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Spina Bifida and Pediatric Cancers

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Abstract

Spina bifida has been reported to co-occur with pediatric cancer, but comprehensive evaluations remained elusive. We investigated this co-occurrence in two large, population-based studies in Taiwan (N=1900 cancer cases, 2,077,137 controls) and Denmark (N=5508 cases, 137,700 controls). Analyses in Denmark were restricted to the period before prenatal diagnostics became available (2004) and pregnancy terminations of fetuses with birth defects became more common. Using national patient and cancer registries, we linked spina bifida and cancer diagnoses among cases and non-cases. The risk of spina bifida among all cancer cases was increased and similar in Denmark [odds ratio (OR)=8.4, 95% confidence interval (CI) 5.1–13.8] and Taiwan (OR=8.5, 95% CI 4.0–17.8), particularly for central nervous system (CNS) tumors (Denmark: OR=16.3, 95% CI 8.1–33.0; Taiwan: OR=26.6, 95% CI 8.5, 83.1), including benign CNS tumors (Denmark: OR=41.5, 95% CI 21.2, 81.4). These findings suggest the need for comprehensive investigation of shared risk factors in the link between spina bifida and pediatric cancer.

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Declaration of Interests Statement

The authors report no conflicts of interest.

Keywords

Spina bifida; Childhood cancer epidemiology; Central nervous system tumors; Folate; Birth defects

Introduction

Spina bifida is a birth defect resulting from failed closure of the neural folds in the first month of gestation, resulting in vertebrae that do not completely form. Global incidence varies by time period and region, with a meta-analysis estimating global risk as 3.5–24.3 per 10,000 pregnancies.[1] It is detected at ultrasound or via alpha-fetoprotein testing in the second trimester. Spina bifida occulta (or closed spinal dysraphism) is the mildest form of the condition and can go unnoticed because the meninges and nerve tissue are covered by skin. Spina bifida aperta (or open spinal dysraphism) is more severe and can result in sensory, motor, or orthopedic impairments, and bowel and bladder dysfunction.

Previous studies have suggested that pediatric cancer risk is higher among children with spina bifida. Early studies on this topic grouped all cancer types together, yet found intriguing suggestions of threefold increased risks.[2,3] Later studies with greater statistical power were able to stratify by cancer type, and reported increased risks for acute lymphoblastic leukemia (ALL), hepatoblastoma, central nervous system (CNS) tumors, Wilms tumor, Ewing sarcoma, and non-rhabdomyosarcoma soft tissue sarcomas, although findings were not always consistent likely due to small sample sizes.[4–10] In addition, spina bifida aperta was reported in family members of Wilms tumor cases.[9] Because both cancer and spina bifida are rare events, however, there are few published studies. Variation in results may occur between studies that relied on birth defect registries, in comparison to studies ascertaining spina bifida by physical exam or imaging. Due to the small number of reports on this topic, additional comprehensive evaluation is needed. We investigated this question in two large population-based studies in Denmark and Taiwan.

Materials and Methods

The Danish and Taiwanese studies were similar in design. In Denmark, spina bifida diagnoses (Supplementary Table 1) were ascertained from the National Patient Registry, while cancer diagnoses in childhood (<20 years) were ascertained from the Danish Cancer Registry.[11] In the main analyses, we limited the study period from the establishment of the National Patient Registry through the time period prior to when prenatal diagnostics became widely available (births 1977–2004). Currently in Denmark, uptake of prenatal diagnostics is at 97% of pregnancies, and 90% of spina bifida pregnancies are terminated.[12] Controls (N=137,700) were randomly selected from the Central Population Register and supplemented with birth records and matched to cases by birth year and sex (25:1 matching rate), although we broke the matching in the present analysis to estimate risks more precisely for these rare conditions. In order to thoroughly describe the co-occurrence of spina bifida and pediatric cancers among Danish children, Supplemental table 2 provides results for the entire study period in Denmark (1968–2016).

