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Neonatal exposure to Per- and polyfluoroalkyl substances, maternal exposure to residential proximity to oil and gas development during pregnancy, parental occupational exposures to organic solvents and childhood cancer risk

A dissertation submitted in partial satisfaction
of the requirements for the degree Doctor of Philosophy
in Epidemiology

by

Yixin Chen

2024

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2024

ABSTRACT OF THE DISSERTATION

Neonatal exposure to Per- and polyfluoroalkyl substances (PFAS), maternal exposure to residential proximity to oil and gas development during pregnancy, parental occupational exposures to organic solvents and childhood cancer risk

by

Yixin Chen

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2024

Professor Beate R. Ritz, Co-Chair

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Childhood cancer, defined as cancer diagnoses in children aged 0 to 19 years, is the second leading cause of death in children in the United States and Europe. The etiology of childhood cancer remains unclear. Established risk factors include genetic predispositions, high dose ionizing radiation, and prior chemotherapy. This dissertation examines three types of environmental exposures in relation to childhood cancer: 1) neonatal exposure to PFAS and the risk of retinoblastoma; 2) maternal residential proximity to oil and gas development during pregnancy and the risk of childhood cancer; and 3) parental occupational exposures to organic solvents and the risk of childhood cancer.

The first study utilized 501 retinoblastoma cases and 899 controls born 1983-2011 from a population-based case-control study. We identified PFOS, PFOA, and PFNA feature intensities in neonatal DBS from California GDSP. Among all children, above-mean PFOS levels increased the risk of retinoblastoma overall (aOR: 1.29; 95% CI: 1.00, 1.67) and unilateral retinoblastoma (aOR: 1.42; 95% CI: 1.03, 1.97). In children of Mexico-born mothers, above-mean PFOS levels increased the risk of retinoblastoma overall (aOR: 1.67; 95% CI: 1.06, 2.66) and bilateral retinoblastoma (aOR: 2.06; 95% CI: 1.12, 3.92). In children of US-born mothers, the risk of unilateral retinoblastoma increased by 15% for each IQR increase in PFOS (95% CI: 0.99, 1.35) and by 71% (95% CI: 1.04, 2.90) for above-mean PFOS levels. PFOA increased the risk of retinoblastoma overall (aOR: 1.41; 95% CI: 1.00, 2.02 for above-mean levels, aOR: 1.06; 95% CI: 0.98, 1.16 per IQR increase) for children of US-born mothers.

The second study utilized the same population-based case-control study in California with children born 1998-2016. We estimated exposure during pregnancy to any well (i.e., active or inactive) and inactive wells located within 1km and 3km of residences and assessed low and high exposures (categorized by median) within this proximity. The risk of medulloblastoma increased among children of mothers exposed to any well within 3km (≥ 1 well: adjusted Odds Ratio (aOR): 1.40; 95% confidence interval (CI): 1.08, 1.82; low, aOR = 1.27; 95% CI = 0.93, 1.74; high, aOR = 1.55; 95% CI = 1.14, 2.11). The risk of rhabdomyosarcoma consistently increased across the exposure levels of any well within 3km (≥ 1 well: aOR = 1.64; 95% CI = 1.28, 2.09; low, aOR = 1.69; 95% CI = 1.28, 2.23; high, aOR = 1.57; 95% CI = 1.16, 2.12). Similar associations were observed for teratoma with any well within 3km (≥ 1 well: aOR = 1.42; 95% CI = 0.99, 2.05; low, aOR = 1.35; 95% CI = 0.88, 2.07; high, aOR = 1.51; 95% CI = 0.98,

2.33). Overall, the results were consistent across the buffer sizes and no differences were found between any well and inactive wells.

The third study utilized a linkage of four Danish data registries, including 10442 cases and 261050 controls born 1968-2013. Using JEMs, we identified and examined the role of parental occupational exposure to 3 hydrocarbon groups (i.e., aromatic, aliphatic/alicyclic, chlorinated hydrocarbons) and 4 individual hydrocarbons (i.e., toluene, DCM, TCE, 1,1,1-TCA) in two biologically relevant time periods: 1) 3 months preconception to birth for fathers; and 2) during pregnancy for mothers and the risk of childhood cancer in offspring. Paternal exposure to aromatic (high: aOR: 1.31; 95% CI: 0.95, 1.81) and chlorinated hydrocarbons (high: aOR: 1.82; 95% CI: 1.18, 2.82) increased the risk of glioma. The risk of AML was higher among fathers highly exposed to aliphatic/alicyclic hydrocarbons (high: aOR: 1.87; 95% CI: 1.24, 2.82). Paternal exposure to 1,1,1-trichloroethane increased the risk of osteosarcoma (high: aOR: 2.29; 95% CI: 1.25, 4.18). The risk of medulloblastoma increased in offspring of mothers ever exposed to DCM (aOR: 1.69; 95% CI: 1.01, 2.84), TCE (aOR: 1.86; 95% CI: 1.12, 3.10), and toluene (aOR: 1.92; 95% CI: 1.07, 3.46). The risk of ALL increased in children of mothers ever exposed to aromatic hydrocarbons (aOR: 1.29; 95% CI: 1.01, 1.64), and 1,1,1-TCA (aOR: 1.30; 95% CI: 1.01, 1.69), while risk of NHL was associated with maternal exposure to chlorinated hydrocarbons (aOR: 1.94; 95% CI: 1.05, 3.57).

The dissertation of Yixin Chen is approved.

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2024

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ABBREVIATIONS AND ACRONYMS

AI/AN	American Indian/Alaska Native
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
aOR	adjusted odds ratio
API	Native Hawaiian/Asian-Pacific-Islander
ASR	age-standardized rate
CI	confidence interval
CNS	central nervous system
DBS	dried blood spots
DCM	methylene chloride
GDSP	Genetic Disease Screening Program
HL	Hodgkin's lymphoma
IARC	International Agency for Research on Cancer
IQR	interquartile range
JEM	job-exposure matrix
NHL	non-Hodgkin lymphoma
NOCCA	the Nordic Occupational Cancer study
NO _x	nitrogen oxides
NO ₂	nitrogen dioxide
OGD	oil and gas development
OR	odds ratio
PAH	polyaromatic hydrocarbon
PFAS	per- and polyfluoroalkyl substances
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
PM	particulate matter

RMS	rhabdomyosarcoma
SES	Socioeconomic status
TCE	trichloroethylene
VOC	Volatile organic compounds
1,1,1-TCA	1,1,1-trichloroethane

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1 Background and introduction

1.1 Dissertation objectives

This dissertation aims to assess the role of three types of environmental exposure including PFAS, oil and gas development, and occupational exposure to hydrocarbon solvents as potential risk factors for the development of childhood cancer.

Briefly, the first study assessed the associations between three types of PFAS (i.e., PFOS, PFOA, and PFNA) identified in neonatal dried blood spots and the risk of retinoblastoma.

The second study assessed the associations between maternal residential proximity to oil and gas development in pregnancy and the risk of childhood cancer. We calculated the number of inactive wells and active wells within 1km, 1-3km, and 3km of the birth addresses. We then examined the ever exposure, low and high exposure categorized by median well counts within the certain buffer size associated with the risk of childhood cancer.

The third study focused on parental occupational exposure to hydrocarbon solvents. We identified hydrocarbon exposures in each industry using Danish version of NOCCA-JEM, which included three hydrocarbon groups (i.e., aromatic, aliphatic/alicyclic, chlorinated hydrocarbons) and five individual hydrocarbons (i.e., toluene, DCM, TCE, PCE, 1,1,1-TCA). We assessed fathers' exposure from 3 months pre-conception to birth and mothers' exposure from conception to birth and the associations with the risk of childhood cancer.

1.2 Childhood cancer: an overview

Childhood cancer, defined as cancer diagnosed in children aged 0 to 19 years, is the 2nd leading cause of death in children, with an expected 9620 childhood cancer cases and 1040 cancer deaths in 2024 in the US.¹ Unlike cancer incidence in adults with large geographic variations, the total incidence of most childhood cancer types is relatively constant geographically (approximately 1.0-2.5 per thousand).² However, ALL, HL, and CNS tumors were more common in high-income countries, while NHL and non-heritable retinoblastoma were more frequent in developing countries.²⁻⁵

Leukemia is the most common childhood cancer, accounting for about 30% of cancer diagnoses.⁶ There are two major types of pediatric leukemia, ALL and AML.⁷ ALL is a malignant neoplasm of the lymphoblasts which exhibits exaggerated and unconditional growth and dysfunction of mounting a normal immune response, and further causes a reduction in normal bone marrow cells.⁸ During 2001-2014 in the US, the overall incidence of childhood ALL (aged < 19 years) was 34.0 per 1 million persons with the highest in children aged 1-4 years (75.2 per 1 million), and among Hispanics (42.9 per 1 million) but the lowest among non-Hispanic Blacks (18.7 per 1 million).⁹ Children of Hispanic origin have high incidence of ALL. As it was reported in a population-based study, using medical data on ~50% of the Mexican children from a large medical system in Mexico, the incidence of leukemia (predominated by ALL) ranked the highest in the principal cancer groups.¹⁰ AML arises from a transformation of hematopoietic progenitor cells, which is characterized by a differentiation block, an increasing number of progenitor cells but a decreasing number of mature blood cells.¹¹ During 2005-2009, the overall incidence of childhood AML (aged ≤ 14 years) was 7.7 per million persons with higher incidence in infants

(18.4 per million) and in children aged 10-14 years (7.7 per million) but lower incidence in children aged 5-9 years (4.3 per million).⁶ Within the US, the ASR of AML in California during 1998-2012 was higher among Hispanic Whites (10.1 per million) and non-Hispanic Whites (9.2 per million).¹⁰

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Denmark has one of the oldest and the most comprehensive cancer registries in the world. It was previously reported having one of the highest incidence rates of childhood cancer (age 0-14) in the world and in the European region.^{13, 14} A Denmark study investigated the time trend of childhood cancer incidence during 72-year study period (1943-2014).¹⁵ Leukemia (26.5%) was the most common cancer type, followed by CNS tumors (23.4%) and lymphomas (12.9%) in Denmark over the entire study period.¹⁵ The incidence of childhood cancer increased by an average of 211 new cases each year over the study period, with a greater increase in more recent years (280 cases during 2006-2014) than in earlier years (168 cases during 1943-1955).¹⁵ Specific cancer types with increasing trends included soft tissue sarcomas, germ cell and gonadal tumors and malignant epithelial tumors.¹⁵

1.3 Retinoblastoma: an overview

Retinoblastoma is the most common primary ocular childhood malignancy with two-thirds diagnosed before 2 and 95% cases diagnosed before 5 years.¹⁶ The incidence of retinoblastoma varied geographically.¹⁶ The incidence was lower in the US (3.6 cases per million children aged under 15) and higher (6-10 cases per million children aged under 15) in Africa, India, and among children of Native American descent in the North American continent.² In the US, the mean age-adjusted incidence of retinoblastoma was 11.8 per million children aged 0-4 years (95% confidence interval (CI) = 10.9-12.8).¹⁷ Around 250-300 new cases are diagnosed in the US yearly, with approximately 1 case in 5,000-20,000 live births.^{18, 19}

The tumorigenesis of retinoblastoma originates from the inactivation of both alleles of *RB1* gene, a tumor suppressor gene located on chromosome 13. This produces a malignant tumor of the retina that may occur unilaterally or bilaterally.²⁰ The two-hit hypothesis was proposed by Knudson to explain the genetic mechanisms underlying retinoblastoma, as two separate mutation events must occur for this cancer to be initiated.²¹ There are two clinical forms of retinoblastoma: hereditary (40%) and non-hereditary (60%).²² In non-heritable retinoblastoma, both mutations occur in a single retinal cell (somatic mutation), while in heritable retinoblastoma, the first *RB1* gene mutation occurs in the germline and predisposes the child to the cancer but a necessary second (somatic) mutation in retinal cells leads to retinoblastoma development.²² All bilateral forms, consisting of 40% of all retinoblastoma cases, are heritable with most cases usually having a first germline *de novo* mutation in gametes of paternal origin.^{22, 23} About 60% cases are unilateral, of which 15% are heritable retinoblastoma.²⁴ Among heritable cases, retinoblastoma can be further classified into: 1) unilateral or bilateral retinoblastoma with no or unknown family

history were classified as sporadic; 2) bilateral retinoblastoma with no or unknown family history were also classified as having a de novo germline mutation; 3) unilateral or bilateral retinoblastoma with family history were classified as familial.²⁵

The geographic variation of retinoblastoma incidence was largely restricted to unilateral cases.²⁶ Thus, the relatively elevated incidence of unilateral retinoblastoma in developing countries indicates a role for infections or other environmental factors to cause *RB1* gene mutations in utero or infancy.²

1.4 Risk factors

1.4.1 Parental age

Parental age has been studied in relation to childhood cancer risks, however there is inconsistency in the findings. The increased risk of cancer associated with advanced parental age may be attributed to higher mutations in paternal germline cells and chromosomal abnormalities during maternal germ cell maturation.^{27, 28} In addition, maternal aging, including changes in estrogen levels, might also affect childhood cancer risks.²⁷

Epidemiologic studies have shown older paternal age increased the risk of leukemia overall and its subtypes (i.e., ALL and AML),^{27, 29-33} Wilms' tumor,^{34, 35} lymphomas including NHL,^{36, 37} brain cancer and CNS tumors,^{27, 28} RMS,³⁸ germ cell tumors,³⁷ retinoblastoma (including bilateral or sporadic hereditary cases),^{37, 39-42} and hepatoblastoma.⁴³ Specifically, paternal age over 35 years was associated with increased risks of overall leukemia and ALL,³⁰ RMS,³⁸ and retinoblastoma including bilateral cases,^{37, 39} while fathers aged over 50 years and 55 years was linked to increased risks of sporadic hereditary retinoblastoma⁴² and Wilms' tumor in the offspring,³⁵ respectively. On the other hand, younger paternal age might increase the risk for ALL in infants and AML.^{33, 44}

Regarding maternal age, findings have also linked aging with retinoblastoma,^{27, 45} leukemia (ALL and AML),^{27, 28, 31, 33, 34, 36, 46} lymphoma,³⁶ CNS tumors,³⁶ neuroblastoma, Wilms' tumor,^{47, 48} gonadal germ cell tumors,⁴⁹ bone tumors, and soft tissue sarcoma.⁵⁰ Maternal age were found to have a U-shaped association with AML risk (i.e., elevated in both youngest and oldest mothers).⁴⁴ Maternal age over 40 years increased the risk of AML, while maternal age under 20 years increased the risk of acute leukemia overall.^{33, 51} Additionally, maternal age over

35 years might elevate the risk of germ cell tumors.⁵² Mothers' older than 30, 35 and 40 years old might increase the risk for RMS, retinoblastoma (including sporadic hereditary cases), and Wilms' tumor, respectively.^{35, 37, 42, 53} Conversely, younger maternal age might increase the risk of hepatoblastoma.⁵⁴

1.4.2 Smoking

Numerous studies have suggested tobacco smoking is a risk factor for childhood cancer as constituents of tobacco can cross the placenta and have direct toxic effect on fetus.⁵⁵ Tobacco smoke can induce mutations in paternal germ cells and has been demonstrated in mice that the mutations were able to be transmitted to their offspring, leading to permanent alterations of their genomic composition.⁵⁶ Also, it can affect sperm morphology, mobility and concentration and to induce oxidative damage in sperm DNA.⁵⁷ Despite numerous studies investigating the association between maternal smoking during pregnancy and the risk of childhood cancer, the associations and the underlying mechanisms still remain unclear. Most studies investigating maternal smoking and leukemia yielded null results^{51, 58-63} and sometimes reported inverse associations.^{64, 65} Results may be impacted by mothers of case children being more likely to under-report their true smoking status.⁶⁶ There is one study that reported a positive dose-response relationship between the number of cigarettes per day smoked by mothers in pregnancy and ALL.⁶⁷ The Childhood Leukemia and Cancer International Consortium linked maternal smoking in pregnancy and increased AML risk only among Hispanic children.⁶⁸ On the other hand, paternal smoking yielded more consistent results. A meta-analysis of 17 case-control studies revealed an increased risk of ALL associated with paternal smoking before conception and during pregnancy, which was supported by a dose-response analysis.⁶⁹ Pooled and meta-analysis

showed paternal lifetime smoking, prenatal and postnatal smoking increased the risk of AML in offspring.⁶⁸ A study investigating acute leukemia overall and suggested a positive dose-response relationship with paternal smoking preconceptionally.⁷⁰

With regards to other cancer types, there was evidence indicating maternal smoking in pregnancy associated with elevated risks of CNS tumors including glioma, and astrocytoma,^{71, 72} retinoblastoma and particularly bilateral retinoblastoma,^{61, 73} NHL among heavy smokers,⁵¹ and neuroblastoma suggested by a meta-analysis.⁷⁴ Paternal smoking preconceptionally was also linked to elevated risks of childhood brain tumors, CNS tumors and particularly astrocytoma,^{75 76} and lymphoma in a positive dose-response relationship.⁷⁰ However, null associations were also seen in maternal smoking and brain tumors,⁷⁷ in maternal/parental smoking and lymphoma as well as brain tumors.⁶³ Null results were also suggested for germ cell tumors among children whose parents smoked.⁷⁸ Based on the existing evidence, the International Agency for Research on Cancer (IARC) has only classified hepatoblastoma as a tobacco-related cancer.⁷⁹ A few studies investigated parental smoking and hepatoblastoma and yielded mixed results. Three studies found an increased hepatoblastoma risk associated with maternal smoking in pregnancy or preconceptionally,^{54, 66, 80} while two suggested null associations between hepatoblastoma and maternal smoking^{81, 82} One study reported marginally positive associations between hepatoblastoma and paternal smoking preconceptionally⁸³. Children were also at higher risk of hepatoblastoma when both of the parents smoked.^{66, 84}

1.4.3 Race and ethnicity

Childhood cancer incidence has been known to vary by race and ethnicity in the US. White children generally have lower risks of most types of childhood cancer compared to children from other races.⁸⁵

It was observed that Hispanic children experienced approximately 10% higher risk of acute leukemia than their White counterparts.⁸⁵ A study in Tennessee revealed the risk of Wilms tumor was more prevalent in Blacks than in Whites and further suggested the role of race-specific biology in Wilms tumor risk.⁸⁶ Ewing sarcoma is much more common in White children than in Asian and Black children.⁸⁵ For extracranial embryonal tumors, a US population-based study revealed a lower incidence of neuroblastoma among minority groups (i.e., Hispanics, Blacks, API, and AI/AN), a higher incidence of retinoblastoma and germ cell tumor but lower incidence of rhabdomyosarcoma among Hispanics, a lower incidence of hepatoblastoma and germ cell tumors among Blacks, and a lower incidence of rhabdomyosarcoma and germ cell tumors among API.⁸⁷ Across nations, the rates of CNS tumor in White American children seem to be 2 to 3 times higher compared to those in children from Latin American nations.⁸⁸ The disparities might be attributable to a combination of genetic and environmental factors, interacting differently across the racial groups.

As suggested, genetic factors only account for 5-10% of childhood cancer risks,⁸⁵ and therefore, the remaining 90-95% result from environmental exposures or their interaction with genetic factors. Certain alleles with a higher frequency among Hispanics might contribute to the increased risk of B-cell ALL among Hispanic children.⁸⁹ Further, early life infection might impact ALL risk differently between Hispanics and non-Hispanic Whites possibly due to

variations in the role of *KIR* genes.⁹⁰ Racial and ethnic disparities in environmental pollution have been recognized as a growing concern. It was reported that in California, African American children had average higher traffic pollution exposures, followed by Hispanic, Asian/Pacific Islander, and non-Hispanic White children.^{91, 92} Other than environmental pollution, parental occupational exposures may also contribute to racial and ethnic differences. For example, paternal occupational exposures to chlorinated hydrocarbons and polycyclic aromatic hydrocarbons were associated with increased risk of childhood leukemia only among Hispanic fathers.⁹³ Notably, Hispanics constitute the largest agricultural workforce in California where the highest amount of pesticides in the US is used. Meanwhile, an increased childhood leukemia risk was associated with fathers exposed to agricultural pesticides.⁹⁴ Taken together, potential environmental and occupational factors contribute to the racial and ethnic differences in childhood cancer risk.

Hispanic origin by maternal birthplace

The *Hispanic paradox* describes the phenomenon that non-US-born Hispanic mothers who immigrate to the US tend to have better pregnancy outcomes than their US-born counterparts, even with high levels of poverty, lower maternal educational attainment, and reduced healthcare access.⁹⁵ This could shed light on the differential childhood cancer risks seen between non-US-born and US-born Hispanic children. According to a population-based case-control study in California, children of non-US-born mothers had lower risks for several childhood cancer types (i.e., glioma, astrocytoma, neuroblastoma, Wilms tumor) than those of US-born Hispanic mothers and non-Hispanic White mothers.⁹⁶ Additionally, the risk of unilateral retinoblastoma increased among children of US-born Hispanic mothers but decreased

among children born to mothers with less than 9 years of education, a group comprised primarily of mothers born in Mexico.³⁹ The underlying reasons for explaining the differences are still unclear, but it might be attributed to the positive influence of traditional culture such as a healthier diet, lower rates of smoking, drinking or drug use during pregnancy.⁹⁵ Further, children of Hispanic origin have high incidence of leukemia, predominantly ALL, in Mexico.¹⁰

1.4.4 Population density

Population density including household density is associated with the frequency of infant exposure to infectious agents, with those residing in higher density areas experiencing earlier exposure to such agents.^{97, 98} Kinlen's 'population-mixing' hypothesis and Greaves' 'delayed-infection' hypothesis have been proposed in recent years for childhood cancer etiology.^{99, 100} Kinlen hypothesized that an unidentified infectious agent from population mixing cause childhood leukemia and NHL, driven by increased contacts between susceptible and infected individuals.⁹⁹ The exposure occurred possibly in perinatal period.¹⁰¹ Greaves suggested that childhood leukemia might arise from abnormal immune responses to common infection(s).¹⁰⁰ Children with weaker immunity due to limited early-life exposures to infectious agents might be susceptible.¹⁰⁰ Direct investigation on the associations between population density and childhood cancer is limited. Some evidence supporting Greaves' hypothesis indicated an elevated risk of ALL for children from low-density areas,¹⁰² from more isolated communities (i.e., farthest from large urban centers),¹⁰³ and from metropolitan regions with low population density areas.¹⁰⁴ On the other hand, some studies suggested an increased risk of childhood leukemia occurred in areas of intermediate population density which had some level of population clustering and thus

aligned with Kinlen's hypothesis that an infectious agent might directly or indirectly contribute to childhood leukemia.^{105, 106}

1.5 PFAS and retinoblastoma

PFAS are synthetic chemicals widely used to make everyday consumer products. PFAS are chemically stable and are able to persist in soil and water once released. Humans can be exposed to PFAS from multiple sources with the primary ones being diet (contaminated food or migration of PFAS from food packaging or cookware), drinking water, consumer products, household dust, and ambient air via routes that include dermal contact, ingestion, and inhalation.¹⁰⁷⁻¹⁰⁹ Of all types of PFAS, legacy long-chain PFAS such as PFOS, PFOA, PFNA are the most produced and previously studied ones in terms of adverse health effects.¹¹⁰ Due to the long half-life of these 'forever chemicals',¹¹¹ PFAS were still detected in >98% of all serum samples in the 2013-2014 National Health and Nutrition Examination Survey (NHANES) participants including children ages 3-11 years.^{112, 113}

Several possible links from experimental and epidemiologic studies have suggested that PFAS might be associated with the increased risk of retinoblastoma. First, the toxicity of PFAS to the eye development in terms of structural integrity of the eye and delayed development of eye function have been suggested in experimental studies,¹¹⁴⁻¹¹⁶ Second, experimental and epidemiologic studies have indicated that PFAS (i.e., PFOS, PFOA, PFNA) can promote oxidative stress and disrupt hormone homeostasis in pregnant women, thus increasing of the risk of preterm birth, low birthweight, fetal death and miscarriage.¹¹⁷⁻¹³⁶ Meanwhile, there is some evidence that retinoblastoma risk may be elevated among preterm birth and infants with very low birthweight from population-based case-control studies.^{137, 138} In addition, with the impacts on

miscarriage, live birth bias will be introduced and impact our observations of retinoblastoma risk to some extent.¹³⁹ Third, PFOA is classified as Group 2B chemical (i.e., possibly carcinogenic to humans) by IARC,¹⁴⁰ based on limited evidence on an increased risk of testicular cancer and kidney cancer. However, no evidence has linked PFAS exposure to any type of eye cancer nor to any type of embryonal tumor. Fourth, immunomodulatory effects of PFAS have been previously described in epidemiologic as well as experimental studies, with PFOA and PFOS particularly exhibiting lower levels of vaccine antibodies and increased risks of infectious diseases.¹⁴¹⁻¹⁵⁰ Further, the US National Toxicology Program declared that PFOA and PFOS are immunotoxins. In our previous study, specific metabolites including linoleic acid, purine and N-Acetylneuraminic acid, as well as the vitamin A metabolism pathway were related to retinoblastoma, suggesting a role for immune response in retinoblastoma.¹⁵¹ Fifth, epidemiologic studies have indicated the disruption of homeostasis among children with prenatal exposure to PFAS. A higher prenatal exposure to PFOA was associated to decreased beta function,¹⁵² increased insulin and leptin levels but lower adiponectin levels in female offspring.¹⁵³ Prenatal PFOS exposure was also associated with altered glucose homeostasis including decreased insulin sensitivity and increased beta-cell function.¹⁵⁴ Metabolomics studies showed higher PFAS including PFOA and PFOS exposure were related to pathways and metabolites involved in altered glucose, lipid and amino acid metabolism in children.¹⁵⁵⁻¹⁶¹ Specifically, the linoleic acid pathway, de novo lipogenesis pathway and fatty acid metabolism pathway, and metabolites including aspartate, tyrosine, taurine, glycine, triacylglycerols, and several free fatty acids were found associated with exposure to PFAS. Importantly, these pathways and metabolites might be altered among retinoblastoma cases.^{151, 162, 163}

1.6 Oil and gas development and childhood cancer

California is among the top-10 oil and top-15 natural gas producing US states.^{164, 165} Major crude oil reservoirs in California are located in Los Angeles basin and in the Central Valley region (e.g., San Joaquin Valley), which account for approximately 4% of the nation's total proved crude oil reserves.^{166, 167} The majority of California's natural gas is extracted from reservoirs also producing oil.¹⁶⁸

