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RESEARCH ARTICLE

Maternal migraine and risk of pediatric cancers

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Abstract

Background: Maternal migraine has been linked to adverse birth outcomes including low birth weight and preterm birth, as well as congenital anomalies in offspring. It has been speculated that this may be due to the use of medications in pregnancy, but lifestyle, genetic, hormonal, and neurochemical factors could also play a role. There is evidence for varying cancer incidences among adults with migraine. Here, we utilized data from national registries in Denmark to examine associations between maternal diagnoses of migraine and risk for cancer in offspring.

Methods: We linked several national registries in Denmark to identify cases from the Cancer Registry among children less than 20 years (diagnoses 1996–2016) and controls from the Central Population Register, matched to cases by birth year and sex (25:1 matching rate). Migraine diagnoses were identified from the National Patient Register using International Classification of Diseases, versions 8 and 10 codes and migraine-specific acute or prophylactic treatment recorded in the National Pharmaceutical Register. We used logistic regression to estimate the risk of childhood cancers associated with maternal migraine.

Results: Maternal migraine was positively associated with risk for non-Hodgkin lymphoma (odds ratio [OR] = 1.70, 95% confidence interval [CI]: 1.01–2.86), central nervous system tumors ([OR = 1.31, 95% CI: 1.02–1.68], particularly glioma [OR = 1.64, 95% CI: 1.12–2.40]), neuroblastoma (OR = 1.75, 95% CI: 1.00–3.08), and osteosarcoma (OR = 2.60, 95% CI: 1.18–5.76).

Conclusions: Associations with maternal migraine were observed for several childhood cancers, including neuronal tumors. Our findings raise questions about the role of lifestyle factors, sex hormones, genetic, and neurochemical factors in the relationship between migraine and childhood cancers.

KEYWORDS
central nervous system tumors, childhood cancer, estrogen, germ cell tumors, migraine, non-Hodgkin lymphoma, osteosarcoma, pregnancy

Abbreviations: CGRP, calcitonin gene-related peptide; CNS, central nervous system; ICD, International Classification of Diseases; NF1, neurofibromatosis 1; NHL, non-Hodgkin lymphoma.

1 | INTRODUCTION

Migraine is a common disorder among adults of childbearing age, affecting 10%–25% of Danish women from adolescence to age 40.[1] Migraine is also common in children, affecting males and females equally with a prevalence of approximately 9%. In women, the prevalence and frequency of migraine is highly influenced by hormonal events. The prevalence of migraine increases dramatically with menarche and decreases significantly after menopause. Migraine frequency decreases during pregnancy, and varies across the menstrual cycle.[2]

Women with migraine are more likely to be smokers and have higher rates of obesity compared to women without migraine.[3] A higher prevalence of comorbid conditions occurs among individuals with migraine (hypertension and other cardiovascular conditions, allergy/asthma).[4–6] Migraine impacts pregnancy, as it has been associated with adverse birth outcomes, including low birth weight and preterm birth.[7,8] It has been linked to congenital anomalies in offspring, leading to speculation that this is due to the use of medications in pregnancy.[9] Additionally, migraine is linked to pregnancy complications—most consistently, preeclampsia[10]—and is also related to severe nausea and vomiting during the pregnancy.[8] In some studies, these risk factors have been related to a higher risk for childhood cancer.[11–15] Maternal migraine has been reported to be associated with a number of disorders in children, including asthma, psychiatric disorders, and infantile colic.[16–18] In contrast, due to its role as a trigger, alcohol use is lower in women with migraine, which may be related to lower pediatric cancer risk in offspring.[3,6,11]

Women with migraine have lower risk of estrogen-receptor-positive and progesterone-receptor-positive breast cancer,[19] supporting the importance of endogenous hormones in migraine. Hypotheses of associating hormone levels in relation to childhood cancer risk have focused on germ cell tumors and osteosarcoma. Estrogens induce osteoclast apoptosis, and also mediate androgen's effects on pubertal growth, skeletal maturation, and bone mass.[20] In mice, estrogen administration can induce testicular carcinoma.[21] A California study of newborn hormone levels and childhood testicular germ cell tumors reported differential effects by age at diagnosis for estriol and androgens, that is, higher estriol appeared to increase the risk for early childhood (<age 5) tumors but decreased risk for cancers in older adolescence.[22]

