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Congenital Heart Disease: Systematic Review

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Risk of Cancer in Patients with Congenital Heart Disease: A Systematic Review and Meta-Analysis

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Keywords
Congenital heart disease · Cancer · Hazard risk · Meta-analysis · Systematic review

Abstract

Introduction: There has been remarkable progress in both diagnosis and treatment of patients with congenital heart disease (CHD), with an increasing number of survivors. Whether patients with CHD are more likely to develop cancer is still a controversial issue. This study aimed to quantitatively estimate the association between patients with CHD and the risk of developing cancer through meta-analysis. ***Methods:*** Web of Science, PubMed, and Embase databases were searched from inception to September 2023 to identify potentially relevant case-control studies and cohort studies that reported risk estimates and confidence intervals (CIs). RevMan software was used to analyze the pooled effect size and test for heterogeneity. The random effect and fixed effect models were applied to the study period. Egger's test was performed to examine publication bias. ***Results:*** We analyzed six studies, consisting of 2 case-control studies and 4 cohort studies comprising 276,124 participants. The overall pooled hazard risk for cancer in patients with CHD was 1.71 (95% CI: 1.28–2.28; $p < 0.01$), with significant heterogeneity ($I^2 = 97\%$, $p < 0.01$). The quantitative analysis of studies indicates that patients with CHD have an increased risk of developing cancer, even after adjusting for chromosomal disorders. ***Conclusion:*** Our study highlights the importance of controlling modifiable factors in cancer prevention and emphasizes the need for health education for patients with CHD in primary care. Given the limited number of studies included in this analysis, further research is needed to accurately quantify the cancer risk of exposed versus unexposed CHD.

Introduction

Congenital heart disease (CHD) refers to a group of structural abnormalities of the heart that are present at birth. It is one of the most common birth defects and ranks among the top five causes of infant mortality, with an estimated global prevalence of about 1.8% in newborn infants [1]. Owing to advances in diagnostic and therapeutic techniques, the survival rate of CHD has greatly improved. A previous study showed that the probability of survival to 35 years of age was even over 80% [2]. As a result, the number of adults with CHD (ACHD) is also increasing, with an estimated 1.2 million in Europe and 1 million in the USA [3]. As the survival rate of the CHD and ACHD populations continues to rise, concerns about

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the long-term quality of life for CHD patients must be taken into account.

Cancer is a major health concern globally, and its risk factors and causes have been extensively studied. In recent years, several studies have found an increased risk of cancer in children and adults with CHD in comparison to the general population [4]. The biologic basis for the link between CHD and cancer is multifaceted and includes gene mutations [5], increased radiation exposure during cardiac therapies or examinations [6], and lifestyle changes due to the disease [7]. However, the observed cancer risks among patients with CHD varied considerably across studies. Of note, Kamptisi et al. [8] discovered that the cancer risk in patients with CHD disappeared when Down syndrome was excluded. Currently, no studies have systematically evaluated the cancer risk of individuals with CHD.

Understanding whether there is an increased risk of cancer in individuals with CHD is crucial for the long-term management and care of CHD patients. Therefore, our research aimed to perform a systematic review and meta-analysis of case-control studies and cohort studies to assess the cancer risk in patients with CHD. This study seeks to enhance our understanding of the potential connection between CHD and cancer and hopes to provide future research directions to improve the long-term prognosis and quality of life for patients with CHD.

Methods

This systematic review and meta-analysis were performed according to the standard PRISMA statement.

Search Strategies

The databases PubMed, Embase, and Web of Science were systematically searched from inception to September 2023. The combination of the following search terms was used to conduct this search: "congenital," "heart or cardiac or cardio*," "defect or abnormal* or malform*," "cancer or tumor or tumour or carcinoma* or sarcoma* or lymphoma or leukemia." The searches were limited to the English language.

