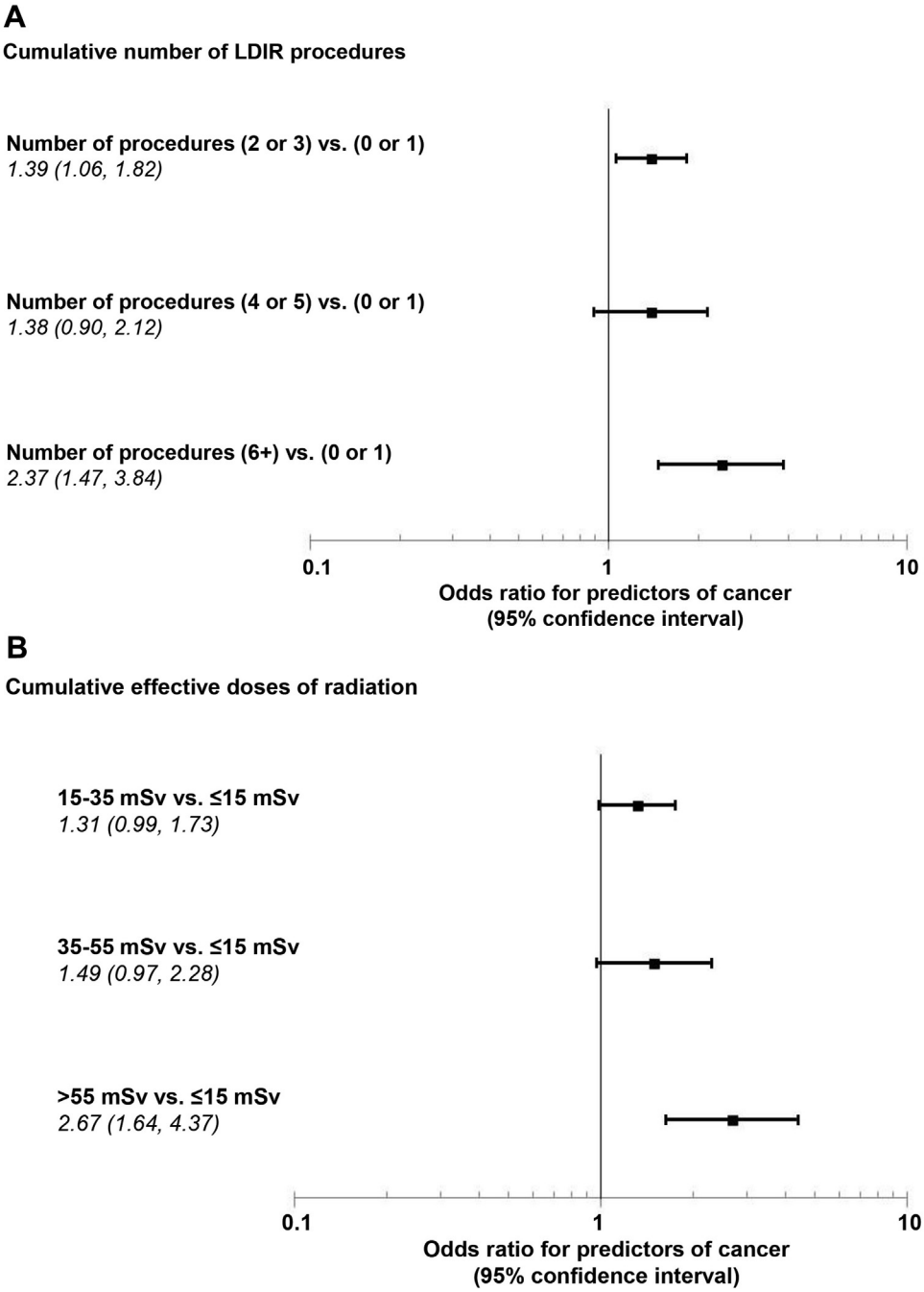

Figure 4. The effect of low-dose ionizing radiation (LDIR) from cardiac procedures on cancer risk in ACHD patients, with LDIR exposure represented as (**A**) cumulative number of procedures or (**B**) cumulative effective dose estimates. (**A**) Plot showing adjusted odds ratios for cancer using 0 or 1 procedure as the reference level. (**B**) Plot showing adjusted odds ratio for cancer using $\leq$ 15 mSv as the reference level.[6]

stomach cancers also appear to be more frequent in patients with Down syndrome than in the general population.[42,43] However, they have a decreased global malignancy burden owing to a low incidence of many adult solid tumours, such as lung cancer, breast cancer, and cervical cancer.[41,44,45]

