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Cancer risks in children with congenital malformations in the nervous and circulatory system—A population based cohort study

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ABSTRACT

Aim: We estimated the age and organ-specific cancer risk for children with a congenital malformation (CM) in the nervous or in the circulatory system.
Methods: We identified 1,709,456 live born singletons in Denmark between 1 January 1977 and 31 December 2007 and excluded children with chromosomal birth defects. Information on CMs was obtained from the Danish National Hospital Register. Information on cancer occurrence was obtained from the Danish Cancer Registry. We applied Cox proportional hazards regression model to estimate hazard ratios (HR) for cancer. Children entered into the CM cohort on the day of birth regardless of when the CM was diagnosed or on the day of CM diagnosis in an alternative analysis.
Results: Overall, 4484 (0.26%) and 24,643 (1.44%) children were diagnosed with a CM in the nervous and in the circulatory system, respectively. Compared with children without any CM, children with a CM in the nervous system had a 5.97 fold (95%CI [confidence interval]: 4.66–7.64) higher risk of cancer, including cancer in the central nervous system (HR = 18.84, 95%CI: 12.67–28.01), in the mesothelial and soft tissue (HR = 15.64, 95%CI: 7.99–30.60), in the skin (HR = 4.91, 95%CI: 2.19–11.0). The associations were stronger early in life. Children with a CM in the circulatory system had a 2.64 fold (95%CI: 2.21–3.16) higher risk of cancer, including cancer in the lymphatic and haematopoietic tissues (HR = 3.22, 95%CI: 2.43–4.27) and cancer in the CNS (HR = 2.40, 95%CI: 1.43–4.02). Some of these associations were weaker in the alternative analysis. Children with subtypes of CM in the two systems showed a higher cancer risk.
Conclusions: Children who were diagnosed with a CM in the nervous system had a substantially higher cancer risk especially early in life. Children diagnosed with a CM in the circulatory system had a moderately higher cancer risk.

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1. Introduction

It is known that children with certain congenital malformations (CM) have a higher cancer risk [1–3]. Reasons for these associations are not well known, but genetic, epigenetic, and environmental causes have been proposed. Children with Down's syndrome have, for example, a higher risk of leukemia [4,5]. Children born with cryptorchidism have a higher risk of testis cancer, which may be related to the abnormal location and higher temperature of the testis during childhood [6,7]. Maternal folic acid deficiency is associated with a higher risk of neural tube defects among their children and may be also related to childhood cancer [8].

Studies have shown that children with a CM in the nervous system or a CM in the circulatory system have a higher cancer risk although the findings are inconsistent [1–3,9–13]. Most studies have focused on the overall cancer risk for children with congenital malformations in broad categories. Chromosomal defects may also play a role [11]. Children with Down's syndrome more often have mental retardation, dementia and congenital heart malformations [14].

We estimated the age and organ-specific cancer risk among children with a non-chromosomal CM in the nervous system or in the circulatory system. Furthermore, we estimated cancer risk for children with subtypes of CM in the two systems.

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2. Methods

2.1. Study population

We identified children born alive in Denmark between 1 January 1977 and 31 December 2007 from the Danish Fertility Database (n = 1,924,672) [15]. We excluded children who were adopted (n = 33,324), had missing information on sex (n = 18), maternal parity (n = 396), gestational age (n = 122,938), had gestational age less than 20 or greater than 45 gestational week (n = 131), had missing information on date of emigration from Denmark (n = 870), or were twins (n = 55,660). We also excluded children who had chromosomal defects (n = 1879) from the study population leaving 1,709,456 children in the final analyses. In Denmark, a unique identification number is assigned to all residents, which enables accurate linkage between all national registers.

2.2. Congenital malformations (CM)

Information on CMs was obtained from the Danish National Hospital Register, which was established in 1977 [16]. It contains information on discharge diagnoses from all inpatients in Danish hospitals from 1977 onwards and outpatients were included from 1995. Diagnostic information was based on the Danish version of the International Classification of Diseases, the 8th revision (ICD-8) from 1977 to 1993, and the 10th revision (ICD-10) from 1994 onwards. We identified CMs in the nervous system by the ICD-8 codes: 740–743 and the ICD-10 codes: Q00–Q07 and CMs in the circulatory system by the ICD-8 codes: 746–747 and the ICD-10 codes: Q20–Q28. Children who had chromosomal defects were identified by ICD-8 code: 759 and the ICD-10 codes: Q90–99. We categorized children into groups according to the types of CM they had and the codes for types of CM are listed in a supplement table (s-table 1). Children with more than one type of congenital malformation were grouped according to the priority shown in s-table 1.