Study Selection

Studies were included if the following criteria were met: (1) the study population had CHD as previously defined; (2) the study design was a case-control study or cohort study; (3) the control subjects were from a healthy population or persons without CHD groups; (4) the study outcomes were adjusted hazard ratio (HR), relative risk, or odds ratio and 95% confidence intervals (CIs) for the incidence ratio of cancer. Articles that studied only specific groups (e.g., only Down syndrome) were excluded. Case reports, comments, editorials, and conference papers were also excluded. Studies of cancers associated with Font surgery were not considered because there have been systematic reviews of hepatocellular carcinoma after Font surgery. Two authors (L.R. and L.Y.) independently conducted an initial screening of the titles and abstracts of all articles using pre-defined inclusion and exclusion criteria. Then, the final eligibility studies for meta-analysis were determined by reviewing the full text. Any disagreements were determined through mutual consultation, with a third author (Y.C.) stepping in to resolve disputes if necessary.

Data Extraction and Quality Assessment

Two authors (L.R. and L.Y.), respectively, extracted the following information from each study: name of the first author, publication year, study period, study design, geographic region, sample size, source of participants, demographic characteristics, types of control groups, duration of follow-up, type of cancer, adjustments, and effect size estimates. Joanna Briggs Institute (JBI) Critical Appraisal Tools for case-control studies and cohort studies were used to appraise the quality of all included studies. For cohort studies, the total score ranged from 0 to 11, whereas for case-control studies, it was between 0 and 10. Discrepancies were settled through consensus-building or third author's arbitration (Y.C.).

Statistical Analysis

Meta-analysis was conducted using RevMan version 5.3 and Stata version 12. Effect size estimates of cancer incidence rates among patients with CHD, such as odds ratio, relative risk, HR, and other necessary raw data, were extracted and finally presented as HR and corresponding 95% CIs. A p value <0.05 was defined as statistically significant. We performed random-effects model or fixed-effects model to pool the overall HRs during the study period. To assess heterogeneity, the Cochran Q test and I^2 statistics were conducted (the I^2 range of 0–50% indicates low heterogeneity, 51–75% indicates moderate heterogeneity, and >75% indicates high heterogeneity). To explore potential heterogeneity, subgroup analyses were performed based on the type of study design and controlled confounders (adjusted for chromosomal disorders). To evaluate the robustness of the results, a sensitivity analysis was conducted using the serial exclusive method. Egger's linear regression test was used to objectively assess the publication bias.

Results

Study Selection

A total of 6,746 records were retrieved from databases in the initial search. After filtering out 963 duplicates, an additional 5,754 irrelevant records were eliminated by reviewing the titles and abstracts. Twenty-nine studies were further evaluated in full text for eligibility. Of these, 23 studies were excluded for the following reasons: 8 studies had no effect estimates, 4 studies were case reports, 5 studies lacked control, and 6 studies had no cancer events as results. Finally, 6 studies, containing 2 case-control studies [9, 10] and four cohort studies [8, 11–13] met the predetermined criteria and were included in the meta-analysis. Figure 1 shows the flow diagram selected for this study.