In Taiwan, cases were ascertained from the Cancer Registry for children born and diagnosed 2004–2014, and spina bifida diagnoses were taken from the National Health Insurance register.[13] Non-cases (N=2,077,137) were cancer-free children born in Taiwan 2004–2014. Prenatal diagnostics were available in Taiwan throughout the study period and uptake is >95% for Down syndrome testing.[14] Abortion is largely prohibited in Taiwan but remains legal for some fetal medical conditions including spina bifida. We do not have information on the rate of induced abortions due to neural tube defects.

We estimated risk for spina bifida among cancer cases using unconditional logistic regression, providing crude results for cancer types with at least 3 cases of spina bifida. Variables considered for adjustment were suggested by the literature.[15] We adjusted for maternal and paternal ages, maternal history of epilepsy, diabetes or gestational diabetes, asthma, viral or bacterial infections in pregnancy, parental country of birth (a proxy for ethnicity[16]), maternal smoking in pregnancy, maternal history of stillbirth, and maternal occupational exposures by use of Job Exposure Matrices (ultraviolet radiation, polycyclic aromatic hydrocarbons, gasoline and diesel exhausts[17]), but none of these variables changed estimates by more than 2%. Therefore, we ultimately adjusted only for maternal age and parity and the matching factors, birth year and sex.

Because spina bifida occulta can go undetected, it is important to consider the timing of the spina bifida diagnosis. In some instances, spina bifida may be detected only as a result of tests or procedures associated with the tumor diagnosis, resulting in overascertainment of spina bifida in cases compared to controls. For this reason, we conducted sensitivity analyses in which we examined risk for cancer among children where the spina bifida was detected prior to the cancer diagnosis or the equivalent date in controls. We restricted this sensitivity analysis to the Danish study because of the larger sample size.

We additionally conducted sensitivity analyses to determine whether the association persisted after exclusion of genetic syndromes associated with spina bifida (using syndromes previously identified[18,19]). However, there were no cancer cases with spina bifida who had ICD codes in their medical records of these syndromes.

Human subjects approvals were obtained from the Danish Data Protection Board, the Taipei City Hospital Research Ethics Committee, and the University of California Los Angeles.

Results

Table 1 presents the descriptive summary for and associations between spina bifida and cancer types. Spina bifida was positively associated with all cancers in Denmark and Taiwan, including similar risk size estimates. The associations were strongest for central nervous system (CNS) tumors with diverse tumor types seen, including both malignant and benign CNS tumors. Although CNS tumors accounted for only 25% of all pediatric cancers in Denmark diagnosed during the study period, 13 of 21 (62%) of the cancer cases with spina bifida had CNS tumors, mostly benign tumors. Similarly, in Taiwan, CNS tumors accounted for 14% of all pediatric cancers; yet, 3 of 7 (43%) of the cancer cases with spina bifida had CNS tumors (the Taiwanese Cancer Registry does not include benign CNS

tumors). Spina bifida additionally was seen with several other cancer types (ALL, neuroblastoma, germ cell tumors, rhabdomyosarcoma, and some rare cancers).

In sensitivity analyses restricted to children where the spina bifida diagnosis occurred prior to cancer diagnosis, we still observed higher risk for all cancers (OR=4.54, 95%CI 2.46, 8.39) and for CNS tumors (OR=8.38, 95%CI 3.32, 21.15).

Discussion

Our study confirmed previously reported associations between childhood cancer and spina bifida.[2–10] In particular, we found associations between spina bifida and CNS tumors, as in other work.[5] However, our study is the first to report on associations with benign CNS tumors. Possible shared risk factors for both spina bifida and pediatric CNS tumors include inadequate folate intake in pregnancy, maternal obesity (which was not documented in Denmark until 2004 and not collected in Taiwanese national databases), certain pharmacologic treatments, and polymorphisms in 5,10-methyl-enetetrahydrofolate reductase (*MTHFR*) and dihydrofolate reductase (*DHFR*) alleles.[15,20,21] Our findings suggest further investigation into these shared links.

