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Original article

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Cancer risk in the siblings of individuals with major birth defects: a large Nordic population-based case-control study

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Abstract

Background: Individuals with major birth defects are at increased risk of developing cancer, indicating a common aetiology. However, whether the siblings of individuals with birth defects are also at an increased risk of cancer is unclear.

Methods: We used nationwide health registries in four Nordic countries and conducted a nested case-control study. We included 40 538 cancer cases (aged 0–46 years) and 481 945 population controls (matched by birth year and country), born between 1967 and 2014. The relative risk of cancer among individuals whose siblings had birth defects was computed with odds ratios (OR) and 95% confidence intervals (CIs), using logistic regression models.

Results: In the total study population (aged 0–46 years), we observed no overall difference in cancer risk between individuals whose siblings had birth defects and those who had unaffected siblings (OR 1.02; 95% CI 0.97–1.08); however, the risk of lymphoid and haematopoietic malignancies was elevated (1.16; 1.05–1.28). The overall risk of childhood cancer (0–19 years) was increased for siblings of individuals who had birth defects (1.09; 1.00–1.19), which was mainly driven by lymphoma (1.35; 1.09–1.66), neuroblastoma (1.51; 1.11–2.05) and renal carcinoma (5.03; 1.73–14.6). The risk of cancer also increased with the number of siblings with birth defects ($P_{trend} = 0.008$).

Conclusion: Overall risk of cancer among individuals (aged 0–46 years) whose siblings had birth defects was not elevated, but the risk of childhood cancer (ages 0–19 years) was increased. Our novel findings are consistent with the common aetiologies of birth defects and cancer, such as shared genetic predisposition and environmental factors.

Keywords: Neoplasms, abnormalities, epidemiology, aetiology, risk, sibling

Key Messages

- The overall cancer risk for individuals (ages 0 to 46 years) whose siblings have a birth defect is not increased.
- The risk of childhood cancer (ages 0–19 years) is elevated among individuals whose siblings have a birth defect.
- Risks vary by age at cancer diagnosis, type of birth defect and type of cancer.
- There is a dose-response relationship between the number of siblings with birth defects and the risk of developing cancer.
- These findings provide evidence consistent with common aetiologies of birth defects and cancer.

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Introduction

The causes of both childhood cancer and birth defects are largely unknown.[1,2] However, individuals with major birth defects are at an increased risk of cancer, particularly during childhood, indicating a possible common aetiology.[3–6] A common aetiology may also imply that relatives of individuals with birth defects are at an increased cancer risk. Indeed, birth defects are known to have an increased recurrence risk in first-degree relatives.[7–9] Moreover, a history of cancer among first-degree family members is associated with increased risk of some childhood cancers.[10] However, whether the siblings of individuals with birth defects are also at increased risk of cancer is not well understood.[11–13]

Previous studies on the association between birth defects and cancer risk among siblings are mostly inconclusive and underpowered; nevertheless, these studies suggest a lack of an overall association.[11–18] There is, however, more evidence for a link between specific birth defects in individuals and cancer development in their siblings. For instance, the following associations have been reported: (i) cancer development in siblings of individuals affected by defects of the nervous system, or the ear, face, and neck [hazard ratio (HR) = 2.61; 95% confidence interval (CI): 1.60–4.27, and 2.47; 1.46–4.18, respectively][11]; (ii) congenital heart defects in siblings and acute lymphatic leukaemia (odds ratio OR = 2.49; 95% CI: 1.23–5.04)[16]; and (iii) any birth defect in siblings and central nervous system (CNS) tumours (OR = 1.82; 95% CI: 1.25–2.65).[17]

In this population-based case-control study conducted in four Nordic countries, we examined the risk of cancer (from childhood to adulthood) in individuals whose siblings had birth defects, and compared it with the risk of cancer in individuals whose siblings did not have birth defects.

Methods

Data sources

We performed a nested case-control study that combined data from the national population-based health registries of four Nordic countries.[19] The use of unique identifiers made an accurate linkage between the registries of the Nordic countries possible. Information on cancer was retrieved from the cancer registries, and information on emigration and deaths was retrieved from the population registries. Information on birth defects among siblings was obtained from the medical birth registries (all countries) and supplemented with information from the patient registries (inpatient diagnoses during the first year of life in Denmark and Sweden), the Register of Congenital Malformations (in Finland) and the Norwegian Cause of Death Registry; see Supplementary Table S1 (available as Supplementary data at *IJE* online) for additional descriptions of the registries accessed in this study. Information on the identity of fathers was only available in Norway.

Source populations

Cases were defined as individuals recorded in the birth registries from 1977 to 2013 in Denmark, from 1994 to 2013 in Finland, from 1967 to 2013 in Norway and from 1973 to 2014 in Sweden, who had a cancer diagnosis recorded in the cancer registries. Only primary cancer diagnoses were included. Controls were frequency matched (case-control ratio 1:10) by country and birth year; individuals who were alive, residing in the country of birth, and with no cancer diagnosis by the end of follow-up were selected as controls. Cases and controls without siblings or with incomplete sibling records (i.e. those with siblings who were born prior to the establishment of the birth registry), and individuals with a major birth defect, were excluded. We know from previous studies that having a birth defect is a risk factor for cancer, and to be able to separate that effect from the effect of having a sibling with a major birth defect, we included only cases and controls without birth defects.

Classification of cancer

Within the total study population, comprising individuals aged 0–46 years, most cancer cases were classified according to the *International Statistical Classification of Diseases and Related Health Conditions*, 10th Revision (ICD-10).[20] Leukaemia and lymphoma cases were classified according to the *International Classification of Diseases for Oncology*, Third edition (ICD-O-3) morphology codes.[21] Cases with non-malignant neoplasms (except for urinary tract tumours, CNS tumours and other intracranial tumours), without verified morphology (except for CNS and other intracranial tumours), or with basal cell carcinomas, were excluded (see Supplementary Table A in Daltveit *et al.*[3] for details).

In the childhood cancer subpopulation (aged 0–19 years), the cancer cases were additionally grouped according to the *International Classification of Childhood Cancer*, Third edition (ICCC-3) [International Agency for Research on Cancer (IARC) 2017].[22,23] Cases with non-malignant neoplasms (except for groups III and Xa), without verified morphology, or those who were not classified by the ICCC-3, were excluded.