Air contamination from the oil and natural gas industry has been a major concern.¹⁶⁹ Air toxics exposures during OGD are generated not only by the development of oil and gas sites and wells (production and injection for enhanced recovery), but also by the transport of materials, drilling, equipment operations, and waste disposal.¹⁷⁰ Emissions from truck traffic (e.g., PM_{2.5}, diesel PM, NO_x, NO₂), BTEX compounds, 1,3-butadiene, n-hexane, and styrene were frequently reported from the associated OGD activities.^{169, 171-173} Among the chemicals identified near active wells, 1,3-butadiene,¹⁷⁴ benzene,¹⁷⁵ diesel exhaust,¹⁷⁶ and formaldehyde¹⁷⁷ are established carcinogens (Group 1), while ethylbenzene is a possible carcinogen (Group 2B).¹⁷⁸

In California, an idle well is a well that has been inactive for over 2 years and has not been properly plugged and abandoned (i.e., sealed and closed).¹⁷⁹ California has a substantial number of abandoned wells including plugged/unplugged abandoned wells (~124,000) and idle wells (~38,000).¹⁸⁰ Yet not all plugged wells have been properly plugged (i.e., permanently sealing the well with a cement plug to prevent leakage to the surface), and the true number of poorly plugged wells is hard to estimate.^{180, 181} A recent project in 2022 has revealed that approximately 40% of over 4000 abandoned wells in Ventura county in California were properly

plugged.¹⁸² Pollutants released from active wells can also be released from abandoned and idle wells.^{180, 183, 184}

According to a national spatial analysis, approximately 17.6 million people in the US live within 1 mile of at least one active oil and/or gas well.¹⁸⁵ More than 4.6 million people live within 1 km of a documented abandoned well.¹⁸³ In California, it was estimated that on average 1.1 million Californians (3.0%) lived within 1km of active wells and approximately 9 million Californians (22.9%) lived within 1km of plugged wells during 2005-2019.¹⁸⁶ A ban on new or reworked oil and gas wells being located within 1km of residences was initiated by the California legislature in September 2022.¹⁸⁷

Only two ecologic and two case-control studies have previously investigated OGD exposures and childhood cancer. An ecologic study in the Amazon basin of Ecuador found an increased risks of childhood leukemia in counties with compared with those without OGD, while a second ecologic study in the same area reported that CNS tumors incidence increased after hydraulic fracturing drilling began.^{188, 189} Furthermore, a case-control study in Pennsylvania reported an elevated risk of ALL among 2-7 year olds with a birth residence within 2 km of OGD activity.¹⁹⁰ A study in rural Colorado instead utilized the address at the time of diagnosis to assign exposure and only found increases in risk of ALL among cases aged 5-24 years, but this study used children diagnosed with other types of cancers as controls.¹⁹¹

1.7 Occupational exposures to organic solvents and childhood cancer

Parental occupational exposures have been frequently investigated in the etiology of childhood cancer. However, the underlying biological mechanisms of how the exposures would impact cancer risk in the offspring remain unknown. During preconception, an increased risk is likely to result from genetic alterations in parental germ cells subsequently passed to the offspring, particularly from paternal sperm.¹⁹² During pregnancy, trans-placental exposure could harm the fetus.^{193, 194}

Occupational studies assessing occupational exposures have relied on self-reported information, employed routine data such as birth certificates to avoid recall bias, and utilized job exposure matrices. The validity of self-reported information can be questionable,^{195, 196} while studies employing routine data may be hampered by inadequate information.¹⁹⁷ Some studies assessed exposures by using job or industry title, which can be problematic, as identical job titles can have vastly different exposures depending on specific activities and the extent to which exposure controls are used.¹⁹⁸

Preconception

Parental preconception exposure can potentially induce mutations in germ cells, including DNA damage and chromosomal aberrations resulting in tumorigenesis in their offspring.¹⁹⁹ Studies found toluene resulted in DNA damage in the sperm of rats, inhalation of PCE led to sperm head abnormalities in male mice, and inhalation of TCE caused depletion of germ cells and spermatogenic arrest in male rats.²⁰⁰⁻²⁰² Despite not specifically associated with germ cells, DCM and 1,1,1-TCA exhibited mutagenicity in a mouse model.²⁰³

A small number of studies have linked parental occupational exposure to organic solvents prior to conception to childhood cancer. With regards to paternal exposures, a study assessing acute nonlymphocytic leukemia found its association with paternal preconception exposure to any solvents including TCE, PCE, and xylene (OR = 2.2, $P < 0.05$).²⁰⁴ Metayer et al., found organic solvents including chlorinated hydrocarbons (OR=1.48; 95% CI = 1.01-2.16) elevated the risk of ALL only among Latino fathers rather than non-Latino fathers in California.⁹³ Increased risks of brain tumors were associated with solvents including benzene and other aromatic solvents (OR=1.76; 95% CI =1.10–2.82).^{205, 206} Increased risks of CNS tumors was also seen among fathers working in the painting industry near conception.²⁰⁷ Our previous study did not find any associations with germ cell tumors.²⁰⁸

Maternal solvent exposure in pre-conceptional period has been linked to leukemia. Specifically, aliphatic (OR = 4.3; 95% CI = 1.8-10.4) and aromatic (OR = 3.8; 95% CI = 1.6-9.2) hydrocarbons including toluene (OR = 4.3; 95% CI = 1.4-13.7) were associated with leukemia.²⁰⁹ Paints, lacquers, and thinners, consisting of exposures to various hydrocarbons, were also linked to ALL and acute nonlymphocytic leukemia.^{204, 210, 211} Some studies grouped solvents together, likely due to small number, suggested solvents or dermal exposure to hydrocarbons was associated with ALL.^{206, 212-214}

Pregnancy

Toxins and stress that mothers experienced during pregnancy lead to altered fetal programming, resulting in permanent changes that affect long-term disease risk.²¹⁵⁻²¹⁷ Inconsistent findings on parental occupational exposures and childhood during pregnancy have been reported. Some studies found maternal exposure in pregnancy to hydrocarbon-related

products including paints, lacquers or thinners, and solvents such as toluene (OR = 2.25; 95% CI = 1.02–4.95), and benzene were associated with the increased risk of leukemia, especially ALL,^{210-212, 218-220} while some studies were limited by small sample sizes.^{219, 221} For other cancer types, maternal exposure to solvents (OR = 2.0; 95%CI = 1.0–4.1) especially aromatic hydrocarbons (OR = 9.2; 95%CI = 2.4–34.3) during pregnancy was linked to neuroblastoma.²²² Our group previously reported null associations between germ cell tumors and maternal exposure to DCM.²⁰⁸

Studies investigating paternal exposure have reported an increased risk of leukemia associated with organic solvents. Specifically, exposure to organic solvents was associated with acute nonlymphocytic leukemia,²⁰⁴ TCE was associated with leukemia (all types combined; exposed cases N = 7; OR = 4.4; 95% CI = 1.2-21.0)²²³ and paternal exposure to inhaled hydrocarbons was associated with leukemia and ALL.²¹⁴ However, the existing evidence is not sufficient to draw conclusions due to the lack of studies and the lack of statistical power in some studies.

Other exposure windows

Some studies investigated exposures before birth and yielded inconsistent results. Maternal exposures to toluene before and during pregnancy was found associated with leukemia (OR = 2.27; 95%CI = 1.1-5.0).²²⁴ For ALL, it was suggested that paternal exposures to aromatic hydrocarbons except benzene (OR = 1.48; 95% CI = 0.97-2.25)²²⁵ as well as maternal exposures to mononuclear aromatic hydrocarbons (OR = 1.64; 95% CI = 1.12-2.41), toluene (OR = 1.88; 95% CI = 1.01-3.47), and 1,1,1-TCE (OR = 7.55; 95% CI = 0.92-61.97) might increase the risk.²¹⁸ Paternal occupations in the painting industry might elevate the risk AML but not ALL.^{225,}

²²⁶ By evaluating paternal occupation at birth, Keegan et al., did not find any form of exposure to hydrocarbons (i.e., inhaled or dermal) and hydrocarbon-related occupations were associated with leukemia including ALL and AML.²²⁷ NHL (OR = 1.64; 95% CI = 1.05-2.58) was linked to maternal exposures to aromatic hydrocarbon solvents around birth.²²⁸ For brain tumors, maternal exposures to solvents and specifically chlorinated solvents (OR = 8.79; 95% CI = 0.96-80.7)²⁰⁵,²²⁹ as well as paternal occupations in painting and printing industries might increase the risk.²²⁶ However, one study did not find any associations between aromatic, aliphatic and alicyclic hydrocarbons and ALL as well as brain cancer.²³⁰ Paternal occupational exposure to lacquer thinner 2 years before birth was associated with an increased risk of neuroblastoma in offspring.²³¹

2 Neonatal per- and polyfluoroalkyl substance exposure in relation to retinoblastoma

2.1 Abstract

Background

Prenatal per- and polyfluoroalkyl substance (PFAS) exposure can disrupt hormonal homeostasis and induce neuro- and immunotoxicity in children. In this exploratory study, we investigated associations between PFAS levels in neonatal dried blood spots and retinoblastoma risk.

Materials and Methods

This study included 501 retinoblastoma cases born from 1983 to 2011 and 899 controls frequency-matched by birth year (20:1 matching ratio), born to 755 US-born and 366 Mexico-born mothers in California. Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA) feature intensities were identified from neonatal blood spots from California newborn Genetic Disease Screening Program. Using logistic regression, we assessed whether a doubling (log₂-unit increase) of PFAS levels or having above-mean levels of PFAS in blood affects retinoblastoma risk overall or its subtypes (i.e., unilateral, bilateral). We also assessed children of US-born and Mexico-born mothers, separately.

Results and Discussion

Among all children, above-mean PFOS levels at birth increased the odds of retinoblastoma overall by 29% (95% Confidence Interval (CI): 1.00, 1.67) and unilateral retinoblastoma by 42% (95% CI: 1.03, 1.97). For children of Mexico-born mothers, we estimated the highest odds of retinoblastoma overall (adjusted odds ratio (aOR): 1.67; 95% CI: 1.06, 2.66) and bilateral retinoblastoma (aOR: 2.06; 95% CI: 1.12, 3.92) with above-mean PFOS levels. Among children

of US-born mothers, higher PFOS levels increased the odds of unilateral retinoblastoma by 15% (95% CI: 0.99, 1.35) for each log₂-unit increase and by 71% among children with above-mean PFOS levels (95% CI: 1.04, 2.90). In addition, for children of US-born mothers, PFOA increased the odds of retinoblastoma overall (aOR: 1.41; 95% CI: 1.00, 2.02 for above-mean levels, aOR: 1.09; 95% CI: 0.98, 1.23 per log₂-unit increase). PFNA was not associated with retinoblastoma risk.

Conclusions

Our results suggested that PFOS and PFOA might contribute to retinoblastoma risk in children born in California.

2.2 Introduction

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals widely used in consumer products and industrial applications because of their stain-proof, water-proof, grease-proof, and heat resistant properties.²³² Humans can be exposed to PFAS from multiple sources with the primary ones being diet (contaminated food or migration of PFAS from food packaging or cookware), drinking water, consumer products, household dust, and ambient air via routes that include dermal contact, ingestion, and inhalation.¹⁰⁷⁻¹⁰⁹

Of all types of PFAS, legacy long-chain PFAS such as perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA) are the most produced and previously studied ones in terms of adverse health effects.¹¹⁰ The phase-out of PFOS and PFOA in the US began in 2000 and 2006,^{233, 234} respectively. Blood concentrations of PFOS and PFOA detected in the US population declined >80% and 60% from 1999 to 2014.²³⁵ But because the half-life of these ‘forever chemicals’ is long,¹¹¹ PFAS were still detected in >98% of all serum samples in 2013-2014 National Health and Nutrition Examination Survey (NHANES) participants including children ages 3-11 years.^{112, 113}

Known adverse health effects of PFAS include disruption of hormonal homeostasis, neuro- and immunotoxicity in children, and there is a growing interest in understanding all of the health impacts of early-life exposure to PFAS on child health.²³⁶ PFAS can be passed from an expectant mother to her developing offspring via placental transfer and breastfeeding.²³⁷ Toxicity to the developing eye was reported in laboratory animals for PFOA and PFOS, with evidence of gene suppression related to the structural integrity of the eye’s lens¹¹⁴ and delayed eye

opening.¹¹⁶ Prenatal PFAS exposure also appears to contribute to adverse birth outcomes such as preterm birth and low birthweight,^{238, 239} which are risk factors for retinoblastoma.^{137, 138} Carcinogenicity of PFAS has been investigated in adults, and PFOA has been classified as a Group 2B carcinogen by the International Agency for Research on Cancer.²⁴⁰

A ‘two-hit hypothesis’ has been proposed by Knudson to explain genetic mechanisms underlying retinoblastoma as two separate mutation events must occur for this cancer to be initiated.²¹ There are two clinical forms of retinoblastoma: hereditary (40%) and non-hereditary (60%).²² In non-heritable retinoblastoma, both mutations occur in a single retinal cell (somatic mutation), while in heritable retinoblastoma, the first *RB1* gene mutation occurs in the germline and predisposes the child to the cancer but a second (somatic) mutation in retinal cells is necessary for retinoblastoma development.²² All bilateral cases are heritable with most cases usually having a first germline *de novo* mutation in gametes of paternal origin.^{22, 23} Among unilateral cases, 10-15% are heritable.²² Several risk factors for retinoblastoma were identified in epidemiologic studies. Older paternal age is considered an independent risk factor for hereditary retinoblastoma.²⁷ Other risk factors with supportive evidence that need further investigation include being the child of a US-born Hispanic mother, exogenous factors such as low-quality diet, maternal pre-pregnancy underweight, air toxics, low sunlight exposure in early life, parental occupational exposure to hazardous agents, and possibly human papillomavirus infection.^{39, 91, 241-245}

To the best of our knowledge, no previous studies have evaluated the association between PFAS and childhood cancer including retinoblastoma. This exploratory study investigates associations between PFAS we identified in dried neonatal blood spots (i.e., PFOS, PFOA, and PFNA) and the risk of developing childhood retinoblastoma.

2.3 Methods

Human subject permissions were obtained from the California Committee for the Protection of Human Subjects, the University of California, Los Angeles, and the University of North Texas.

Study population and sample collection

Our study population belongs to the Smoking and Embryonal Tumor Study, a large population-based case-control study of all childhood cancers. Children born in California from 1983 to 2011 and aged ≤ 5 years at diagnosis were included. Cases were selected from the California Cancer Registry, and controls were frequency-matched by year of birth (20:1 matching ratio) and randomly selected from California birth rolls.³⁹ For our untargeted metabolomics sub-study, 1,400 mother-child pairs (501 retinoblastoma cases and 899 controls) with available neonatal blood spots were randomly selected from this study population.

In California, neonatal blood samples are routinely obtained from newborns by heel-sticks between 12 to 48 hours after birth and placed on specialized filter paper, dried at room temperature for at least 3 hours, and mailed to the state laboratory for analyses.²⁴⁶ After routine genetic testing, leftover blood spots are stored at -20°C by the California newborn Genetic Disease Screening Program. We previously reported that the metabolites assessed on these blood spots are largely stable with some variation by the type of metabolite over the years.²⁴⁷ We obtained each mother-child pair's data from birth records, including demographic and gestational information. Samples considered outliers based on their metabolomic profiles ($N = 10$) were excluded from our analyses. Our final sample included 497 retinoblastoma cases and 893 control children.

High-resolution metabolomics

Neonatal blood spots were analyzed using liquid chromatography with high resolution mass spectrometry (LC-HRMS; Thermo Scientific Fusion Orbitrap Tribrid Mass Spectrometer) using established methods.²⁴⁸ Samples were punched using a 5mm hole punch and treated with 2:1 acetonitrile in water (containing a mixture of stable isotopic internal standards). Samples were mixed for 12 hours at 0-4 °C in the dark, and then centrifuged to remove particulate matter. The resulting supernatant was analyzed in triplicate using hydrophilic interaction liquid chromatography (HILIC) with positive electrospray ionization (ESI) and C18 hydrophobic reversed-phase chromatography with negative ESI for quantification of PFAS.²⁴⁹ The mass spectrometer was operated using ESI mode at a resolution of 120,000 and a mass-to-charge ratio (m/z) range 85-1275. Blood spot samples were analyzed in batches of 40. To evaluate system performance, we used two separate quality assessment methods. Our first QC sample was NIST 1950,²⁵⁰ which was analyzed at the beginning and end of the entire analytical run. The second QC sample (Q-Std) included commercially purchased plasma pooled from an unknown number of males and females. Q-Std was analyzed at the beginning, middle, and end of each batch of 40 samples for normalization and batch effect evaluation. Raw data files were extracted and aligned using *apLCMS*²⁵¹ with modifications by *xMSanalyzer*.²⁵² Uniquely detected ions consisted of mass-to-charge ratio (m/z), retention time (rt), and ion abundance, referred to as metabolite features. Prior to data analysis, metabolite features were batch corrected using wavelet analysis.²⁵³

PFAS identification was conducted by matching accurate mass and retention time to authentic reference standards analyzed under identical conditions using tandem mass spectrometry.²⁵⁴ We were able to identify PFOS, PFOA, and PFNA in our blood sample. The

m/z ratio was 498.9302 for PFOS, 412.9666 for PFOA, and 462.9629 for PFNA, while the retention time was 120 seconds for PFOS, 77 seconds for PFOA and 137 seconds for PFNA.

Statistical analysis

We report means, standard deviations (SDs), medians, and interquartile ranges (IQRs) for detected PFAS in dried blood spots. For participants with PFAS levels below the detection limits, we used a value equal to half of the minimum feature intensity observed for each PFAS. All PFAS feature intensities were log2-transformed prior to analysis.

The PFAS were only weakly correlated ($|r| < 0.15$). We applied unconditional logistic regression models to determine associations between PFOS, PFOA, PFNA, and retinoblastoma (all cases, unilateral and bilateral only), to investigate each PFAS individually. A model including all available PFAS (i.e., PFOS, PFOA, PFNA) was additionally performed to assess the impacts of all PFAS on retinoblastoma. Covariates we considered for adjustment including maternal age, paternal age, maternal race and ethnicity, US-born mother, mother's education attainment, mother's payment for prenatal care, census-based neighborhood socioeconomic status (SES).²⁵⁵ These characteristics have been associated with retinoblastoma and/or PFAS exposure.^{27, 39, 256-258} In addition to birth year, the matching factor, we adjusted for maternal age (<20, 20-29, ≥ 30), maternal race and ethnicity (White non-Hispanic, Hispanic of any race, other), US-born mother (Yes/No), mother's years of education (≤ 11 years, 12 years, 13-15 years, ≥ 16 years), and census-based neighborhood SES in our final model. We assessed associations of retinoblastoma with log2-transformed PFAS feature intensities as continuous variables as well as after dichotomizing PFAS exposure (above vs. below mean). Data from 1999-2000 and 2003-2004 NHANES showed that non-Hispanic white women in the US had higher serum

concentrations of PFAS including PFOS, compared to Mexican Americans.²⁵⁹ Although we have previously observed maternal birthplace to be related to retinoblastoma risk among Hispanics,⁹⁶ the sample size did not allow us to assess associations stratified by maternal birthplace and race and ethnicity. Therefore, we conducted stratified analyses based on maternal birthplace, either US-born or Mexico-born women (all ethnic groups, combined).

All statistical tests were performed using R version 4.2.2.

2.4 Results

In our study population, the average age of diagnosis for unilateral retinoblastoma was 22.1 months (SD = 14.5 months), while the average age of diagnosis for bilateral retinoblastoma was 9.3 months (SD = 8.7 months). **Table 2-1** presents the demographic characteristics of the 1,390 study subjects. Among all, 755 (54.3%) children had US-born mothers, 366 (26.3%) had Mexico-born mothers and 269 (19.4%) had mothers born in other foreign countries. A greater proportion of fathers of cases were ≥ 30 years of age (57.9%, 288 of 497) than of controls (53.1%, 474 of 893). Parents of children with bilateral retinoblastoma had more years of formal education, with 22.0% of mothers and 22.5% of fathers having at least a college degree versus 16% of parents in controls.

Due to the similarity of results between the model with all three PFAS and the models for each individual PFAS, we only reported results for PFAS from each individual model. **Table 2-2** shows the log2-transformed PFAS feature distribution in our study. Mean values for PFAS were all slightly higher in cases than in controls, but median values were similar. More cases had an above-mean value for PFOS and PFOA than controls (PFOS: 74.9% vs. 70.3%; PFOA: 75.9% vs. 73.5%), but this was reversed for PFNA (PFNA: 71.2% of cases vs. 75.1% of controls).

Among children of Mexico-born mothers, cases tended to have lower measures for PFOA and PFNA than controls, but not for PFOS. For cases and controls, children with US-born mothers had higher PFOS measures than those children with Mexico-born mothers.

Table 2-3 shows the associations between prenatal PFAS exposure and retinoblastoma. We observed that in children with above-mean PFOS measure the odds of developing retinoblastoma were increased (adjusted odds ratio (aOR) = 1.29; 95% confidence interval (CI): 1.00, 1.67), especially among unilateral cases (aOR = 1.42; 95% CI: 1.03, 1.97). This was seen in children of US-born mothers for unilateral retinoblastoma (aOR = 1.71; 95% CI: 1.04, 2.90), and in children of Mexico-born mothers for retinoblastoma overall (aOR = 1.67, 95% CI: 1.06, 2.66) but especially for bilateral cases (aOR = 2.06; 95% CI: 1.12, 3.92). For unilateral disease, the odds were slightly elevated among children of US-born mothers for PFOS [per IQR increase aOR = 1.15; 95% CI: 0.99, 1.35] and for PFOA (per IQR increase aOR = 1.09; 95% CI: 0.98, 1.23) when we used a continuous measure. With above the mean PFOA, the odds of retinoblastoma were increased by 41% (95% CI: 1.00, 2.02), compared to children of US-born mothers with below the mean PFOA. Among children of Mexico-born mothers, we found null associations of all retinoblastoma with exposure to PFOA and PFNA when using either a continuous measure or dichotomized exposure.

2.5 Discussion

This is the first study linking prenatal PFAS exposure to retinoblastoma. We utilized PFAS metabolomic intensities in neonatal dried blood spots and found positive associations for retinoblastoma at higher levels of PFOS, especially unilateral retinoblastoma among all children. When stratifying by maternal birthplace, children of US-born mothers were more likely to

develop unilateral retinoblastoma with higher prenatal PFOS exposure, while for children of Mexico-born mothers we found stronger associations with bilateral retinoblastoma. An increased odds in retinoblastoma was also estimated for higher levels of PFOA among children of US-born mothers, although no associations were observed among all children and children of Mexico-born mothers.

Several pathways involved in lipid metabolism such as fatty acid metabolism and the glycerophospholipid pathway are known to be related to retinoblastoma.^{151, 163} Fatty acid metabolism has been found to be disturbed among overweight and obese Hispanic children,¹⁵⁶ while the glycerophospholipid pathway was altered among children diagnosed with nonalcoholic fatty liver disease related to PFAS exposure.¹⁶¹ In addition, a meta-analysis reported perturbations in lipid metabolism with PFAS exposure.²⁶⁰ The common pathways altered by PFAS exposure and previously reported to coincide with retinoblastoma cancer status supports the link we found between PFAS and retinoblastoma.

In our previous study, specific metabolites including linoleic acid, purine and N-Acetylneuraminic acid, as well as the vitamin A metabolism pathway as being related to retinoblastoma, suggesting a role for immune response in retinoblastoma.¹⁵¹ Although findings are not entirely consistent, immunomodulatory effects of PFAS have been previously described in epidemiologic as well as experimental studies.¹⁴¹ For example, PFAS exposure was associated with lower levels of vaccine antibodies (especially for PFOA, PFNA, PFOS, Perfluorodecanoic acid (PFDA)),¹⁴²⁻¹⁴⁵ and increased risks of infectious diseases (especially for PFOA, PFOS).¹⁴⁷⁻¹⁵⁰ Experimental studies suggested serum IgM and/or IgG concentrations to be negatively associated with PFOA^{261, 262} and PFOS.^{263, 264} The US National Toxicology Program declared

that PFOA and PFOS are immunotoxins, thus it is possible that prenatal PFAS exposures affect children's risk of retinoblastoma by impacting immune responses.²⁶⁵

Our findings showed stronger associations of PFOS exposure with unilateral retinoblastoma among children of US-born mothers, compared to those with Mexico-born mothers. One reason for the differences in the observed PFAS burden may be that US-born persons tend to consume lower-quality diets, including more fast food, compared to Mexican-born Americans.^{266, 267}

PFAS coatings are commonly used for fast food packaging due to their grease-proof properties,²⁶⁸ and serum PFOS levels were previously found to be positively associated with the consumption of fast food, pizza, and microwave popcorn.²⁶⁹ Furthermore, low-quality diets, including more fried foods, have previously been associated with higher risk of retinoblastoma.²⁷⁰ Because of the different dietary habits, children of US-born mothers might have higher PFOS levels than children of Mexico-born mothers, which subsequently puts them at a higher risk of unilateral retinoblastoma.

Increased odds of bilateral retinoblastoma were only seen among children of Mexico-born mothers. PFOS and PFOA may disturb spermatogenesis, causing chromosomal aneuploidies and DNA fragmentation of sperm cells.²⁷¹ Since a first germline *de novo* mutation, which is mostly from gametes of paternal origin, is necessary for the development of bilateral retinoblastoma,^{22, 23} it is possible that paternal or maternal exposure to PFAS preconceptionally predisposes the offspring to an increased risk of bilateral retinoblastoma. However, we did not have further information on specific mutations nor information on parental exposures to PFAS before conception, which might confound the associations between children's prenatal PFAS exposure and the odds of bilateral retinoblastoma.

Exposure to PFNA showed mostly inverse associations, with confidence intervals crossing the null. However, PFNA was reported to cause miscarriage in several epidemiologic studies.¹³² If PFNA reduced fetal survival, a live birth bias could occur,¹³⁹ and could explain our inverse associations for PFNA.

The study population consisted of retinoblastoma cases randomly selected from the California Genetic Disease Screening Program. Thus, we avoided selection bias due to differential participation in our study as neonatal bloodspots are obtained from more than 99% of all California children. The use of metabolomic markers and state records avoids recall bias.

We acknowledge several limitations. First, there may be confounding due to unknown or unmeasured parental risk factors such as maternal diet including fast food consumption. Second, we assumed that the one-time collection of neonatal blood spots was representative of average exposure of PFAS during pregnancy. Maternal serum PFAS and cord blood PFAS concentration were found to be strongly correlated.²⁷² Furthermore, it has been reported that the elimination of PFOS, PFOA, PFNA from serum increases throughout pregnancy, with serum PFAS concentrations decreasing by 3-7% per month.^{273, 274} Hence, the average exposure for neonates during pregnancy, considering the shorter half-life, should be higher than the levels we detected.

This is the first paper to examine PFAS in relation to any type of pediatric cancer. Our study suggests adverse effects of prenatal exposure to PFAS, especially PFOS and PFOA, on retinoblastoma. Children of US-born mothers might be at higher risk of unilateral retinoblastoma with the exposure of PFOS and PFOA, while children of Mexico-born mothers might be at higher risk of bilateral retinoblastoma with the exposure of PFOS. Our study is warranted for

further investigation on PFAS and childhood retinoblastoma and specifically among US-born and Mexico-born Mexican Americans.

