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Smoking in pregnancy and risk of cancer among young children: a population-based study

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Abstract

Smoking during pregnancy is a plausible risk factor for childhood cancer, yet previous studies have yielded conflicting results, and few prospective studies have been published.

Data on maternal smoking were obtained from California birth certificates. We linked California birth certificates (births 2007–2011) with California Cancer Registry records for childhood cancer cases (diagnosed January 2007 – September 2013) that were ages 5 or younger at diagnosis (N cases=2,021). Controls (N=40,356) were frequency-matched by birth year and randomly selected from birth certificate records. We used unconditional logistic regression to obtain odds ratios (OR) and 95% confidence intervals (CI) to assess the association between smoking during pregnancy and childhood cancer.

We observed positive associations for gliomas (OR=1.8, 95% CI: 1.0–3.4) and retinoblastoma (OR=3.0, 95% CI: 1.4–6.6), particularly bilateral retinoblastoma (OR=9.4, 95% CI 3.6–24.7) with maternal smoking in pregnancy.

Maternal smoking during pregnancy may be a risk factor for retinoblastoma and certain types of childhood brain tumors.

Keywords

tobacco; childhood cancer epidemiology; pregnancy; retinoblastoma; brain tumors; leukemia

Introduction

Smoking is the leading cause of cancer worldwide, and the constituents of tobacco rapidly cross the placenta and are found in cord blood and fetal tissues.[1] Most of the epidemiologic literature on parental smoking and childhood cancer is comprised of retrospective case-

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control studies which collected data via parental interview. These studies may be subject to selective participation, recall biases, or a limited willingness to disclose smoking status in pregnancy to research interviewers. There remains a need for prospective population-based studies.

Materials and Methods

In 2007, California began collecting maternal smoking information on the birth certificate. Data on maternal smoking, demographics, and pregnancy and birth-related factors are abstracted by hospital clerks from the medical record, reported by the mother's physician or midwife, or self-reported by mothers.

We linked California birth certificates (births 2007–2011) with California Cancer Registry records for childhood cancer cases (diagnosed January 2007–September 2013) that were ages 5 or younger at diagnosis. Controls were frequency-matched by year of birth. Detailed methods have been previously published.[2] We estimated adjusted odds ratios among cancer types with ≥5 exposed cases only, and additionally estimated risk for hepatoblastoma because parental smoking was classified as a cause of hepatoblastoma by the International Agency for Research on Cancer.[3] Cancer types were categorized using International Classification of Childhood Cancer (ICCC) codes, however in order to compare results to other studies, we additionally examined risk among all gliomas, high-grade, and low-grade gliomas, defining these subtypes using International Classification of Diseases for Oncology (ICD-O-3) codes as categorized by the Central Brain Tumor Registry of the United States (CBTRUS).[4] Thus glioma cases overlap with astrocytoma cases. Odds ratios (OR) and 95% confidence intervals were ascertained using unconditional logistic regression, with adjustment for the child's birth year (matching variable), the race/ethnicity of the mother (White non-Hispanic vs. all others), and maternal years of education. Additional adjustment for the number of prenatal care visits and the source of payment for prenatal care (a socioeconomic indicator, as described previously[2]) did not change results and were left out of final models.

Data were collected on smoking status in the three months pre-pregnancy and within each trimester, however smoking status was strongly correlated across trimesters (r~0.77–0.91). Thus our analysis examined ever smoking during any point in pregnancy in the main results.

Results

Compared to mothers of cases, a slightly higher proportion of control mothers smoked in the 3 months before pregnancy (3.8% vs. 3.2%). During pregnancy, however, smoking was more common among case mothers (1st trimester, 2.7%; 2nd trimester, 2.1%; 3rd trimester, 1.8%) than among control mothers (1st trimester, 2.5%; 2nd trimester, 1.8%; 3rd trimester, 1.7%). Hence, of all the mothers who smoked prior to pregnancy, 16% of case mothers and 34% of control mothers quit smoking during the 1st trimester.