Classification of exposure

The exposure of interest was having a sibling(s) with a birth defect(s). Siblings were defined as individuals sharing the same biological mother. For Norway, analyses for individuals sharing the same mother and father were also carried out. Major birth defects among siblings were classified using ICD-10 codes, according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT).[24] Minor congenital anomalies, according to EUROCAT Guide 1.4, Section 3.2, were excluded.[24]

Statistical analysis

We computed ORs with 95% CIs using unconditional logistic regression models. All models were adjusted for the matching factors (i.e. country and birth year). We performed sensitivity analyses adjusting for maternal smoking (information that was not available at the beginning of the study period) and maternal age, using a complete case approach for handling missing data. In addition, cancer risk was evaluated in relation to age at diagnosis, sex and the number of siblings with birth defects (i.e. 0, 1 or ≥2). Tests for linear trends were performed using orthogonal polynomial contrasts.[25] Sensitivity analyses of cancer risk among only full siblings were performed using the Norwegian dataset. All analyses were performed using Stata version 17 software (StataCorp LLC, College Station, TX, USA).

Results

During the study period, we identified 40 538 cancer cases (aged 0–46 years) and 481 945 matched controls (Table 1). The median age at cancer diagnosis was 22 years. The proportions of individuals who had siblings with birth defects was equal between the cases and controls (3.7% in both groups). The most common malignancies in the total study population were lymphoid and haematopoietic malignancies ($n = 9864$), genitourinary cancers ($n = 8112$) and CNS tumours ($n = 7082$) (Figure 1).

A total of 38% ($n = 15\,458$) of the cancer cases were childhood cancers, affecting individuals aged 0–19 years, which were classified using ICCC-3 (Table 1). For this subpopulation, the median age at cancer diagnosis was 8 years; 4% of the childhood cancer cases had siblings with birth defects, versus 3.6% of the controls. The primary childhood cancers were leukaemia ($n = 3962$), CNS tumours (n = 3742) and lymphomas ($n = 1997$) (Figure 2).

Risk of any and specific cancers

Using the ICD-10 classification within the total study population, we observed no overall cancer risk between individuals whose siblings had birth defects and individuals whose siblings did not have birth defects (OR = 1.02; 95% CI: 0.97–1.08) (Figure 1). However, we detected an increased risk of lymphoid and haematopoietic malignancies (1.16; 1.05–1.28), specifically, acute lymphatic leukaemia (1.17; 1.00–1.37), among individuals whose siblings had birth defects.

Using the ICCC-3 classification within the subpopulation of children and adolescents with childhood cancer, we found an overall increased cancer risk for individuals whose siblings had birth defects (1.09; 1.00–1.19), compared with matched controls (Figure 2). In addition, we observed increased risks of lymphoma (1.35; 1.09–1.66), neuroblastoma (1.51; 1.11–2.05), neuroblastoma in combination with ganglioneuroblastoma (1.43; 1.04–1.96) or with other peripheral nervous cell tumours (5.93; 1.70–20.7), and renal carcinoma (5.03; 1.73–14.6); the two latter groups had few exposed cases (<5).

We observed no strong sex differences in the association between having siblings with birth defects and overall cancer risk (Supplementary Tables S2 and S3, available as Supplementary data at *IJE* online). Moreover, adjusting for maternal age and maternal smoking did not impact on the results (data not shown).

Risk of cancer by age at diagnosis

Using the ICD-10 classification within the total study population revealed that the overall association between having a sibling with birth defects and cancer risk was 1.15 (0.99–1.34) in adolescents (aged 15–19 years), 1.07 (0.98–1.17) in children (aged 0–14 years) and 1.00 (0.93–1.08) in adults (aged ≥20 years) (Table 2). Among adults, having a sibling with birth defects was associated with an increased risk of CNS tumours (1.29; 1.05–1.57) and kidney cancer (1.90; 1.10–3.27).

In the subpopulation with childhood cancer classified by ICCC-3, the OR for the development of any cancer was 1.19 (1.01–1.39) among adolescents and 1.06 (0.96–1.17) among children (Table 3). The adolescents had the highest risk of developing neuroblastoma (6.50; 1.84–22.9), renal tumours (4.17; 1.23–14.1) and leukaemia (1.61; 1.08–2.42), specifically acute myeloid leukaemia (2.38; 1.20–4.72). The risk of gonadal tumours was also increased for adolescents who had siblings with birth defects (1.56; 1.03–2.35). Children who had siblings with birth defects were most at risk of developing lymphomas (1.44; 1.09–1.89) and neuroblastomas (1.42; 1.03–1.96). The subgroup of adolescents had higher ORs for most cancers than the subpopulation of children, except for lymphomas (excluding non-Hodgkin lymphoma), malignant melanomas and CNS tumours.

Risk of cancer by the number of siblings with birth defects

Among individuals aged 0–46 years with two or more siblings, the OR for cancer development increased with the number of siblings with birth defects ($P_{trend} = 0.008$) (Table 4). The OR for cancer development in individuals with one sibling with birth defects was 1.02 (95% CI: 0.96–1.09) and was1.42 (1.10–1.86) for individuals with two or more siblings with birth defects, compared with individuals with two or more siblings with no birth defects. A similar trend was observed for lymphoid and haematopoietic malignancies, in particular acute lymphatic leukaemia. For cases with at least two siblings with birth defects, the most common defect among siblings was congenital heart defects (40%), followed by limb defects (32%) (Supplementary Table S4, available as Supplementary data at *IJE* online).

Using the ICCC-3 classification in the subpopulation of children and adolescents revealed that the OR for cancer development in individuals with one sibling with birth defects was 1.06 (95% CI: 0.96–1.17) and 1.38 (0.91–2.11) for individuals with two or more affected siblings ($P_{trend} = 0.13$). Moreover, the OR for leukaemia development increased with number of affected siblings ($P_{trend} = 0.009$).

Risk of cancer and specific birth defects among siblings

Using the ICD-10 classification in the total study population showed that no single specific birth defect was associated with overall cancer risk (Supplementary Table S5, available as Supplementary data at *IJE* online).

