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Cancer risk in siblings of children with congenital malformations

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ABSTRACT

Purpose: Cancer and birth defects cluster in families more often than expected by chance, but the reasons are neither well known nor well studied.
Methods: From singletons born alive in Denmark between 1 January 1977 and 31 December 2007, we identified children who had no congenital malformations but had a full or half sibling with a congenital malformation (CM) diagnosed in the first year of life; this constituted the exposed group, while children whose siblings had no such condition constituted a reference group. We estimated cancer risks for children who had a full sibling or a half sibling with a CM using a Cox proportional hazards regression model. To control for confounding related to change of family structure, we estimated cancer risks for children from core families and children from broken families separately. Children were followed from birth up to 30 years of age (median follow-up 13.6 years). We obtained information on CMs and cancer from the Danish National Hospital Register and the Danish Cancer Registry.
Results: We identified 991,454 (78%) children from core families with 53,995 children who had a full sibling with a CM and 277,773 (22%) children from broken families with 7200 children who had a full sibling with a CM and 6194 children who had a half sibling with a CM. Children who had a full sibling with a CM from both core and broken families showed, in general, no increased cancer risk compared with children whose siblings had no CM, except in the case of children who had a full sibling with a CM in the nervous system (HR = 2.61, 95%CI: 1.60–4.27) or in the eye, ear, face, or neck (HR = 2.47, 95%CI: 1.46–4.18). Children who had a half sibling with a CM seemed to have a higher cancer risk in early adulthood (HR = 1.87, 95%CI: 0.98–3.56).
Conclusions: Children who had a full sibling with a CM had no increased risk of cancer except for those who had a full sibling with a CM in the nervous system or in the eye, ear, face or neck. Children with a half-sibling with a CM tended to have an increased cancer risk in early adulthood, perhaps a result of chance. This study should be replicated using other data sources.

1. Background

Cancer and birth defects may share common risk factors of genetic or environmental origin, since cancer and birth defects cluster in families more often than expected [1,2]. It is known that children with certain congenital malformations (CMs) have a higher risk of cancer, for which genetic, epigenetic, and environmental causes have been proposed [3–5].

Some studies, although not all, show that siblings of children with lymphoblastic leukemia, sarcoma, or brain cancer had an excess risk of CM [6–10]. One study addressed overall cancer risk in full siblings to children with CMs and found no increased risks [11].

In this study, we estimated cancer risk among children who had no CMs but had a full or half sibling with a CM. We also examined cancer risks in children whose sibling had a specific type of CM.

2. Methods

2.1. Study population (identification of siblings)

Among children born alive in Denmark between 1 January 1977 and 31 December 2007 and recorded in the Danish Fertility Database (N = 2,070,604) [12], we identified those who had no CMs

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but had a full or half sibling with a CM as the exposed group. Children who were registered with the same mother and same father were identified as full siblings. Children who had the same mother but a different father or the same father but a different mother were identified as half siblings. If a child had both a full sibling and a half sibling with a CM, they were grouped in the category of children with a full sibling with a CM. We excluded: adopted children; children from one-child families or from families with a multiple birth; children from families that had children born abroad, had their first migration date into Denmark or had a child born before 1977; children from a family with a missing value on maternal parity or coding error on birth records; and children from families in which all children had CMs and there were no discordant pairs of siblings in terms of CM. Ultimately, we used data on 1,269,227 children who had no recorded CM in the first year of life and had at least one sibling.

2.2. Congenital malformations (CMs)

Information on CMs was obtained from the Danish National Hospital Register, which was established in 1977 [13]. It contained information on discharge diagnoses from all inpatients in Danish hospitals from 1977 onwards; 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 children with CMs by the ICD-8 codes of 740-759 and the ICD-10 codes of Q00-Q99 and children who had chromosomal defects according to an ICD-8 code of 759 and ICD-10 codes of Q90-99. We also identified children with an isolated minor CM according to three digital ICD-10 codes provided in the EUROCAT (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Section-3.2.pdf) for children born in 1994 onwards. In this study, we estimated the cancer risk for children with a sibling with major congenital malformations diagnosed during the first year of life by excluding chromosomal defects and minor defects, since chromosomal defects like Down syndrome are related to a higher cancer risk, probably because of a shared genetic background between the two conditions.

2.3. Cancer

Information on cancer occurrence was obtained from the Danish Cancer Registry [14], which had data on all cancer cases since 1943. From 1973–1977, the registry used a modified ICD-7 code but changed to ICD-O codes in 1978, which then have been converted into the ICD-10 codes. We identified malignant neoplasm 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, only the

Table 1
Characteristics of the study population.

	Children whose sibling had no CM		Children with a full sibling with a CM		Children with a half sibling with a CM	
	No.	%	No.	%	No.	%
Children from core families						
	N = 937,459		N = 53,995			
Sex of child						
Boys	480,351	51.2	27,648	51.2	–	
Girls	457,108	48.8	26,347	48.8	–	
Maternal age at birth (years)						
<25	197,910	21.1	11,697	21.7	–	
25–29	387,724	41.4	21,229	39.3	–	
30–39	344,589	36.8	20,552	38.1	–	
40+	7236	0.8	517	1.0	–	
Parity at birth						
1	399,933	42.7	19,315	35.8	–	
2	404,072	43.1	22,097	40.9	–	
3+	133,454	14.2	12,583	23.3	–	
Gestational age at birth (weeks)						
<37	32,558	3.5	2322	4.3	–	
37–42	863,625	92.1	49,344	91.4	–	
>42	6902	0.7	416	0.8	–	
missing	34,374	3.7	1913	3.5	–	
Children from broken families						
	N = 264,379		N = 7200		N = 6194	
Sex of child						
Boys	135,129	51.1	3748	52.1	3077	49.7
Girls	129,250	48.9	3452	47.9	3117	50.3
Maternal age at birth (years)						
<25	90,366	34.2	2354	32.7	2156	34.8
25–29	83,390	31.5	2380	33.1	1704	27.5
30–39	85,921	32.5	2361	32.8	2166	35.0
40+	4702	1.8	105	1.5	168	2.7
Parity at birth						
1	122,233	46.2	2117	29.4	3649	58.9
2	90,265	34.1	2953	41.0	1303	21.0
3+	51,881	19.6	2130	29.6	1242	20.1
Gestational age at birth (weeks)						
<37	12,342	4.7	375	5.2	402	6.5
37–42	240,977	91.1	6554	91.0	5482	88.5
>42	2016	0.8	58	0.8	42	0.7
Missing	9044	3.4	213	3.0	268	4.3

CM, congenital malformation, defined as a major congenital malformation diagnosed in the first year of life.