2.6 Figures and tables

Table 2-1. Demographic characteristics of the study population

Characteristics, N (%)	Control (N = 893)	Case (N = 497)	
		Unilateral (N = 279)	Bilateral (N = 218)
Birth Year			
1983-1990	185 (20.7)	51 (18.3)	20 (9.2)
1991-2000	353 (39.5)	111 (39.8)	98 (45.0)
2001-2011	355 (39.8)	117 (41.9)	100 (45.9)
Maternal birthplace			
US	483 (54.1)	156 (55.9)	116 (53.2)
Mexico	236 (26.4)	66 (23.7)	64 (29.4)
Other foreign countries	174 (19.5)	57 (20.4)	38 (17.4)
Maternal Age			
<20	100 (11.2)	25 (9.0)	23 (10.6)
20-29	462 (51.7)	159 (57.0)	106 (48.6)
≥30	331 (37.1)	95 (34.1)	89 (40.8)
Paternal Age			
<20	32 (3.6)	10 (3.6)	10 (4.6)
20-29	387 (43.3)	115 (41.2)	68 (31.2)
≥30	474 (53.1)	150 (53.8)	138 (63.3)
Missing	0	4	2
Maternal race/ethnicity			
White non-Hispanics	303 (33.9)	83 (29.8)	69 (31.7)
Hispanic of any race	422 (47.3)	131 (47.0)	105 (48.2)
Other/not specified	168 (18.8)	65 (23.3)	44 (20.2)
Paternal race/ethnicity			
White non-Hispanics	261 (29.2)	81 (29.0)	63 (28.9)
Hispanic of any race	407 (45.6)	125 (44.8)	102 (46.8)
Other/not specified	225 (25.2)	73 (26.2)	53 (24.3)
Census-based socioeconomic status index level			
1 (Low)	194 (21.7)	71 (25.5)	51 (23.4)
2	248 (27.8)	62 (22.2)	61 (28.0)
3	196 (22.0)	63 (22.6)	39 (17.9)
4	135 (15.1)	50 (17.9)	45 (20.6)
5 (High)	116 (13.0)	32 (11.5)	21 (9.6)
Missing	4	1	1
Maternal Education			
≤11 years	252 (28.2)	68 (24.4)	71 (32.6)
12 years	233 (26.1)	80 (28.7)	52 (23.9)
13-15 years	155 (17.4)	56 (20.1)	35 (16.1)
≥ 16 years	145 (16.2)	46 (16.5)	48 (22.0)

Missing	108	29	12
Paternal Education			
≤11 years	214 (24.0)	66 (23.7)	59 (27.1)
12 years	226 (25.3)	78 (28.0)	54 (24.8)
13-15 years	146 (16.4)	40 (14.3)	31 (14.2)
≥ 16 years	142 (15.9)	52 (18.6)	49 (22.5)
Missing	165	43	25

Table 2-2. The distribution of PFAS ^a in the study population, by case-control status and maternal birthplace

	All cases (N = 497)		Unilateral (N = 279)		Bilateral (N = 218)		Control (N = 893)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Among all mothers								
PFOS	15.5 (2.9)	16.2 (1.6)	15.6 (2.8)	16.3 (1.6)	15.4 (3.0)	16.1 (1.7)	15.4 (2.9)	16.2 (1.8)
PFOA	17.0 (3.3)	18.2 (1.8)	17.1 (3.2)	18.1 (1.9)	17.0 (3.5)	18.2 (1.6)	16.8 (3.5)	18.1 (2.0)
PFNA	15.7 (1.3)	16.0 (0.9)	15.6 (1.4)	16.0 (0.9)	15.7 (1.2)	16.0 (0.8)	15.6 (1.4)	16.1 (0.8)
Among US-born mothers								
	All cases (N = 272)		Unilateral (N = 156)		Bilateral (N = 116)		Control (N = 483)	
PFOS	16.1 (2.1)	16.4 (1.5)	16.3 (2.0)	16.5 (1.4)	16.0 (2.2)	16.3 (1.6)	15.9 (2.5)	16.4 (1.6)
PFOA	17.1 (3.2)	18.2 (1.6)	17.2 (2.9)	18.0 (1.6)	17.0 (3.6)	18.3 (1.5)	16.8 (3.6)	18.1 (2.0)
PFNA	15.6 (1.4)	16.0 (0.9)	15.6 (1.5)	16.0 (1.0)	15.7 (1.3)	16.1 (0.9)	15.6 (1.5)	16.1 (0.8)
Among Mexico-born mothers								
	All cases (N = 130)		Unilateral (N = 66)		Bilateral (N = 64)		Control (N = 236)	
PFOS	14.7 (3.6)	15.9 (1.8)	14.6 (3.6)	15.9 (1.9)	14.7 (3.5)	15.9 (1.5)	14.4 (3.3)	15.6 (2.4)
PFOA	16.7 (3.6)	18.1 (2.2)	16.3 (3.9)	17.9 (2.7)	17.1 (3.2)	18.2 (1.5)	17.0 (3.4)	18.1 (1.7)
PFNA	15.6 (1.4)	15.9 (0.8)	15.6 (1.4)	15.9 (0.9)	15.5 (1.4)	15.9 (0.7)	15.7 (1.4)	16.0 (0.7)
Dichotomized above-mean exposure ^b								
Among all mothers								
PFOS, N (%)	372 (74.9)		214 (76.7)		158 (72.5)		628 (70.3)	
PFOA, N (%)	377 (75.9)		208 (74.6)		169 (77.5)		656 (73.5)	
PFNA, N (%)	354 (71.2)		193 (69.2)		161 (73.9)		671 (75.1)	
Among US-born mothers								
	All cases (N = 272)		Unilateral (N = 156)		Bilateral (N = 116)		Control (N = 483)	
PFOS, N (%)	224 (82.4)		134 (85.9)		90 (77.6)		378 (78.3)	
PFOA, N (%)	210 (77.2)		120 (76.9)		90 (77.6)		345 (71.4)	
PFNA, N (%)	190 (69.9)		108 (69.2)		82 (70.7)		356 (73.7)	
Among Mexico-born mothers								
	All cases (N = 130)		Unilateral (N = 66)		Bilateral (N = 64)		Control (N = 236)	
PFOS, N (%)	85 (65.4)		41 (62.1)		44 (68.8)		126 (53.4)	
PFOA, N (%)	92 (70.8)		42 (63.6)		50 (78.1)		181 (76.7)	

PFNA, N (%)	93 (71.5)	45 (68.2)	48 (75.0)	178 (75.4)
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Note:

^a The descriptive statistics were calculated on the log2-transformed scale.

^b The exposures were dichotomized based on mean value of the log2-transformed PFAS feature intensities of all study population (N = 1,390)

Abbreviations: SD, standard deviation; IQR, interquartile range; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctane sulfonic acid; PFOA, perfluorooctanoic Acid; PFNA, perfluorononanoic acid.

Table 2-3. Effect estimates and 95% confidence interval for retinoblastoma in relation to prenatal PFAS exposure ^a

	PFOS		PFOA		PFNA	
	Crude OR ^c (95% CI)	Adjusted OR (95% CI)	Crude OR ^c (95% CI)	Adjusted OR (95% CI)	Crude OR ^c (95% CI)	Adjusted OR (95% CI)
Per IQR increase						
<i>Among all mothers^d</i>						
Retinoblastoma	1.02 (0.95, 1.09)	1.02 (0.95, 1.09)	1.03 (0.97, 1.09)	1.03 (0.97, 1.09)	1.00 (0.94, 1.07)	1.00 (0.94, 1.07)
Unilateral cases	1.03 (0.95, 1.13)	1.03 (0.95, 1.14)	1.03 (0.96, 1.12)	1.04 (0.96, 1.13)	0.98 (0.91, 1.06)	0.98 (0.91, 1.06)
Bilateral cases	1.00 (0.91, 1.09)	0.99 (0.91, 1.09)	1.02 (0.94, 1.11)	1.02 (0.94, 1.11)	1.03 (0.94, 1.13)	1.03 (0.94, 1.13)
<i>Among US-born mothers^e</i>						
Retinoblastoma	1.09 (0.97, 1.23)	1.09 (0.97, 1.23)	1.06 (0.97, 1.15)	1.06 (0.98, 1.16)	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
Unilateral cases	1.14 (0.99, 1.34)	1.15 (0.99, 1.35)	1.08 (0.97, 1.21)	1.09 (0.98, 1.23)	0.99 (0.90, 1.09)	0.98 (0.89, 1.09)
Bilateral cases	1.03 (0.90, 1.22)	1.02 (0.88, 1.20)	1.03 (0.93, 1.16)	1.04 (0.94, 1.17)	1.02 (0.91, 1.16)	1.02 (0.91, 1.16)
<i>Among Mexico-born mothers^e</i>						
Retinoblastoma	1.04 (0.93, 1.17)	1.04 (0.93, 1.17)	0.96 (0.86, 1.08)	0.97 (0.86, 1.09)	0.96 (0.85, 1.09)	0.95 (0.84, 1.08)
Unilateral cases	1.03 (0.90, 1.20)	1.04 (0.90, 1.22)	0.91 (0.80, 1.05)	0.93 (0.81, 1.08)	0.99 (0.86, 1.17)	0.99 (0.85, 1.17)
Bilateral cases	1.06 (0.92, 1.25)	1.04 (0.89, 1.23)	1.02 (0.88, 1.22)	1.02 (0.87, 1.22)	0.93 (0.80, 1.10)	0.92 (0.78, 1.09)
Above mean exposure VS Below mean exposure^b						
<i>Among all mothers^d</i>						
Retinoblastoma	1.32 (0.91, 1.95)	1.29 (1.00, 1.67)	1.37 (0.97, 1.95)	1.16 (0.90, 1.50)	0.81 (0.58, 1.13)	0.79 (0.62, 1.02)
Unilateral cases	1.40 (1.03, 1.93)	1.42 (1.03, 1.97)	1.06 (0.78, 1.45)	1.10 (0.81, 1.51)	0.73 (0.54, 0.98)	0.73 (0.54, 0.99)
Bilateral cases	1.16 (0.84, 1.63)	1.14 (0.82, 1.62)	1.30 (0.92, 1.86)	1.29 (0.91, 1.85)	0.89 (0.64, 1.26)	0.88 (0.62, 1.25)
<i>Among US-born mothers^e</i>						
Retinoblastoma	1.28 (1.00, 1.65)	1.30 (0.89, 1.93)	1.15 (0.89, 1.48)	1.41 (1.00, 2.02)	0.79 (0.62, 1.02)	0.81 (0.58, 1.14)
Unilateral cases	1.69 (1.05, 2.85)	1.71 (1.04, 2.90)	1.33 (0.88, 2.06)	1.43 (0.94, 2.22)	0.80 (0.54, 1.19)	0.82 (0.54, 1.23)
Bilateral cases	1.01 (0.62, 1.67)	0.95 (0.58, 1.60)	1.45 (0.90, 2.38)	1.45 (0.90, 2.40)	0.82 (0.52, 1.29)	0.81 (0.51, 1.30)
<i>Among Mexico-born mothers^e</i>						

Retinoblastoma	1.68 (1.08, 2.64)	1.67 (1.06, 2.66)	0.74 (0.46, 1.20)	0.76 (0.47, 1.26)	0.78 (0.49, 1.29)	0.77 (0.46, 1.28)
Unilateral cases	1.43 (0.82, 2.52)	1.42 (0.80, 2.58)	0.53 (0.30, 0.96)	0.57 (0.31, 1.05)	0.70 (0.39, 1.30)	0.70 (0.38, 1.32)
Bilateral cases	2.08 (1.16, 3.84)	2.06 (1.12, 3.92)	1.13 (0.59, 2.28)	1.18 (0.61, 2.42)	0.90 (0.48, 1.76)	0.90 (0.46, 1.84)

Note:

^a The exposure assessment was based on the log2-transformed scale.

^b The exposures were dichotomized based on mean value of the log2-transformed PFAS feature intensities of all study population (N = 1,390)

^c The crude model was adjusted for birth year (matching factor)

^d The adjusted model was adjusted for birth year (matching factor), maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES

^e The adjusted model was adjusted for birth year (matching factor), maternal age, maternal race and ethnicity, maternal education attainment, census tract SES

Abbreviations: OR, odds ratio; CI, confidence interval; IQR, interquartile range; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctane sulfonic acid; PFOA, perfluorooctanoic Acid; PFNA, perfluorononanoic acid.

3 Maternal residential exposure to oil and gas development in California and the risk of childhood cancer

3.1 Abstract

Background

Oil and gas development (OGD) releases air pollutants that were previously linked to childhood cancer. A small number of studies have linked active OGD to childhood acute leukemia and central nervous system tumors. This study investigates associations between maternal residential exposure to oil and gas wells in pregnancy and the risk of childhood cancer in California.

Material and Methods

Cases were identified from the California Cancer Registry and controls were randomly selected from the California Birth Registry (20:1 frequency-matched by birth year: 1998-2016). We estimated exposure during pregnancy to any well (i.e., active or inactive) and inactive wells located within 1km and 3km of residences and also assessed low and high exposures according to the median well count within this proximity. We used unconditional logistic regression models to estimate cancer risks in the exposed (≥ 1 well, low/high exposure within 1 and 3km) compared to those considered unexposed (living within 3-10km of any well).

Results

The risk of medulloblastoma increased among children of mothers exposed to any well within 3km (≥ 1 well: adjusted Odds Ratio (aOR): 1.40; 95% confidence interval (CI): 1.08, 1.82; low, aOR = 1.27; 95% CI = 0.93, 1.74; high, aOR = 1.55; 95% CI = 1.14, 2.11). The risk of rhabdomyosarcoma consistently increased across the exposure levels of any well within 3km (≥ 1

well: aOR = 1.64; 95% CI = 1.28, 2.09; low, aOR = 1.69; 95% CI = 1.28, 2.23; high, aOR = 1.57; 95% CI = 1.16, 2.12). Similar associations were observed for teratoma with any well within 3km (≥ 1 well: aOR = 1.42; 95% CI = 0.99, 2.05; low, aOR = 1.35; 95% CI = 0.88, 2.07; high, aOR = 1.51; 95% CI = 0.98, 2.33). Overall, the results were consistent across the buffer sizes and no differences were found between any well and inactive wells.

Conclusions

Our study suggests that OGD may affect the risk of developing several types of rare childhood cancers.

3.2 Introduction

Approximately 17.6 million Americans live within 1 mile of an active oil and/or gas well,¹⁸⁵ while over 4.6 million live within 1 km of documented abandoned wells.¹⁸³ In California, many actively operated oil and natural gas wells are sited in the densely populated Los Angeles area, with 70% of active wells located within 500m of a home, school, or hospital.²⁷⁵ Approximately 1.7 million people live within 1 mile of an active oil and gas well in the Los Angeles Basin.²⁷⁶ A ban on new or reworked oil and gas wells located within 1km of residences was passed by the California legislature in September 2022.¹⁸⁷

Air toxics exposures during oil and gas development (OGD) are generated not only by the development of oil and gas sites and wells (production and injection for enhanced recovery), but also by the transport of materials, drilling, equipment operations, and waste disposal.¹⁷⁰ There has been a gradual decrease in California's crude oil and natural gas production since 1985.^{165, 277} Nevertheless, in 2023, California was still ranked the seventh-largest producer of crude oil among all US states.¹⁶⁴ Most of California's natural gas is extracted from reservoirs which also produce oil.¹⁶⁸

OGD produces multiple environmental hazards. Air emissions of toxics can occur at the wellhead, in controlled burns (flaring), from produced water storage pits and tanks, and by diesel-powered equipment and trucks.^{169, 171-173, 278} A review identified numerous air pollutants associated with unconventional OGD (i.e., the use of hydraulic fracturing techniques) including 1,3-butadiene, benzene, diesel exhaust, ethylbenzene, formaldehyde, hydrogen sulfide, methane, nitrogen oxides, ozone, and particulate matter (PM).²⁷⁹ Among the chemicals identified near

active wells, 1,3-butadiene,¹⁷⁴ benzene,¹⁷⁵ diesel exhaust,¹⁷⁶ and formaldehyde¹⁷⁷ are established carcinogens (Group 1), while ethylbenzene is a possible carcinogen (Group 2B).¹⁷⁸

California has a substantial number of abandoned wells including both plugged and unplugged abandoned (no longer in use; ~124,000) and idle wells (wells not producing, but capable of being reactivated; ~38,000).¹⁸⁰ Not all plugged wells have been properly plugged (i.e., permanently sealing the well with a cement plug to prevent leakage to the surface), and the true number of poorly plugged wells is difficult to estimate.^{180, 181} In Ventura County, California, a 2022 report found that 40% of more than 4000 abandoned wells were not properly plugged.¹⁸² Similarly, idle wells require proper closure to prevent the release of contaminants into the air.^{180,}
¹⁸¹ The same pollutants released from active wells can also be released from abandoned and idle wells.^{180, 183, 184}

Only two ecologic and two case-control studies have previously investigated OGD exposures and childhood cancer. An ecologic study in the Amazon basin of Ecuador found an increased risks of childhood leukemia in counties with compared with those without OGD, while a second ecologic study reported that central nervous system (CNS) tumor incidence increased after hydraulic fracturing drilling began in the same area.^{188, 189} Furthermore, a case-control study in Pennsylvania reported an elevated risk of acute lymphoblastic leukemia (ALL) among 2-7 year olds with a birth residence within 2 km of OGD activity.¹⁹⁰ A study in rural Colorado instead utilized the address at the time of diagnosis to assign exposure and only found increases in risk of ALL among cases aged 5-24 years, but it is difficult to interpret the results of this study because it used children diagnosed with other types of cancers as controls.¹⁹¹

To our knowledge, there are no published studies that considered OGD exposures in relation to other types of childhood cancer, despite that studies of exposure to the ambient air toxics released by OGD suggested increased risks of germ cell tumors, retinoblastoma, and Wilms tumor as well as leukemia and CNS tumor.²⁸⁰⁻²⁸⁵ Our study sought to explore the potential increase in the risks of various types of childhood cancer in offspring associated with maternal residential exposure to OGD in pregnancy. Furthermore, we aimed to evaluate whether cancers are increased within the 1km distance from OGD sites, as suggested by the California legislature, or if greater distances should be considered.

3.3 Methods

Study population

For this population-based case-control study,²⁸⁶ all childhood cancer cases diagnosed between 1983 and 2018 were ascertained from the California Cancer Registry. Using a probabilistic linkage program (LinkPlus; CDC, Atlanta, GA), 89% of cases were matched to a California birth certificate (births 1983-2016) by first and last names, dates of birth, and social security number if available. Cancers were classified according to the International Classification of Childhood Cancer, version 3 (ICCC-3) extended classification recode (**Table S3-1**). Controls were frequency-matched to cases by year of birth (20:1 matching ratio) but otherwise selected at random from among all California births.

Exposure assessment

We obtained active and inactive oil and gas well records including monthly production data from the California Department of Conservation, Geologic Energy Management Division (CalGEM).²⁸⁷ CalGEM began recording well information in 1915, but the earliest year of accessible production data was 1977. CalGEM data included the address of the well (latitude and

longitude) and monthly production volume (barrels of oil and/or cubic meters of natural gas). Production wells could transition between active and inactive status throughout the study period. To assign prenatal exposure to oil and gas wells, we integrated the geocoded well data with the residential addresses of children at birth, the conception date (i.e., the first date of the last menstrual period), and the date of birth.

Production data was not available for every well. For the wells with available production data, we defined well status (i.e., active or inactive) based on well production during the entire pregnancy period for each child. A production well was defined as active if it ever produced at least one unit of oil or natural gas during the entire pregnancy period. Otherwise, the well was considered inactive. When production data was not available for the well, we relied on the well status and spud date (i.e., when drilling begins) provided by CalGEM. If the spud date was later than the start date of our study period (i.e., the earliest conception date of our study population which was February 14, 1997) and preceded the date of a child's birth, and the well status was recorded as "active" or "new", we called it 'active'. Since all wells had a well status and approximately 51% of them had production data, we considered wells missing spud dates as having been drilled prior to our study period. In this case, 'missingness' was probably a result of inadequate documentation of wells drilled prior to 1977. If the spud date was missing or occurred prior to the study period, or the well status was "idle", "plugged" (permanently sealed and abandoned), "plugged only" (sealed but not yet abandoned), or "unknown", the well was considered inactive.

Because electronic birth certificates in California only included zip code information prior to 1998, we restricted our study to births with a full street address recorded, i.e. births between

1998 and 2016.²⁸⁸ Children with missing gestational age (N = 11038), nonviable or improbably long gestational age (<20 weeks or >45 weeks; N = 4556), nonviable or implausible birthweight (<500g or >6800g; N = 242), and children with missing sex information (N = 3) were excluded. We also excluded births to mothers living outside of 10km of any well during pregnancy (excluded N = 88981, 3.2% of the total population); i.e. all participants lived within 10km of at least one well (active or inactive type) (**Figure 1**).

We calculated the number of active wells, inactive wells, and any wells (i.e., inactive and active wells combined) located within 1km or 3km of a residential address at birth. We chose the 3km buffer because it was the smallest distance threshold that allowed for adequate statistical power for estimating effects for most cancer types. Furthermore, it has been suggested that beyond 3km, air toxics concentrations decrease to background levels due to dispersion.²⁷⁶ The restriction to the exposure within a 1km buffer was not only to investigate the distance suggested by California legislature but also because prior literature suggested that the strongest health risks with OGD-related exposures may occur within this distance.²⁸⁹⁻²⁹²

Statistical Analyses

To estimate the effects of exposures on childhood cancer risk, we performed unconditional logistic regression with adjustment for birth year (matching variable) and possible confounders. We examined the effects of exposure to at least one well (any type and inactive well) within 1km and 3km of the birth address during pregnancy on the risk of childhood cancer. In this study, we refer to any well as exposure to at least one well of any type (active or inactive), while we refer to inactive wells as the exposure to at least one inactive well. Because of the heavily right-skewed distribution of well counts, we further classified the exposure level by the median. Well counts above the median were classified as high exposed while non-zero well counts below the

median were classified as low exposed. We then estimated effects of high exposure and low exposure to any well and inactive wells on the risk of childhood cancer to explore potential exposure-response relationships.

There were 6245 cases and 120002 controls included in the 1km analyses of exposure, with the referent group as 3-10 km (i.e., with wells within 3-10 km but no wells within 3km of the birth address). In the analysis of residing within 3km, which also had the referent group as 3-10km, the sample size included 9487 cases and 183834 controls. We excluded pregnant mothers living outside the 10km buffer to reduce the potential for unmeasured confounding and enhance comparability of exposed and unexposed pregnancies.

For confounding adjustment, in addition to birth year, in our minimally adjusted model we included the source of payment for prenatal care (private insurance vs. Medi-Cal, other government source, self-pay, or military; this variable is a proxy for socioeconomic status),²⁹³ census-based neighborhood socioeconomic status (SES),²⁹⁴ census-tract population density, and residence in rural or urban area (as defined by the US Department of Agriculture).^{294, 295} These characteristics have been associated with childhood cancer and/or with oil and gas development.²⁹⁶⁻³⁰⁰ A directed acyclic graph (**Figure S3-1**) was constructed for confounder selection. In fully adjusted models, we additionally adjusted for maternal race and ethnicity, maternal age, and maternal education. As results were similar to the minimally adjusted models, we only reported results from the minimally adjusted models.

Because minorities are likely to be disproportionately affected by OGD and the risk of childhood cancer is known to vary by race and ethnicity,^{186, 301} whenever sample size allowed, we conducted stratified analysis by maternal race and ethnicity. As there were <10 exposed cases

observed among African American, Asian/ Pacific Islander, and Native American for most cancer types, the stratified analyses were limited to non-Hispanic White and Hispanic mothers.

Because traffic-related air pollution has previously been linked to elevated childhood cancer risks,³⁰² sensitivity analysis was performed by further controlling for residential exposure to traffic-related nitrogen oxides in ambient air in pregnancy among mothers for whom this information was available (mothers of births 1998-2007).⁹² However, we only had sufficient power to conduct this sensitivity analyses at the 3km distance.

In addition, we limited the exposed group to those living within 1-3km of any well in order to determine if the California legislature's 1km restriction is sufficient.

We further restricted to children with ALL aged 2-7 years at diagnosis to assess the risk associated with active wells, in order to compare our results with the case-control study in Pennsylvania.¹⁹⁰

Statistical analyses were completed using SAS 9.4 (SAS, Cary, NC). We reported results in each category when exposed cases were ≥ 10 . For stratified analysis by maternal race and ethnicity, we only reported results when exposed cases in each category were ≥ 10 in both non-Hispanic White and Hispanic groups.

3.4 Results

Mothers of cases were more likely to be 30 years of age and older compared to mothers of controls (**Table 3-1**). Parents of cases were more likely to be non-Hispanic White, use private insurance/HMO/Blue Cross Blue Shield, and were more likely to reside in census tracts with

higher socioeconomic status (SES) and lower population density, compared to controls. Other demographic and socioeconomic characteristics were similar in cases and controls.

Approximately 78% of all wells were inactive. Families living within 1km or 3km of any well were more likely to be from minority groups (i.e., Hispanic, Black), to use Medi-Cal/Other government/self-pay insurance, to reside in urban areas, and to reside in census tracts with either the lowest or the highest SES. Children were also more likely to be born low birthweight when mothers lived within 1km or 3km of any well (**Table 3-2**) or any inactive well (**Table S3-2**).

The risk of medulloblastoma increased among children of mothers exposed to any well within 3km (**Table S3-3, Figures 3-2 and 3-3**, adjusted Odds Ratio (aOR) = 1.40; 95% Confidence Interval (CI) = 1.08, 1.82). There was no notable difference between mothers with low and high exposure (low, aOR = 1.27; 95% CI = 0.93, 1.74; high, aOR = 1.55; 95% CI = 1.14, 2.11).

The risk of rhabdomyosarcoma increased among children of mothers exposed to any well within 3km (**Table S3-3, Figures 3-2 and 3-3**, aOR = 1.64; 95% CI = 1.28, 2.09) with increases across both exposure levels (low, aOR = 1.69; 95% CI = 1.28, 2.23; high, aOR = 1.57; 95% CI = 1.16, 2.12).

The risk of teratoma increased among children of mothers exposed to any well within 3km (**Table S3-3, Figures 3-2 and 3-3**, aOR = 1.42; 95% CI = 0.99, 2.05). When we stratified the exposure level, we observed similar increases in teratoma in mothers with low and high exposure (low, aOR = 1.35; 95% CI = 0.88, 2.07; high, aOR = 1.51; 95% CI = 0.98, 2.33).

