Congenital heart disease and the risk of cancer: The importance of understanding associated comorbidities

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Congenital heart disease (CHD) is the most common birth defect affecting nearly 9 per 1000 live births.[1] Survival for patients with CHD has dramatically increased over the last several decades with nearly 97% of patients expected to reach adulthood.[2] With this rise in life expectancy, there has been a parallel rise in the need to understand the burden of acquired diseases in this patient population. This knowledge is critical for the assessment of contributing factors to morbidity and mortality, identification of modifiable risk factors and the implementation of CHD specific care guidelines aimed at addressing this complex array of comorbidities.

Prior work has demonstrated an association between CHD and cancer.[3] The present study published in the *The Lancet Regional Health-Europe* by Karazisi et al expands this understanding by evaluating the risk of cancer from birth to adulthood.[4] Leveraging the broad and longitudinal nature of the Swedish Health Registry, the authors identified 89,000 patients with CHD and compared them to age and sex matched controls. They found that the risk of cancer in CHD was 23% higher as compared to the control group (HR 1·23, 95% CI 1·19-1·27). Interestingly, this risk remains elevated (HR 1·18, 95% CI 1·14-1·22) even when accounting for genetic syndromes and organ transplantation. The risk was highest among younger patients (0-17 years of age, HR 3·2, 95% CI 2.·9-3·56) and those born in later cohorts (1990-2017, HR 2·88 [95% CI 2·57-3·22]). Malignancies of the skin had the highest incident rate ratio among the whole CHD population as compared to controls; but among the youngest age group (0-17 years) the most common cancer diagnosis were those of primary lymphoid and hematopoietic origin. While congenital heart surgery did not increase the risk of cancer overall, there was an increase in risk amongst children who had CHD surgery at less than 1 year of age.

The present study underscores the far-reaching implications of CHD on overall health. CHD has been associated with distinct syndromes, and some of these entities, in turn, have been linked with a variety of extracardiac pathologies including gastrointestinal malformations, orthopedic abnormalities, and certain oncologic processes (e.g. Trisomy 21 with leukemia).[5] In this paper the authors observed a persistent elevation in cancer risk even when accounting for known syndromes and organ transplantation, suggesting that the genetic underpinnings of CHD likely have vast consequences outside of the cardiovascular system due to the shared developmental nature of these genes across various systems. This finding is in keeping with prior work by Seidman et al. who identified several loss of function genetic variants in CHD patients that code regulatory proteins.[6] This observation underscores how CHD may have significant extracardiac associations in the absence of a distinct syndrome.

The findings of this paper also highlight the need to understand how CHD management may predispose patients to acquired disease. While radiation exposure has previously been hypothesized to be a contributing risk factor for cancer in CHD, the authors of this paper shed light on a potential additional source.[7] Specifically, the study observed an increased risk of cancer in patients who underwent congenital heart surgery (and presumed thymectomy) in the first year of life. There is some suggestion that neonatal thymectomy alters the immunologic T-cell profile and may accelerate immunosenescence, thereby increasing the risk of cancer.[8] Additional studies using granular clinical data and long-term follow-up are needed, but this finding highlights the need to further explore how CHD management may increase a predisposition to developing cancer, and how, if possible, we can modify these risks without compromising survival.

The work presented by Karazisi et al. has several strengths and limitations. Use of a national registry provides a unique opportunity for longitudinal follow-up, a feature that is crucial for epidemiologic studies seeking to understand the evolution of disease over the course of a lifetime. It also provides an opportunity to address confounding due to era or exposure time. However, Karazisi et al. were limited by the lack of clinical granularity, such as radiation dose and procedures such as cardiac catheterizations. There may be some misclassification due to the evolution of diagnosis codes over time.

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Nonetheless, this important and impressive work presented by Karazisi et al. has added to the limited but now growing body of knowledge for patients with CHD. As survival continues to improve, so must our attention to issues that extend beyond cardiovascular health. The associated comorbidities observed in patients with CHD, either as a consequence of management, lifestyle, or genetic underpinning, require further study, and the findings presented in this paper provide the groundwork for additional research.

Contributors

Erika Mejia: writing of first draft of manuscript

Joseph Rossano: editing and critical revision of the manuscript

Declaration of interests

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