The deletion of 22q11.2 is a genetic syndrome associated with conotruncal CHD. There are reports of malignancy in several patients with 22q11.2 deletion syndrome, including atypical teratoid/rhabdoid tumours, lymphoma, neuroblastoma, acute lymphoblastic leukemia, osteosarcoma, thyroid carcinoma, Wilms tumour, and hepatoblastoma.[46-54] Some genes within the deleted region may play a role in both heart development and tumour suppressor or tumourogenesis genes with increased incidence of malignancy.[51]

The renin-angiotensin system pathologies (RASopathies) provide evidence that a mutation in genes in a specific pathway can cause dysregulation and consequences in both development and oncogenesis. The RASopathies are a group of autosomal dominant disorders with overlapping phenotypic features, which may include cardiac malformations, craniofacial dysmorphology,

neurocognitive impairment, cutaneous, and musculoskeletal and ocular abnormalities, and an increased cancer risk. They are caused by pathogenic variants in genes that encode proteins in or with close interaction with RAS−mitogen-activated protein kinase pathway, which plays an important role in regulating cellular growth, differentiation, and senescence, all of which are crucial to normal development.[55] For example, Noonan syndrome is explained by mutation of the protein tyrosine phosphatase nonreceptor type 11 gene in 50% of cases. A cardiovascular feature is observed in 80%-90% of affected individuals, and pulmonary valve stenosis is seen in ∼ 40% of patients. These patients are at an approximately 8-fold increased risk for leukemia and solid tumours.[55-58]

Fanconi anemia is an autosomal and X-linked recessive disease with cancer predisposition. It is associated with developmental abnormalities and can be diagnosed in newborns with birth defects that suggest the VACTERL spectrum of abnormalities (vertebral anomalies, anal atresia, cardiac anomalies, tracheo-esophageal fistula with esophageal atresia, and structural,[59] renal, and limb anomalies).[60] Patients with Fanconi anemia and VACTERL phenotype have a worse prognosis than patients with milder phenotypes and have earlier onset of cancer. The early identification of this high-risk subgroup of patients should lead to earlier cancer surveillance.[60]

Specific Cancers and Specific CHD Conditions

Fontan circulation and hepatocellular carcinoma

Long-term liver dysfunction is an increasingly recognized complication of CHD with univentricular physiology palliated by means of the Fontan procedure.[61] The procedure, which evolved over several decades, maintains near-normal systemic oxygenation while inducing a state of systemic venous hypertension with passive venous congestion of the liver and relatively decreased cardiac output. Moreover, a variety of chronic liver diseases may occur in ACHD patients, including viral hepatitis,[62] nonalcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and primary biliary cholangitis. These can increase the risk for cirrhosis. Furthermore, patients with univentricular physiology may already have liver damage before creation of the Fontan circulation due to chronically elevated right atrial pressure, as was highlighted by an autopsy study.[63]

Hepatic complications occurring after Fontan procedures have been associated with the duration of the Fontan circulation,[61,64,65] ventricular dysfunction,[65] and elevated central pressures.[64] Hepatic dysfunction may lead to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).

Diagnosis of HCC is not obvious in Fontan patients. The typical kinetics of enhancement of HCC may be altered due to high systemic venous pressure and low cardiac output in these patients. Therefore, elevation of alpha-fetoprotein may be helpful in making the diagnosis of HCC. Studies reporting HCC are case series,[66-68] so the exact risk of HCC in the Fontan population with cirrhosis has yet to be determined; this risk is estimated to be 1.5%-5% per year.[61,68] In a multicentre case series study, the median duration from Fontan operation to HCC diagnosis was 22 (range 2-36) years.[68] Of the 33 patients with HCC, mortality after the diagnosis of HCC was high: 18 (55%) died during a median follow-up of 26 (range 1-51) months. As life expectancy has improved in Fontan patients, the incidence of HCC may increase in this population.

Pheochromocytoma and paraganglioma in cyanotic CHD

Pheochromocytoma and paraganglioma are rare neuroendocrine tumours arising from the neuroendocrine cells, presenting with a known incidences of 0.2%-0.6% in patients with hypertension in the general population and 0.6% in children with hypertension.[69] In the past decade, a convincing body of evidence pointed to a link between genetic neuroendocrine tumour syndromes and the chronic hypoxia pathway. The association of neuroendocrine tumours in patients with cyanotic CHD, mainly pheochromocytoma and paraganglioma, was first described in a 1964 case series: 5 of 21 patients with histologically proven pheochromocytoma seen at Johns Hopkins Hospital (Baltimore, MD) from 1901 to 1962 had cyanotic CHD.[70] This association has been repeatedly reported anecdotally in case reports.[69-74] Using a nationally representative discharge database, Opotowsky et al. recently reported that cyanotic ACHD patients had an increased odds ratio (6.0, CI 2.6-13.7; $P < 0.0001$) for pheochromocytoma and paraganglioma development compared with those without cyanotic CHD.[75] A Korean study focused on pheochromocytoma after a Fontan operation.[73] Among 283 Fontan patients, 7 were diagnosed with pheochromocytoma, reaching a prevalence of 2.5%, which is high compared with the general population.[73] Although rare, these tumours are often associated with significant adverse cardiovascular events, such as arrhythmia, hypertension, and heart failure, particularly in patients with an existing cardiovascular disease. Whether the risk for these neuroendocrine tumours is increased in cyanotic CHD owing to chronic hypoxia only or to the combination of chronic hypoxia with an underlying genetic susceptibility is not elucidated. Clinical suspicion and early biochemical screening with imaging should be kept in mind in cyanotic patients.