The use of the ICCC-3 classification in the subgroup of children and adolescents revealed an increased cancer risk for individuals whose sibling had birth defects affecting the nervous system (1.40; 1.03–1.91) (Supplementary Table S6, available as Supplementary data at *IJE* online). We next investigated the link between the risk of developing childhood cancer and having a sibling with a specific birth defect, and found the following associations: nervous system defects and risk of lymphoma (2.16; 1.11–4.20), genital or urinary defects and germ cell tumours (2.28; 1.13–4.59 and 2.83; 1.17–6.88, respectively) and limb defects and neuroblastoma (1.99; 1.03–3.86) (Supplementary Tables S7 and S8, available as Supplementary data at *IJE* online).

Risk of cancer among full siblings

Sensitivity analyses performed in the Norwegian study population did not indicate large differences in cancer risk between individuals who had maternal siblings with birth defects (n cases with affected siblings = 568) or those who had full siblings with birth defects ($n = 481$). The relative risk of cancer among all Norwegians with maternal siblings with birth defects was 1.07 (0.98–1.17) and 1.13 (1.03–1.24), after exclusion of half-siblings. The same was observed for the childhood cancer cases [maternal siblings ($n = 216$): 1.07 (0.96–1.28) and full siblings ($n = 194$): 1.08 (0.93–1.25)].

Table 1. Population characteristics of the total study population (aged 0–46 years) and the subpopulation of children and adolescents (aged 0–19 years)

	Subpopulation of children and adolescents (aged 0–19 years)		Total study population (aged 0–46 years)	
	Cases[a]	Controls	Cases[b]	Controls
Study population	15 458 (8.9%)	157 329 (91.1%)	40 538 (7.8%)	481 945 (92.2%)
Sibling with major birth defects	612 (4.0%)	5738 (3.6%)	1509 (3.7%)	18 022 (3.7%)
Number of siblings with birth defects				
0	14 846 (96.0%)	151 591 (96.4%)	39 029 (96.3%)	463 923 (96.3%)
1	587 (3.8%)	5552 (3.5%)	1447 (3.6%)	17 490 (3.6%)
≥2	25 (0.2%)	186 (0.1%)	62 (0.2%)	532 (0.1%)
Sex[c]				
Males	8433 (54.6%)	80 934 (51.4%)	19 987 (49.3%)	248 682 (51.6%)
Females	7025 (45.4%)	76 395 (48.6%)	20 551 (50.7%)	233 263 (48.4%)
Birthweight (g)				
<2500	572 (3.7%)	6175 (3.9%)	1530 (3.8%)	18 547 (3.8%)
2500–3999	11 526 (74.6%)	121 921 (77.5%)	31 544 (77.8%)	381 257 (79.1%)
≥4000	3313 (21.4%)	28 863 (18.3%)	7368 (18.2%)	81 059 (16.8%)
Missing	47 (0.3%)	370 (0.2%)	96 (0.2%)	1082 (0.2%)
Gestational age (weeks)				
<37	829 (5.4%)	8100 (5.1%)	2014 (5.0%)	23 675 (4.9%)
37–41	12 869 (83.3%)	131 183 (83.4%)	32 831 (81.0%)	395 167 (82.0%)
≥42	1356 (8.8%)	13 960 (8.9%)	4419 (10.9%)	49 889 (10.4%)
Missing	404 (2.6%)	4086 (2.6%)	1274 (3.1%)	13 214 (2.7%)
In vitro fertilization[d]				
No	7291 (47.2%)	74 669 (47.5%)	8754 (21.6%)	89 553 (18.6%)
Yes	103 (0.7%)	851 (0.5%)	108 (0.3%)	911 (0.2%)
Not collected	8064 (52.2%)	81 809 (52.0%)	31 676 (78.1%)	391 481 (81.2%)
Maternal smoking[e]				
No	7262 (76.0%)	73 728 (75.6%)	10 125 (72.0%)	139 943 (70.3%)
Yes	1587 (16.6%)	16 633 (17.1%)	2647 (18.8%)	40 592 (20.4%)
Missing[f]	711 (7.4%)	7151 (7.3%)	1281 (9.1%)	18 453 (9.3%)
Not collected	6609 (42.8%)	66 968 (42.6%)	27 766 (68.5%)	301 410 (62.5%)
Maternal age (years)				
<25	3996 (25.9%)	44 563 (28.3%)	15 733 (38.8%)	182 548 (37.9%)
25–29	5747 (37.2%)	58 323 (37.1%)	14 685 (36.2%)	177 359 (36.8%)
30–34	4089 (26.5%)	39 617 (25.2%)	7657 (18.9%)	93 408 (19.4%)
≥35	1626 (10.5%)	14 826 (9.4%)	2463 (6.1%)	28 630 (5.9%)
Paternal age (years)[g]				
<25	1063 (6.9%)	11 216 (7.1%)	4725 (11.7%)	43 868 (9.1%)
25–29	2226 (14.4%)	22 886 (14.5%)	6726 (16.6%)	64 168 (13.3%)
30–34	2065 (13.4%)	21 417 (13.6%)	4389 (10.8%)	43 900 (9.1%)
≥35	1511 (9.8%)	15 093 (9.6%)	2540 (6.3%)	26 344 (5.5%)
Missing	8593 (55.6%)	86 717 (55.1%)	22 158 (54.7%)	303 665 (63.0%)
Year of birth				
<1970	215 (1.4%)	2044 (1.3%)	2185 (5.4%)	19 001 (3.9%)
1970–79	1724 (11.2%)	17 863 (11.4%)	14 609 (36.0%)	154 014 (32.0%)
1980–89	3822 (24.7%)	38 277 (24.3%)	12 694 (31.3%)	183 756 (38.1%)
1990–99	5868 (38.0%)	59 135 (37.6%)	7061 (17.4%)	81 841 (17.0%)
2000–09	3408 (22.0%)	35 276 (22.4%)	3558 (8.8%)	38 134 (7.9%)
≥2010	421 (2.7%)	4734 (3.0%)	431 (1.1%)	5199 (1.1%)
Age at cancer diagnosis (years)[h]				
0–4	5755 (37.2%)	–	7188 (17.7%)	–
5–9	2982 (19.3%)	–	3637 (9.0%)	–
10–14	2723 (17.6%)	–	3133 (7.7%)	–
15–19	3998 (25.9%)	–	4345 (10.7%)	–
20–29	–	–	11 385 (28.1%)	–
30–39	–	–	9356 (23.1%)	–
≥40	–	–	1494 (3.7%)	–
Year of cancer diagnosis[h]				
<1980	448 (2.9%)	–	700 (1.7%)	–
1980–89	1343 (8.7%)	–	2630 (6.5%)	–
1990–99	4170 (27.0%)	–	6608 (16.3%)	–
2000–09	6265 (40.5%)	–	16 471 (40.6%)	–
≥2010	3232 (20.9%)	–	14 129 (34.9%)	–