We observed positive associations for glial tumors and retinoblastoma with maternal smoking in pregnancy, with a particularly elevated risk estimate for bilateral retinoblastoma (Table 1). With regards to central nervous system tumor subtypes, gliomas (OR=1.8, 95%

confidence interval 1.0–3.4) were elevated. We also observed an elevated risk estimate for astrocytomas, which made up 123 of the 194 gliomas (adjusted OR=2.0, 95% confidence interval 0.9, 4.2).

We additionally examined the risk from smoking by trimester of pregnancy for gliomas and retinoblastomas. The adjusted estimates for gliomas were fairly similar across trimesters (1st trimester, OR=1.7; 2nd trimester, OR=1.6; 3rd trimester, OR=1.5) whereas adjusted estimates for retinoblastoma appeared to steadily increase with each subsequent trimester (1st trimester, OR=3.1; 2nd trimester, OR=4.5; 3rd trimester, OR=5.0).

The prevalence of smoking was high among mothers of children with both low grade gliomas (4/53 cases, 7.6%) and high-grade gliomas (1/14 cases, 7.1%). Other cancer types were generally null excepting leukemia where point estimates were below unity, with wide confidence intervals.

Discussion

In this records-based prospective study, we observed increased risk for two major types of childhood cancers. Among all cancers, smoking quit rates during the 1st trimester were higher among control mothers than among case mothers, and the prevalence of smoking in pregnancy was particularly high for bilateral retinoblastoma (15.4%). Children with bilateral retinoblastoma carry a germline mutation in one allele of a retinal progenitor cell, due to *RB1* inheritance from a parent, *de novo* mutation in parental germline cells, or due to a mutation that occurs during very early embryonic development; these children lose the second allele somatically during the pregnancy. Only a small number of studies have reported on maternal smoking and retinoblastoma, but several have reported increased effect estimates.[5–7] Of these, one study reported an increased risk for maternal smoking in the first trimester and bilateral retinoblastoma (OR=3.7),[7] and another study an increase with sporadic heritable disease (OR=2.0), which typically presents as bilateral;[5] the third study did not stratify by laterality. Our findings for astrocytoma support those seen in another prospective investigation.[8]

The decreased risk we observed with acute lymphoblastic leukemia (ALL) has been reported in other prospective studies[6, 9–11] and may be due to competing risks such as miscarriage or the development of fatal birth defects.[12] If so, our results for all cancer types might be underestimated. Further, this would explain the seemingly counterintuitive results seen in studies which have examined leukemia risk according to cigarettes per day. Several of these studies have reported an higher risk estimate for ALL with light smoking (e.g. <6 or <10 cigarettes per day) but then decreasing point estimates with heavier smoking,[13–18] with reported effect estimates as low as 0.26 for maternal smoking of more than 30 cigarettes per day.[16]

Many women attempt to quit smoking during pregnancy, and the smoking patterns exhibited often involve attempts to cut down, quit, followed by relapsing and attempting to quit again. Overall, between 20–50% of female smokers attempt to quit or reduce their smoking during pregnancy;[19] of these women, roughly half quit successfully, and the other half change their

smoking intensity multiple times.[20] As such, the complex pattern of smoking during pregnancy could not be captured with our study design. Nondifferential misclassification may also be expected due to errors in recall or due to poor willingness to disclose smoking to medical providers, due to the stigma attached to smoking during pregnancy in the United States. Thus there are concerns for the accuracy of medical-record abstracted smoking status in our data. Validation studies of maternal smoking status on birth certificates suggest that smoking has moderate sensitivity (74–89%) but high specificity (99%),[21, 22] which should be expected to slightly attenuate effect estimates.

California residents smoke less than residents of other US States, with current smoking reported by 17% of adult males and 10% of adult females in 2011.[23] The prevalence of smoking that we observed on birth certificates is lower than that reported among pregnant California women in a 2003 survey (8.7%)[24] although adult smoking rates may dropped since that survey was published, as they have done nationally.[25] In addition, the proportion of births from Hispanic and Asian/Pacific Islander women have risen in California across the last several decades, and those women are less likely to smoke in pregnancy than women of other ethnic groups (3% of Hispanic women and 2% of Asian/Pacific Islander women smoke in pregnancy, as compared to 14% of White non-Hispanics).[26] In the present study, 52% of mothers were Hispanic and 10% were Asian/Pacific Islander.