We consistently observed inverse associations between neuroblastoma and any well within 3km at all exposure levels (**Table S3-3, Figures 3-2 and 3-3**, ≥ 1 well, aOR = 0.66; 95% CI = 0.51, 0.87; low, aOR = 0.63; 95% CI = 0.44, 0.90; high, aOR = 0.70; 95% CI = 0.50, 1.00)

For the above cancer types, we observed consistent associations across the buffer sizes (**Figures 3-2, 3-3, 3-4, 3-5**) (i.e., within 1km (**Tables S3-5 and S3-6**), 1-3km (**Tables S3-7 and S3-8**) and 3km (**Tables S3-3 and S3-4**)), and estimates were similar between any well (**Figures 3-2, 3-3**) and inactive wells (**Figures 3-4 and 3-5**).

The risk of retinoblastoma increased among children of mothers highly exposed to inactive well within 3km (**Tables S3-4, Figures 3-4 and 3-5**, low, aOR = 0.99; 95% CI = 0.72, 1.37; high: aOR = 1.32; 95% CI = 0.97, 1.81), although we did not observe an association between exposure to any well and the risk of retinoblastoma (**Table S3-3, Figures 3-2 and 3-3**).

Retinoblastoma was also not associated with exposure to any well (**Table S3-5, Figures 3-2 and 3-3**) or inactive wells (**Table S3-6, Figures 3-4 and 3-5**) within 1km.

The risk of osteosarcoma was weakly associated with exposure to any well within 3km (**Table S3-3, Figures 3-2 and 3-3**, aOR = 1.19; 95% CI = 0.86, 1.64), while the association was more evident among those with low exposure (low, aOR = 1.50; 95% CI = 1.06, 2.14; high, aOR = 0.83; 95% CI = 0.53, 1.29). Comparing inactive wells to any well within 3km, we observed consistent associations for exposure to at least one well and low exposure, while there was a moderate increase for those with high exposure to inactive wells (**Table S3-4, Figures 3-4 and 3-5**, ≥ 1 well: aOR = 1.37; 95% CI = 0.97, 1.97; low, aOR = 1.34; 95% CI = 0.89, 2.02; high, aOR = 1.40; 95% CI = 0.90, 2.17). However, osteosarcoma was not associated with any well

(**Table S3-5, Figures 3-2 and 3-3**) or inactive wells within 1km (**Table S3-6, Figures 3-4 and 3-5**).

Stratified analysis revealed that the risk of glioma varied for exposure within 1km between children of non-Hispanic White and Hispanic mothers. Within 1 km of any well, we observed an increase in the risk of glioma among children of non-Hispanic White mothers with high exposure only (**Table S3-9**, aOR = 1.41; 95% CI = 1.02, 1.94), but not among children of Hispanic mothers. However, results were null for both Hispanic and non-Hispanic White for exposure to any well within 3km.

The risk of retinoblastoma also varied between children of Hispanic and non-Hispanic White mothers. In children of Hispanic mothers, the risk of retinoblastoma consistently increased with the exposure to any well within 3km (**Table S3-10**, ≥ 1 well, aOR = 1.53; 95% CI = 1.11, 2.11; low, aOR = 1.49; 95% CI = 1.03, 2.15; high, aOR = 1.58; 95% CI = 1.08, 2.30). However, we did not see such associations in children of non-Hispanic White mothers. Estimates were similar when we examined the exposure to any well within 1km in Hispanic mothers, while we did not have sufficient power to estimate the risk among children of non-Hispanic White mothers within the same distance.

In addition, we found a moderate increase in the risk of non-Hodgkin lymphoma (NHL) among children of Hispanic mothers exposed to any well and those with high exposure within 1km (≥ 1 any well: aOR: 1.32; 95% CI: 0.89, 1.95; low: aOR: 1.23; 95% CI: 0.76, 2.01; high: aOR: 1.43; 95% CI: 0.86, 2.35), but we lacked sufficient exposed cases in children of non-Hispanic White mothers to assess the risk. Furthermore, we found no notable differences in NHL risk for the exposure within 3km between children of non-Hispanic White and Hispanic mothers.

Overall, we did not observe any difference in cancer risk in two racial and ethnic groups for the exposure to inactive wells (**Table S3-11 and S3-12**), compared to the results for exposure to any well within the same distance.

In sensitivity analyses further adjusting for residential exposure to nitrogen oxide levels in pregnancy, results did not change (**Table S3-13**). In sensitivity analyses done to compare to a previous study,¹⁹⁰ we did not find an association between ALL and exposure to active wells within 3km (≥ 1 active well: aOR: 0.96; 95% CI: 0.85, 1.09) among children aged 2-7 years, which was consistent across all three buffer sizes.

3.5 Discussion

In this population-based case-control study of various types of childhood cancers in California, we assessed OGD-related environmental pollution from inactive and active wells in pregnancy. We found increased risks of medulloblastoma, rhabdomyosarcoma and teratoma, with exposure to any type and inactive wells. Results for retinoblastoma and osteosarcoma were inconsistent. In 2022, California legislation prohibited new or reworked oil and gas wells within 1km of residences.¹⁸⁷ Our findings support this legislation and emphasize the importance of properly plugging and regulating inactive oil and gas wells within 1km of residences. Additionally, continued risk increases at the 1-3km distance suggest that a 3km buffer distance should be additionally considered for prevention of childhood cancers.

We did not find any associations with ALL, in contrast to a study in Pennsylvania that investigated active OGD sites only and found an elevated risk of ALL among children aged 2-7 living within 2km of the wells.¹⁹⁰ When we limited to children aged 2-7 years and examined the exposures to active wells for comparison with this study, we also found null associations. The

difference could be due to several reasons. First, that investigation had a different definition of the unexposed group (having no active wells within 2km), while our study defined children living within 3-10km of any well as unexposed. Second, their findings of an increased risk of ALL (aOR = 2.80; 95% CI = 1.11, 7.05) with perinatal exposure was based on only 7 exposed cases within 2km, while our study included 65 cases within 1km and 316 cases within 3km exposed to at least 1 active well for children in the same age range. Further, our study included far more inactive wells, and there are differences between active and inactive OGD sites (e.g., traffic-related pollution, noise, and excessive and inappropriate lighting).^{171, 184, 303} The presence and concentration of OGD-related air toxics (e.g., benzene) may also vary between and within US oil and gas reservoirs,²⁷⁶ which may also contribute to the observed differences in cancer risks between states.

The risk of medulloblastoma was consistently increased across all of our exposure measures. Although the Pennsylvania ecologic study suggested an increase in the risk of all CNS tumors in the area after hydraulic fracturing drilling began,¹⁸⁹ it is not comparable to our results because medulloblastoma only accounted for 12% of CNS tumor cases in our study. Prenatal exposures to air toxics including PAH has previously been found to increase the risk of medulloblastoma.²⁸³

Few studies have investigated environmental toxics in relation to rhabdomyosarcoma. In the two published studies that investigated rhabdomyosarcoma and traffic exposure, no associations were reported.^{91, 92} An increased risk of rhabdomyosarcoma was associated with residential proximity to factories emitting chemical pollution, however this study grouped chemicals together and relied on small numbers of exposed cases.⁵³

In stratified analysis, we found the risk of retinoblastoma increased among Hispanics only, while the risk of glioma increased among non-Hispanic Whites. In California, Hispanic and non-Hispanic Black individuals have higher exposure to several well types (i.e., active, long-idle, plugged and abandoned wells) than non-Hispanic White and non-Hispanic Asian individuals.¹⁸⁶ In our study, the prevalence of exposure to any wells and inactive wells was ~10% higher among highly exposed Hispanic mothers of children with retinoblastoma, compared to highly exposed non-Hispanic White mothers. This may have contributed to our observation of an elevated risk of retinoblastoma among children of Hispanic mothers only. Epidemiologic studies found that children of Hispanic origin have generally a lower risk of developing glioma than non-Hispanic White children.^{96, 296, 304} Yet, little is known about the underlying mechanisms for these glioma risk differences by Hispanic ethnicity.

Inverse associations between neuroblastoma and OGD exposure may result from unmeasured confounding or random errors. Maternal use of multivitamin has been extensively associated with childhood leukemia, brain tumors and neuroblastoma.³⁰⁵⁻³⁰⁹ In our study, we also observed the risk of childhood ALL, acute myeloid leukemia, and glioma might be associated with OGD exposure in a negative direction despite across null. The increased risk in medulloblastoma may suggest possible differences in genetic and histological features because a previous metabolomic study suggested that neuroblastoma was metabolically distinct from retinoblastoma and medulloblastoma, although they all originate from neuroectodermal tissue.^{162, 310} For the determinants of multivitamin use, although we attempted to adjust for maternal race and ethnicity, education and SES, we were not able to control for health behavior related factors such as alcohol intake and smoking, leading to possible unmeasured confounding.³¹¹⁻³¹⁵

Mothers' exposure to air pollution in pregnancy increases oxidative stress and induces genetic and epigenetic changes, possibly leading to a greater cancer risk in the offspring.³¹⁶ Our team previously found that maternal exposure to traffic-related air pollution in pregnancy contributes to oxidative stress and inflammation in newborn children.³¹⁷ Oxidative stress plays an important role in several cancers including childhood brain tumors such as glioma and medulloblastoma, and NHL.³¹⁸⁻³²³ The cord blood of newborns exposed to traffic-related air toxics in utero revealed bulky DNA adducts and micronuclei.³²⁴ Furthermore, biomarkers of genotoxicity biomarkers such as shortened telomere length, chromosomal aberrations, and micronucleus were increased in individuals exposed to traffic.³²⁵ All of these could be plausible biologic mechanisms for OGD-related air toxics affecting childhood cancer risk.

This population-based cohort which is large for a study of rare childhood cancers allowed us to examine several types of childhood cancer with an adequate sample size. The reliance on state records meant recall bias and selective study participation were avoided.

Our study may be subject to potential live birth bias if living closer to wells and having higher exposures to air toxics cause fetal loss in pregnant women.¹³⁹ Studies have reported elevated risks of stillbirth, infant death, and spontaneous abortion associated with exposure to OGD-related pollution³²⁶ or residential proximity of oil fields.³²⁷ In addition, we relied upon the child's address from the birth certificate, which could introduce exposure misclassification among families that moved in pregnancy. It is estimated that approximately 9-32% of pregnant mothers relocate during pregnancy with median distances moved ranging from 4.2-10km.³²⁸⁻³³¹ Given the low to moderate percentage of women expected to move in pregnancy, and those who do, moved within small distances, our 1 and 3 km exposure buffer likely captured the majority of

exposure to OGD near residences. Furthermore, exposure misclassification may have occurred in both cases and controls because the database may not have provided complete or accurate records of all OGD wells. Although we lacked the information for California, we may have underestimated the number of wells, suggested by studies in other states (e.g., the average percent error was 29-45% in Pennsylvania and Wyoming, comparing aeromagnetic surveys to the state database).³³² The resulting exposure misclassification would be nondifferential, likely biasing our estimates toward the null. We had planned to examine exposure to at least 1 active well and to explore exposure-response relations by production volume. However, we found that there were not enough active wells with records for production volumes available to closely examine the risk of childhood cancer. In addition, we did not examine wells producing crude oil and wells producing natural gas separately, because of the small number of wells producing natural gas.

Given California legislation that new or reworked oil and gas wells are banned within 1 km of residences,¹⁸⁷ our study re-emphasizes the importance of regulating oil and gas wells situated near residential areas. Furthermore, minority groups including Hispanics and Blacks are more likely to live within 1km of any well. The findings suggest OGD may affect the risk of developing several childhood cancers.

3.6 Figures and tables

Table 3-1. Demographic and socioeconomic characteristics of children born 1998-2016 in California

Characteristics	Cases N = 9487	Controls N = 183834
Child's sex, N (%)		
Male	5178 (54.6)	93500 (50.9)
Female	4309 (45.4)	90334 (49.1)
Maternal age, N (%)		
19 or less	751 (7.9)	17343 (9.4)
20-24 years old	1929 (20.3)	41458 (22.6)
25-29 years old	2448 (25.8)	49344 (26.8)
30-34 years old	2504 (26.4)	44754 (24.3)
35 and older	1855 (19.6)	30935 (16.8)
Maternal race and ethnicity, N (%)		
White non-Hispanic	2858 (30.1)	48954 (26.6)
Hispanic of any race	5186 (54.7)	100271 (54.5)
Black	405 (4.3)	11153 (6.1)
Asian/Pacific Islander	830 (8.8)	19470 (10.6)
American Indian	21 (0.2)	512 (0.3)
Other	72 (0.8)	1614 (0.9)
Missing	115	1860
Paternal race and ethnicity, N (%)		
White non-Hispanic	2791 (29.4)	47576 (25.9)
Hispanic of any race	4785 (50.4)	92631 (50.4)
Black	477 (5.0)	11896 (6.5)
Asian/Pacific Islander	726 (7.7)	16868 (9.2)
American Indian	20 (0.2)	424 (0.2)
Other	72 (0.8)	1498 (0.8)
Missing	616	12941
Source of payment for prenatal care, N (%)		
Private insurance/HMO/Blue Cross, Blue Shield	5177 (54.6)	87820 (47.8)
Medi-Cal/Other government/self-pay	4272 (45.0)	94900 (51.6)
Missing	38	1114
Residency in rural/urban area, N (%)		
Rural	320 (3.4)	6013 (3.3)
Urban	9166 (96.6)	177790 (96.7)
Missing	1	31
Census tract level socioeconomic status		
Lowest	2760 (29.1)	58620 (31.9)
Lower middle	2241 (23.6)	43749 (23.8)

Middle	1756 (18.5)	33216 (18.1)
Upper middle	1502 (15.8)	27265 (14.8)
Highest	1224 (12.9)	20912 (11.4)
Missing	4	72
Census tract population per square mile, (Mean +/- STD)	8830.2 +/- 8560.4	9317.6 +/- 8873.8
Age of cancer diagnosis, years (Mean +/- STD)	6.0 +/- 5.1	NA

Table 3-2. The distribution of demographic characteristics and pregnancy outcomes between cases and controls exposed to any well

	Cases, N = 9487			Controls, N = 183834		
	Within 1km	Within 3km	3-10km	Within 1km	Within 3km	3-10km
Maternal age, N (%)						
19 or less	132 (27.3)	400 (53.3)	351 (46.7)	2888 (26.0)	9135 (52.7)	8208 (47.3)
20-24 years old	316 (25.1)	988 (51.2)	941 (48.8)	6913 (25.8)	21553 (52.0)	19905 (48.0)
25-29 years old	424 (26.2)	1254 (51.2)	1194 (48.8)	8459 (26.1)	25421 (51.5)	23923 (48.5)
30-34 years old	411 (25.1)	1276 (51.0)	1228 (49)	8086 (27.6)	23514 (52.5)	21240 (47.5)
35 and older	336 (26.9)	943 (50.8)	912 (49.2)	5877 (28.8)	16432 (53.1)	14503 (46.9)
Maternal race and ethnicity, N (%)						
White non-Hispanic	441 (21.4)	1238 (43.3)	1620 (56.7)	7623 (21.8)	21648 (44.2)	27306 (55.8)
Hispanic of any race	934 (28.5)	2844 (54.8)	2342 (45.2)	18003 (28.7)	55578 (55.4)	44693 (44.6)
Black	83 (33.6)	241 (59.5)	164 (40.5)	2384 (33.0)	6319 (56.7)	4834 (43.3)
Asian/Pacific Islander	134 (25.3)	434 (52.3)	396 (47.7)	3615 (29.1)	10655 (54.7)	8815 (45.3)
American Indian	14 <5	7 (66.7)	72 (33.3)	233 (20.5)	279 (45.5)	279 (54.5)
Other	12 (25.5)	37 (51.4)	35 (48.6)	265 (23.4)	747 (46.3)	867 (53.7)
Source of payment for prenatal care, N (%)						
Private insurance/HMO/Blue Cross, Blue Shield	863 (24.9)	2573 (49.7)	2604 (50.3)	15401 (26)	44072 (50.2)	43748 (49.8)
Medi-Cal/Other government/self-pay	753 (27.4)	2275 (53.3)	1997 (46.8)	16655 (27.7)	51444 (54.2)	43456 (45.8)
Residency in rural/urban area, N (%)						
Rural	44 (18.4)	125 (39.1)	195 (60.9)	743 (16.7)	2306 (38.4)	3707 (61.6)
Urban	1575 (26.2)	4735 (51.7)	4431 (48.3)	31476 (27.2)	93732 (52.7)	84058 (47.3)
Census tract level socioeconomic status						

	518	1555	1205	11030	33765	24855
Lowest	(30.1)	(56.3)	(43.7)	(30.7)	(57.6)	(42.4)
	343	1168	1073	7015	22746	21003
Lower middle	(24.2)	(52.1)	(47.9)	(25.0)	(52.0)	(48.0)
	246	801	955	4761	15234	17982
Middle	(20.5)	(45.6)	(54.4)	(20.9)	(45.9)	(54.1)
	279	711	791	5023	13259	14006
Upper middle	(26.1)	(47.3)	(52.7)	(26.4)	(48.6)	(51.4)
	232	622	602	4385	11007	9905
Highest	(27.8)	(50.8)	(49.2)	(30.7)	(52.6)	(47.4)
Low birthweight (birthweight <2500g)	125	342	4323	2031	6126	5585
	(29.2)	(53.0)	(48.9)	(26.7)	(52.3)	(47.7)
	1494	4519	303	30192	89929	82194
No	(25.7)	(51.1)	(47.0)	(26.9)	(52.2)	(47.8)
	10	34	4586	287	858	715
Small-for-gestational-age	(20.0)	(45.9)	(48.7)	(28.6)	(54.5)	(45.5)
	1609	4827	303	31936	95197	87064
No	(26.0)	(51.3)	(47.0)	(26.8)	(52.2)	(47.8)
Preterm birth (gestational age <37 weeks)	188	564	4065	3371	10229	9149
	(25.1)	(50.1)	(48.6)	(26.9)	(52.8)	(47.2)
	1431	4297	40	28852	85826	78630
No	(26.0)	(51.4)	(54.1)	(26.8)	(52.2)	(47.8)
	41	127	4489	662	2097	2188
Pre-eclampsia or eclampsia	(23.0)	(48.1)	(48.7)	(23.2)	(48.9)	(51.1)
	1578	4734	561	31561	93958	85591
No	(26.0)	(51.3)	(49.9)	(26.9)	(52.3)	(47.7)
	24	77	3909	464	1508	1482
Pre-gestational diabetes	(21.2)	(46.4)	(48.2)	(23.8)	(50.4)	(49.6)
	1419	4193	137	27569	82050	74483
No	(26.6)	(51.8)	(51.9)	(27.0)	(52.4)	(47.6)
Gestational diabetes (available for births 2007+)	23	81	1314	431	1460	1636
	(18.4)	(44.3)	(48.8)	(20.9)	(47.2)	(52.8)
	497	1381	89	9249	27437	25896
No	(27.4)	(51.2)	(53.6)	(26.3)	(51.4)	(48.6)

Figure 3-1. Flow chart of study population for analysis

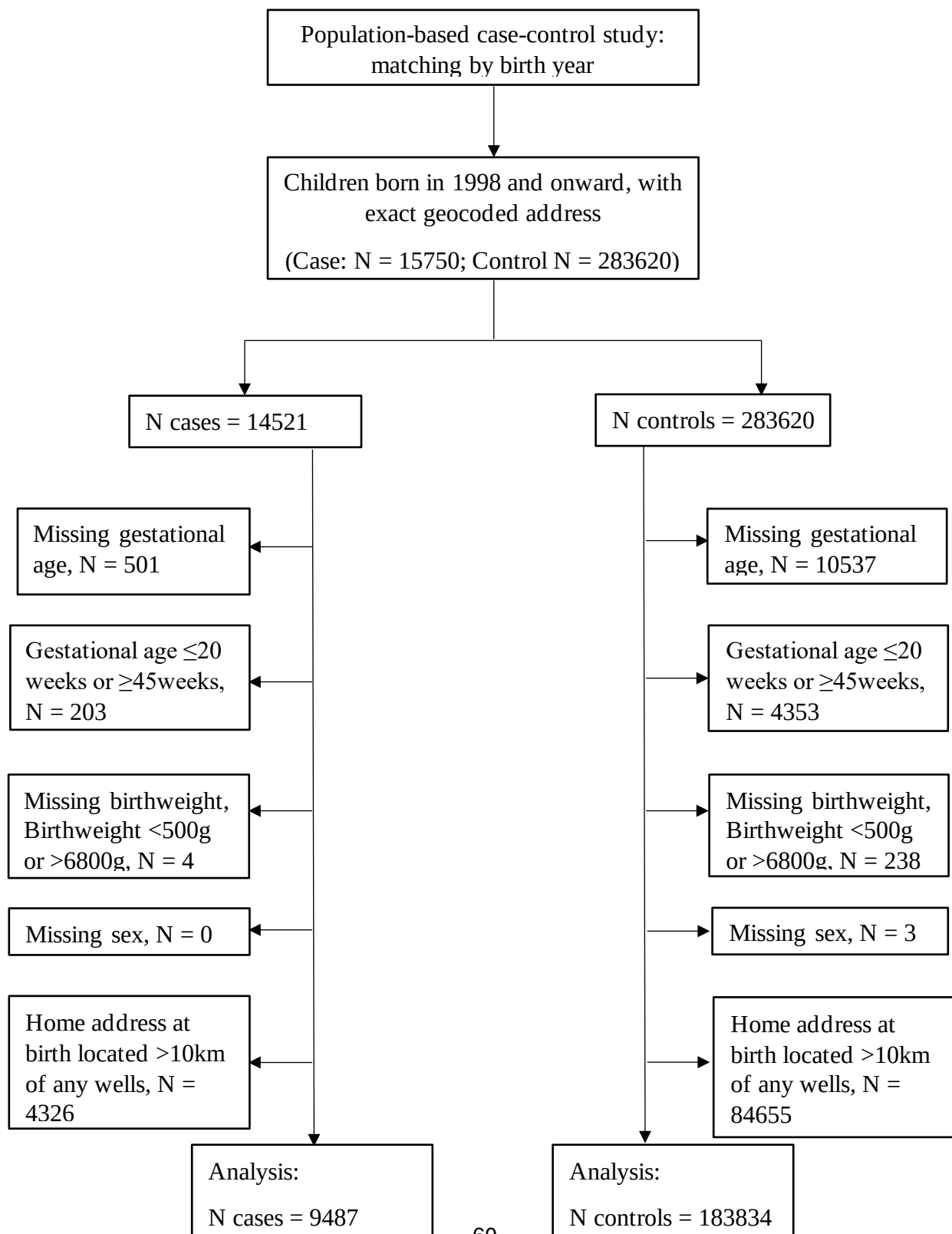


Figure 3-2. Childhood cancer risk associated with exposure to at least 1 any well

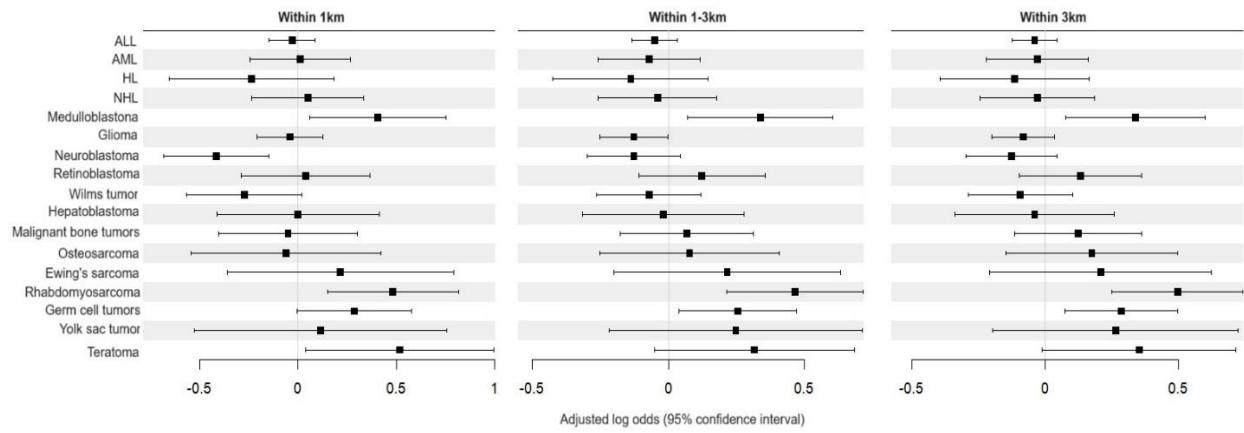


Figure 3-3. Childhood cancer risk associated with low/high exposure to any well

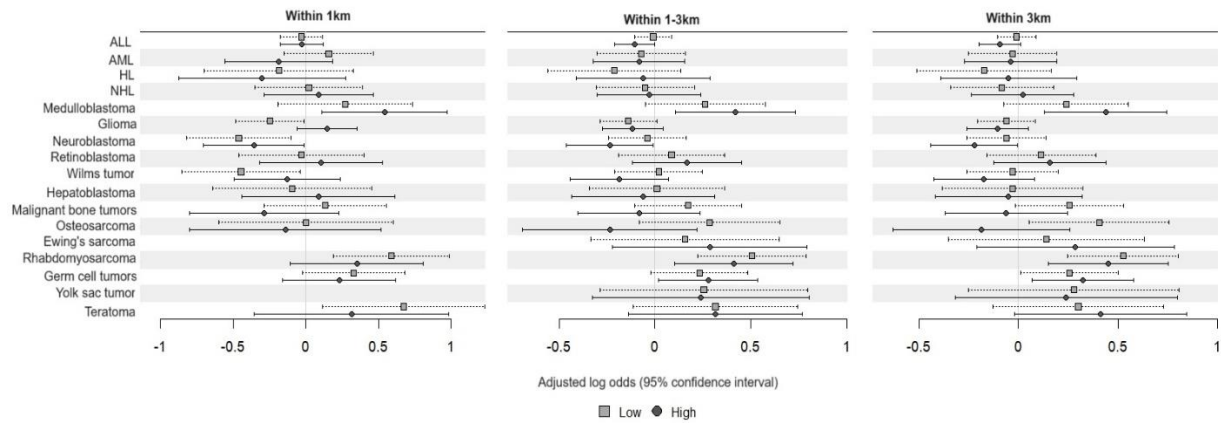


Figure 3-4. Childhood cancer risk associated with exposure to at least 1 inactive well