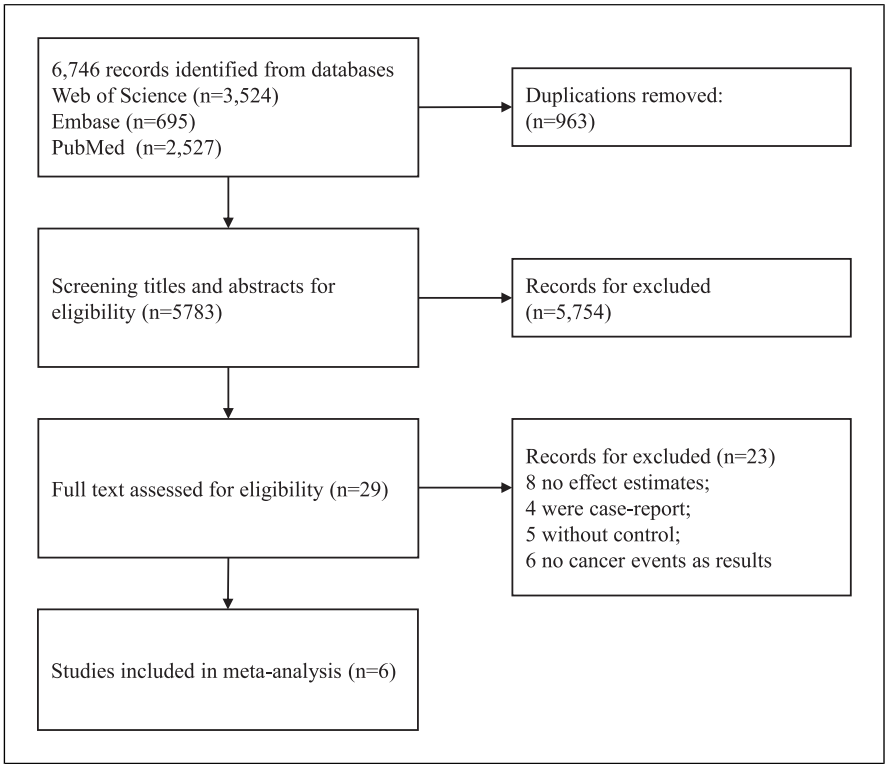

Fig. 1. Flowchart of study selection process.

Study Characteristics

The six studies included 276,124 patients with CHD. Two of these studies were from North America [11, 12], one was a multicenter study [9], and three were conducted in Sweden [8, 10, 13] with the main cohorts being the Swedish birth register and the cancer register. The mean follow-up duration ranged from 9.3 to 58.8 years. Three studies [8, 11, 12] evaluated the risk of cancer in children and young patients (under 20 years) with CHD. All six studies were classified as high quality. The detailed subject and characteristic descriptions are displayed in Table 1.

Outcome Findings

The cancer risk estimate is summarized in Figure 2. The pooled overall HRs in the meta-analysis using a random-effects model revealed that there is an increased risk of cancer in individuals with CHD (HR = 1.71, 95% CI: 1.28–2.28), with significant heterogeneity in the Cochran *Q* test (I^2 = 97%, p < 0.01). Publication bias was assessed using Egger's regression test, and no evidence of publication bias or small study effects was found in this meta-analysis (t = 1.86, p = 0.136).

Subgroup and Sensitivity Analyses

Since there was significant heterogeneity in the studies, we conducted subgroup analyses according to the type of study, population, region, and adjustment factors to investigate potential sources of heterogeneity (Table 2). Among different geographic regions, subgroup analyses revealed that the hazard risk association between cancer and CHD in North America was 2.72 (95% CI: 2.13–3.47), which was higher than that in the Nordic region (HR = 1.41, 95% CI: 1.05–1.89). According to the different study populations, the risk of cancer was found to be higher in adolescents with CHD (HR = 1.77, 95% CI: 1.19–2.62), while this difference did not reach statistical significance in the adult population. Based on five studies that controlled the confounder of chromosomal disorders, the pooled risk of cancer in CHD patients was 1.54 (95% CI: 1.24–1.91). However, unadjusted chromosomal disorders showed a higher risk of cancer among patients with CHD (HR = 2.24, 95% CI: 2.01–2.50). In order to test the robustness of the study results, we conducted leave-one-out jackknife sensitivity analysis. The analysis results demonstrated good robustness, and the increased risks remained consistent (Table 3).

Discussion

In this analysis of 276,124 individual participants from two case-control studies and four cohort studies, our pooled data analysis demonstrates that CHD was significantly linked with an increased risk of cancer. To our

Table 1. Study characteristics

Author	Study period	Study design	Area	Sample size	Source of participants	Control	Age	Follow-up period	Quality assessment
Botto et al. [11]	1983–2006	Retrospective cohort	USA, Utah, Arizona, Iowa	11,211	Nonchromosomal birth defects identified from birth surveillance programs database and vital records databases	Children without birth defects	0–14 years	9.3 years	8
Collins et al. [12]	1988–2006	Retrospective cohort	USA, California	25,981	California Birth Defects Monitoring Program Registry and California Cancer Registry and excluded patients with chromosomal anomalies	Children without CHD	<15 years	NA	8
Daltveit et al. [9]	1967–2014	Case-control	Nordic countries (Denmark, Finland, Norway, Sweden)	60,516	National population-based health registries and medical birth registries and excluded patients with chromosomal anomalies	Individuals without birth defects	23 years (median)	NA	9
Kampitsi et al. [8]	1973–2015	Prospective cohort	Sweden	66,892	Swedish Medical Birth Register and Swedish Cancer Register and adjusted for Down syndrome	Individuals without CHD	<20 years	15.1 years	8
Karazisi et al. [10]	1930–2017	Case-control	Sweden	89,542	Swedish National Inpatient Register, Swedish National Outpatient Register, the Swedish Cause of Death Register and excluded patients with syndromes and organ transplant recipients	Individuals without CHD	52.6 years (mean)	58.8 years	8
Mandalenakis et al. [13]	1970–2011	Prospective cohort	Sweden	21,982	Swedish Patient and Cause of Death Registers	Healthy individuals	<41 years	26.6 years	9