Interpretation of results and comparison to other studies should be considered in light of the younger age of the children in our study (<6 years at diagnosis). Exposures during pregnancy may be most relevant for childhood cancers which are diagnosed at younger ages. Further, variation in histologic subtype by age for central nervous system and germ cell cancers, among other cancer types, should limit generalizability to older cohorts.[4] In contrast, as the embryonal tumors (neuroblastoma, Wilms tumor, retinoblastoma) occur primarily in younger childhood, most cases diagnosed during the study period would have been included in our analysis.

If a child's cancer is diagnosed during pregnancy or at birth, medical personnel might be more vigilant in reporting smoking on the birth certificate. However, this was unlikely to have biased our results because by California law, births must be registered with the State within 10 days of the child's birth. In our data, there were no cases of glioma, astrocytoma, or retinoblastoma diagnosed prior to two weeks of age whose mothers were smokers. A limitation of our study design was that it did not allow exclusion of cases with a family history of disease. We also lacked covariate information on possible confounders such as maternal alcohol consumption, occupational pesticide exposure, and paternal smoking, which could introduce residual confounding.

As we were able to include only 5 years of California births, the sample size of our study was small and data should be viewed as preliminary. Nonetheless our findings corroborate other prospective studies. Further research might ascertain smoking by cotinine assay, and it may be insightful for future meta-analyses on maternal smoking and childhood cancer to compare findings between prospective and retrospective studies.

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Abbreviations

ALL	Acute Lymphoblastic Leukemia
CBTRUS	Central Brain Tumor Registry of the United States
CI	Confidence Interval
ICCC	International Classification of Childhood Cancer
ICD-O-3	International Classification of Diseases for Oncology
OR	Odds Ratio

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Novelty and Impact

This article is one of the few prospective, population-based studies of maternal pregnancy smoking and childhood cancer, with smoking status collected by medical record review. We report increased risk of retinoblastoma and some childhood brain tumors with maternal smoking during pregnancy.

Table 1

Prevalence of maternal smoking during pregnancy and risk of childhood cancer

Cancer	ICCC or ICD-0 code	N smoked in pregnancy/total N	% smoked in pregnancy	Crude OR [a]	Adjusted OR (95% CI) [b]
Controls	----	1056/40356	2.6	Referent	Referent
All cancers	011–999	56/2021	2.8	1.1	1.0 (0.8, 1.4)
Leukemias	011–015	8/469	1.7	0.6	0.6 (0.3–1.3)
Acute lymphoblastic leukemia	011	4/282	1.4	0.5	---
Acute myeloid leukemia	012	1/136	0.7	0.3	---
Central nervous system tumors	031–036	13/308	4.2	1.6	1.3 (0.7–2.4)
Gliomas	*c*	12/194	6.2	2.4	1.8 (1.0–3.4)
Intracranial & intraspinal embryonal tumors	033	2/91	2.2	0.8	---
Neuroblastoma	041	7/238	2.9	1.1	1.2 (0.5–2.5)
Retinoblastoma	050	7/125	5.6	2.2	3.0 (1.4–6.6)
Bilateral	050	6/39	15.4	7.0	9.4 (3.6–24.7)
Wilms tumor	061	6/148	4.1	1.6	1.3 (0.6–3.0)
Hepatoblastoma	071	2/84	2.4	0.9	1.2 (0.3–5.2)
Rhabdomyosarcoma	091	1/58	1.7	0.6	---
Germ cell tumors	101–105	2/75	2.7	1.0	---

[a] Adjusted for the matching variable, birth year.

[b] Adjusted for birth year, maternal race/ethnicity, and maternal years of education.

[c] CBTRUS definition of gliomas, ICD-O-3 codes: 9380-9384, 9391-9460, 9480; low-grade gliomas: 9380, 9382-9384, 9410-9413, 9420, 9424, 9450; high-grade gliomas: 9401, 9440-9442, 9451, 9460, 9480.[4]