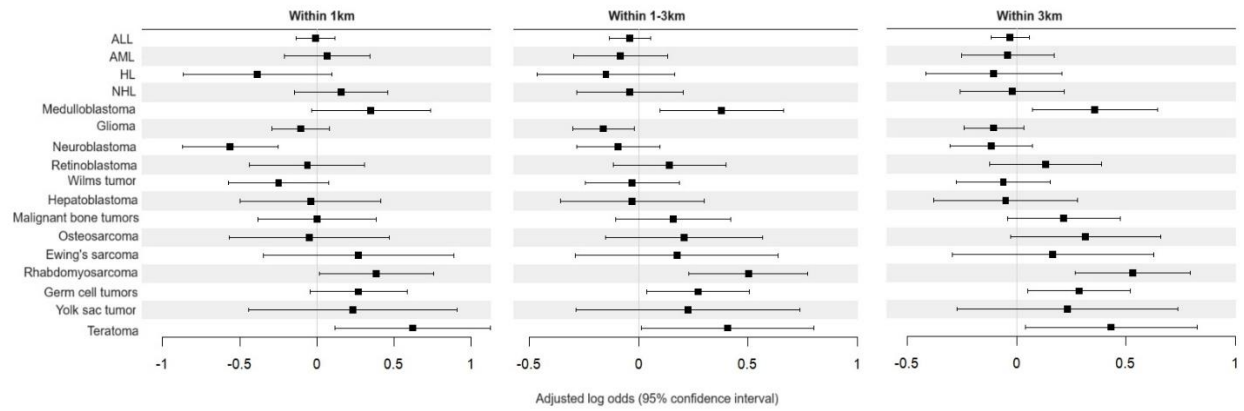
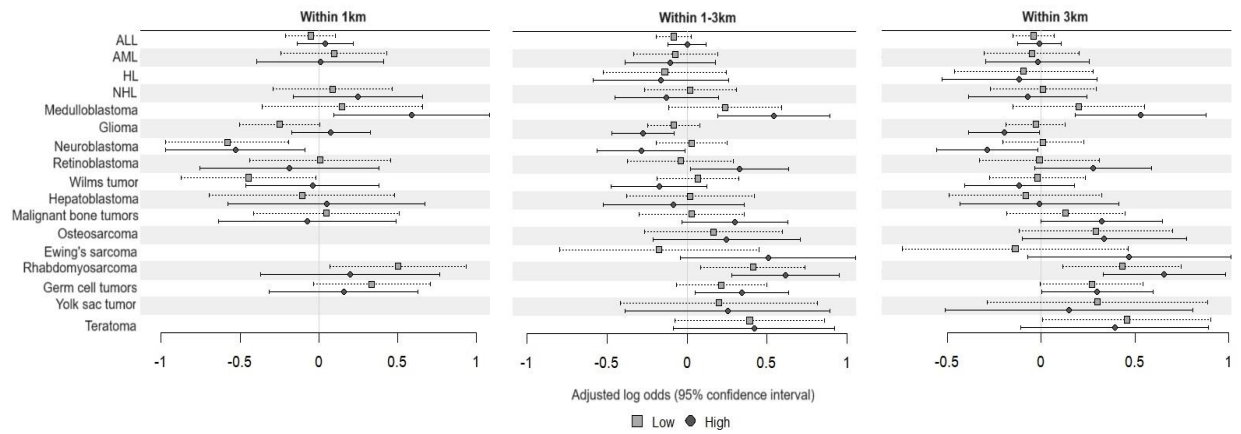


Figure 3-5. Childhood cancer risk associated with low/high exposure to inactive well



3.7 Supplementary materials

Table S3-1. National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program International Classification of Childhood Cancer (ICCC)

Disease	Code	Number of cases living within 10km of any well
Acute lymphoblastic leukemia ^a	001-004	2489
Acute myeloid leukemia ^a	005	463
Hodgkin lymphoma ^a	009	211
Non-Hodgkin lymphoma ^a	010-014	363
Glioma ^a	024-026	1134
Medulloblastoma ^a	020	243
Neuroblastoma ^a	033	565
Retinoblastoma ^a	035	310
Wilms tumor ^a	036	425
Hepatoblastoma ^a	042	182
Malignant bone tumors ^a	045-053	284
Osteosarcoma ^a	045	158
Ewing's sarcoma ^a	047	95
Rhabdomyosarcoma ^a	054	281
Germ cell tumors ^a	071-091	372
Yolk sac tumor ^b	9071	79
Teratoma ^b	9080-9084, 9090-9091	126

^a Based on Extended classification recodes

^b Based on International Classification of Diseases for Oncology, 3rd Edition (ICD-O) code

Table S3-2. The distribution of demographic characteristics and pregnancy outcomes between cases and controls exposed to inactive wells

	Cases, N = 9487			Controls, N = 183834		
	Within 1km	Within 3km	3-10km	Within 1km	Within 3km	3-10km
Maternal age, N (%)						
19 or less	105 (21.7)	256 (34.1)	351 (46.7)	2259 (20.4)	5761 (33.2)	8208 (47.3)
20-24 years old	239 (19.0)	634 (32.9)	941 (48.8)	5291 (19.7)	13746 (33.2)	19905 (48)
25-29 years old	330 (20.4)	801 (32.7)	1194 (48.8)	6566 (20.3)	16343 (33.1)	23923 (48.5)
30-34 years old	304 (18.5)	858 (34.3)	1228 (49.0)	6327 (21.6)	15179 (33.9)	21240 (47.5)
35 and older	261 (20.9)	645 (34.8)	912 (49.2)	4561 (22.4)	10550 (34.1)	14503 (46.9)
Maternal race and ethnicity, N (%)						
White non-Hispanic	334 (16.2)	823 (28.8)	1620 (56.7)	5815 (16.6)	14165 (28.9)	27306 (55.8)
Hispanic of any race	715 (21.8)	1831 (35.3)	2342 (45.2)	14043 (22.4)	35429 (35.3)	44693 (44.6)
Black	63 (25.5)	145 (35.8)	164 (40.5)	1829 (25.3)	3555 (31.9)	4834 (43.3)
Asian/Pacific Islander	104 (19.6)	319 (38.4)	396 (47.7)	2846 (22.9)	7212 (37.0)	8815 (45.3)
American Indian	7 <5	7 (33.3)	7 (33.3)	55 (15.7)	152 (29.7)	279 (54.5)
Other	9 (19.1)	28 (38.9)	35 (48.6)	205 (18.1)	469 (29.1)	867 (53.7)
Source of payment for prenatal care, N (%)						
Private insurance/HMO/Blue Cross, Blue Shield	663 (19.1)	1736 (33.5)	2604 (50.3)	11887 (20.1)	28618 (32.6)	43748 (49.8)
Medi-Cal/Other government/self-pay	573 (20.8)	1448 (33.9)	1997 (46.7)	12987 (21.6)	32578 (34.3)	43456 (45.8)
Residency in rural/urban area, N (%)						
Rural	21 (8.8)	69 (21.6)	195 (60.9)	501 (11.3)	1424 (23.7)	3707 (61.6)
Urban	1218 (20.3)	3124 (34.1)	4431 (48.3)	24499 (21.2)	60139 (33.8)	84058 (47.3)
Census tract level socioeconomic status						

	366	973	1205	8134	20514	24855
Lowest	(21.2)	(35.3)	(43.7)	(22.7)	(35.0)	(42.4)
	293	788	1073	6021	15354	21003
Lower middle	(20.7)	(35.2)	(47.9)	(21.5)	(35.1)	(48.0)
	185	549	955	3711	10325	17982
Middle	(15.4)	(31.3)	(54.4)	(16.3)	(31.1)	(54.1)
	215	475	791	3830	8362	14006
Upper middle	(20.1)	(31.6)	(52.7)	(20.1)	(30.7)	(51.4)
	179	406	602	3299	6996	9905
Highest	(21.5)	(33.2)	(49.2)	(23.1)	(33.5)	(47.4)
Low birthweight (birthweight <2500g)	99	208	303	1590	3902	5585
	(23.1)	(32.2)	(47.0)	(20.9)	(33.3)	(47.7)
	1140	2986	4323	23414	57677	82194
No	(19.6)	(33.8)	(48.9)	(20.8)	(33.5)	(47.8)
	9	23	40	219	515	715
Small-for-gestational-age	(18.0)	(31.1)	(54.1)	(21.9)	(32.7)	(45.5)
	1230	3171	4586	24785	61064	87064
No	(19.9)	(33.7)	(48.7)	(20.8)	(33.5)	(47.8)
Preterm birth (gestational age <37 weeks)	152	374	561	2652	6539	9149
	(20.3)	(33.2)	(49.9)	(21.2)	(33.7)	(47.2)
	1087	2820	4065	22352	55040	78630
No	(19.8)	(33.7)	(48.6)	(20.8)	(33.5)	(47.8)
	35	71	137	536	1434	2188
Pre-eclampsia or eclampsia	(19.7)	(26.9)	(51.9)	(18.8)	(33.5)	(51.1)
	1204	3123	4489	24468	60145	85591
No	(19.8)	(33.9)	(48.7)	(20.9)	(33.5)	(47.7)
	19	52	89	355	980	1482
Pre-gestational diabetes	(16.8)	(31.3)	(53.6)	(18.2)	(32.8)	(49.6)
	1072	2743	3909	21339	52339	74483
No	(20.1)	(33.9)	(48.2)	(20.9)	(33.4)	(47.6)
Gestational diabetes (available for births 2007+)	18	61	102	349	1044	1636
	(14.4)	(33.3)	(55.7)	(16.9)	(33.7)	(52.8)
	390	929	1314	7260	17726	25896
No	(21.5)	(34.5)	(48.8)	(20.7)	(33.2)	(48.6)

Table S3-3. Associations between exposures to any type of oil and gas wells during pregnancy within 3km of home addresses at birth and childhood cancers for births in CA, 1998 – 2016

Cancer type	Exposure category	Exposed cases, N (%)	Crude model, OR (95% CI) ^a	Adjusted model, OR (95% CI) ^b
Controls	≥1 wells	96055 (52.3)	Ref	Ref
	Low	48633 (26.5)	Ref	Ref
	High	47422 (25.8)	Ref	Ref
Acute lymphoblastic leukemia	≥1 wells	1270 (51.0)	0.95 (0.88, 1.03)	0.96 (0.88, 1.04)
	Low	668 (26.8)	0.99 (0.90, 1.09)	0.99 (0.90, 1.09)
	High	602 (24.2)	0.92 (0.83, 1.01)	0.91 (0.82, 1.01)
Acute myeloid leukemia	≥1 wells	238 (51.4)	0.97 (0.81, 1.17)	0.97 (0.80, 1.17)
	Low	120 (25.9)	0.97 (0.77, 1.21)	0.97 (0.78, 1.22)
	High	118 (25.5)	0.98 (0.78, 1.22)	0.96 (0.76, 1.21)
Hodgkin lymphoma	≥1 wells	102 (48.3)	0.84 (0.64, 1.10)	0.89 (0.67, 1.17)
	Low	50 (23.7)	0.81 (0.58, 1.13)	0.84 (0.60, 1.18)
	High	52 (24.6)	0.86 (0.62, 1.20)	0.95 (0.67, 1.33)
Non-Hodgkin lymphoma	≥1 wells	187 (51.5)	0.96 (0.78, 1.18)	0.97 (0.78, 1.20)
	Low	89 (24.5)	0.90 (0.70, 1.17)	0.92 (0.71, 1.19)
	High	98 (27.0)	1.02 (0.80, 1.30)	1.02 (0.79, 1.32)
Medulloblastoma	≥1 wells	143 (58.8)	1.31 (1.01, 1.69)	1.40 (1.08, 1.82)
	Low	68 (28.0)	1.23 (0.90, 1.67)	1.27 (0.93, 1.74)
	High	75 (30.9)	1.39 (1.03, 1.87)	1.55 (1.14, 2.11)
Glioma	≥1 wells	555 (48.9)	0.87 (0.78, 0.98)	0.92 (0.82, 1.04)
	Low	290 (25.6)	0.90 (0.78, 1.04)	0.94 (0.81, 1.08)
	High	265 (23.4)	0.85 (0.73, 0.98)	0.90 (0.77, 1.05)

Neuroblastoma	≥1 wells	274 (48.5)	0.87 (0.74, 1.03)	0.88 (0.74, 1.04)
	Low	149 (26.4)	0.93 (0.77, 1.14)	0.94 (0.77, 1.15)
	High	125 (22.1)	0.80 (0.65, 0.99)	0.80 (0.64, 0.99)
Retinoblastoma	≥1 wells	174 (56.1)	1.18 (0.94, 1.48)	1.14 (0.91, 1.44)
	Low	86 (27.7)	1.15 (0.88, 1.51)	1.12 (0.85, 1.47)
	High	88 (28.4)	1.21 (0.92, 1.58)	1.17 (0.88, 1.55)
Wilms tumor	≥1 wells	209 (49.2)	0.89 (0.74, 1.08)	0.91 (0.75, 1.11)
	Low	114 (26.8)	0.96 (0.76, 1.20)	0.97 (0.77, 1.22)
	High	95 (22.4)	0.82 (0.65, 1.05)	0.84 (0.65, 1.08)
Hepatoblastoma	≥1 wells	93 (51.1)	0.97 (0.72, 1.30)	0.96 (0.71, 1.29)
	Low	47 (25.8)	0.97 (0.68, 1.38)	0.97 (0.68, 1.38)
	High	46 (25.3)	0.97 (0.68, 1.39)	0.95 (0.66, 1.38)
Malignant bone tumors	≥1 wells	153 (53.9)	1.05 (0.83, 1.33)	1.13 (0.89, 1.43)
	Low	91 (32.0)	1.24 (0.95, 1.62)	1.29 (0.98, 1.69)
	High	62 (21.8)	0.86 (0.64, 1.17)	0.94 (0.69, 1.28)
Osteosarcoma	≥1 wells	87 (55.1)	1.10 (0.80, 1.51)	1.19 (0.86, 1.64)
	Low	57 (36.1)	1.43 (1.01, 2.02)	1.50 (1.06, 2.14)
	High	30 (19.0)	0.77 (0.50, 1.18)	0.83 (0.53, 1.29)
Ewing's sarcoma	≥1 wells	53 (55.8)	1.14 (0.76, 1.71)	1.23 (0.81, 1.86)
	Low	26 (27.4)	1.11 (0.68, 1.81)	1.15 (0.70, 1.88)
	High	27 (28.4)	1.18 (0.73, 1.91)	1.33 (0.81, 2.19)
Rhabdomyosarcoma	≥1 wells	176 (62.6)	1.53 (1.20, 1.94)	1.64 (1.28, 2.09)

Germ cell tumors	Low	96 (34.2)	1.64 (1.25, 2.17)	1.69 (1.28, 2.23)
	High	80 (28.5)	1.40 (1.05, 1.88)	1.57 (1.16, 2.12)
	≥1 wells	219 (58.9)	1.30 (1.06, 1.60)	1.33 (1.08, 1.65)
	Low	108 (29.0)	1.27 (0.99, 1.62)	1.29 (1.01, 1.65)
Yolk sac tumor	High	111 (29.8)	1.33 (1.04, 1.70)	1.38 (1.07, 1.78)
	≥1 wells	47 (59.5)	1.35 (0.86, 2.12)	1.30 (0.82, 2.06)
	Low	24 (30.4)	1.36 (0.80, 2.32)	1.32 (0.78, 2.25)
	High	23 (29.1)	1.34 (0.79, 2.29)	1.27 (0.73, 2.23)
Teratoma	≥1 wells	76 (60.3)	1.39 (0.97, 1.98)	1.42 (0.99, 2.05)
	Low	37 (29.4)	1.34 (0.87, 2.04)	1.35 (0.88, 2.07)
	High	39 (31.0)	1.44 (0.95, 2.19)	1.51 (0.98, 2.33)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, the matching variable

^b Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density

Table S3-4. Associations between exposures to inactive oil and gas wells during pregnancy within 3km of home addresses at birth and childhood cancers for births in CA, 1998 – 2016

Cancer type	Exposure category	Exposed cases, N (%)	Crude model, OR (95% CI) ^a	Adjusted model, OR (95% CI) ^b
Controls	≥1 wells	61579 (41.2)	Ref	Ref
	Low	34029 (22.8)	Ref	Ref
	High	27550 (18.5)	Ref	Ref
Acute lymphoblastic leukemia	≥1 wells	828 (40.4)	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)
	Low	450 (22.0)	0.95 (0.86, 1.06)	0.96 (0.86, 1.07)
	High	378 (18.5)	0.99 (0.88, 1.11)	0.99 (0.88, 1.11)
Acute myeloid leukemia	≥1 wells	151 (40.2)	0.96 (0.78, 1.18)	0.96 (0.78, 1.19)
	Low	82 (21.8)	0.94 (0.73, 1.21)	0.95 (0.74, 1.23)
	High	69 (18.4)	0.98 (0.75, 1.28)	0.98 (0.74, 1.29)
Hodgkin lymphoma	≥1 wells	67 (38.1)	0.87 (0.64, 1.17)	0.90 (0.66, 1.23)
	Low	38 (21.6)	0.89 (0.61, 1.28)	0.91 (0.63, 1.32)
	High	29 (16.5)	0.84 (0.56, 1.27)	0.89 (0.59, 1.35)
Non-Hodgkin lymphoma	≥1 wells	120 (40.5)	0.97 (0.77, 1.22)	0.98 (0.77, 1.24)
	Low	68 (23.0)	0.99 (0.75, 1.31)	1.01 (0.76, 1.34)
	High	52 (17.6)	0.94 (0.69, 1.28)	0.93 (0.68, 1.28)
Medulloblastoma	≥1 wells	95 (48.7)	1.35 (1.02, 1.79)	1.43 (1.07, 1.90)
	Low	46 (23.6)	1.19 (0.84, 1.68)	1.22 (0.86, 1.74)
	High	49 (25.1)	1.56 (1.11, 2.20)	1.70 (1.20, 2.42)
Glioma	≥1 wells	351 (37.7)	0.86 (0.76, 0.99)	0.90 (0.79, 1.04)
	Low	212 (22.8)	0.94 (0.81, 1.11)	0.97 (0.83, 1.14)
	High	139 (14.9)	0.77 (0.64, 0.92)	0.82 (0.67, 0.98)

Neuroblastoma	≥1 wells	179 (38.1)	0.88 (0.73, 1.06)	0.89 (0.74, 1.08)
	Low	112 (23.8)	1.00 (0.80, 1.24)	1.01 (0.81, 1.25)
	High	67 (14.3)	0.74 (0.56, 0.96)	0.75 (0.57, 0.98)
Retinoblastoma	≥1 wells	112 (45.2)	1.18 (0.92, 1.51)	1.14 (0.88, 1.47)
	Low	53 (21.4)	1.01 (0.74, 1.39)	0.99 (0.72, 1.37)
	High	59 (23.8)	1.39 (1.02, 1.88)	1.32 (0.97, 1.81)
Wilms tumor	≥1 wells	141 (39.5)	0.93 (0.76, 1.16)	0.94 (0.76, 1.17)
	Low	81 (22.7)	0.97 (0.75, 1.26)	0.98 (0.76, 1.27)
	High	60 (16.8)	0.89 (0.67, 1.18)	0.89 (0.66, 1.19)
Hepatoblastoma	≥1 wells	61 (40.7)	0.98 (0.71, 1.36)	0.95 (0.69, 1.33)
	Low	32 (21.3)	0.94 (0.63, 1.40)	0.92 (0.61, 1.38)
	High	29 (19.3)	1.04 (0.68, 1.58)	0.99 (0.65, 1.52)
Malignant bone tumors	≥1 wells	110 (45.6)	1.19 (0.92, 1.53)	1.24 (0.96, 1.61)
	Low	56 (23.2)	1.09 (0.80, 1.50)	1.14 (0.83, 1.56)
	High	54 (22.4)	1.31 (0.95, 1.80)	1.38 (1.00, 1.91)
Osteosarcoma	≥1 wells	64 (47.4)	1.27 (0.91, 1.79)	1.37 (0.97, 1.93)
	Low	35 (25.9)	1.26 (0.84, 1.89)	1.34 (0.89, 2.02)
	High	29 (21.5)	1.29 (0.84, 1.99)	1.40 (0.90, 2.17)
Ewing's sarcoma	≥1 wells	34 (44.7)	1.15 (0.73, 1.81)	1.18 (0.75, 1.88)
	Low	14 (18.4)	0.85 (0.47, 1.57)	0.87 (0.48, 1.60)
	High	20 (26.3)	1.51 (0.89, 2.58)	1.60 (0.93, 2.76)
Rhabdomyosarcoma	≥1 wells	121 (53.5)	1.64 (1.26, 2.13)	1.70 (1.31, 2.22)

Germ cell tumors	Low		1.49 (1.09, 2.05)	1.54 (1.12, 2.11)
	High	61 (27.0)	1.82 (1.32, 2.50)	1.93 (1.39, 2.68)
	≥1 wells	60 (26.5)	1.34 (1.06, 1.68)	1.33 (1.05, 1.68)
		144 (48.5)		
Yolk sac tumor	Low		1.31 (1.00, 1.72)	1.31 (1.00, 1.73)
	High	78 (26.3)	1.37 (1.03, 1.83)	1.35 (1.00, 1.81)
	≥1 wells	66 (22.2)	1.34 (0.81, 2.21)	1.26 (0.76, 2.09)
		30 (48.4)		
Teratoma	Low		1.38 (0.76, 2.48)	1.35 (0.75, 2.43)
	High	17 (27.4)	1.30 (0.68, 2.47)	1.16 (0.60, 2.25)
	≥1 wells	13 (21.0)	1.54 (1.05, 2.26)	1.54 (1.04, 2.28)
		54 (51.9)		
	Low		1.60 (1.02, 2.50)	1.58 (1.01, 2.48)
	High	31 (29.8)	1.47 (0.89, 2.40)	1.48 (0.90, 2.46)
		23 (22.1)		

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, the matching variable

^b Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density

Table S3-5. Associations between exposures to any type of oil and gas wells during pregnancy within 1km of home addresses at birth and childhood cancers for births in CA, 1998 – 2016

Cancer type	Exposure category	Exposed cases, N (%)	Crude model, OR (95% CI) ^a	Adjusted model, OR (95% CI) ^b
Controls	≥1 wells	32223 (26.9)	Ref	Ref
	Low	16437 (13.7)	Ref	Ref
	High	15786 (13.2)	Ref	Ref
Acute lymphoblastic leukemia	≥1 wells	437 (26.4)	0.98 (0.88, 1.09)	0.97 (0.86, 1.09)
	Low	221 (13.3)	0.97 (0.84, 1.12)	0.97 (0.84, 1.12)
	High	216 (13.0)	0.99 (0.85, 1.14)	0.97 (0.84, 1.13)
Acute myeloid leukemia	≥1 wells	86 (27.7)	1.05 (0.82, 1.34)	1.01 (0.78, 1.30)
	Low	50 (16.1)	1.20 (0.88, 1.62)	1.17 (0.86, 1.59)
	High	36 (11.6)	0.89 (0.63, 1.27)	0.83 (0.57, 1.20)
Hodgkin lymphoma	≥1 wells	31 (22.1)	0.75 (0.51, 1.12)	0.79 (0.52, 1.20)
	Low	17 (12.1)	0.80 (0.48, 1.34)	0.83 (0.50, 1.40)
	High	14 (10.0)	0.70 (0.40, 1.22)	0.74 (0.42, 1.32)
Non-Hodgkin lymphoma	≥1 wells	71 (28.7)	1.08 (0.82, 1.43)	1.05 (0.79, 1.40)
	Low	34 (13.8)	1.01 (0.70, 1.46)	1.02 (0.70, 1.47)
	High	37 (15.0)	1.16 (0.81, 1.65)	1.09 (0.75, 1.59)
Medulloblastoma	≥1 wells	51 (33.8)	1.39 (0.99, 1.95)	1.50 (1.06, 2.13)
	Low	23 (15.2)	1.23 (0.78, 1.93)	1.31 (0.82, 2.07)
	High	28 (18.5)	1.56 (1.02, 2.37)	1.72 (1.12, 2.65)
Glioma	≥1 wells	198 (25.5)	0.93 (0.79, 1.09)	0.96 (0.81, 1.13)
	Low	80 (10.3)	0.74 (0.58, 0.93)	0.78 (0.61, 0.98)
	High	118 (15.2)	1.13 (0.93, 1.38)	1.16 (0.94, 1.42)

Neuroblastoma	≥1 wells	73 (20.1)	0.69 (0.53, 0.89)	0.66 (0.51, 0.87)
	Low	34 (9.3)	0.63 (0.44, 0.90)	0.63 (0.44, 0.90)
	High	39 (10.7)	0.75 (0.54, 1.05)	0.70 (0.50, 1.00)
Retinoblastoma	≥1 wells	53 (0028.0)	1.07 (0.78, 1.47)	1.04 (0.75, 1.44)
	Low	25 (13.2)	1.00 (0.65, 1.53)	0.97 (0.63, 1.49)
	High	28 (14.8)	1.15 (0.77, 1.73)	1.11 (0.73, 1.70)
Wilms tumor	≥1 wells	62 (22.3)	0.79 (0.60, 1.05)	0.76 (0.56, 1.01)
	Low	26 (9.4)	0.65 (0.43, 0.98)	0.64 (0.43, 0.97)
	High	36 (12.9)	0.93 (0.66, 1.33)	0.88 (0.61, 1.27)
Hepatoblastoma	≥1 wells	33 (27.0)	1.02 (0.69, 1.53)	1.00 (0.66, 1.51)
	Low	15 (12.3)	0.92 (0.53, 1.59)	0.91 (0.53, 1.59)
	High	18 (14.8)	1.14 (0.68, 1.88)	1.09 (0.64, 1.84)
Malignant bone tumors	≥1 wells	44 (25.1)	0.90 (0.64, 1.27)	0.95 (0.67, 1.36)
	Low	27 (15.4)	1.08 (0.71, 1.63)	1.14 (0.75, 1.74)
	High	17 (9.7)	0.71 (0.43, 1.18)	0.75 (0.45, 1.26)
Osteosarcoma	≥1 wells	24 (25.3)	0.90 (0.57, 1.43)	0.94 (0.58, 1.52)
	Low	13 (13.7)	0.95 (0.53, 1.72)	1.00 (0.55, 1.83)
	High	11 (11.6)	0.85 (0.45, 1.60)	0.87 (0.45, 1.68)
Ewing's sarcoma ^c	≥1 wells	17 (28.8)	1.09 (0.62, 1.91)	1.24 (0.70, 2.22)
Rhabdomyosarcoma	≥1 wells	57 (35.2)	1.47 (1.07, 2.03)	1.62 (1.16, 2.26)
	Low	33 (20.4)	1.67 (1.13, 2.47)	1.80 (1.21, 2.68)
	High	24 (14.8)	1.27 (0.81, 1.97)	1.42 (0.90, 2.24)

Germ cell tumors	≥1 wells		1.31 (0.99, 1.72)	1.33 (0.99, 1.77)
		74 (32.6)		
	Low	40 (17.6)	1.38 (0.97, 1.95)	1.39 (0.98, 1.98)
	High	34 (15.0)	1.23 (0.85, 1.78)	1.26 (0.85, 1.85)
Yolk sac tumor ^c	≥1 wells	15 (31.9)	1.30 (0.70, 2.40)	1.12 (0.59, 2.13)
Teratoma	≥1 wells	28 (35.9)	1.52 (0.96, 2.42)	1.68 (1.04, 2.71)
	Low	17 (21.8)	1.81 (1.04, 3.14)	1.96 (1.12, 3.42)
	High	11 (14.1)	1.22 (0.64, 2.35)	1.37 (0.70, 2.67)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, the matching variable