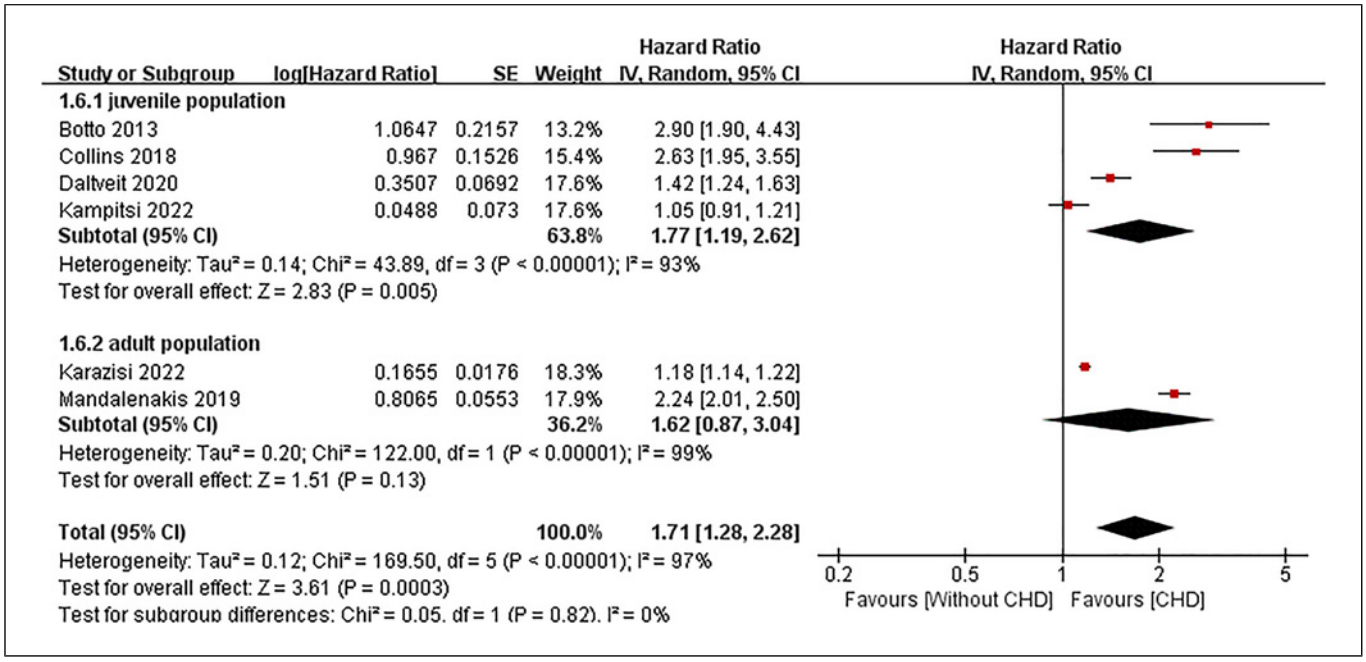

Fig. 2. Forest plot demonstrates the cancer risk in juvenile and adult populations with CHD compared to those without CHD. CHD, congenital heart disease; CI, confidence interval; df, degrees of freedom.