[a] Classified according to the International Classification of Childhood Cancer. Third edition (ICCC-3).
[b] Classified according to the International Statistical Classification of Diseases and Related Health Conditions, 10th Revision (ICD-10).
[c] Differences between cases and controls caused by birth sex ratio and differences in cancer risk for males and females in the study population.
[d] Reported from 1984 onwards in Norway, and from 1995 onwards in Sweden; not included for Denmark.
[e] Information recorded from 1991 onwards in Denmark, from 1998 onwards in Norway and from 1982 onwards in Sweden.
[f] Percentage missing during the time period that this information was available.
[g] Not reported in Sweden.
[h] Only reported for cases.

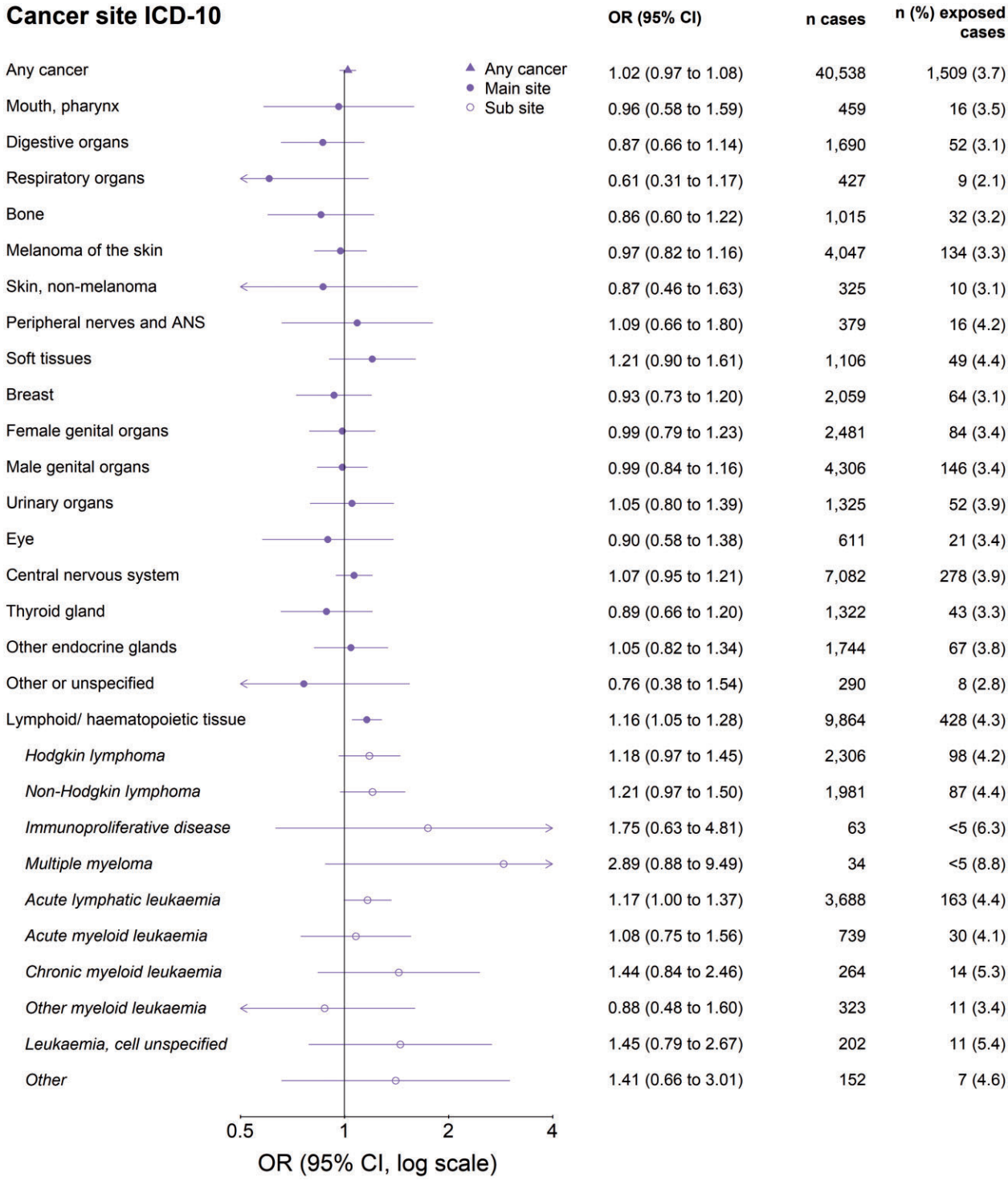

Figure 1. Total or specific cancer risk (according to ICD-10) for individuals (aged 0–46 years) with siblings who had any major birth defect. ORs were adjusted for matching variables (i.e. birth year and country). ICD-10, International Statistical Classification of Diseases and Related Health Conditions, Tenth edition; OR, odds ratio; CI, confidence interval; ANS, autonomic nervous system

Discussion

In this population-based nested case control study, using data from national health registries in four Nordic countries, we observed a 7% and a 15% increase in overall cancer risk among children and adolescents, respectively, whose siblings had birth defects. However, in the total study population of individuals aged 0–46 years, having a sibling with a birth defect did not increase overall cancer risk. Having a sibling with birth defects was instead associated with an increased risk of developing specific malignancies. Individuals whose siblings had birth defects had a 16% increased risk of lymphoid and haematopoietic malignancies. This was observed across all ages (i.e. children, adolescents and adults). In addition, we detected an increased risk of CNS tumours and kidney cancer among adults; an increased risk of neuroblastoma, renal tumours, leukaemia and gonadal tumours among adolescents;