^b Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density

^c The results for low/high exposure were not reported because the number of exposed cases was less than 10

Table S3-6. Associations between exposures to inactive oil and gas wells during pregnancy within 1km of home addresses at birth and childhood cancers for births in CA, 1998 – 2016

Cancer type	Exposure category	Exposed cases, N (%)	Crude model, OR (95% CI) ^a	Adjusted model, OR (95% CI) ^b
Controls	≥1 wells	25004 (22.2)	Ref	Ref
	Low	14428 (12.8)	Ref	Ref
	High	10576 (9.4)	Ref	Ref
Acute lymphoblastic leukemia	≥1 wells	342 (21.9)	0.99 (0.87, 1.11)	0.99 (0.87, 1.12)
	Low	189 (12.1)	0.95 (0.81, 1.10)	0.95 (0.81, 1.11)
	High	153 (9.8)	1.04 (0.88, 1.23)	1.04 (0.87, 1.24)
Acute myeloid leukemia	≥1 wells	70 (23.7)	1.10 (0.84, 1.43)	1.07 (0.81, 1.41)
	Low	41 (13.9)	1.12 (0.80, 1.56)	1.10 (0.79, 1.54)
	High	29 (9.8)	1.07 (0.73, 1.57)	1.01 (0.68, 1.52)
Hodgkin lymphoma ^c	≥1 wells	21 (16.2)	0.66 (0.42, 1.06)	0.68 (0.42, 1.10)
Non-Hodkin lymphoma	≥1 wells	62 (26.1)	1.23 (0.92, 1.64)	1.17 (0.87, 1.59)
	Low	32 (13.4)	1.09 (0.74, 1.58)	1.09 (0.75, 1.60)
	High	30 (12.6)	1.42 (0.96, 2.09)	1.28 (0.85, 1.93)
Medulloblastoma	≥1 wells	38 (27.5)	1.34 (0.92, 1.94)	1.42 (0.97, 2.09)
	Low	18 (13.0)	1.10 (0.66, 1.81)	1.16 (0.70, 1.93)
	High	20 (14.5)	1.66 (1.03, 2.68)	1.80 (1.10, 2.96)
Glioma	≥1 wells	142 (19.7)	0.86 (0.72, 1.03)	0.90 (0.75, 1.09)
	Low	69 (9.6)	0.73 (0.56, 0.93)	0.78 (0.60, 1.00)
	High	73 (10.1)	1.05 (0.82, 1.34)	1.08 (0.84, 1.38)
Neuroblastoma	≥1 wells	50 (14.7)	0.61 (0.45, 0.82)	0.57 (0.42, 0.78)
	Low	27 (7.9)	0.57 (0.39, 0.85)	0.56 (0.38, 0.83)

Retinoblastoma	High	23 (6.7)	0.65 (0.43, 1.00)	0.59 (0.38, 0.92)
	≥1 wells	37 (21.4)	0.96 (0.67, 1.39)	0.94 (0.65, 1.37)
	Low	23 (13.3)	1.05 (0.67, 1.63)	1.01 (0.65, 1.59)
Wilms tumor	High	14 (8.1)	0.85 (0.49, 1.48)	0.83 (0.47, 1.47)
	≥1 wells	50 (18.8)	0.82 (0.60, 1.11)	0.78 (0.56, 1.07)
	Low	23 (8.6)	0.66 (0.43, 1.01)	0.64 (0.42, 0.99)
Hepatoblastoma	High	27 (10.2)	1.03 (0.69, 1.54)	0.96 (0.63, 1.46)
	≥1 wells	25 (21.9)	1.00 (0.64, 1.55)	0.96 (0.61, 1.52)
	Low	13 (11.4)	0.91 (0.51, 1.63)	0.90 (0.50, 1.62)
Malignant bone tumors	High	12 (10.5)	1.11 (0.61, 2.03)	1.05 (0.56, 1.95)
	≥1 wells	36 (21.6)	0.96 (0.66, 1.38)	1.00 (0.68, 1.46)
	Low	22 (13.2)	1.00 (0.64, 1.57)	1.05 (0.66, 1.66)
Osteosarcoma ^c	High	14 (8.4)	0.89 (0.51, 1.55)	0.93 (0.53, 1.63)
	≥1 wells	19 (21.1)	0.93 (0.56, 1.54)	0.95 (0.57, 1.61)
	Ewing's sarcoma ^c	14 (25.0)	1.16 (0.63, 2.13)	1.31 (0.71, 2.44)
Rhabdomyosarcoma	≥1 wells	41 (28.1)	1.37 (0.95, 1.96)	1.47 (1.02, 2.14)
	Low	27 (18.5)	1.55 (1.02, 2.37)	1.65 (1.07, 2.54)
	High	14 (9.6)	1.11 (0.63, 1.94)	1.22 (0.69, 2.15)
Germ cell tumors	≥1 wells	57 (27.1)	1.30 (0.96, 1.76)	1.31 (0.96, 1.80)
	Low	36 (17.1)	1.42 (0.98, 2.04)	1.40 (0.97, 2.03)
	High	21 (10.0)	1.14 (0.72, 1.80)	1.17 (0.73, 1.88)
Yolk sac tumor ^c	≥1 wells	13 (28.9)	1.44 (0.76, 2.75)	1.26 (0.64, 2.47)

Teratoma ^c	≥1 wells	24 (32.4)	1.68 (1.03, 2.74)	1.86 (1.12, 3.07)
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Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, the matching variable

^b Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density

^c The results for low/high exposure were not reported because the number of exposed cases was less than 10

Table S3-7. Associations between exposures to any oil and gas wells during pregnancy within 1-3km of home addresses at birth and childhood cancers for births in CA,1998 – 2016

Cancer type	Exposure category	Exposed cases, N (%)	Crude model, OR (95% CI) ^a	Adjusted model, OR (95% CI) ^b
Controls	≥1 wells	93664 (51.6)	Ref	Ref
	Low	47732 (26.3)	Ref	Ref
	High	45932 (25.3)	Ref	Ref
Acute lymphoblastic leukemia	≥1 wells	1232 (50.3)	0.95 (0.88, 1.03)	0.95 (0.87, 1.03)
	Low	655 (26.7)	0.99 (0.90, 1.09)	0.99 (0.90, 1.09)
	High	577 (23.5)	0.91 (0.82, 1.00)	0.90 (0.81, 1.00)
Acute myeloid leukemia	≥1 wells	231 (50.7)	0.97 (0.80, 1.16)	0.93 (0.77, 1.12)
	Low	117 (25.7)	0.96 (0.77, 1.20)	0.93 (0.74, 1.17)
	High	114 (25.0)	0.97 (0.78, 1.22)	0.92 (0.72, 1.16)
Hodgkin lymphoma	≥1 wells	98 (47.3)	0.82 (0.63, 1.08)	0.87 (0.65, 1.15)
	Low	48 (23.2)	0.79 (0.57, 1.11)	0.81 (0.57, 1.14)
	High	50 (24.2)	0.86 (0.61, 1.20)	0.94 (0.66, 1.33)
Non-Hodgkin lymphoma	≥1 wells	184 (51.1)	0.97 (0.79, 1.19)	0.96 (0.77, 1.19)
	Low	92 (25.6)	0.95 (0.74, 1.23)	0.95 (0.73, 1.22)
	High	92 (25.6)	0.99 (0.77, 1.27)	0.97 (0.74, 1.27)
Medulloblastoma	≥1 wells	140 (58.3)	1.31 (1.02, 1.70)	1.40 (1.07, 1.82)
	Low	68 (28.3)	1.25 (0.92, 1.70)	1.30 (0.95, 1.77)
	High	72 (30.0)	1.38 (1.02, 1.86)	1.52 (1.11, 2.08)
Glioma	≥1 wells	535 (48.0)	0.86 (0.77, 0.97)	0.88 (0.78, 1.00)
	Low	275 (24.7)	0.87 (0.76, 1.01)	0.87 (0.75, 1.01)
	High	260 (23.3)	0.86 (0.74, 0.99)	0.89 (0.76, 1.04)

Neuroblastoma	≥1 wells	269 (48.0)	0.88 (0.74, 1.03)	0.88 (0.74, 1.04)
	Low	148 (26.4)	0.94 (0.77, 1.15)	0.96 (0.78, 1.17)
	High	121 (21.6)	0.80 (0.65, 0.99)	0.79 (0.63, 0.99)
Retinoblastoma	≥1 wells	169 (55.4)	1.17 (0.94, 1.47)	1.13 (0.90, 1.43)
	Low	82 (26.9)	1.12 (0.85, 1.47)	1.09 (0.83, 1.44)
	High	87 (28.5)	1.23 (0.94, 1.61)	1.18 (0.89, 1.57)
Wilms tumor	≥1 wells	208 (49.1)	0.91 (0.75, 1.10)	0.93 (0.77, 1.13)
	Low	117 (27.6)	1.00 (0.80, 1.26)	1.02 (0.81, 1.28)
	High	91 (21.5)	0.81 (0.64, 1.04)	0.83 (0.64, 1.07)
Hepatoblastoma	≥1 wells	92 (50.8)	0.98 (0.73, 1.32)	0.98 (0.73, 1.32)
	Low	48 (26.5)	1.01 (0.71, 1.43)	1.01 (0.71, 1.44)
	High	44 (24.3)	0.96 (0.67, 1.38)	0.94 (0.65, 1.37)
Malignant bone tumors	≥1 wells	147 (52.9)	1.04 (0.82, 1.31)	1.07 (0.84, 1.37)
	Low	87 (31.3)	1.21 (0.92, 1.58)	1.19 (0.90, 1.57)
	High	60 (21.6)	0.86 (0.64, 1.17)	0.92 (0.67, 1.27)
Osteosarcoma	≥1 wells	83 (53.9)	1.08 (0.78, 1.48)	1.08 (0.78, 1.51)
	Low	54 (35.1)	1.38 (0.97, 1.96)	1.33 (0.92, 1.92)
	High	29 (18.8)	0.77 (0.50, 1.18)	0.79 (0.50, 1.24)
Ewing's sarcoma	≥1 wells	52 (55.3)	1.15 (0.77, 1.73)	1.24 (0.82, 1.89)
	Low	26 (27.7)	1.13 (0.69, 1.84)	1.17 (0.72, 1.92)
	High	26 (27.7)	1.17 (0.72, 1.91)	1.33 (0.80, 2.21)
Rhabdomyosarcoma	≥1 wells	168 (61.5)	1.49 (1.17, 1.90)	1.59 (1.24, 2.05)

Germ cell tumors	Low		1.62 (1.23, 2.14)	1.66 (1.25, 2.20)
	High	93 (34.1)	1.36 (1.01, 1.83)	1.51 (1.11, 2.06)
	≥1 wells	75 (27.5)	1.28 (1.04, 1.58)	1.29 (1.04, 1.60)
		211 (58.0)		
Yolk sac tumor	Low		1.25 (0.98, 1.61)	1.26 (0.98, 1.62)
	High	105 (28.8)	1.31 (1.03, 1.68)	1.32 (1.02, 1.71)
	≥1 wells	106 (29.1)	1.33 (0.84, 2.09)	1.28 (0.80, 2.03)
		45 (58.4)		
Teratoma	Low		1.33 (0.78, 2.28)	1.29 (0.75, 2.21)
	High	23 (29.9)	1.33 (0.77, 2.28)	1.27 (0.72, 2.23)
	≥1 wells	22 (28.6)	1.37 (0.95, 1.96)	1.37 (0.95, 1.98)
		73 (59.3)		
	Low		1.36 (0.89, 2.08)	1.37 (0.89, 2.10)
	High	37 (30.1)	1.38 (0.90, 2.11)	1.37 (0.87, 2.15)
		36 (29.3)		

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, the matching variable

^b Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density

Table S3-8. Associations between exposures to inactive oil and gas wells during pregnancy within 1-3km of home addresses at birth and childhood cancers for births in CA, 1998 – 2016

Cancer type	Exposure category	Exposed cases, N (%)	Crude model, OR (95% CI) ^a	Adjusted model, OR (95% CI) ^b
Controls	≥1 wells	59630 (40.5)	Ref	Ref
	Low	32870 (22.3)	Ref	Ref
	High	26760 (18.2)	Ref	Ref
Acute lymphoblastic leukemia	≥1 wells	798 (39.6)	0.97 (0.88, 1.06)	0.96 (0.87, 1.05)
	Low	422 (20.9)	0.93 (0.83, 1.04)	0.92 (0.83, 1.03)
	High	376 (18.6)	1.01 (0.90, 1.14)	1.00 (0.89, 1.13)
Acute myeloid leukemia	≥1 wells	145 (39.2)	0.95 (0.77, 1.17)	0.92 (0.74, 1.14)
	Low	80 (21.6)	0.95 (0.74, 1.23)	0.93 (0.71, 1.20)
	High	65 (17.6)	0.95 (0.72, 1.25)	0.90 (0.68, 1.20)
Hodgkin lymphoma	≥1 wells	63 (36.6)	0.84 (0.62, 1.15)	0.86 (0.63, 1.18)
	Low	35 (20.3)	0.84 (0.58, 1.24)	0.87 (0.59, 1.27)
	High	28 (16.3)	0.84 (0.55, 1.27)	0.85 (0.56, 1.31)
Non-Hodgkin lymphoma	≥1 wells	117 (39.9)	0.97 (0.77, 1.23)	0.96 (0.75, 1.22)
	Low	68 (23.2)	1.02 (0.77, 1.36)	1.02 (0.76, 1.35)
	High	49 (16.7)	0.91 (0.66, 1.25)	0.88 (0.64, 1.22)
Medulloblastoma	≥1 wells	94 (48.5)	1.38 (1.04, 1.83)	1.46 (1.10, 1.94)
	Low	46 (23.7)	1.23 (0.87, 1.74)	1.27 (0.89, 1.80)
	High	48 (24.7)	1.57 (1.12, 2.22)	1.72 (1.21, 2.44)
Glioma	≥1 wells	332 (36.4)	0.84 (0.74, 0.97)	0.85 (0.74, 0.98)
	Low	201 (22.1)	0.93 (0.79, 1.09)	0.92 (0.78, 1.08)
	High	131 (14.4)	0.74 (0.61, 0.90)	0.76 (0.63, 0.93)

Neuroblastoma	≥1 wells	175 (37.6)	0.89 (0.74, 1.07)	0.91 (0.75, 1.10)
	Low	110 (23.6)	1.02 (0.82, 1.27)	1.03 (0.82, 1.28)
	High	65 (13.9)	0.73 (0.56, 0.96)	0.75 (0.57, 0.99)
Retinoblastoma	≥1 wells	111 (44.9)	1.21 (0.94, 1.55)	1.15 (0.89, 1.49)
	Low	50 (20.2)	0.99 (0.72, 1.37)	0.96 (0.69, 1.34)
	High	61 (24.7)	1.47 (1.09, 1.99)	1.39 (1.02, 1.89)
Wilms tumor	≥1 wells	140 (39.3)	0.96 (0.77, 1.18)	0.97 (0.78, 1.20)
	Low	85 (23.9)	1.06 (0.82, 1.36)	1.07 (0.83, 1.38)
	High	55 (15.4)	0.84 (0.62, 1.12)	0.84 (0.62, 1.13)
Hepatoblastoma	≥1 wells	60 (40.3)	1.00 (0.72, 1.39)	0.97 (0.70, 1.35)
	Low	34 (22.8)	1.03 (0.70, 1.53)	1.02 (0.68, 1.51)
	High	26 (17.4)	0.96 (0.62, 1.48)	0.92 (0.59, 1.43)
Malignant bone tumors	≥1 wells	104 (44.3)	1.16 (0.90, 1.50)	1.17 (0.90, 1.52)
	Low	50 (21.3)	1.01 (0.73, 1.40)	1.03 (0.74, 1.43)
	High	54 (23.0)	1.35 (0.98, 1.85)	1.35 (0.97, 1.88)
Osteosarcoma	≥1 wells	60 (45.8)	1.23 (0.88, 1.74)	1.23 (0.86, 1.76)
	Low	31 (23.7)	1.15 (0.76, 1.76)	1.18 (0.77, 1.82)
	High	29 (22.1)	1.34 (0.87, 2.06)	1.28 (0.81, 2.03)
Ewing's sarcoma	≥1 wells	33 (44.0)	1.15 (0.73, 1.82)	1.19 (0.75, 1.90)
	Low	13 (17.3)	0.82 (0.44, 1.53)	0.84 (0.45, 1.57)
	High	20 (26.7)	1.56 (0.92, 2.66)	1.66 (0.96, 2.87)
Rhabdomyosarcoma	≥1 wells	114 (52.1)	1.59 (1.22, 2.08)	1.65 (1.26, 2.17)

Germ cell tumors	Low	58 (26.5)	1.47 (1.07, 2.02)	1.51 (1.09, 2.09)
	High	56 (25.6)	1.75 (1.26, 2.42)	1.85 (1.32, 2.58)
	≥1 wells	140 (47.8)	1.34 (1.07, 1.69)	1.31 (1.04, 1.66)
	Low	72 (24.6)	1.25 (0.94, 1.65)	1.24 (0.93, 1.64)
Yolk sac tumor	High	68 (23.2)	1.46 (1.09, 1.94)	1.41 (1.05, 1.89)
	≥1 wells	29 (47.5)	1.34 (0.81, 2.21)	1.25 (0.75, 2.09)
	Low	15 (24.6)	1.26 (0.68, 2.32)	1.22 (0.66, 2.27)
	High	14 (23.0)	1.44 (0.77, 2.69)	1.29 (0.68, 2.45)
Teratoma	≥1 wells	51 (50.5)	1.50 (1.02, 2.22)	1.50 (1.01, 2.23)
	Low	28 (27.7)	1.49 (0.94, 2.37)	1.48 (0.93, 2.36)
	High	23 (22.8)	1.51 (0.92, 2.47)	1.52 (0.92, 2.52)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, the matching variable

^b Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density

Table S3-9. Associations between exposures to any type of oil and gas wells during pregnancy within 1km of home addresses at birth and childhood cancers, by race and ethnicity, for births in CA between 1998 – 2016

Cancer type	Exposure category	Non-Hispanic White		Hispanic	
		Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a	Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a
Controls	≥1 wells	7623 (21.8)	Ref	18003 (28.7)	Ref
	Low	3558 (10.2)	Ref	9643 (15.4)	Ref
	High	4065 (11.6)	Ref	8360 (13.3)	Ref
Acute lymphoblastic leukemia	≥1 wells	102 (23.0)	1.02 (0.80, 1.28)	285 (28.3)	0.98 (0.85, 1.13)
	Low	46 (10.4)	1.00 (0.73, 1.37)	142 (14.1)	0.92 (0.76, 1.10)
	High	56 (12.6)	1.03 (0.76, 1.38)	143 (14.2)	1.06 (0.88, 1.28)
Glioma	≥1 wells	73 (23.1)	1.08 (0.82, 1.42)	92 (26.3)	0.89 (0.69, 1.14)
	Low	23 (7.3)	0.73 (0.47, 1.13)	41 (11.7)	0.76 (0.54, 1.06)
	High	50 (15.8)	1.41 (1.02, 1.94)	51 (14.6)	1.05 (0.76, 1.43)
Neuroblastoma	≥1 wells	29 (20.5)	0.81 (0.53, 1.23)	30 (18.9)	0.59 (0.39, 0.89)
	Low	15 (10.6)	0.94 (0.55, 1.63)	13 (8.2)	0.48 (0.27, 0.85)
	High	14 (9.9)	0.69 (0.39, 1.23)	17 (10.7)	0.72 (0.43, 1.21)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract SES-index, population density, household unit density

Table S3-10. Associations between exposures to any types of oil and gas wells during pregnancy within 3km of home addresses at birth and childhood cancers, by race and ethnicity, for births in CA between 1998 – 2016

Cancer type	Exposure category	Non-Hispanic White		Hispanic	
		Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a	Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a
Controls	≥1 wells	21648 (44.2)	Ref	55578 (55.4)	Ref
	Low	11467 (23.4)	Ref	27990 (27.9)	Ref
	High	10181 (20.8)	Ref	27588 (27.5)	Ref
Acute lymphoblastic leukemia	≥1 wells	270 (44.1)	0.98 (0.83, 1.15)	823 (53.3)	0.92 (0.83, 1.02)
	Low	138 (22.5)	0.95 (0.78, 1.17)	423 (27.4)	0.94 (0.83, 1.06)
	High	132 (21.6)	1.01 (0.82, 1.25)	400 (25.9)	0.90 (0.79, 1.02)
Acute myeloid leukemia	≥1 wells	46 (36.5)	0.73 (0.50, 1.07)	142 (55)	0.98 (0.76, 1.26)
	Low	23 (18.3)	0.69 (0.43, 1.10)	75 (29.1)	1.06 (0.79, 1.41)
	High	23 (18.3)	0.79 (0.49, 1.28)	67 (26.0)	0.90 (0.66, 1.23)
Hodgkin lymphoma	≥1 wells	25 (36.8)	0.72 (0.43, 1.19)	64 (53.3)	0.94 (0.65, 1.36)
	Low	11 (16.2)	0.60 (0.31, 1.17)	32 (26.7)	0.91 (0.58, 1.40)
	High	14 (20.6)	0.86 (0.46, 1.62)	32 (26.7)	0.99 (0.63, 1.55)
Non-Hodgkin lymphoma	≥1 wells	59 (44.0)	1.01 (0.71, 1.44)	101 (57.1)	1.01 (0.75, 1.37)
	Low	33 (24.6)	1.06 (0.70, 1.61)	42 (23.7)	0.86 (0.59, 1.25)
	High	26 (19.4)	0.95 (0.60, 1.51)	59 (33.3)	1.18 (0.83, 1.69)
Medulloblastoma	≥1 wells	49 (55.7)	1.59 (1.03, 2.45)	82 (62.6)	1.45 (1.01, 2.07)
	Low	26 (29.5)	1.58 (0.96, 2.61)	36 (27.5)	1.23 (0.79, 1.89)
	High	23 (26.1)	1.60 (0.94, 2.74)	46 (35.1)	1.70 (1.13, 2.58)

Glioma	≥1 wells		0.93 (0.76,		0.91 (0.76,
		181 (42.7)	1.13)	281 (52.1)	1.08)
	Low		0.91 (0.71,		0.92 (0.75,
		94 (22.2)	1.16)	144 (26.7)	1.13)
	High		0.95 (0.73,		0.90 (0.72,
		87 (20.5)	1.22)	137 (25.4)	1.11)
Neuroblastoma	≥1 wells		0.99 (0.74,		0.81 (0.63,
		94 (45.4)	1.31)	126 (49.4)	1.05)
	Low		1.13 (0.81,		0.83 (0.62,
		55 (26.6)	1.56)	65 (25.5)	1.12)
	High		0.82 (0.56,		0.79 (0.58,
		39 (18.8)	1.20)	61 (23.9)	1.09)
Retinoblastoma	≥1 wells		0.72 (0.44,		1.53 (1.11,
		27 (38.0)	1.19)	114 (65.9)	2.11)
	Low		0.74 (0.41,		1.49 (1.03,
		14 (19.7)	1.36)	56 (32.4)	2.15)
	High		0.70 (0.37,		1.58 (1.08,
		13 (18.3)	1.34)	58 (33.5)	2.30)
Wilms tumor	≥1 wells		0.83 (0.58,		1.03 (0.78,
		51 (40.2)	1.20)	120 (54.8)	1.35)
	Low		0.85 (0.55,		1.11 (0.82,
		27 (21.3)	1.32)	67 (30.6)	1.52)
	High		0.82 (0.51,		0.93 (0.66,
		24 (18.9)	1.32)	53 (24.2)	1.31)
Hepatoblastoma	≥1 wells		0.95 (0.53,		1.04 (0.70,
		22 (44.9)	1.70)	56 (55.4)	1.55)
	Low		1.02 (0.52,		1.08 (0.67,
		12 (24.5)	2.03)	29 (28.7)	1.72)
	High		0.87 (0.40,		1.00 (0.61,
		10 (20.4)	1.86)	27 (26.7)	1.65)
Malignant bone tumors	≥1 wells		1.00 (0.66,		1.15 (0.83,
		43 (44.8)	1.52)	88 (57.1)	1.59)
	Low		1.14 (0.71,		1.26 (0.87,
		26 (27.1)	1.84)	51 (33.1)	1.82)
	High		0.82 (0.47,		1.02 (0.67,
		17 (17.7)	1.46)	37 (24.0)	1.54)
Osteosarcoma	≥1 wells		1.46 (0.82,		1.05 (0.67,
		27 (52.9)	2.59)	45 (54.2)	1.63)
	Low		1.73 (0.92,		1.27 (0.78,
		17 (33.3)	3.25)	29 (34.9)	2.07)
	High		1.13 (0.52,		0.78 (0.43,
		10 (19.6)	2.44)	16 (19.3)	1.42)
Rhabdomyosarcoma	≥1 wells		1.22 (0.77,		1.53 (1.09,
		37 (48.7)	1.93)	98 (64.5)	2.15)

Germ cell tumor	Low	19 (25.0)	1.17 (0.67, 2.04)	53 (34.9)	1.57 (1.07, 2.30)
	High	18 (23.7)	1.28 (0.71, 2.28)	45 (29.6)	1.49 (0.99, 2.24)
	≥1 wells	47 (50.5)	1.26 (0.83, 1.92)	133 (61.6)	1.31 (0.99, 1.73)
	Low	27 (29.0)	1.38 (0.85, 2.22)	62 (28.7)	1.20 (0.86, 1.68)
	High	20 (21.5)	1.12 (0.65, 1.93)	71 (32.9)	1.43 (1.03, 1.99)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract SES-index, population density, household unit density

Table S3-11. Associations between exposures to inactive oil and gas wells during pregnancy within 1km of home addresses at birth and childhood cancers, by race and ethnicity, for births in CA between 1998 – 2016

Cancer type	Exposure category	Non-Hispanic White		Hispanic	
		Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a	Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a
Controls	≥1 wells	5815 (17.6)	Ref	14043 (23.9)	Ref
	Low	3019 (9.1)	Ref	8582 (14.6)	Ref
	High	2796 (8.4)	Ref	5461 (9.3)	Ref
Acute lymphoblastic leukemia	≥1 wells	82 (19.3)	1.08 (0.84, 1.38)	217 (23.1)	0.97 (0.83, 1.13)
	Low	37 (8.7)	0.96 (0.68, 1.36)	122 (13.0)	0.89 (0.73, 1.08)
	High	45 (10.6)	1.20 (0.87, 1.67)	95 (10.1)	1.09 (0.87, 1.36)
Glioma	≥1 wells	55 (18.4)	1.08 (0.80, 1.46)	62 (19.4)	0.78 (0.59, 1.04)
	Low	20 (6.7)	0.76 (0.48, 1.20)	34 (10.6)	0.72 (0.50, 1.03)
	High	35 (11.7)	1.44 (1.00, 2.08)	28 (8.8)	0.89 (0.59, 1.32)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract SES-index, population density, household unit density