Prevention and Screening

The most common types of cancer in ACHD patients mirror those of the general population.[7] For these reasons, age-appropriate cancer screening for ACHD patients is recommended.[76] Alarmingly, ACHD patients, particularly those with severe CHD, are underscreened for malignancies such as cervical, breast, and colon cancer, with significantly lower rates of Papanicolaou tests, mammograms, and colonoscopies than the general population.[77] In one study, 58%, 37%, and 44% of adults with, respectively, simple, moderate, and complex CHD had adequate cancer screening, and this decreased as New York Heart Association functional class increased.[77] It is possible that screening compliance rates may be influenced by competing medical comorbidities, such as the severity of disease, and that a focus on the underlying CHD may divert attention from cancer surveillance.[77] Physicians should strive to meet the screening recommendations for the general population (Table 2).

Patients and physicians should be aware of LDIR associated with medical studies and procedures. The small risk of inducing malignancy has to be weighed against the potential

Table 2. Suggested guidelines for screening cancer in CHD patients

Cancer type	Recommendations
Breast[90,*]	Women 40-49: screening with mammography not recommended, individual decision; Women 50-74: mammography every 2-3 years; Clinical breast (self)examination not recommended
Cervical[91,†]	Women < 25: no routine screening; Women 25-69: Pap test every 3 years; Women ≥ 70 who have undergone adequate screening (ie, 3 successive negative Pap test results in the past 10 years): routine screening may stop; Women ≥ 70: continued screening until 3 negative test results have been obtained; No recommendation for HPV testing
Colorectal[92]	Adults 50-74: screening with fecal testing every 2 years or flexible sigmoidoscopy every 10 years; Adults ≥ 75: no screening. We recommend not using colonoscopy as a screening test for colorectal cancer.
Prostate[93]	Recommendation against PSA-based screening
Lung[94,‡]	Adults 55-74 with ≥ 30 pack-year smoking history, who smoke or quit smoking < 15 years ago: low-dose computed tomography every year up to 3 consecutive years
Liver[67,86,95]	CHD patients 10 years after Fontan completion (or earlier if there is evidence of failure of the Fontan circulation): yearly screening with laboratory evaluation; Imaging of liver by ultrasound every 2 years; All patients who underwent cardiac surgery in or before 1992 should be screened for hepatitis B and C; Recommendation against the use of alpha-fetoprotein alone

* These recommendations apply to women aged 40-74 years who are not at increased risk of breast cancer (ie, women with a personal or family history of breast cancer, women who are carriers of gene mutations such as BRCA1 or BRCA2 or who have a first-degree relative with these gene mutations, and women who had chest radiation therapy before age 30 or within the past 8 years).

† These recommendations apply to women with no symptoms of cervical cancer who are or have been sexually active, regardless of sexual orientation. They do not apply to women with symptoms of cervical cancer (eg, abnormal vaginal bleeding), women with previous abnormal results on screening (unless they have been cleared to return to normal screening), women who do not have a cervix (because of hysterectomy), women who are immunosuppressed (eg, as a result of organ transplantation, chemotherapy, chronic corticosteroid treatment, or HIV infection), or women who have limited life expectancy such that they would not benefit from screening.

‡ These recommendations apply to adults 18 years of age and older who are not suspected of having lung cancer. These recommendations do not apply to adults with previous lung cancer or with signs or symptoms of lung cancer.