We also observed positive associations between germ cell tumors and spina bifida. In another study, authors could not find such compelling associations, due to having only one exposed case.[6] However, in a study of testicular cancer patients which examined all patients via radiograph, spina bifida was more than twofold more prevalent among cases than controls.[22] In the current study, both the germ cell and benign CNS cases included teratomas. This finding is in line with existing literature, which suggested associations between dysraphic processes and teratoma.[23] Many CNS teratomas occur in midline structures, possibly derived from cell rests at sites of early neural tube closure. Of the 15 CNS tumors with co-occurring spina bifida in our Danish study, 12 (80%) had a tumor of the spinal cord (ICD-O-1 192.2 and ICD-O-3 C72.0). It is hypothesized that teratomas and dysraphic effects may share a common process of dysembryogenesis, based on the pluripotential nature of the developing caudal spinal cord.[23]

In addition to spina bifida, consistent associations between other head and spine anomalies and CNS tumors have been reported among children.[5] Studies which elucidated specific anomalies identified craniosynostosis, holoprosencephaly, microcephaly, and hydrocephalus (which may be secondary to the tumor) as co-occurring defects.[4,5]

Several limitations should be considered when interpreting our results. Because spina bifida occulta can go unnoticed, the greater medical surveillance that occurs with a cancer diagnosis may result in an ascertainment bias. Indeed, we observed evidence of this bias, as our effect estimates were attenuated — yet still elevated — when we restricted analyses to children among whom spina bifida was diagnosed prior to cancer or the equivalent date in controls. With regards to benign tumors (which also may go undetected), it is somewhat likely that children with spina bifida would have experienced a lifetime of greater medical surveillance, resulting in a greater likelihood of ascertainment of benign tumors. The universal and free medical care available to all residents in Denmark might have limited

some errors in ascertainment, although we could not preclude such bias from impacting our results.

Our study design did not allow for medical record review. Underreporting of genetic syndromes would have occurred in the time period prior to the more detailed ICD-10 coding of diagnoses. Nonetheless, our study has some notable strengths such as its population-based design and its use of comprehensive virtually complete national cancer registries and medical records.

In our study of two populations of differing ethnicities, our study confirmed results seen elsewhere[2–10] and suggests further investigation into both shared genetic and environmental risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Atta CA, Fiest KM, Frolkis AD, Jette N, Pringsheim T, St Germaine-Smith C, et al. Global Birth Prevalence of Spina Bifida by Folic Acid Fortification Status: A Systematic Review and Meta-Analysis. Am J Public Health. 2016;106(1):e24–34. doi: 10.2105/AJPH.2015.302902. [PubMed: 26562127]
2. Botto LD, Flood T, Little J, Fluchel MN, Krikov S, Feldkamp ML, et al. Cancer risk in children and adolescents with birth defects: a population-based cohort study. PLoS One. 2013;8(7):e69077. doi: 10.1371/journal.pone.0069077. [PubMed: 23874873]
3. Fisher PG, Reynolds P, Von Behren J, Carmichael SL, Rasmussen SA, Shaw GM. Cancer in children with nonchromosomal birth defects. J Pediatr. 2012;160(6):978–983. doi: 10.1016/j.jpeds.2011.12.006. [PubMed: 22244463]
4. Lupo PJ, Schraw JM, Desrosiers TA, Nembhard WN, Langlois PH, Canfield MA, et al. Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births. JAMA Oncol. 2019. doi: 10.1001/jamaoncol.2019.1215.
5. Johnson KJ, Lee JM, Ahsan K, Padda H, Feng Q, Partap S, et al. Pediatric cancer risk in association with birth defects: A systematic review. PLoS One. 2017;12(7):e0181246. doi: 10.1371/journal.pone.0181246. [PubMed: 28749971]
6. Narod SA, Hawkins MM, Robertson CM, Stiller CA. Congenital anomalies and childhood cancer in Great Britain. Am J Hum Genet. 1997;60(3):474–485. [PubMed: 9042906]
7. Venkatramani R, Spector LG, Georgieff M, Tomlinson G, Krailo M, Malogolowkin M, et al. Congenital abnormalities and hepatoblastoma: a report from the Children's Oncology Group (COG) and the Utah Population Database (UPDB). Am J Med Genet Part A. 2014;164A(9):2250–2255. doi: 10.1002/ajmg.a.36638. [PubMed: 24934283]
8. Mertens AC, Wen W, Davies SM, Steinbuch M, Buckley JD, Potter JD, et al. Congenital abnormalities in children with acute leukemia: a report from the Children's Cancer Group. J Pediatr. 1998;133(5):617–623. doi: 10.1016/s0022-3476(98)70100-3. [PubMed: 9821417]