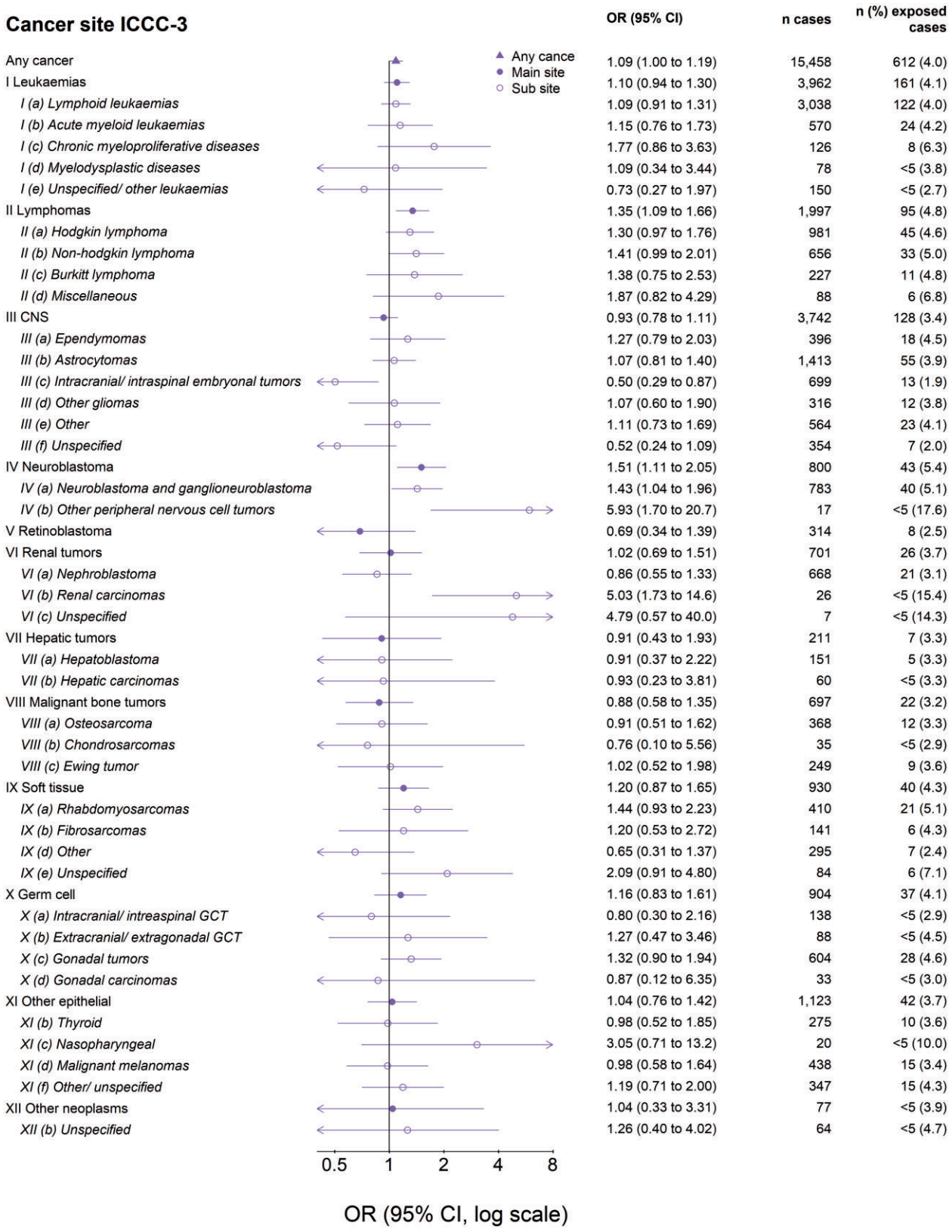

Figure 2. Total or specific childhood cancer risk (according to ICCC-3) for children and adolescents (aged 0–19 years) with siblings who had any major birth defect. ORs adjusted for matching variables (i.e. birth year and country). ICCC-3, International Classification of Childhood Cancer, Third edition; OR, odds ratio; CI, confidence interval; CNS, central nervous system; GCT, germ cell tumour

and an increased risk of lymphomas and neuroblastomas among children. In addition, cancer risk increased with the number of siblings with birth defects. In the total study population, individuals with one sibling with a birth defect had no increase in cancer risk whereass individuals with two or more siblings with birth defects had a 42% increase in

Table 2 Total or specific cancer risk (using the ICD-10 classification) for individuals (aged 0–46 years) with siblings who had any major birth defect, stratified by age at diagnosis