In two small studies, increased incidence of central nervous system (CNS) tumors[23] and all cancer types combined[24] were reported in children of mothers with migraine. Migraine was also reported to be higher in children with neurofibromatosis 1 (NF1), a genetic condition that predisposes to several pediatric cancers, including rhabdomyosarcoma and optic pathway glioma.[25] A study in Denmark showed that migraine was higher in childhood cancer survivors; however, authors attributed that to greater medical surveillance or treatment effects.[26]

A recent publication examined migraine and cancer risk in Danish adults, which indicated an increased risk of neurological cancers.[27] Here, we utilized data from several national registries in Denmark to examine associations between maternal diagnoses of migraine and risk for cancer in her offspring.

2 | METHODS

As described elsewhere,[28] cancer cases were identified from the Cancer Registry among children less than 20 years of age (diagnoses 1996–2016). Cases were linked to the Central Population Register, based on the unique 10-digit identifier applied to all residents since 1968, which provided demographic information and identified the parents of each child. Controls were matched to cases by birth date and sex (25:1 matching rate) and selected at random from the Central Population Register; these children were free of cancer at the date of diagnosis of their corresponding case. We then linked these files to the Medical Births Registry to obtain gestational information, the National Patient Register for information on medical conditions, and the National Pharmaceutical Register for information on filled prescriptions. In order to have thorough information on factors at the time of pregnancy, eligibility criteria for the study was that children in the study were born in Denmark. This study was approved by the human subjects protection boards of the Danish Data Protection Agency, the University of California, Los Angeles, and the University of North Texas.

Migraine diagnoses were taken from the National Patient Register using International Classification of Disease, version 8 (ICD-8) codes until 1993 and a Danish extended version of ICD-10 coding thereafter (ICD-8: 346.0x; ICD-10: G43x, O993A2, Z033B), and procedure codes (BAHY2, MN02C, MNO2CX). ICD-9 was not used during the study period.[26] We additionally identified patients with migraine via their use of prescribed migraine-specific acute or prophylactic treatments (Table S1). We additionally examined the relation with migraine in the child. Because headache can be an early sign of a tumor, we planned to conduct a lagged analysis. However, small sample sizes prevented us from conducting this analysis, as only nine cases had a migraine diagnosis at least 1 year prior to cancer diagnosis.

Initial analyses focused on osteosarcoma and germ cell tumors with the hypothesis of hormonally mediated effects.[20,29] However, as previous reports have suggested associations between migraine and other cancers in adults,[4,27,30] we also decided to investigate all cancer types in children for which we had adequate sample size (five or more exposed cases). Other cancer predisposition syndromes that are related to headache, tuberous sclerosis (0.26%), and Li–Fraumeni syndrome (0%) had very small numbers in our data and their exclusion did not change results.

We used unconditional logistic regression to estimate the risk of childhood cancer associated with a maternal migraine diagnosis. Covariates considered for inclusion in final models were suggested by the scientific literature.[4,5,10,13,15,31–33] Final models adjusted for sex and birth date (matching factors), as well as maternal age, and conditions obtained from the National Patient Register: maternal history of neurofibromatosis, asthma, and epilepsy (ever/never lifetime diagnosis); gestational diabetes (diagnosis during the index pregnancy); and ischemic heart disease and depression (diagnosis before the index child's birth). Other risk factors considered for inclusion in models were urbanicity of residence, maternal country of birth, maternal hypertension or preeclampsia, anxiety, anemia, hyperemesis gradivarum,

sleep apnea, or ICD code indicating alcohol or illicit drug use in pregnancy (ICDs previously published[34]). Following the analytic strategy suggested by Maldonado and Greenland, we did not include these in final models, because each of these factors did not change beta values by less than 10%.[35] As they are on the cancer pathway, we did not adjust for congenital anomalies as they do not fulfill the definition of a confounder.