9. Kajtar P, Weisenbach J, Mehes K. Association of Wilms tumour with spina bifida occulta. Eur J Pediatr. 1990;149(8):594–595.
10. Mehes K, Weisenbach J, Kajtar P. Association of Wilms tumor with spinal dysraphism. Pediatr Hematol Oncol. 2003;20(3):261–264. [PubMed: 12637224]
11. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. Cancer Epidemiol. 2017;49202–215. doi: 10.1016/j.canep.2017.06.010.
12. Bodin CR, Rasmussen MM, Tabor A, Westbom L, Tiblad E, Ekelund CK, et al. Ultrasound in Prenatal Diagnostics and Its Impact on the Epidemiology of Spina Bifida in a National Cohort from Denmark with a Comparison to Sweden. BioMed Res Int. 2018;20189203985. doi: 10.1155/2018/9203985.
13. Heck JE, Lee PC, Wu CK, Tsai HY, Ritz B, Arah OA, et al. Gestational risk factors and childhood cancers: A cohort study in Taiwan. Int J Cancer. In Press. doi: 10.1002/ijc.32905.
14. Lin SY, Hsieh CJ, Chen YL, Shaw SW, Lin MW, Chen PC, et al. The impact of Down syndrome screening on Taiwanese Down syndrome births: a nationwide retrospective study and a screening result from a single medical centre. PLoS One. 2013;8(9):e75428. doi: 10.1371/journal.pone.0075428. [PubMed: 24147155]
15. Donnan J, Walsh S, Sikora L, Morrissey A, Collins K, MacDonald D. A systematic review of the risks factors associated with the onset and natural progression of spina bifida. Neurotoxicology. 2017;6120–31. doi: 10.1016/j.neuro.2016.03.008.
16. Heck JE, He D, Janzen C, Federman N, Olsen J, Ritz B, et al. Fetal programming and Wilms tumor. Pediatr Blood Cancer. 2019;66(1):e27461. doi: 10.1002/pbc.27461. [PubMed: 30255546]
17. Kauppinen T, Heikkila P, Plato N, Woldbaek T, Hansen J, Kristjansson V, et al. Construction of job-exposure matrices for the Nordic Occupational Cancer Study (NOCCA). Acta Oncol. 2009;48(5):791–800. [PubMed: 19225948]
18. Lowry RB, Bedard T, MacFarlane AJ, Crawford S, Sibbald B, Agborsangaya BC. Prevalence rates of spina bifida in Alberta, Canada: 2001–2015. Can we achieve more prevention? Birth Defects Res. 2019;111(3):151–158. doi: 10.1002/bdr2.1438. [PubMed: 30561844]
19. Seaver LH, Stevenson RE. Syndromes with neural tube defects In: Wyszynski DF, ed. Neural tube defects: From origin to treatment. Oxford, UK: Oxford University Press; 2006.
20. Johnson KJ, Cullen J, Barnholtz-Sloan JS, Ostrom QT, Langer CE, Turner MC, et al. Childhood brain tumor epidemiology: a Brain Tumor Epidemiology Consortium review. Cancer Epidemiol Biomarkers Prev. 2014;23(12):2716–2736. doi: 10.1158/1055-9965.EPI-14-0207. [PubMed: 25192704]
21. Milne E, Greenop KR, Bower C, Miller M, van Bockxmeer FM, Scott RJ, et al. Maternal use of folic acid and other supplements and risk of childhood brain tumors. Cancer Epidemiol Biomarkers Prev. 2012;21(11):1933–1941. doi: 10.1158/1055-9965.EPI-12-0803. [PubMed: 22941336]
22. Agostini S, Magrini SM, Simoncini R, Biti G, Villari N, Giannardi G. Association between testicular cancer and spina bifida occulta. Acta Oncol. 1991;30(5):579–581. doi: 10.3109/02841869109092421. [PubMed: 1892674]
23. Koen JL, McLendon RE, George TM. Intradural spinal teratoma: evidence for a dysembryogenic origin. Report of four cases. J Neurosurg. 1998;89(5):844–851. doi: 10.3171/jns.1998.89.5.0844. [PubMed: 9817426]
24. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. Neuro-oncology. 2013;15 Suppl 2ii1–56. doi: 10.1093/neuonc/not151.