Cancer site (ICD-10[a])	Children (aged 0–14 years)			Adolescents (aged 15–19 years)			Adults (aged ≥ 20 years)		
	Cases	Exposed cases	OR[b] (95% CI)	Cases	Exposed cases	OR[b] (95% CI)	Cases	Exposed cases	OR[b] (95% CI)
Any cancer	13 958	561 (4.0%)	1.07 (0.98–1.17)	4345	183 (4.2%)	1.15 (0.99–1.34)	22 235	765 (3.4%)	1.00 (0.93–1.08)
Mouth, pharynx	100	7 (7.0%)	1.95 (0.90–4.21)	69	5 (7.2%)	2.02 (0.81–5.03)	290	<5 (1.4%)	0.39 (0.14–1.04)
Digestive organs	318	12 (3.8%)	1.01 (0.57–1.80)	132	5 (3.8%)	1.01 (0.41–2.46)	1240	35 (2.8%)	0.83 (0.59–1.16)
Colon	66	5 (7.6%)	2.01 (0.81–5.01)	80	<5 (3.8%)	1.00 (0.31–3.17)	562	20 (3.6%)	1.04 (0.66–1.62)
Rectum, rectosigmoid	<5	0	–	9	0	–	275	8 (2.9%)	0.89 (0.44–1.81)
Liver	234	7 (3.0%)	0.80 (0.38–1.70)	20	<5 (5.0%)	1.42 (0.19–10.6)	81	<5 (2.5%)	0.66 (0.16–2.69)
Respiratory organs	75	0	–	43	<5 (9.3%)	2.84 (1.01–7.97)	309	5 (1.6%)	0.48 (0.20–1.16)
Lung, trachea	25	0	–	26	<5 (11.5%)	3.53 (1.06–11.8)	233	5 (2.1%)	0.63 (0.26–1.52)
Bone	523	16 (3.1%)	0.82 (0.50–1.34)	264	9 (3.4%)	0.92 (0.47–1.79)	228	7 (3.1%)	0.91 (0.43–1.93)
Melanoma of the skin	100	<5 (4.0%)	1.12 (0.41–3.05)	326	11 (3.4%)	0.94 (0.51–1.71)	3621	119 (3.3%)	0.98 (0.81–1.17)
Skin, non-melanoma	44	0	–	39	0	–	242	10 (4.1%)	1.22 (0.65–2.31)
Peripheral nerves and ANS	322	14 (4.3%)	1.13 (0.66–1.94)	24	<5 (4.2%)	1.14 (0.15–8.46)	33	<5 (3.0%)	0.78 (0.11–5.72)
Soft tissues	550	24 (4.4%)	1.16 (0.77–1.75)	177	11 (6.2%)	1.74 (0.94–3.20)	379	14 (3.7%)	1.07 (0.63–1.83)
Breast	<5	0	–	<5	0	–	2055	64 (3.1%)	0.94 (0.73–1.20)
Female genital organs	110	<5 (3.6%)	0.98 (0.36–2.65)	115	<5 (2.6%)	0.70 (0.22–2.21)	2256	77 (3.4%)	1.01 (0.80–1.27)
Cervix, uterus	<5	0	–	5	0	–	1746	58 (3.3%)	0.98 (0.76–1.28)
Ovary etc.	90	<5 (4.4%)	1.19 (0.44–3.25)	102	<5 (2.9%)	0.79 (0.25–2.49)	348	13 (3.7%)	1.08 (0.62–1.88)
Male genital organs	154	<5 (1.9%)	0.52 (0.16–1.62)	414	21 (5.1%)	1.44 (0.93–2.24)	3738	122 (3.3%)	0.96 (0.80–1.15)
Testicular	137	<5 (2.2%)	0.58 (0.19–1.83)	409	21 (5.1%)	1.46 (0.94–2.27)	3703	121 (3.3%)	0.96 (0.80–1.15)
Urinary organs	890	31 (3.5%)	0.92 (0.64–1.32)	43	<5 (7.0%)	1.90 (0.59–6.14)	392	18 (4.6%)	1.37 (0.85–2.20)
Kidney (excluding renal pelvis)	844	27 (3.2%)	0.84 (0.58–1.24)	26	<5 (11.5%)	3.32 (0.99–11.1)	231	14 (6.1%)	1.90 (1.10–3.27)
Eye	532	17 (3.2%)	0.83 (0.51–1.35)	17	0	–	62	<5 (6.5%)	1.84 (0.67–5.07)
Central nervous system	3930	150 (3.8%)	1.02 (0.86–1.20)	836	28 (3.3%)	0.91 (0.63–1.33)	2316	100 (4.3%)	1.29 (1.05–1.57)
Thyroid gland	95	<5 (4.2%)	1.10 (0.40–2.98)	189	8 (4.2%)	1.12 (0.55–2.28)	1038	31 (3.0%)	0.83 (0.58–1.19)
Other endocrine glands	642	28 (4.4%)	1.20 (0.82–1.75)	230	8 (3.5%)	0.92 (0.45–1.86)	872	31 (3.6%)	0.97 (0.68–1.39)
Lymphoid/haematopoietic tissue	5459	243 (4.5%)	1.18 (1.04–1.35)	1403	64 (4.6%)	1.26 (0.98–1.62)	3002	121 (4.0%)	1.15 (0.96–1.38)
Hodgkin lymphoma	370	19 (5.1%)	1.41 (0.89–2.23)	663	28 (4.2%)	1.16 (0.79–1.70)	1273	51 (4.0%)	1.14 (0.86–1.50)
Non-Hodgkin lymphoma	909	46 (5.1%)	1.37 (1.01–1.84)	275	11 (4.0%)	1.13 (0.62–2.06)	797	30 (3.8%)	1.09 (0.76–1.57)
Acute lymphocytic leukaemia	3241	139 (4.3%)	1.13 (0.95–1.34)	256	12 (4.7%)	1.29 (0.72–2.31)	191	12 (6.3%)	1.76 (0.98–3.16)
Acute myeloid leukaemia	453	18 (4.0%)	1.05 (0.66–1.69)	85	5 (5.9%)	1.61 (0.65–3.98)	201	7 (3.5%)	0.97 (0.46–2.07)
Chronic myeloid leukaemia	71	<5 (5.6%)	1.53 (0.56–4.19)	37	<5 (5.4%)	1.40 (0.34–5.82)	156	8 (5.1%)	1.42 (0.70–2.90)
Other myeloid leukaemia	128	<5 (1.6%)	0.41 (0.10–1.67)	44	<5 (9.1%)	2.51 (0.90–7.01)	151	5 (3.3%)	0.85 (0.35–2.07)
Leukaemia, unspecified cell type	164	10 (6.1%)	1.64 (0.86–3.10)	8	0	–	30	<5 (3.3%)	0.88 (0.12–6.45)

ANS, autonomic nervous system; CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Conditions, Tenth edition; OR, odds ratio.
[a] Subsites with less than five cases in all age groups were excluded.
[b] Adjusted for matching variables (i.e. birth year and country).

cancer risk, indicating a dose-response relationship. Together, these findings provide evidence consistent with common aetiologies of birth defects and cancer, such as a shared genetic predisposition and/or shared environmental factors. Both (epi)genetic and environmental factors have been suggested as common causes of birth defects and cancer, by previous research.[26]

Strengths and limitations

Our study had several strengths, including the use of nationwide population-based registries, with accurate information and close to complete coverage.[19] The study also included a larger sample size than previous studies, which allowed us to investigate relations between specific birth defects and specific cancer types. Moreover, the study included individuals born over a 46-year period, enabling us to investigate cancer risk among children, adolescents and adults.

Our study also had several limitations, such as differences in birth defect ascertainment, which occurred both over time and between countries. In addition, despite the large sample size, investigation of specific combinations of birth defects and cancer types had limited statistical power and multiple comparisons could have yielded spurious associations. We also had limited information on possible confounding factors or common causes other than maternal smoking and maternal age. We excluded cases and controls who themselves had a record of a major birth defect; it is possible that misclassification could have occurred and thus distorted the associations. However, this is unlikely to fully explain the observed associations. In addition, the main analyses were performed for maternal siblings, possibly underestimating the risks we observed. However, sensitivity analyses in the Norwegian dataset revealed no discernible differences between cancer risk associated with birth defects in full siblings and cancer risk associated with birth defects in maternal siblings.