Table 2. Subgroup analysis of cancer risk in patients with CHD

Subgroup analysis	Number of studies	Effect size		Cochran *Q* test	
		HR (95% CI)	*p* value	heterogeneity (%)	*p* value
Study design					
Cohort	4	2.02 (1.23, 3.32)	0.005	96	<0.01
Case-control	2	1.29 (1.07, 1.54)	0.006	91	<0.01
Population					
Juvenile population	4	1.77 (1.19, 2.62)	0.005	93	<0.01
Adult population	2	1.62 (0.87, 3.04)	0.13	99	<0.01
Region					
USA	2	2.72 (2.13, 3.47)	<0.01	0	0.71
North European	4	1.41 (1.05, 1.89)	0.020	98	<0.01
Confounders					
Adjusted for chromosomal anomalies	5	1.54 (1.24, 1.91)	<0.01	93	<0.01

knowledge, no previous quantitative analysis of pooled participant data has considered HR as an estimate of effect and assessed the association of cancer risk events in patients with CHD, representing a novel contribution to the existing evidence. Previous studies have shown a higher standardized incidence of cancer in patients with CHD [14, 15], and our findings confirm the association between CHD patients and the risk of cancer. But our findings were contrary to those in the research by Kampitisi et al., which found that the cancer risk remained elevated in patients with CHD even after adjusting for patients with chromosomal disorders (HR = 1.54). Noticeably, the results of subgroup analysis could not prove an increased cancer risk in ACHD. The age of the adult population in this study was considerably older, which may introduce survivor bias.

Table 3. Sensitivity analysis of cancer risk in patients with CHD

Sensitivity analysis	Effect size		Cochran *Q* test	
	HR (95% CI)	*p* value	heterogeneity (%)	*p* value
Random model	1.71 (1.28, 2.28)	<0.01	97	<0.01
Fixed model	1.27 (1.23, 1.31)	<0.01	97	<0.01
Omitting Botto 2013	1.57 (1.18, 2.08)	0.002	97	<0.01
Omitting Collins 2018	1.57 (1.18, 2.08)	0.002	97	<0.01
Omitting Daltveit 2020	1.79 (1.24, 2.57)	0.002	98	<0.01
Omitting Kampitsi 2022	1.89 (1.37, 2.61)	<0.01	98	<0.01
Omitting Karazisi 2022	1.86 (1.32, 2.62)	<0.01	96	<0.01
Omitting Mandalenakis 2019	1.54 (1.24, 1.91)	<0.01	93	<0.01

CHD may influence the risk of cancer through several mechanisms. First, exposure to low-dose ionizing radiation (LDIR) could be a potential factor contributing to the elevated risk of cancer. Many diagnostic and interventional procedures for CHD involve the use of LDIR. Patients with CHD are often exposed to diagnosis and therapy with LDIR from a young age, sometimes even from birth, which leads to a higher cumulative burden of ionizing radiation [16]. A large single-center cohort study, which focused on describing cumulative radiation exposure in children with CHD, found that over 70% of the children were exposed to less than 3 mSv/year, but 5.3% were exposed to more than 20 mSv/year [17]. Previous evidence has suggested that high cumulative doses of radiation do increase the risk of cancer [18]. Another cohort study, based on data from the Quebec CHD database, also demonstrated that higher exposure to LDIR was associated with a higher risk of cancer [19]. Of which, 81–95% of the total cumulative radiation exposure was from high-exposure imaging techniques such as cardiac catheterization and chest CT scans [20].

Second, the presence of underlying genetic mutations or genetic disorders may be another significant factor in the increased risk of developing cancer. Patients exposed to radiation-induced DNA damage and chromosome aberrations raise their susceptibility to cancer, especially in child population [21]. Children have a 3–4 times higher risk of developing cancer compared to adults due to their large numbers of rapidly dividing cells, longer life expectancy, and increased vulnerability to the carcinogenic effects of radiation [22, 23]. Additionally, dysregulation or deletion of various developmental genes may contribute to both cardiac development and the development of cancer. Take one of the most common genetic disorders, Down syndrome, a complex disorder caused by trisomy of chromosome 21 (Hsa21), which is associated with an approximately 50% incidence of CHD and an over 10-fold risk of hematological malignancy [9, 24]. Studies have demonstrated that certain genes within the deleted region may play a prominent role in tumor suppression, tumorigenicity, and tumor cell cycle progression, thereby contributing to the increased incidence of malignancy [25].