In sensitivity analyses, we attempted adjustment for maternal smoking at the first prenatal visit and maternal pre-pregnancy body mass index, which are available only for a portion of the study period; however, these did not change results. An earlier analysis of Danish registries did not find maternal smoking to be associated with most childhood cancer types.[36] Germ cell tumors can exhibit sex-specific risk factors.[37] To determine if there were sex-specific effects of migraine, we conducted sensitivity analyses stratifying by child's sex for germ cell tumor in the maternal analyses. Finally, because migraine prevalence changes across adulthood with a peak in women at age 25,[38] we stratified results by maternal age at child's birth (age ±30); although statistical power was limited, results were similar by maternal age at child's birth (data not shown).

We considered three time periods of migraine diagnosis: first, when the first migraine diagnosis in the medical record (or prescription in the pharmaceutical register) occurred before or during the index pregnancy, as it may be associated with the intake of migraine medications in pregnancy. Second, we examined a migraine diagnosis at any time prior to the child's cancer diagnosis. Third, we examined a diagnosis at any time in the study period to 2016. Because stress is a migraine trigger, maternal migraine diagnoses could have increased after the child's cancer diagnosis, resulting in reverse causality. As we observed similar effect estimates across the three different time periods, we present in main results the migraine diagnoses occurring prior to the child's cancer diagnosis, with the other time periods presented in Table S2.

To determine if the increased risk may be due to medications rather than due to the disease itself (confounding by indication), we conducted stratified analyses by two exposures: migraine disease diagnosis and migraine medication use.

3 | RESULTS

Detailed demographic characteristics of cases and controls have been previously published.[28] Compared to mothers without migraine, mothers with migraine were younger and were more likely to have been born in Denmark (Table 1). These mothers were more likely to have a history of asthma or epilepsy and more likely to have been diagnosed with ischemic heart disease before or during the index pregnancy. Among children with congenital anomalies, 4% had mothers with a history of migraine.

In logistic regression analyses (Table 2), maternal migraine was positively associated with risk for non-Hodgkin lymphoma (NHL; odds ratio [OR] = 1.70, 95% confidence interval [CI]: 1.01–2.86), CNS tumors (particularly glioma: OR = 1.64, 95% CI: 1.12–2.40), neuroblastoma (OR = 1.75, 95% CI: 1.00–3.08), and osteosarcoma (OR = 2.60, 95% CI: 1.18–5.76). Elevated point estimates were also seen with retinoblastoma (OR = 1.75, 95% CI: 0.72–4.25) and other leukemias (OR = 2.09, 95% CI: 0.88–4.94) with wide CIs.

When stratifying mothers with migraine by migraine medication use, we did not observe differences in offspring cancer risk between users and nonusers of migraine medication in pregnancy (Table 3).

4 | DISCUSSION

This is among the first studies to examine associations between maternal migraine diagnosis and risk of cancer in children. The prevalence of migraine that we observed among controls (17%) is comparable to that seen in Danish self-reported national surveys.[1] We observed increases in osteosarcoma in relation to a maternal diagnosis of migraine, and in exploratory analyses, increased risk of childhood CNS tumors, neuroblastoma, and NHL. Data did not support that intake of migraine-specific medications could be responsible for the observed associations, which if confirmed elsewhere, is potentially an important public health message for pregnant women with migraine. In Denmark, 86.4% of patients with migraine are treated with migraine-specific medications at the time of their initial diagnosis, with only 7% receiving nonspecific medications such as non-steroidal anti-inflammatory drugs (NSAIDS), opioids, or paracetamol (acetaminophen).[39]

Three epidemiologic studies (one underpowered) suggested possible increases in brain tumors in adult patients with a history of migraine.[27,30,40] These associations were observed after lagging medications by 3 years from migraine diagnoses.[30] A study in Denmark also reported increased migraine in childhood cancer survivors.[26] Nevertheless, as headache is a frequent early symptom of a brain tumor, it is difficult to disentangle whether these associations in adults were due to reverse causality. We adjusted for NF1, but there is a possibility for residual confounding among persons with undiagnosed NF1 and therefore, the associations that we observed with CNS tumors should be interpreted with caution.