Comparison with other studies

Previous studies have reported no association between having a sibling with a birth defect and overall cancer risk, with two of the studies based on data overlapping with our data.[11,12,14] Our findings for the total study population are consistent with these conclusions. However, we did observe a small increase in overall childhood cancer risk. Increased risk of overall childhood cancer has been suggested previously in a small study by Savitz *et al.*[13]

Table 3 Total and specific childhood cancer risk (calculated using the ICCC-3 classification) in children and adolescents (aged 0–19 years) who had siblings with any major birth defect, stratified by age at diagnosis

Cancer site (ICCC-3)	Children (aged 0–14 years)			Adolescents (aged 15–19 years)		
	Cases	Exposed cases	OR[a] (95% CI)	Cases	Exposed cases	OR[a] (95% CI)
Any cancer	11 460	444 (3.9%)	1.06 (0.96–1.17)	3998	168 (4.2%)	1.19 (1.01–1.39)
I Leukaemia	3523	136 (3.9%)	1.04 (0.88–1.24)	439	25 (5.7%)	1.61 (1.08–2.42)
I (a) Lymphoid leukaemia	2782	110 (4.0%)	1.07 (0.88–1.30)	256	12 (4.7%)	1.33 (0.74–2.37)
I (b) Acute myeloid leukaemia	460	15 (3.3%)	0.88 (0.53–1.48)	110	9 (8.2%)	2.38 (1.20–4.72)
II Lymphomas	1068	55 (5.1%)	1.44 (1.09–1.89)	929	40 (4.3%)	1.23 (0.90–1.69)
II (a) Hodgkin lymphoma	332	17 (5.1%)	1.45 (0.89–2.36)	649	28 (4.3%)	1.23 (0.84–1.79)
II (b) Non-Hodgkin lymphoma	441	22 (5.0%)	1.38 (0.89–2.11)	215	11 (5.1%)	1.50 (0.82–2.75)
II (c) Burkitt lymphoma	180	10 (5.6%)	1.57 (0.83–2.97)	47	<5 (2.1%)	0.59 (0.08–4.26)
II (d) Miscellaneous	79	6 (7.6%)	2.09 (0.91–4.81)	9	0	–
III CNS	3008	108 (3.6%)	0.98 (0.81–1.19)	734	20 (2.7%)	0.74 (0.48–1.16)
III (a) Ependymomas	342	16 (4.7%)	1.30 (0.78–2.14)	54	<5 (3.7%)	1.05 (0.26–4.31)
III (b) Astrocytoma	1166	49 (4.2%)	1.15 (0.86–1.53)	247	6 (2.4%)	0.67 (0.30–1.50)
III (c) Intracranial/intraspinal embryonal tumours	628	12 (1.9%)	0.51 (0.29–0.91)	71	<5 (1.4%)	0.39 (0.05–2.79)
III (d) Other gliomas	231	9 (3.9%)	1.09 (0.56–2.13)	85	<5 (3.5%)	1.00 (0.32–3.17)
III (e) Other	396	15 (3.8%)	1.03 (0.61–1.72)	168	8 (4.8%)	1.31 (0.64–2.67)
III (f) Unspecified	245	7 (2.9%)	0.76 (0.36–1.61)	109	0	–
IV Neuroblastoma	784	40 (5.1%)	1.42 (1.03–1.96)	16	<5 (18.8%)	6.50 (1.84–22.9)
IV (a) Neuroblastoma and ganglioneuroblastoma	773	39 (5.0%)	1.41 (1.02–1.94)	10	<5 (10.0%)	3.19 (0.40–25.3)
V Retinoblastoma	314	8 (2.5%)	0.69 (0.34–1.39)	0	–	–
VI Renal tumours	679	23 (3.4%)	0.93 (0.61–1.41)	22	<5 (13.6%)	4.17 (1.23–14.1)
VI (a) Nephroblastoma	659	20 (3.0%)	0.83 (0.53–1.29)	9	<5 (11.1%)	2.73 (0.34–22.0)
VII Hepatic tumours	191	6 (3.1%)	0.85 (0.38–1.93)	20	<5 (5.0%)	1.45 (0.19–10.8)
VII (a) Hepatoblastoma	150	5 (3.3%)	0.91 (0.37–2.23)	<5	0	–
VIII Malignant bone tumours	443	12 (2.7%)	0.75 (0.42–1.33)	254	10 (3.9%)	1.11 (0.59–2.10)
VIII (a) Osteosarcoma	225	5 (2.2%)	0.61 (0.25–1.48)	143	7 (4.9%)	1.41 (0.66–3.03)
VIII (c) Ewing tumour	171	6 (3.5%)	0.98 (0.43–2.22)	78	<5 (3.8%)	1.08 (0.34–3.43)
IX Soft tissue	676	28 (4.1%)	1.15 (0.79–1.68)	254	12 (4.7%)	1.36 (0.76–2.43)
IX (a) Rhabdomyosarcomas	358	18 (5.0%)	1.41 (0.87–2.26)	52	<5 (5.8%)	1.65 (0.52–5.32)
X Germ cell	344	12 (3.5%)	0.96 (0.54–1.70)	560	25 (4.5%)	1.28 (0.86–1.92)
X (c) Gonadal tumours	157	<5 (2.5%)	0.69 (0.26–1.87)	447	24 (5.4%)	1.56 (1.03–2.35)
XI Other epithelial	366	13 (3.6%)	0.98 (0.56–1.70)	757	29 (3.8%)	1.07 (0.74–1.56)
XI (b) Thyroid	90	<5 (3.3%)	0.89 (0.28–2.82)	185	7 (3.8%)	1.03 (0.48–2.19)
XI (d) Malignant melanomas	103	<5 (3.9%)	1.10 (0.40–2.98)	335	11 (3.3%)	0.94 (0.52–1.72)
XI (f) Other/unspecified	145	6 (4.1%)	1.14 (0.50–2.59)	202	9 (4.5%)	1.23 (0.63–2.40)

CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, Third edition; OR, odds ratio.
[a] Adjusted for matching variables (i.e. birth year and country).