See s-table 1 as supplementary file. Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2014.04.001.

2.3. Cancer

Information on cancer occurrence was obtained from the Danish Cancer Registry [17], which contains data on all cancer cases since 1943. From 1973 to 1977, the registry used a modified ICD-7 code but changed to ICD-O codes in 1978, which have been converted into the ICD-10 codes. We identify malignant neoplasms diagnoses using the ICD-7 codes (140–207) in 1977 and the ICD-10 codes (C00–C97) between 1978 and 2007. If a person was diagnosed with two or more cancers, the diagnosis obtained at the youngest age was included in the analysis.

2.4. Statistical analyses

We estimated the overall and organ-specific cancer risk for children with a CM in the nervous and circulatory system using a Cox proportional hazards regression model (STATA 11, Stata Corp, College Station, TX), compared with children without any diagnosis of congenital malformation. Age of the children was used as the time scale in the Cox regression analyses [18]. Children were followed from birth until the time of cancer diagnosing, death, emigration, or 31 December 2007, whichever came first and children entered the CM cohort on the day of birth regardless of when the CM was diagnosed. Some children had the CM diagnosis after cancer diagnosis and we conducted an alternative analysis, in which, children entered the CM cohort on the day they were diagnosed with a CM. Children who were diagnosed with cancer before birth (n = 19) and children who were diagnosed with a CM and cancer on the same day (n = 4) were given 0.5 day of follow up time. We adjusted for calendar year and sex of the child in the main analysis and presented the crude estimates in the subanalyses due to a limited number of cancer cases.

We estimated cancer risks in 3 age periods (the first year of life, between 1 and 15 years of age, and above 15 years of age). We estimated cancer risk according to types of CM in the nervous and circulatory system. We stratified the analyses according to gender. Some with 'congenital' hydrocephalus may have acquired this by an undetected cancer and we estimated the cancer risk among children who had a CM in the nervous system by excluding children with congenital hydrocephalus to reduce the risk of reverse causation.

3. Results

Among 1,709,456 children, 4484 (0.26%) were diagnosed with a CM in the nervous system with 631 (14.1%) children having multiple CM in the system, 24,643 (1.44%) were diagnosed with a CM in the circulatory system with 7356 (29.9%) children having multiple CM in the system, and 340 children had CMs in the two systems. More than 60% of children were diagnosed with a CM in the first year of life (66.0% for CM in the nervous system and 61.7% for CM in the circulatory system). Among 1,547,126 children without any CM, 3264 (0.21%) children were diagnosed with cancer while 64 (1.43%) were diagnosed with cancer among children with a CM in the nervous system (of them, 18 were diagnosed with cancer before the diagnosis of CM) and 125 (0.51%) were diagnosed with cancer among children with a CM in the circulatory system (of them, 75 were diagnosed with cancer before the diagnosis of CM). Table 1 shows the characteristics of children according to their CM diagnosis.

Children with a CM in the nervous system had an almost six fold higher overall cancer risk compared with children without CMs (Table 2a). These children also had a higher risk of cancer in the CNS, in the mesothelial and soft tissue, in the skin, and in the lymphatic and haematopoietic tissues, especially the first two types of cancer. Children with a CM in the circulatory system had a 2.64 fold higher overall risk of cancer compared with children without CMs (Table 2b). These children also had a higher risk of cancer in the urinary tract, in the lymphatic and haematopoietic tissues, in the CNS, in the mesothelial and soft tissue, and in the skin (Table 2b). In the analyses where children entered the CM cohort on the day they were diagnosed with a CM, the estimated cancer risk decreased when there were children whose CM's diagnosis often occurred after the cancer diagnosis while the estimated risk of cancer increased when there were not (Tables 2a and 2b).

Children with a CM in the nervous system had a higher cancer incidence, especially early in life, than children with a CM in the circulatory system (Table 3). The association between a CM in the nervous system and overall cancer risk was stronger in the first year of life and the association remained in childhood and early adulthood (Table 3). The association between a CM in the nervous system and a cancer in the CNS was especially stronger in the first year of life but then it decreased. The strong association between a CM in the nervous system and cancer in the mesothelial and soft tissue, however, remained in up to 30 years of follow up time. The findings were consistent when children entered the CM cohort at the time of CM diagnosis (Table 3). Children with a CM in the circulatory system showed a constant higher risk of cancer in the childhood and the associations were weaker in the analyses when children entered the CM cohort at the time of diagnosis.

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