Changes in sex hormones across the menstrual cycle are believed to be a trigger for migraine. Compared to controls, across the menstrual cycle, females with migraine have higher prolactin (which can reduce serum estrogen) and gonadotropin-releasing hormone, lower testosterone, and varying estrogen: higher than controls in the follicular phase but lower than controls in the luteal phase.[41,42] Greater migraine severity was related to lower estrogen.[41] These variations may explain women with migraine's lower risk of estrogen-receptor-positive and progesterone-receptor-positive breast cancer.[19] However, studies of another hormonally mediated cancer, epithelial ovarian cancer, showed no clear pattern.[4,27,43]

While an earlier study in Danish adults did not find associations with hormonally mediated cancers,[27] prenatal hormone exposures may act differently than hormonal exposures in adults. Exogenous hormone-mediated effects (estradiol, progesterone) have been suggested in neuroblastoma.[11,44] In neural cells, both estradiol and progesterone influence neuronal survival.[45] Further, estradiol modified the toxic effects of chemicals (methylmercury and thimerosal) in neuroblastoma

TABLE 1 Demographics and medical history of mothers with and without migraine.

Characteristics	Mothers with migraine *N* (%)	Mothers without migraine *N* (%)	Crude OR (95% CI)
Age (mean, SD)	29.6 (4.9)	29.9 (4.8)	
<24	1685 (15.0)	7024 (12.9)	Ref
25–29	3917 (35.0)	18,636 (34.3)	0.89 (0.84–0.95)
30–34	3756 (33.5)	19,335 (35.6)	0.84 (0.79–0.90)
35+	1849 (16.5)	9343 (17.2)	0.89 (0.82–0.96)
Mothers' birth place			
Denmark	9967 (89.1)	47,682 (87.9)	Ref
Other Europe and North America	416 (3.7)	2430 (4.5)	0.85 (0.76–0.94)
Other	806 (7.2)	4130 (7.6)	0.96 (0.89–1.04)
Maternal medical history			
Asthma (lifetime)	638 (5.7)	1912 (3.5)	1.65 (1.51–1.81)
Epilepsy (lifetime)	878 (7.8)	1733 (3.2)	2.56 (2.36–2.79)
Gestational diabetes during the index pregnancy	159 (1.4)	806 (1.5)	1.04 (0.87–1.23)
Ischemic heart disease before or during the index pregnancy	286 (2.6)	1055 (1.9)	1.43 (1.26–1.64)
Neurofibromatosis	6 (0.1)	16 (<0.1)	1.80 (0.70–4.60)

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 2 Risk of childhood cancer in relation to maternal diagnosis of migraine before child's cancer diagnosis, 1996–2016.

	Maternal diagnosis of migraine		
Cancer type	*N* (%)	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Controls	6180 (10.6)	Reference	Reference
Acute lymphocytic leukemia	50 (9.9)	1.09 (0.81–1.47)	1.08 (0.80–1.46)
Acute myeloid leukemia	11 (10.8)	1.13 (0.60–2.15)	1.11 (0.59–2.12)
Other leukemia	7 (20.0)	2.06 (0.87–4.85)	2.09 (0.88–4.94)
Hodgkin lymphoma	13 (13.7)	0.91 (0.50–1.64)	0.92 (0.51–1.67)
Non-Hodgkin lymphoma	19 (18.8)	1.66 (0.99–2.77)	1.70 (1.01–2.86)
Burkitt lymphoma	8 (17.4)	1.58 (0.72–3.47)	1.85 (0.84–4.09)
Central nervous system tumors	78 (14.3)	1.37 (1.07–1.75)	1.31 (1.02–1.68)
Intracranial and intraspinal embryonal tumors	33 (15.9)	1.26 (0.86–1.84)	1.29 (0.88–1.89)
Glioma	34 (15.8)	1.69 (1.16–2.46)	1.64 (1.12–2.40)
Neuroblastoma	15 (12.4)	1.79 (1.03–3.13)	1.75 (1.00–3.08)
Retinoblastoma	6 (10.2)	1.67 (0.70–4.01)	1.75 (0.72–4.25)
Wilms tumor	8 (9.2)	1.12 (0.53–2.35)	1.07 (0.50–2.27)
Bone tumors	14 (17.1)	1.50 (0.83–2.71)	1.47 (0.81–2.67)
Osteosarcoma	9 (24.3)	2.73 (1.25–5.98)	2.60 (1.18–5.76)
Germ cell tumors	11 (12.6)	1.00 (0.53–1.92)	1.00 (0.52–1.91)
Males	6 (3.4)	0.84 (0.35–1.99)	0.82 (0.34–1.95)
Females	5 (5.0)	1.32 (0.50–3.49)	1.39 (0.52–3.71)
Melanoma	6 (16.2)	1.01 (0.42–2.47)	1.03 (0.42–2.52)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Crude OR: adjusted for sex and birth date.