Table 4 Number of siblings with birth defects and risk of cancer[a]

Cancer site (ICD-10/ICCC-3)	One sibling with birth defects		Two or more siblings with birth defects		
	Cases	OR[b] (95% CI)	Cases	OR[b] (95% CI)	P_{trend}
Total study population (aged 0–46 years)[c]					
Any cancer	1091	1.02 (0.96–1.09)	62	1.42 (1.10–1.86)	0.008
Melanoma of the skin	97	1.04 (0.85–1.28)	6	1.65 (0.73–3.69)	0.23
Female genital organs	67	1.11 (0.86–1.42)	5	2.10 (0.87–5.09)	0.10
Male genital organs	104	0.98 (0.80–1.19)	7	1.65 (0.78–3.48)	0.19
Central nervous system	200	1.02 (0.89–1.18)	8	0.99 (0.49–2.00)	0.99
Lymphoid/haematopoietic tissue	309	1.14 (1.01–1.28)	20	1.76 (1.13–2.76)	0.01
Hodgkin lymphoma	70	1.18 (0.93–1.51)	5	2.09 (0.87–5.06)	0.10
Acute lymphocytic leukaemia	113	1.08 (0.89–1.31)	10	2.26 (1.21–4.26)	0.01
Children and adolescents (aged 0–19 years)[d]					
Any cancer	446	1.06 (0.96–1.17)	25	1.38 (0.91–2.11)	0.13
Leukaemia (ICCC-3 group I)	109	0.99 (0.81–1.20)	11	2.27 (1.23–4.18)	0.009

CI, confidence interval; ICCC-3, International Classification of Childhood Cancer, Third edition; ICD-10, International Statistical Classification of Diseases and Related Health Conditions, 10th Revision; OR, odds ratio.
[a] The reference category is an individual with two or more siblings with no birth defects.
[b] Adjusted for matching variables (i.e. birth year and country).
[c] ICD-10 classification.
[d] ICCC-3 classification. Sites with less than five cases in any of the exposure categories are not included in the table.

Using Danish data, Sun *et al.*[11] reported a 2.6-fold increase in cancer risk for individuals who had a full sibling with a nervous system birth defect. Combining data from four Nordic countries, we observed a 1.4-fold increase in childhood cancer risk for individuals whose maternal siblings were affected by birth defects in the nervous system. Sun *et al.*[11] also reported

a 2.5-fold increase in the risk of developing any cancer for individuals who had a sibling with ear, face and neck birth defects, which was not supported by our data (0.76; 0.28–2.10). Infante-Rivard *et al.*[16] reported a 2.5-fold increase in the risk of developing acute lymphatic leukaemia for children who had siblings with congenital heart defects, but we observed no increase in this risk (0.98; 0.71–1.36). Partap *et al.*[17] observed a 1.8-fold increased risk of childhood CNS tumour among children who had siblings with birth defects, which was also not observed in our study (0.93; 0.78–1.11). Mertens *et al.*[18] found no association between having siblings with birth defects and the risk of acute leukaemia in childhood, consistent with our findings.

The cancer risk associated with having a sibling with birth defects in our study was lower than that of having one's own birth defect observed in the same source population previously (children: OR = 1.1 versus 1.9, adults: OR = 1.0 versus 1.2).[3,6] Having any major birth defect of one's own was associated with an increased risk of several specific cancers,[3,6] but having a sibling with any birth defect was only associated with an increased risk of lymphoid and haematopoietic malignancies (with similar effect estimates: own birth defect: OR = 1.2,[3] sibling with birth defects: OR = 1.16). For childhood cancer, we observed increased risk in three combinations of birth defects and cancers that were present for both own and sibling's birth defects: (i) nervous system defects and any childhood cancer (own: OR = 6.1[3], sibling's: OR = 1.4); (ii) urinary system defects and germ cell tumours (own: OR = 3.9[3], sibling's: OR = 2.8); and (iii) limb defects and neuroblastoma (own: OR = 2.5,[3] sibling's: OR = 2.0). If the common causes of both birth defects and cancer are mostly genetic/environmental risk factors, we would have expected the same association for one's own birth defects as for siblings' birth defects. However, we observed far fewer birth defect-cancer associations between siblings' birth defects compared with one's own defects, and having a birth defect was a stronger risk factor for cancer than having a sibling with a birth defect. This could indicate that many birth defect-cancer associations are linked to prenatal developmental errors, but not all. Assuming that a higher number of siblings with birth defects indicate a higher burden of genetic or persistent environmental risk factors, the observation of increased cancer risk by the number of siblings with birth defects could be compatible with some birth defect-cancer associations being linked to genetic/shared environmental factors. Together, these findings reflect the heterogeneity of both the exposure (birth defect) and outcome (cancer) and the complexity of the relationships that likely involve multiple different combinations of embryonic, genetic/epigenetic and/or persistent environmental risk factors.

Conclusion

We found that although having a sibling with birth defects did not raise the overall cancer risk, the risk of childhood cancer was slightly elevated. In addition, we revealed the existence of a dose-response relationship between the number of siblings with birth defects and the OR for developing cancer. Our novel findings provide evidence consistent with common aetiologies of birth defects and cancer, such as shared genetic predisposition and environmental factors. Further research into possible mechanisms should be pursued.

Ethics approval

The study was approved by the Ethics Committees of Norway (2015/317/REK vest) and Stockholm, Sweden (2015/1642–31/2) and by the Data Protection Agency of Denmark (2015–57-0002). Permission to use health register data in Finland was granted by the Finnish Institute of Health and Welfare after consultation with the Data Protection Authority (THL/68/5.05/2014 and THL/909/5.05/2015).

Data availability

The datasets analysed during the current study cannot be shared because of national data sharing regulations; however, the raw data can be obtained directly from the relevant registries.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

T.B., A.E. and K.K. designed and planned the study. T.B., I.G., M.G. and H.T.S. gained access to the data. D.S.D. performed data analysis and drafted the manuscript with support from T.B., A.E. and K.K. All authors were involved in the interpretation of results, manuscript revision, and approval of the final version.

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Conflict of interest

None declared.

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