Third, patients with CHD may also be more susceptible to some specific cancers as a result of particular treatment approaches. The most prevalent instance is following Fontan surgeries, which result in a markedly elevated risk of HCC. When a child is born with a single functional ventricle, the Fontan operation is typically the preferred course of therapy. Nevertheless, persistent ischemia and elevated systemic venous pressure following the surgery may result in Fontan-related liver disease, where HCC is a significant late complication [26, 27].

Furthermore, the American Cancer Society states that children and adolescents should engage in at least 1 h of moderate or vigorous activity per day to help prevent cancer [28]. However, young patients with CHD tend to have a lower capacity to perform aerobic exercise and can tolerate a lower exercise load than healthy controls of the same age [29]. In addition to limited physical exercise capacity, these patients also have low self-efficacy of physical activity and overprotection from their parents [30]. Such lifestyle adaptations and changes also elevate the risk of cancer in patients with CHD.

Previous studies have found that only 16% of patients had been screened for cancer prior to diagnosis, while 22% had stage IV disease at the time of cancer diagnosis [31]. These data underscore the importance of cancer screening for priority patients in routine primary care. Given the current known cancer risk in patients with CHD, important strategies to modify modifiable risk factors are warranted. For example, doctors should choose protocols

with LDIR exposure when providing medical services to young patients. Additionally, policymakers can establish tailored cancer screening strategies for patients with CHD to prioritize early cancer prevention and enhance the rate of early cancer screening. What is more, primary care physicians can provide patients with health knowledge about diet and physical activity to assist them in adopting a healthy lifestyle.

Our study has many noteworthy advantages. To the best of all that we know, this comprises the first systematic study which utilizes quantitative methods to assess the cancer risk in patients with CHD. Another strength is the rigorous methodology and high-quality evaluation of the studies. We applied subgroup analyses to investigate potential sources of heterogeneity and to obtain precise and reliable risk estimates throughout the process. Notably, the majority of our study utilized registry-based data from countries with universal health coverage, which are nationwide cohorts that encompass all patients with CHD.

Of course, there are still some limitations to this study. First, although subgroup analyses were performed, potential heterogeneity remained. Given the underlying mechanisms of CHD and cancer, it is possible to interconnect the complexity and variability of CHD and cancer. Second, a proportion of patients with complex CHD might die from the underlying condition before developing cancer, potentially underrating the results. Third, although cohort studies are extensive, there are limited data available for quantitative synthesis due to significant variations in follow-up periods, wide age ranges of included subjects, diverse types of heart disease, etc. Consequently, it is challenging to analyze factors like age stratification, the type and severity of CHD and cancer in detail to ascertain cancer risk. Moreover, there may be some regional selection bias in the results due to the fact that only developed countries in North America and Europe had reports included in the meta-analysis. We believe that the findings of this meta-analysis, despite some limitations, provide quantifiable evidence to assess the risk of cancer in CHD patients.

The results are often underestimated. Additionally, the available data for quantitative synthesis in cohort studies is limited, preventing a more detailed analysis of factors such as age stratification and the type of CHD and cancer to determine cancer risk. Furthermore, there may be regional selection bias in the results due to the inclusion of reports only from developed countries in North America and Europe. Despite these limitations, we believe that this meta-analysis provides quantifiable evidence to assess the risk of cancer in CHD patients.

Conclusion

The results of this quantitative analysis indicate that patients with CHD have an increased risk of developing cancer, even after adjusting for chromosomal disorders. Our study highlights the importance of controlling modifiable factors in cancer prevention and emphasizes the need for health education for patients with CHD in primary care. Given the limited number of studies included in this analysis, further research is needed to investigate the cancer risk of different subtypes of CHD, accurately quantify the cancer risk of exposure versus non-exposure to CHD, and explore the underlying mechanisms.

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Statement of Ethics

Ethical statements do not apply as this study is based exclusively on published literature.

Conflict of Interest Statement

Regarding this paper, the authors have no conflicts of interest.

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Author Contributions

L.R., F.M., and Y.L. contributed to the study's conceptualization and design. L.R. and Y.L. contributed to the data analysis. L.R. wrote the initial manuscript. F.M. and Y.C. contributed to the manuscript's critical revision.

Data Availability Statement

All data analyzed during this study are included in this manuscript. Further inquiries can be directed to the corresponding author.

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