Table S3-12. Associations between exposures to inactive oil and gas wells during pregnancy within 3km of home addresses at birth and childhood cancers, by race and ethnicity, for births in CA between 1998 – 2016

Cancer type	Exposure category	Non-Hispanic White		Hispanic	
		Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a	Exposed cases, N (%)	Adjusted model, OR (95% CI) ^a
Controls	≥1 wells	14165 (34.2)	Ref	35429 (44.2)	Ref
	Low	8652 (20.9)	Ref	18922 (23.6)	Ref
	High	5513 (13.3)	Ref	16507 (20.6)	Ref
Acute lymphoblastic leukemia	≥1 wells	176 (34.0)	0.97 (0.80, 1.17)	519 (41.9)	0.91 (0.81, 1.03)
	Low	98 (18.9)	0.89 (0.71, 1.12)	277 (22.3)	0.92 (0.80, 1.05)
	High	78 (15.1)	1.10 (0.85, 1.41)	242 (19.5)	0.91 (0.79, 1.06)
Acute myeloid leukemia	≥1 wells	30 (27.3)	0.74 (0.48, 1.13)	93 (44.5)	1.02 (0.77, 1.34)
	Low	19 (17.3)	0.77 (0.46, 1.27)	44 (21.1)	0.92 (0.65, 1.30)
	High	11 (10.0)	0.69 (0.36, 1.31)	49 (23.4)	1.13 (0.80, 1.58)
Non-Hodgkin lymphoma	≥1 wells	43 (36.4)	1.11 (0.76, 1.63)	59 (43.7)	0.94 (0.66, 1.33)
	Low	28 (23.7)	1.20 (0.78, 1.87)	31 (23.0)	0.95 (0.62, 1.45)
	High	15 (12.7)	0.97 (0.55, 1.70)	28 (20.7)	0.93 (0.59, 1.45)
Medulloblastoma	≥1 wells	35 (47.3)	1.68 (1.06, 2.68)	51 (51.0)	1.41 (0.95, 2.11)
	Low	22 (29.7)	1.73 (1.02, 2.93)	19 (19.0)	0.97 (0.57, 1.64)
	High	13 (17.6)	1.61 (0.85, 3.05)	32 (32.0)	1.99 (1.26, 3.14)
Glioma	≥1 wells	114 (31.9)	0.91 (0.72, 1.14)	176 (40.6)	0.89 (0.73, 1.08)
	Low	75 (21.0)	0.98 (0.76, 1.28)	105 (24.2)	0.98 (0.78, 1.24)
	High	39 (10.9)	0.79 (0.56, 1.12)	71 (16.4)	0.77 (0.59, 1.00)

Neuroblastoma	≥1 wells		1.03 (0.75, 1.40)	79 (38.0)	0.79 (0.60, 1.06)
	Low	64 (36.2)	1.22 (0.86, 1.72)	41 (19.7)	0.77 (0.54, 1.10)
	High	46 (26.0)	0.72 (0.44, 1.20)	38 (18.3)	0.82 (0.57, 1.18)
Wilms tumor	≥1 wells	18 (10.2)	0.89 (0.59, 1.34)	82 (45.3)	1.07 (0.79, 1.43)
	Low	35 (31.5)	0.97 (0.61, 1.56)	45 (24.9)	1.10 (0.77, 1.57)
	High	23 (20.7)	0.77 (0.42, 1.43)	37 (20.4)	1.02 (0.70, 1.50)
Malignant bone tumors	≥1 wells	12 (10.8)	1.07 (0.68, 1.69)	62 (48.4)	1.22 (0.86, 1.74)
	Low	30 (36.1)	1.00 (0.57, 1.73)	33 (25.8)	1.20 (0.79, 1.82)
	High	17 (20.5)	1.18 (0.64, 2.19)	29 (22.7)	1.26 (0.81, 1.96)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: reference

^a Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract SES-index, population density, household unit density

Table S3-13. Sensitivity analysis with the adjustment of ambient nitrogen oxides level ^a of home address in pregnancy for exposure to oil and gas wells (any and inactive wells) within 3km

Cancer type	Exposure category	Exposed cases, N (%)	Any well, OR (95% CI)	Exposed cases, N (%)	Inactive well, OR (95% CI)
Controls	≥1 wells	26940 (52.8)	Ref	16999 (41.4)	Ref
	Low	13683 (26.8)	Ref	9481 (23.1)	Ref
	High	13257 (26.0)	Ref	7518 (18.3)	Ref
Acute lymphoblastic leukemia	≥1 wells	351 (50.6)	0.92 (0.79, 1.07)	214 (38.4)	0.89 (0.74, 1.06)
	Low	175 (25.2)	0.91 (0.75, 1.09)	120 (21.5)	0.90 (0.73, 1.11)
	High	176 (25.4)	0.93 (0.77, 1.13)	94 (16.9)	0.87 (0.69, 1.11)
Acute myeloid leukemia	≥1 wells	65 (47.4)	0.86 (0.61, 1.21)	39 (35.1)	0.80 (0.54, 1.19)
	Low	30 (21.9)	0.75 (0.49, 1.15)	20 (18)	0.72 (0.44, 1.19)
	High	35 (25.5)	1.00 (0.65, 1.52)	19 (17.1)	0.91 (0.54, 1.52)
Non-Hodkin lymphoma ^b	≥1 wells	24 (52.2)	0.97 (0.53, 1.76)	16 (42.1)	0.96 (0.50, 1.85)
Medulloblastoma	≥1 wells	39 (65.0)	1.76 (1.02, 3.03)	26 (55.3)	1.82 (1.01, 3.27)
	Low	20 (33.3)	1.70 (0.92, 3.14)	10 (21.3)	1.23 (0.58, 2.61)
	High	19 (31.7)	1.84 (0.97, 3.51)	16 (34)	2.68 (1.37, 5.23)
Glioma	≥1 wells	138 (49.5)	0.96 (0.75, 1.22)	88 (38.4)	0.97 (0.74, 1.27)
	Low	71 (25.4)	0.94 (0.71, 1.26)	55 (24.0)	1.06 (0.77, 1.46)
	High	67 (24.0)	0.97 (0.72, 1.32)	33 (14.4)	0.84 (0.57, 1.23)
Neuroblastoma	≥1 wells	113 (51.1)	0.93 (0.71, 1.23)	73 (40.3)	0.99 (0.73, 1.34)
	Low	60 (27.1)	1.01 (0.73, 1.39)	47 (26.0)	1.13 (0.80, 1.60)
	High	53 (24.0)	0.85 (0.60, 1.20)	26 (14.4)	0.80 (0.52, 1.24)

Retinoblastoma	≥1 wells	97 (61.8)	1.37 (0.98, 1.91)	62 (50.8)	1.38 (0.96, 1.99)
	Low	48 (30.6)	1.35 (0.92, 1.99)	26 (21.3)	1.08 (0.68, 1.71)
	High	49 (31.2)	1.39 (0.94, 2.07)	36 (29.5)	1.78 (1.16, 2.73)
Wilms tumor	≥1 wells	74 (50.7)	1.00 (0.71, 1.39)	49 (40.5)	1.01 (0.70, 1.46)
	Low	39 (26.7)	0.99 (0.67, 1.47)	26 (21.5)	0.95 (0.60, 1.49)
	High	35 (24.0)	1.00 (0.65, 1.52)	23 (19.0)	1.10 (0.68, 1.77)
Hepatoblastoma	≥1 wells	35 (53.0)	1.05 (0.64, 1.73)	23 (42.6)	1.08 (0.62, 1.86)
	Low	17 (25.8)	1.00 (0.55, 1.81)	11 (20.4)	0.93 (0.47, 1.85)
	High	18 (27.3)	1.11 (0.60, 2.04)	12 (22.2)	1.26 (0.64, 2.49)
Malignant bone tumors ^b	≥1 wells	18 (64.3)	1.74 (0.79, 3.83)	14 (58.3)	2.02 (0.89, 4.60)
Rhabdomyosarcoma	≥1 wells	48 (60.0)	1.40 (0.89, 2.22)	35 (52.2)	1.57 (0.97, 2.56)
	Low	24 (30.0)	1.34 (0.79, 2.29)	17 (25.4)	1.35 (0.75, 2.45)
	High	24 (30.0)	1.48 (0.85, 2.57)	18 (26.9)	1.87 (1.04, 3.38)
Germ cell tumors	≥1 wells	57 (67.1)	1.76 (1.11, 2.79)	41 (59.4)	1.93 (1.19, 3.14)
	Low	29 (34.1)	1.77 (1.05, 2.98)	22 (31.9)	1.86 (1.06, 3.26)
	High	28 (32.9)	1.75 (1.01, 3.03)	19 (27.5)	2.02 (1.11, 3.68)
Yolk sac tumor ^b	≥1 wells	21 (67.7)	1.86 (0.86, 4.02)	15 (60.0)	1.94 (0.86, 4.34)
Teratoma	≥1 wells	28 (66.7)	1.66 (0.86, 3.22)	22 (61.1)	2.17 (1.10, 4.29)
	Low	13 (31.0)	1.55 (0.73, 3.31)	11 (30.6)	1.86 (0.84, 4.13)
	High	15 (35.7)	1.80 (0.83, 3.87)	11 (30.6)	2.63 (1.17, 5.90)

Abbreviation: CI: confidence interval; OR: odds ratio; Ref: Reference

^a Adjusted for birth year, source of payment for prenatal care, residence in rural/urban area, census tract socioeconomics-index, population density, ambient nitrogen oxides level

^b The results for low/high exposure were not reported because the number of exposed cases was less than 10

Figure S3-1. Directed acyclic graph for confounder selection

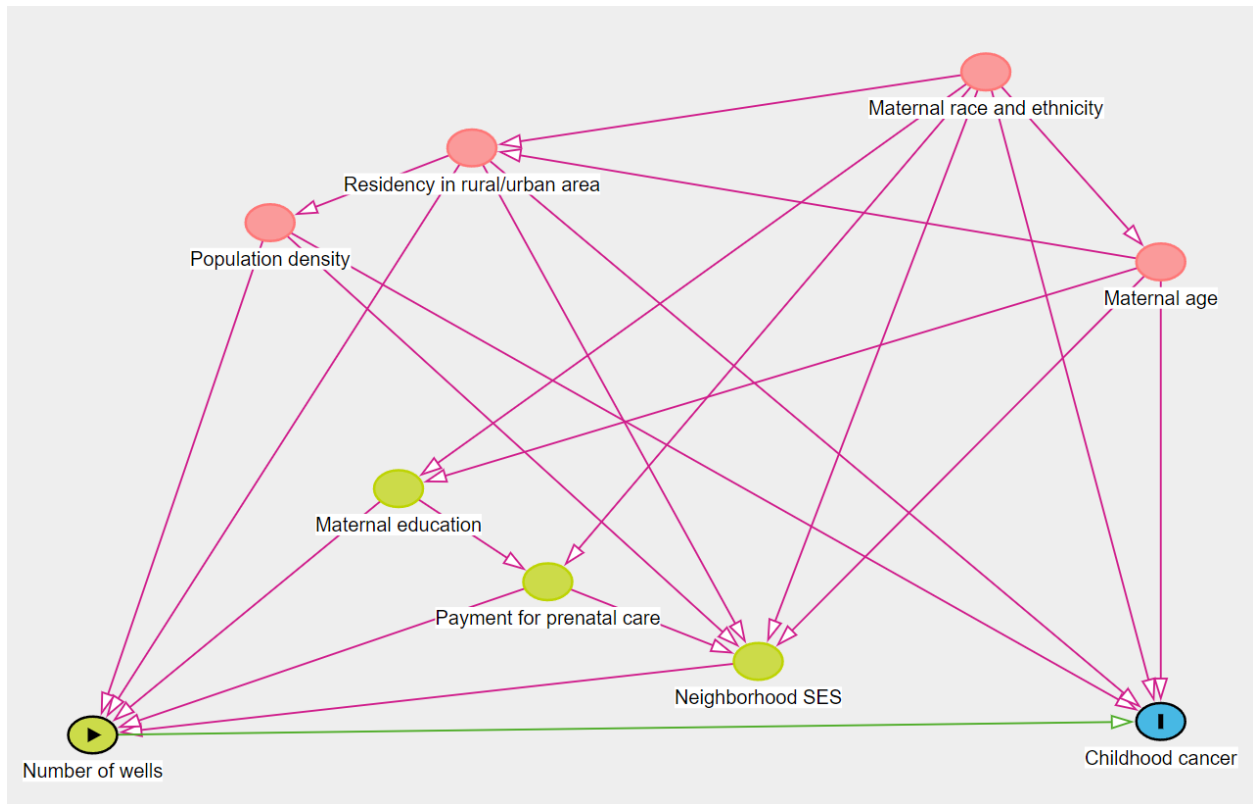


Figure legend:

Abbreviation: SES, Socioeconomic status

4 Childhood cancer risk in offspring in mothers occupationally exposed to hydrocarbon solvents

4.1 Abstract

Background: Little is known about maternal occupational exposure to hydrocarbons and offspring cancer risk. We aimed to estimate childhood cancer risk associated with maternal exposure to aliphatic/alicyclic, aromatic, and chlorinated hydrocarbons, and methylene chloride, trichloroethylene, 1,1,1-trichloroethane, and toluene.

Methods: This case-control study included all cancer cases diagnosed at age <20 years, born 1968-2013 in Denmark. A total of 10,442 cases (diagnosed 1968-2016) were matched to 261,050 cancer-free controls (25:1 matching ratio). Maternal occupational exposure to hydrocarbons during pregnancy was determined from a job-exposure matrix. We performed conditional logistic regression to estimate offspring cancer risks from hydrocarbon exposures adjusting for maternal age, birthplace and child's birthplace.

Results: For medulloblastoma, we observed strong associations with maternal occupational exposure to chlorinated hydrocarbons (adjusted odds ratio (aOR): 2.29; 95% confidence interval (CI): 1.24, 4.25) including the individual ones: trichloroethylene (aOR: 1.86; 95% CI: 1.12, 3.10), methylene chloride (aOR: 1.69; 95% CI: 1.01, 2.84). The risk of medulloblastoma also increased with aliphatic/alicyclic hydrocarbons (aOR: 1.80; 95% CI: 0.98, 3.30) and toluene (aOR: 1.92; 95% CI: 1.07, 3.46). The risk of NHL increased by 94% with the exposure to chlorinated hydrocarbons (aOR; 1.94; 95% CI: 1.05, 3.57). We found moderate associations of ALL with aromatic hydrocarbons (aOR; 1.29; 95% CI: 1.01, 1.64) and 1,1,1-trichloroethane

(aOR; 1.30; 95% CI: 1.01, 1.69). A possible increase in germ cell tumors was associated with maternal exposure to aromatic hydrocarbons (aOR: 1.44; 95% CI: 0.91, 2.26).

Conclusions: We saw increased risks in medulloblastoma, NHL, ALL, and possibly germ cell tumors in offspring of mothers occupationally exposed to solvents in pregnancy over a span of 50 years in Denmark. Workplace protection from solvents is warranted in pregnant women to reduce childhood cancer risk.

4.2 Introduction

Toluene, trichloroethylene (TCE), perchloroethylene (PCE), methylene chloride (DCM), and 1,1,1-trichloroethane (1,1,1-TCA) are hydrocarbons extensively employed in various industries and products, including petroleum refining, dry cleaning, printing, and metal degreasing.^{240, 333-335} According to the International Agency for Research on Cancer (IARC), TCE is a Group 1 carcinogen, while PCE, 1,1,1-TCA and DCM are Group 2A carcinogens.^{240, 333-335} These chemicals can pass through the placenta, leading to altered fetal programming and permanent changes that affect the risk of childhood cancer.^{215, 336-341} Maternal exposures to hydrocarbon solvents in pregnancy was suspected to be involved in the development of childhood cancer in epidemiologic studies.

Because women generally have been less likely to work during pregnancy, especially in prior generations, studies addressing offspring carcinogenic effects of maternal occupational exposure to solvents in offspring are often limited by insufficient sample size and statistical power.³⁴² Hence, more studies are needed to support the evidence. Only one previous study reported a moderate increase in the risk of childhood leukemia associated with maternal occupational exposure to mononuclear aromatic hydrocarbons in pregnancy.²¹⁸ Other studies investigating specific hydrocarbons/hydrocarbon groups (i.e., chlorinated, aromatic or aliphatic hydrocarbons, 1,1,1-TCA, PCE, TCE, DCM and toluene) yielded null associations with acute lymphoblastic leukemia (ALL) or were underpowered.^{93, 218, 343} ALL was however positively associated with maternal occupational exposure to paints, thinners or lacquers which contain a mixture of hydrocarbons in pregnancy.^{210, 211} There are few published studies investigating other cancer types, and some had low statistical power.^{82, 205, 222, 229, 344-346}

The evaluation of maternal occupational exposure in pregnancy in relation to childhood cancer risk can be greatly assisted by large register-based studies. Here, we aimed to investigate the risk of various types of cancer in Danish children from maternal pregnancy exposure to four individual hydrocarbons (toluene, DCM, TCE, and 1,1,1-TCA), as well as three primary subgroups of hydrocarbons (chlorinated, aliphatic/alicyclic, and aromatic hydrocarbons). We intended to examine PCE but lacked statistical power due to its low prevalence in Denmark (exposure prevalence among mothers of controls: 2.5%).

4.3 Methods

Data sources and study population

For this population-based study, we linked four registries with a 10-digit unique personal identification number allocated to each Danish resident: the Central Population Registry (established in 1968),³⁴⁷ the Cancer Registry (established in 1942),³⁴⁸ the Supplementary Pension Fund (established in 1964),³⁴⁹ and the Medical Birth Registry (computerized since 1973).³⁵⁰ Details of these registries were reported previously.^{34, 351}

This study included all childhood cancer cases born 1968-2013 and diagnosed in 1968-2016 in Denmark, aged 0-19 at diagnosis. We identified cancer cases from the Danish Cancer Registry with cancer types ascertained based on the International Classification of Childhood Cancer, Version 1 until 2003 and Version 3 thereafter. Histologic subtypes of cancer were classified according to the International Classification of Diseases for Oncology (ICD-O), Version 1 until 2003 and Version 3 thereafter. We classified medulloblastoma using ICD-O classifications recommended by the Central Brain Tumor Registry of the United States.³⁵² Cancer-free children who were alive at the date of diagnosis of the corresponding case were randomly selected from

the Central Population Registry and were matched to cases by birth date and sex (25:1 ratio). If 25 controls with the corresponding case's birthday could not be identified, we widened the search by 1 day (on either side), then 2 days, etc, until a sufficient number of controls were selected.

The Medical Birth Registry provided gestational information, from which we obtained gestational age. When gestational age was missing, we used multiple imputation to estimate it, as previously described.³⁵³ Date of conception was calculated by subtracting the child's gestational age in days from their birth date.

For this record-based study, informed consent was not required. Approval for this study was received from the Danish Data Protection Agency and the human subjects' protection board at the University of California, Los Angeles, and the University of North Texas.

Exposure assessment

Maternal occupational records were extracted from the Supplementary Pension Fund Register. Participation in the Supplementary Pension Fund is mandatory for all salaried employees in Denmark aged 18-66 years and working at least 9 hours per week (in 1978, individuals ages 16-17 years were also included). Students, the unemployed including stay-at-home parents, the self-employed, and individuals born before April 1st, 1897 are not included in this system.³⁴⁹ The self-employment rate in Denmark over the past decade has been stable at about 8%.³⁵⁴ The Register keeps track of the start/end dates, company name, a unique company number and the personal identification number for each employment entry. Maternal employment was categorized according to a Danish 5-digit extended version of the United Nation's International Standard Industrial Classification of All Economic Activities codes.³⁵⁵

The Danish version of the Nordic Occupational Cancer Study Job Exposure Matrices (NOCCA JEM) was developed from Finnish JEM templates.³⁵⁶ Based on the Danish JEM, we identified industries with hydrocarbon exposure. The construction of JEMs for hydrocarbon groups (chlorinated, aliphatic/alicyclic, aromatic hydrocarbons) was primarily based on expert assessments in 1968-1974, while the JEMs for individual hydrocarbons (toluene, TCE, DCM, 1,1,1-TCA) were constructed from estimated annual mean levels of exposure (ppm) based on workplace-based biomonitoring and ambient air measurements since 1975.^{356, 357} Using both exposure assessment methods led to slight inconsistencies where the expert-derived broader hydrocarbon groups did not encompass all measurement-based individual hydrocarbons. For instance, workplaces with toluene measurements might not have been categorized as exposed to aromatic hydrocarbons by experts. Similarly, workplaces with measurements of DCM, TCE, or 1,1,1-TCA might not have consistently fallen under the broader category of chlorinated hydrocarbon exposures.

Using this study, our group previously reported associations for childhood cancer and parents who worked in industries with frequent exposure to hydrocarbons (e.g., painting and printing industries and the iron, metal works, and foundries industries).^{208, 226, 358}

We excluded children for whom maternal occupational history could not be identified during the exposure window of interest. We classified a pregnant woman as ever exposed to each hydrocarbon if she had ever been employed in the exposed industry during the index child's pregnancy. The JEM assigned an exposure level and the probability of exposure for each hydrocarbon within each industry by time period (1960-1974, 1975-1984, and ≥ 1985),³⁵⁶ based on which we calculated exposure intensity for exposed industries. However, because analyses

were underpowered, we were not able to evaluate potential exposure-response relationships between exposure intensity and the risk of childhood cancer. Thus, we presented results for ever exposure. Paternal exposure to hydrocarbon solvents were identified and classified, based on the same JEM and using the same approach.

Statistical analyses

We used frequencies (percentages) for categorical variables and means (standard deviations) for continuous variables to describe population characteristics, comparing cases and controls. We calculated the frequencies and percentages of mothers in our study employed in industries exposed to each hydrocarbon group.

We conducted conditional logistic regression analyses to estimate the risk of childhood cancer associated with maternal occupational exposure to hydrocarbons in pregnancy, controlling for possible confounders.

Based on previous research, we created a directed acyclic graph (**Supplemental Figure 1**) for confounder selection.^{205, 208, 358, 359} The Central Population Registry and the Medical Birth Registry provided us with information on parental, child, and gestational factors. The confounders we had available for adjustment included maternal age (continuous), maternal birthplace (Denmark/Other Europe/North America/Asia/Africa/Other), and child's birthplace (urban/small town/rural residence). In addition, we attempted to control for maternal smoking status (ever smoked vs. non-smoker), as it is a suspected risk factor for childhood cancer.⁶¹ However, maternal smoking status at the first prenatal visit was only recorded during half of the study period (1991+). Using a prediction model of maternal smoking,³⁶⁰ we imputed maternal smoking status using predictors including birthweight, birth year, and maternal socioeconomic

status (SES) as a proxy for maternal education, parity, and maternal birthplace as a proxy for maternal race. With additional adjustment for maternal smoking status, results did not change more than minimally, therefore maternal smoking was not included in the final models.

Sensitivity analyses

Some industries expose workers to multiple hydrocarbon solvents and we present Pearson correlations for the 3 hydrocarbon groups and the 4 individual hydrocarbons. To address potential confounding by co-exposure to other hydrocarbons, we conducted sensitivity analyses that restricted to mothers who were employed in industries with exposure to only one of the hydrocarbon groups. This sensitivity analysis was not feasible for individual hydrocarbon solvents due to co-exposures.

Weak Pearson correlations were observed between paternal and maternal occupational exposures (correlation coefficient: 0.09-0.12). To ensure our findings for maternal exposures were not confounded by paternal exposures, we conducted sensitivity analyses in which we excluded children whose fathers were also occupationally exposed to hydrocarbons.

We also conducted sensitivity analyses in which we classified women with no employment record during pregnancy as unexposed and included them into the reference group.

All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA). We only report risk estimates when the number of exposed cases was ≥ 10 .

4.4 Results

As presented in **Table 4-1**, the demographic characteristics of children as well as parents are similar for cases and controls.

Mothers exposed to chlorinated hydrocarbons were commonly employed as laboratory assistants (N = 2238, 37.7%), printers (N = 1436, 24.2%), painters, lacquerers, and floor layers (N = 632, 10.7%). For aliphatic/alicyclic hydrocarbons, exposed mothers were commonly employed as machine and engine mechanics (N = 2563, 33.6%), printers (N = 1686, 22.1%), and wooden surface finishers (N = 1415, 18.6%). For aromatic hydrocarbons, exposed mothers were commonly employed as printers (N = 1686, 19.0%), bench carpenters (N = 1084, 12.2%), on maintenance crews and as supervisors (N = 816, 9.2%) (**Table S4-1**). Examining chlorinated hydrocarbons only, mothers were employed as laboratory assistants, metal plating and coating workers, and lithographers. The aliphatic/alicyclic hydrocarbons only group included mothers employed as machine and engine mechanics and wooden surface finishers. The aromatic hydrocarbons only group most often included mothers employed as service station attendants, bench carpenters, plastic product workers and maintenance crews and supervisors.

Maternal occupational exposure to the three hydrocarbon groups (**Table S4-2**) was moderately to highly correlated. Stronger correlations were observed between the four individual hydrocarbons, with the strongest correlation for DCM and TCE (Pearson correlation coefficient = 0.93, **Table S4-3**).

Maternal exposure to aliphatic/alicyclic hydrocarbons was associated with medulloblastoma (**Table 4-2**, adjusted odds ratio (aOR): 1.80; 95% confidence interval (CI): 0.98, 3.30) and weakly also with ALL (aOR: 1.25; 95% CI: 0.95, 1.63) that strengthened slightly in sensitivity analysis of maternal exposure to aliphatic/alicyclic hydrocarbons only (**Table S4-4**, aOR: 1.49; 95% CI: 1.05, 2.09).

Aromatic hydrocarbons were associated with an increased risk of ALL (**Table 4-2**, aOR: 1.29; 95% CI: 1.01, 1.64). There were also suggestive associations with medulloblastoma (aOR: 1.64; 95% CI: 0.92, 2.94) and germ cell tumors (aOR: 1.44; 95% CI: 0.91, 2.26) the later again strengthened in sensitivity analyses of maternal exposure to aromatic hydrocarbons only (**Table S4-4**, aOR: 2.00; 95% CI: 1.22, 3.28). When excluding children with both parents exposed, the effect estimates for maternal exposure increased for medulloblastoma (**Table S4-5**, aOR: 2.02; 95% CI: 1.07, 3.82) but decreased for germ cell tumors (aOR: 1.22; 95% CI: 0.68, 2.20).