Table 1.

Prevalence of spina bifida among cancer cases and controls in Denmark and Taiwan, and the associations of spina bifida with cancers

Cancer	ICD-O-1 and ICD-O-3 codes of cancer cases with spina bifida	Total N	N with spina bifida (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Denmark, 1978–2004[1]					
Controls	-----	137700	63 (0.05)	Referent	
All cancers	All[2]	5508	21 (0.38)	8.4 (5.1, 13.7)	8.4 (5.1, 13.8)
Acute Lymphoblastic Leukemia	9821/3	1014	2 (0.20)	-----	
CNS tumors (benign and malignant)	8850/0, 9080/0, 9080/1, 9084/0, 9391/3, 9400/3, 9550/0, 9990/0	1355	13 (0.95)	16.4 (8.1, 33.0)	16.3 (8.1, 33.0)
--*Ependymoma*	9391/3	101	1 (0.99)	-----	
--*Glioma*[3]	9400/3, 9391/3	689	3 (0.44)	9.6 (3.0, 30.7)	
--*Benign tumors*	8850/0, 9080/0, 9080/1, 9084/0, 9550/0, 9990/0	543	10 (1.8)	41.1 (21.0, 80.6)	41.5 (21.2, 81.4)
Taiwan, 2004–2014[4]					
Controls	-----	2077137	912 (0.04)	Referent	Referent
All cancers	All	1900	7 (0.37)	8.4 (4.0,17.7)	8.5 (4.0,17.8)
Central nervous system tumors	9400/3, 9421/3, 9470/3	260	3 (1.2)	26.6 (8.5, 83.1)	-----
Germ cell tumors	9071/3, 9080/3	183	3 (1.6)	38.0 (12.1,119.0)	-----

1. Analyses in Danish children are limited to the time period between the initiation of the National Patient Register (1977) through the availability of prenatal diagnostics (2004), after which abortions for spina bifida increased. Non-CNS cancer types with only one case of spina bifida were excluded from the table: germ cell tumor, neuroblastoma, rhabdomyosarcoma, and dermatofibrosarcoma. Models adjusted for the matching factors, birth year and age. Adjusted models additionally adjust for maternal age and parity.

2. ICD-O-1 or ICD-O-3 morphology was not available for 1 cases with spina bifida.

3. Glioma was identified by ICD-O codes as defined by the Central Brain Tumor Registry of the United States.[24]

4. The histologic type of the other cancer case in Taiwan could not be released due to data use restrictions for conditions with N<3. Adjusted models included maternal age and parity.