cardiovascular risks for which these procedures are needed and the resulting decrease in morbidity and mortality expected with their use. Physicians ordering and performing cardiac imaging should justify the clinical need for a procedure and ensure that exposure is "as low as reasonably achievable" without sacrificing quality of care. Consensus recommendations regarding strategies to optimize imaging during LDIR cardiac procedures were published recently.[78] The goal of these recommendations is to optimize the study quality at the lowest achievable dose. Launched in 2011, the **Im**proving **P**ediatric and **A**dult **C**ongenital **T**reatments (IMPACT) registry focuses on evaluating the use, adverse events, and outcomes associated with diagnostic and interventional catheterization procedures in children and adults with CHD.[79] The IMPACT registry showed a reduced radiation exposure during CHD catheterization procedures decided according to best practices.[80] The results have yet to be published, but there was a decrease in radiation exposure in early and late adapters compared with nonadapters. The usefulness of repeated procedures that may have nonradiation substitutes needs judicious consideration. Fortunately, technologic advances have already allowed procedure doses to be reduced. Although federal regulation exists to monitor radiation exposure in health care workers, there have been no directives for patients so far. The development of an "electronic patient passport" that patients with CHD would carry with them, containing an overview of their CHD history and cumulative lifetime exposure, has been suggested.[81] Consensus regarding appropriate screening and surveillance modalities to depict liver pathologies in Fontan patients is lacking. Current ACHD guidelines give little direction on how to conduct screening for liver diseases in this population. European guidelines suggest noninvasive hepatic evaluation (with the use of ultrasound) for fibrosis, cirrhosis, and HCC.[82] The 2018 American guidelines mention the vulnerability of the liver in Fontan patients and suggest imaging of the liver (with the use of ultrasound, magnetic resonance [MR] imaging, or CT) and blood tests of liver function for liver diseases after Fontan surgery.[83] Canadian guidelines also state that hepatic congestion may lead to cardiac cirrhosis and hepatic neoplasms.[84] On the other hand, hepatologic societies do not address cardiac cirrhosis.[85] Based on the available evidence, some teams recommend yearly screening for laboratory evaluation and annual, or biannual, screening for other evaluations,[67] such as liver ultrasound (with shear-wave elastrography if available).[86] Screening should be initiated in collaboration with the hepatologist 10 years after Fontan completion, or earlier if there is evidence of failure of the Fontan circulation.[67,86,87] CT or MR imaging may be recommended at the discretion of the hepatologist or if a suspicious liver nodule is identified. The use of alpha-fetoprotein alone is controversial and should be combined with ultrasound.[85] Moreover, patients with evidence of liver disease and patients who underwent cardiac surgery before 1992 should have their serologies checked for hepatitis B and C. Indeed, before 1992, testing methods were not sensitive enough to detect the hepatitis C virus in the national blood supply.

Recommendations for cancer surveillance in patients with RASopathies and other genetic conditions have been made.[88] In most of these syndromes, routine cancer surveillance is probably not warranted owing to the low prevalence of cancer but prompt assessment in case of clinical symptoms is

justified. To date, no screening recommendation exists for patients with Down syndrome. Because their risk for solid tumours is lower than that of the general population, timing for screening tests has yet to be determined. For example, radiation exposure from mammograms and anaesthesia exposure from subsequent testing also pose a risk to patients. Regarding patients with 22q11.2 deletion syndrome, the true incidence of malignancy is not known. Only more extensive analyses will allow tailored surveillance recommendations to be made. Until such time as additional data become available, caregivers of patients with 22q11.2 deletion syndrome should be vigilant regarding malignancy.

Knowledge Gaps

Many research questions remain, and substantial work still needs to be done. Whether cancer screening for adult malignancies needs to be applied more aggressively in the ACHD population is an important issue. Radiation-induced solid cancers may occur at younger ages than in the general population.[29] More data are needed in children with CHD for whom longitudinal follow-up is available. Studies to determine the possible impact of a threshold effect will also prove pivotal for policy recommendations to improve prevention. This point has to be studied in the ACHD population to guide specific recommendation and to ascertain whether earlier screening is necessary. Furthermore, the susceptibility of ACHD patients to the effects of LDIR involves several mechanisms that are still unknown and have to be part of this complex equation. Finally, the effect of chemotherapy on the congenitally abnormal heart has not been explored. In such difficult situations, it would seem appropriate to adjust chemotherapeutic regimens in the setting of an underlying ventricular dysfunction. To date, no study has been conducted in this area and data need to be collected to assess the safety of such treatments in this population.

Conclusion

Although great progress has been made in the management of ACHD patients, the presence of noncardiac morbidities affects the long-term outcomes of individuals with CHD. The question now becomes, "is the glass half empty or half full?"[89] Adults with CHD often have a complex multisystem disease that requires particular clinical attention in our efforts to influence outcomes. There is evidence that cancer risk is significantly elevated in patients with CHD owing to exposure to medical LDIR, known or yet unknown genetic disorders, or pathophysiologic predisposition. There is currently no clear consensus regarding appropriate screening for cancer and surveillance modalities in CHD patients, but every effort should be made to avoid the "malignant price of cardiac care."[81] We propose judicious adherence to the cancer prevention policies for non-ACHD populations until more evidence becomes available. An interdisciplinary and global approach is required to bridge the knowledge gap in this field. Physicians who care for patients with ACHD should be aware of this cancer predisposition and therefore focus on their patients' needs beyond cardiovascular disease.

Disclosures

The authors have no conflicts of interest to disclose.

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