[b]Adjusted OR: additionally adjusted for maternal age, and maternal history of neurofibromatosis, asthma, epilepsy (lifetime), gestational diabetes (index pregnancy), and ischemic heart disease (before birth), depression (before birth).

TABLE 3 Risk of childhood cancer in relation to maternal diagnosis of migraine before child's cancer diagnosis and migraine treatment medication use during index pregnancy, Danish National Prescription Registry, 1996–2016.

Cancer type	Exposure stratum	*N* (%)	Crude OR[a]	Adjusted OR[b]
Controls		61,096 (96.9)		
All cancers	Non-exposed	2422 (96.1)	Ref	Ref
	Migraine medication use prescription, but no migraine diagnosis in the medical record	7 (0.3)	1.23 (0.58–2.64)	1.22 (0.57–2.62)
	Migraine diagnosis recorded, but no prescription for migraine-specific medication	89 (3.5)	1.29 (1.04–1.60)	1.26 (1.01–1.56)
	Migraine diagnosis and medication use	<5		

Abbreviation: OR, odds ratio.

[a]Crude OR: adjusted for sex and birth year.

[b]Adjusted OR: additionally adjusted for maternal age, and maternal history of neurofibromatosis, asthma, epilepsy (lifetime), gestational diabetes (index pregnancy), and ischemic heart disease (before birth), depression (before birth).

cell lines.[46] Estrogen can also have neuroprotective effects.[47] Evidence has been mixed for a role of estrogens in NHL,[48,49] and a study in adults did not find associations between migraine and NHL.[27]

Other possible mechanisms for the association between migraine and childhood cancer include genetic and/or neurochemical factors. Migraine has a high level of heritability within families, but the specific genetic factors underlying this heritability are poorly understood. Neurochemical mediators of migraine may also play a role. There is now substantial evidence that neuropeptides, particularly calcitonin gene-related peptide (CGRP), play a primary role in migraine. It has been established that CGRP plays a role in bone growth, and it has been speculated that CGRP could also be involved in the modulation of cancer.[50]

Although lifestyle factors vary between women with and without migraine, adjustment for smoking and maternal body mass index did not change our results. We lacked information on maternal alcohol use; however, lower alcohol use should be expected among women with migraine.[6] We had no information on maternal physical activity nor sleep disturbances; however, neither factor has been previously associated with childhood cancer risk. Data were not available for over-the-counter analgesics, however, at present there is no compelling evidence of links between childhood cancers and maternal intake of over-the-counter medications.[51]

The strengths of this study include the reliance on nationwide and validated registries for ascertaining diagnoses, with no concerns for recall error. However, the validity of migraine diagnoses in the National Patient Register is unknown. Migraine is typically underdiagnosed, so it is possible that phenotypic features of migraine that lead to more reliable diagnosis (such as aura) are overrepresented in the migraine diagnosis cohort. We lacked information on mothers' hormone levels, and we also lacked information on offspring sex hormone levels, which may be correlated with maternal sex hormones[52] and may independently impact the child's cancer risk.

In conclusion, although the sample size was small, we observed associations between maternal migraine and several childhood cancers, affirming the results of two small prior studies,[23,24] and contributing to an increasing literature linking cancer and migraine.[26,27] Our findings raise questions about the role of lifestyle factors, sex hormones, genetics, and neurochemical factors in the etiology of these cancers. We did not observe associations between cancer and maternal migraine medication use, but the sample size was limited; therefore, these findings require replication.

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CONFLICT OF INTEREST STATEMENT

Authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Danish National Registries. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Danish National Registries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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