Chlorinated hydrocarbons were associated with medulloblastoma (**Table 4-2**, aOR: 2.29; 95% CI: 1.24, 4.25) and non-Hodgkin lymphoma (NHL, aOR: 1.94; 95% CI: 1.05, 3.57), and the later further increased (**Table S4-4**, aOR: 2.81; 95% CI: 1.42, 5.56) when we investigated maternal exposure to chlorinated hydrocarbons only.

Toluene, an aromatic hydrocarbon, was associated with medulloblastoma (**Table 4-3**, aOR: 1.92; 95% CI: 1.07, 3.46) and suggestive but weakly with glioma (aOR: 1.29; 95% CI: 0.92, 1.79) and ALL (aOR: 1.23; 95% CI: 0.94, 1.59).

As subtypes of chlorinated hydrocarbons, TCE (**Table 4-3**, aOR: 1.86; 95% CI: 1.12, 3.10) and DCM (aOR: 1.69; 95% CI: 1.01, 2.84) were also positively associated with the risk of medulloblastoma. In addition, we observed associations with ALL for 1,1,1-TCA (aOR: 1.30; 95% CI: 1.01, 1.69) and suggestive but weakly for TCE (aOR: 1.18; 95% CI: 0.94, 1.48). We also observed suggestive but weak associations for germ cell tumors and TCE (aOR: 1.32; 95% CI: 0.87, 2.01), 1,1,1-TCA (aOR: 1.29; 95% CI: 0.79, 2.10), and DCM (aOR: 1.27; 95% CI: 0.84, 1.94).

The associations discussed above remained largely unchanged when we excluded children with both parents exposed and when mothers with missing occupational history were reclassified as unexposed (**Table S4-5, S4-6, S4-7, and S4-8**).

4.5 Discussion

Our study is one of only few nationwide studies using register-based datasets and a JEM approach to assess maternal occupational exposure to various hydrocarbon solvents. Furthermore, this research was conducted in a country with high female employment during the study period (>80%).³⁶¹ We found medulloblastoma was associated with all hydrocarbons we investigated except 1,1,1-TCA that we could not evaluate due to too few exposed cases, with 64-129% increase in risk. The risk of NHL increased by 94% with exposure to chlorinated hydrocarbons. In addition, our study suggested only a slight increase in the risks of ALL associated with aromatic and aliphatic hydrocarbons, toluene 1,1,1-TCA, and TCE, while a slight increase in germ cell tumors was found with exposure to aromatic hydrocarbons and all chlorinated hydrocarbon subtypes.

The increase in medulloblastoma risk we found for most hydrocarbon solvents we examined has not been reported previously. While a previous study reported an increased risk of brain tumors with maternal solvent exposure, these researchers did not investigate medulloblastoma specifically likely due to small sample size.²²⁹ In a study of ambient air exposures, prenatal exposure to toluene (an aromatic solvent) and TCE and DCM (chlorinated solvents) was not associated with medulloblastoma, however ambient air exposures are likely to be far lower than those encountered in occupational settings.²⁸³ There is growing knowledge that brain tumors including medulloblastoma involve the aryl hydrocarbon receptor (AhR).³⁶² Impairment and

overexpression of AhR disrupts cell cycle regulation of cerebellar neuronal precursors, potentially promoting medulloblastoma.³⁶³ Furthermore, toluene, TCE and DCM are known for their neurotoxicity.^{364, 365} Due to their lipophilicity, these agents can easily cross the blood-brain barrier,^{366, 367} causing pathologic changes that lead to the impairment of coordination and balance, cognition, visual and auditory function, as well as sleep cycle abnormalities.^{364, 365, 368} However, only polycyclic aromatic hydrocarbons but not other hydrocarbons are well-known to activate the AhR and induce gene mutations.^{362, 369}

Prior studies of ALL found associations with maternal occupational exposures to aromatic, aliphatic/alicyclic hydrocarbons, and with TCE, toluene and 1,1,1-TCA specifically.^{93, 211, 218, 219, 343} These studies, some with small sample sizes, relied on interviews to obtain occupational histories and may have been subject to recall bias. Our study instead used a JEM for exposure assessment that is not affected by this potential bias.^{356, 370} Studies have shown that ALL is likely to originate from chromosomal translocations generated in utero.^{371, 372} Chromosomal aberrations have also been proposed as a biomarker for the risk of developing hematologic cancers.³⁷³ A few studies have reported associations between genotoxic effects including chromosomal aberrations and occupational exposure to paints and aromatic hydrocarbons including benzene and toluene.³⁷⁴⁻³⁷⁹ In addition, the oxidative metabolites of trichloroethylene including chloral/chloral hydrate are shown to be genotoxic, leading to an increase level of chromosomal aberrations.³⁸⁰

Our study is the first study to report an increased risk of childhood NHL with maternal occupational exposure to chlorinated hydrocarbons in pregnancy. Previously, it has been shown that adults occupationally exposed to chlorinated hydrocarbons were at greater risk of NHL.^{381, 382} Maternal exposure to hydrocarbon solvents including TCE in pregnancy may impact the

development of immune system in newborns, indicated by epidemiologic and experimental studies. The immunotoxicity of TCE was extensively studied mostly in experimental studies,³⁸³ and it was suggested that gestational exposure to TCE in mice may lead to epigenetic changes of CD4+ T cells.³⁸⁴ Maternal exposure to TCE in pregnancy was associated with a lower level of interleukin-2-producing T cells in neonatal cord blood,³⁸⁵ suggesting a compromised immune system.³⁸⁶ Despite inconsistent, some studies have reported maternal occupational exposure to solvents was associated with a higher risk of allergic diseases including wheezing, asthma, hay fever and atopic eczema, indicating a vulnerable immune system.³⁸⁷ It is likely that maternal exposure to solvents impair the immune system of newborns, increasing the risk of childhood NHL, as immune deficiency is a risk factor for childhood NHL.³⁸⁸

We found an increased risk of germ cell tumors with aromatic hydrocarbons, as well as DCM, TCE and 1,1,1-TCA (chlorinated hydrocarbons). There are few epidemiologic studies on maternal occupational exposure to hydrocarbon solvents and germ cell tumors. Two previous studies have linked maternal occupational exposure to chemicals or solvents to an increased risk of malignant germ cell tumors, without specifying chemical types.^{389, 390} A California study reported an increased risk of germ cell tumors in children associated with maternal ambient DCM exposure in pregnancy.³⁹¹ Given the carcinogenicity of DCM, TCE and 1,1,1-TCA, maternal exposure to these hydrocarbons may disrupt the differentiation and migration of primordial germ cells in the early embryo, possibly promoting the development of germ cell tumors.^{240, 333, 392}

Co-exposures were likely to occur in our study. In sensitivity analyses examining the exposure to only one hydrocarbon group, the effect estimates remained elevated, which meant

our study had minimal impacts from co-exposure confounding between hydrocarbon groups. However, we were not able to evaluate exposure to any of the individual hydrocarbons alone due to sample size issues and because most workers are exposed to multiple solvents in their jobs. Our findings regarding individual hydrocarbons need to be interpreted with caution because of the moderate to high correlation between individual hydrocarbons resulting in potential co-exposure confounding. Our sensitivity analyses to remove influences from paternal exposure suggested comparable findings, which meant paternal exposure did not confound the associations we observed. In addition, the sensitivity analyses including parents without records of employment in the unexposed group (stay-at-home parents, students, and self-employed individuals, whose records are not in the Supplementary Pension Fund system) yielded similar results, suggesting our study were not subject to selection bias.

Our study may introduce non-differential misclassification, biasing the results towards the null. JEMs are known to suffer from exposure misclassification as workers have different jobs – some more exposed than others – and pregnant women may be assigned different job tasks, and thus may not have been as highly exposed to hydrocarbons despite having an industry code that suggests it. We were unable to assess trimester specific exposures since few parents changed their jobs in pregnancy. Mothers were typically employed in the same industry throughout pregnancy (in our study, only 8.8% of mothers changed their jobs in pregnancy). Furthermore, our results for all cancer outcomes most likely represent first and second and early third trimester exposures, as after 1980 all women in Denmark begin maternity leave 4 weeks prior to birth, and also are allowed to initiate maternity leave earlier if pregnancy conditions warrant it.

Increased risks of fetal loss and spontaneous abortion have been previously reported among pregnant women occupationally exposed to high levels of solvents in dry cleaning and painting industries.^{393, 394} Thus, our study which only included live births, and our study design excluded mothers who were unable to conceive, may have been affected by live birth bias.

Maternal exposure to hydrocarbon solvents at workplace in pregnancy may lead to a higher risk of childhood cancer including medulloblastoma, ALL, NHL, and possibly germ cell tumors. We encourage maternal workplace safety for children's health.

4.6 Figures and tables

Table 4-1. Demographic, gestational, parental characteristics of population cases and controls, 1968-2013

Characteristics	Cases (N = 10442) N (%)	Controls (N = 261050) N (%)
Child's sex		
Male	5303 (50.8)	132575 (50.8)
Female	5139 (49.2)	128475 (49.2)
Child's birthplace		
Urban	3496 (33.5)	84946 (32.5)
Small towns	3358 (32.2)	85645 (32.8)
Rural	3588 (34.4)	90459 (34.7)
Paternal age, (Mean $\pm$ Standard Deviation)	30.4 $\pm$ 6.0	30.4 $\pm$ 5.9
Maternal age, (Mean $\pm$ Standard Deviation)	27.6 $\pm$ 5.1	27.6 $\pm$ 5.0
Paternal birthplace		
Denmark	9514 (91.1)	240222 (92.0)
Other Europe	333 (3.2)	7813 (3.0)
North America	33 (0.3)	526 (0.2)
Asia	106 (1.0)	2827 (1.1)
Africa	79 (0.8)	1795 (0.7)
Other	255 (2.4)	5923 (2.3)
Missing	122	1944
Maternal birthplace		
Denmark	9677 (92.7)	242389 (92.9)
Other Europe	325 (3.1)	7916 (3.0)
North America	24 (0.2)	458 (0.2)
Asia	121 (1.2)	3486 (1.3)
Africa	56 (0.5)	1335 (0.5)
Other	214 (2.1)	4889 (1.9)
Missing	25	577
Family socioeconomic status ^a		
1 (highest)	1042 (10.0)	26243 (10.1)
2	1360 (13.0)	34071 (13.1)
3	1574 (15.1)	40928 (15.7)
4	2773 (26.6)	69577 (26.7)
5 (lowest)	1572 (15.1)	39155 (15.0)
Missing	2121	51076
Maternal smoking status ^b		
Smoker	1058 (10.1)	24976 (9.6)
Non-smoker	2942 (28.2)	75375 (28.9)
Missing	224	5249

^a Missing data on family socioeconomic status increased over time due to changes in Danish tax law

^b Data for maternal smoking were only available for births from 1991 and onward

Table 4-2. Odds ratios and 95% confidence intervals for associations between maternal occupational exposure to 3 major hydrocarbon groups and offspring cancer risks, (N = 189151)

Cancer types	Aliphatic/alicyclic hydrocarbons			Aromatic hydrocarbons			Chlorinated hydrocarbons		
	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	7332 (4.0)	Ref	Ref	8525 (4.7)	Ref	Ref	5700 (3.1)	Ref	Ref
ALL	60 (5.0)	1.24	1.25 (0.95, 1.63)	74 (6.2)	1.28	1.29 (1.01, 1.64)	42 (3.5)	1.05	1.04 (0.76, 1.43)
NHL	<10 ^b	***	***	12 (6)	1.35	1.39 (0.76, 2.53)	12 (6)	2.00	1.94 (1.05, 3.57)
Medulloblastoma	12 (6.9)	1.80	1.80 (0.98, 3.30)	13 (7.5)	1.64	1.64 (0.92, 2.94)	12 (6.9)	2.32	2.29 (1.24, 4.25)
Glioma	36 (4.7)	1.24	1.24 (0.88, 1.76)	36 (4.7)	1.04	1.04 (0.74, 1.47)	24 (3.1)	1.11	1.09 (0.72, 1.66)
Germ cell tumors	13 (3.8)	0.96	0.97 (0.55, 1.71)	21 (6.1)	1.42	1.44 (0.91, 2.26)	<10 ^b	***	***
Neuroblastoma	<10 ^b	***	***	10 (3.6)	0.84	0.83 (0.44, 1.59)	<10 ^b	***	***

Note:

^a Odds ratios adjusted for maternal age, maternal race, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma

Table 4-3. Odds ratios and 95% confidence intervals for associations between maternal occupational exposure to individual hydrocarbons and offspring cancer risks, (N = 189151)

Cancer types	Cases, N (%)	Toluene		Methylene chloride		Trichloroethylene		1,1,1-Trichloroethane	
		Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	7755 (4.3)	Ref	Ref	11308 (6.2)	Ref	Ref	11088 (6.1)	Ref	Ref
ALL	62 (5.2)	1.22	1.23 (0.94, 1.59)	81 (6.8)	1.09	1.11 (0.88, 1.39)	85 (7.1)	1.17	1.18 (0.94, 1.48)
AML	<10 ^b	***	***	13 (5.3)	0.85	0.88 (0.50, 1.56)	14 (5.8)	0.97	1.00 (0.58, 1.75)
HL	<10 ^b	***	***	15 (5.0)	0.74	0.74 (0.44, 1.26)	15 (5.0)	0.75	0.75 (0.44, 1.27)
NHL	<10 ^b	***	***	11 (5.5)	0.88	0.91 (0.49, 1.69)	10 (5.0)	0.81	0.83 (0.44, 1.59)
Medulloblastoma	13 (7.5)	1.92	1.92 (1.07, 3.46)	17 (9.8)	1.71	1.69 (1.01, 2.84)	18 (10.3)	1.88	1.86 (1.12, 3.10)
Glioma	39 (5.1)	1.29	1.29 (0.92, 1.79)	49 (6.4)	1.10	1.09 (0.81, 1.47)	36 (4.7)	1.16	1.16 (0.86, 1.55)
Malignant bone tumors	<10 ^b	***	***	15 (5.6)	0.83	0.84 (0.49, 1.42)	13 (4.9)	0.71	0.71 (0.40, 1.25)
Germ cell tumors	13 (3.8)	0.91	0.92 (0.52, 1.61)	25 (7.3)	1.24	1.27 (0.84, 1.94)	25 (7.3)	1.29	1.32 (0.87, 2.01)
Teratoma	<10 ^b	***	***	10 (7.4)	1.18	1.18 (0.61, 2.29)	<10 ^b	***	***
Neuroblastoma	<10 ^b	***	***	15 (5.5)	1.00	1.02 (0.60, 1.74)	17 (6.2)	1.16	1.18 (0.71, 1.96)
Wilms tumor	<10 ^b	***	***	12 (5.8)	0.87	0.88 (0.48, 1.59)	12 (5.8)	0.88	0.89 (0.49, 1.60)

Note:

^a Odds ratios adjusted for maternal age, maternal race, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

4.7 Supplementary materials

Table S4-1. Prevalence of industry employment with the exposure to hydrocarbons among the exposed mothers

Hydrocarbon group	Industry	N	%
Chlorinated hydrocarbons			
Total exposed N = 5934	Laboratory assistants	2238	37.7
	Printers	1436	24.2
	Painters, lacquerers, and floor layers	632	10.7
	Cookers and furnacemen (chemical processes)	463	7.8
	Footwear workers, etc.	353	6.0
	Lithographers	250	4.2
	Occupation in graphics, etc.	178	3.0
	Lasters and sole fitters etc.	117	2.0
	Rubber products workers	85	1.4
	Laundry workers	74	1.3
	Metal plating and coating work	67	1.1
	Shoe sewers	14	0.2
	Leather cutters for footwear	11	0.2
	Chemists	10	0.2
	Refinery workers, other occupations in the chemical industry	6	0.1
Aliphatic/alicyclic hydrocarbons			
Total exposed N = 7620	Machine and engine mechanics	2563	33.6
	Printers	1686	22.1
	Wooden surface finishers	1415	18.6
	Painters, lacquerers, and floor layers	633	8.3
	Cookers and furnacemen (chemical processes)	469	6.2
	Footwear workers, etc.	353	4.6
	Occupation in graphics, etc.	178	2.3
	Lasters and sole fitters etc.	117	1.5
	Rubber products workers	84	1.1
	Laundry workers	73	1.0
	Upholsterers	18	0.2
	Shoe sewers	14	0.2
	Leather cutters for footwear	11	0.1
	Refinery workers, other occupations in the chemical industry	6	0.1
Aromatic hydrocarbons			
Total exposed N = 8862	Printers	1686	19.0
	Chemists	1569	17.7
	Bench carpenters	1528	17.2

Plastic product workers	1084	12.2
Maintenance crews and supervisors	816	9.2
Painters, lacquerers and floor layers	631	7.1
Cookers and furnacemen (chemical processes)	465	5.2
Footwear workers, etc.	353	4.0
Service station attendants	230	2.6
Occupation in graphics, etc.	178	2.0
Lasters and sole fitters etc.	117	1.3
Rubber products workers	84	0.9
Laundry workers	72	0.8
Upholsterers	18	0.2
Shoe sewers	14	0.2
Leather cutters for footwear	11	0.1
Refinery workers, other occupations in the chemical industry	6	0.1

Table S4- 2. Correlation coefficients between 3 major hydrocarbon groups

	Chlorinated hydrocarbons	Aromatic hydrocarbons	Aliphatic/alicyclic hydrocarbons
Chlorinated hydrocarbons	1		
Aromatic hydrocarbons	0.71	1	
Aliphatic/alicyclic hydrocarbons	0.52	0.70	1

Table S4-3. Correlation coefficients between specific hydrocarbons

	Methylene Chloride	Toluene	1,1,1- Trichloroethane	Trichloroethylene
Methylene Chloride	1			
Toluene	0.62	1		
1,1,1-Trichloroethane	0.76	0.41	1	
Trichloroethylene	0.93	0.58	0.81	1

Table S4-4. Sensitivity analysis for mothers exposed to one hydrocarbon group only and the associations with offspring cancer risks, (N = 189151)

Cancer types	Aliphatic/alicyclic hydrocarbons only			Aromatic hydrocarbons only			Chlorinated hydrocarbons only		
	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	3833 (2.1)	Ref	Ref	5475 (3.0)	Ref	Ref	2907 (1.6)	Ref	Ref
ALL	36 (3)	1.48	1.49 (1.05, 2.09)	52 (4.3)	1.40	1.40 (1.05, 1.86)	21 (1.8)	1.00	0.98 (0.63, 1.53)
NHL	<10 ^b	***	***	<10 ^b	***	***	10 (5.0)	3.03	2.81 (1.42, 5.56)
Glioma	21 (2.7)	1.31	1.32 (0.84, 2.06)	23 (3)	0.99	1.00 (0.65, 1.52)	11 (1.4)	0.98	0.96 (0.52, 1.77)
Germ cell tumors	10 (2.9)	1.43	1.46 (0.76, 2.79)	18 (5.2)	1.96	2.00 (1.22, 3.28)	<10 ^b	***	***

Note:

^a Odds ratios adjusted for maternal age, maternal birthplace, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma

Table S4-5. Sensitivity analysis for the associations with hydrocarbon groups, excluding children with fathers also exposed to hydrocarbons

Cancer types	Aliphatic/alicyclic hydrocarbons N = 186109 ^a			Aromatic hydrocarbons N = 186233 ^b			Chlorinated hydrocarbons N = 187634 ^c		
	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^d	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^d	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^d
Controls	4537 (2.5)	Ref	Ref	5601 (3.1)	Ref	Ref	4250 (2.4)	Ref	Ref
ALL	39 (3.3)	1.28	1.29 (0.93, 1.80)	54 (4.6)	1.41	1.41 (1.06, 1.87)	33 (2.8)	1.10	1.09 (0.76, 1.55)
Medulloblastoma	<10 ^e	***	***	11 (6.4)	2.02	2.02 (1.07, 3.82)	<10 ^e	***	***
Glioma	21 (2.8)	1.22	1.23 (0.79, 1.92)	27 (3.6)	1.20	1.19 (0.80, 1.77)	16 (2.1)	0.98	0.97 (0.58, 1.60)
Germ cell tumors	<10 ^e	***	***	12 (3.6)	1.21	1.22 (0.68, 2.20)	<10 ^e	***	***

Note:

^a The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons

^b The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons

^c The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons

^d Odds ratios adjusted for maternal age, maternal birthplace, and child's birthplace

^e Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI, confidence interval; ALL, acute lymphoblastic leukemia

Table S4-6. Sensitivity analysis for the associations with individual hydrocarbons, excluding children with fathers also exposed to hydrocarbons

Cancer types	Toluene N = 186035 ^a			Methylene chloride N = 184629 ^b			Trichloroethylene N = 184672 ^c			1,1,1-Trichloroethane N = 186186 ^d		
	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^e	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^e	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^e	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^e
Controls	4771 (2.7)	Ref	Ref	6973 (3.9)	Ref	Ref	6805 (3.8)	Ref	Ref	4983 (2.8)	Ref	Ref
ALL	40 (3.4)	1.28	1.27 (0.93, 1.77)	51 (4.4)	1.11	1.12 (0.84, 1.49)	54 (4.6)	1.20	1.22 (0.92, 1.61)	41 (3.5)	1.27	1.29 (0.94, 1.78)
Medulloblastoma	<10 ^e	***	***	11 (6.5)	1.89	1.88 (0.99, 3.54)	10 (6.0)	1.77	1.76 (0.91, 3.43)	<10 ^e	***	***
Glioma	23 (3.1)	1.28	1.28 (0.84, 1.97)	34 (4.5)	1.24	1.23 (0.87, 1.75)	33 (4.4)	1.26	1.26 (0.88, 1.80)	27 (3.6)	1.36	1.35 (0.91, 2.01)
Germ cell tumors	<10 ^e	***	***	15 (4.5)	1.21	1.25 (0.74, 2.13)	15 (4.5)	1.25	1.29 (0.76, 2.19)	11 (3.3)	1.22	1.26 (0.68, 2.34)

Note:

^a The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons^b The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons^c The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons^d The number indicates the study population excluding children of fathers who were also exposed to hydrocarbons^e Odds ratios adjusted for maternal age, maternal birthplace, and child's birthplace^f Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI, confidence interval; ALL, acute lymphoblastic leukemia

Table S4-7. Classifying mothers missing occupational history in pregnancy as the unexposed: odds ratios and 95% confidence intervals for associations between maternal occupational exposure to 3 major hydrocarbon groups and offspring cancer risks (N=271492)

Cancer types	Aliphatic/alicyclic hydrocarbons			Aromatic hydrocarbons			Chlorinated hydrocarbons		
	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	7332 (2.8)	Ref	Ref	8525 (3.3)	Ref	Ref	5700 (2.2)	Ref	Ref
ALL	60 (5.0)	1.36	1.35 (1.04, 1.76)	74 (6.2)	1.40	1.39 (1.10, 1.77)	42 (3.5)	1.15	1.14 (0.83, 1.56)
NHL	<10 ^b	***	***	12 (6)	1.33	1.38 (0.76, 2.49)	12 (6)	1.96	1.94 (1.06, 3.54)
Medulloblastoma	12 (6.9)	1.98	1.97 (1.08, 3.60)	13 (7.5)	1.80	1.81 (1.01, 3.22)	12 (6.9)	2.54	2.60 (1.41, 4.80)
Glioma	36 (4.7)	1.32	1.32 (0.94, 1.86)	36 (4.7)	1.11	1.11 (0.79, 1.56)	24 (3.1)	1.18	1.17 (0.77, 1.77)
Germ cell tumors	13 (3.8)	0.99	0.99 (0.56, 1.73)	21 (6.1)	1.45	1.45 (0.93, 2.28)	<10 ^b	***	***
Neuroblastoma	<10 ^b	***	***	10 (3.6)	0.90	0.91 (0.48, 1.72)	<10 ^b	***	***

Note:

^a Odds ratios adjusted for maternal age, maternal race, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI, confidence interval; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma

Table S4-8. Classifying mothers missing occupational history in pregnancy as the unexposed: odds ratios and 95% confidence intervals for associations between paternal occupational exposure to specific hydrocarbons and offspring cancer risks (N=271492)

Cancer types	Cases, N (%)	Toluene		Methylene chloride			Trichloroethylene			1,1,1-Trichloroethane		
		Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	7755 (3.0)	Ref	Ref	11308 (4.3)	Ref	Ref	11088 (4.3)	Ref	Ref	7812 (3.0)	Ref	Ref
ALL	62 (5.2) <10 ^b	1.33	1.33 (1.02, 1.72)	81 (6.8)	1.20	1.20 (0.96, 1.51)	85 (7.1)	1.27	1.28 (1.03, 1.61)	64 (5.3)	1.40	1.41 (1.09, 1.82)
AML	<10 ^b	***	***	13 (5.3)	0.93	0.95 (0.54, 1.67)	14 (5.8)	1.05	1.08 (0.62, 1.86)	11 (4.5)	1.29	1.31 (0.71, 2.43)
HL	<10 ^b	***	***	15 (5.0)	0.70	0.71 (0.42, 1.20)	15 (5.0)	0.71	0.72 (0.43, 1.21)	12 (4.0)	0.79	0.81 (0.45, 1.45)
NHL	<10 ^b	***	***	11 (5.5)	0.87	0.90 (0.49, 1.66)	10 (5.0)	0.81	0.83 (0.44, 1.58)	<10 ^b	***	***
Medulloblastoma	13 (7.5)	2.11	2.10 (1.18, 3.76)	17 (9.8)	1.88	1.87 (1.12, 3.13)	18 (10.3)	2.06	2.05 (1.24, 3.38)	<10 ^b	***	***
Glioma	39 (5.1)	1.37	1.37 (0.99, 1.90)	49 (6.4)	1.17	1.17 (0.87, 1.57)	36 (4.7)	1.24	1.24 (0.92, 1.65)	50 (6.5)	1.24	1.24 (0.88, 1.74)
Malignant bone tumors	<10 ^b	***	***	15 (5.6)	0.91	0.91 (0.54, 1.54)	13 (4.9)	0.77	0.77 (0.44, 1.35)	11 (4.1)	0.87	0.86 (0.47, 1.59)
Germ cell tumors	13 (3.8) <10 ^b	0.94	0.93 (0.53, 1.63)	25 (7.3)	1.28	1.29 (0.86, 1.95)	25 (7.3)	1.32	1.34 (0.88, 2.02)	18 (5.2)	1.30	1.31 (0.81, 2.12)
Teratoma	<10 ^b	***	***	10 (7.4)	1.25	1.24 (0.64, 2.38)	<10 ^b	***	***	10 (7.4)	1.20	1.19 (0.55, 2.57)
Neuroblastoma	<10 ^b	***	***	15 (5.5)	1.08	1.10 (0.65, 1.87)	17 (6.2)	1.26	1.28 (0.78, 2.12)	13 (4.7)	1.34	1.36 (0.77, 2.41)
Wilms tumor	<10 ^b	***	***	12 (5.8)	0.91	0.91 (0.51, 1.64)	12 (5.8)	0.92	0.92 (0.51, 1.66)	<10 ^b	***	***

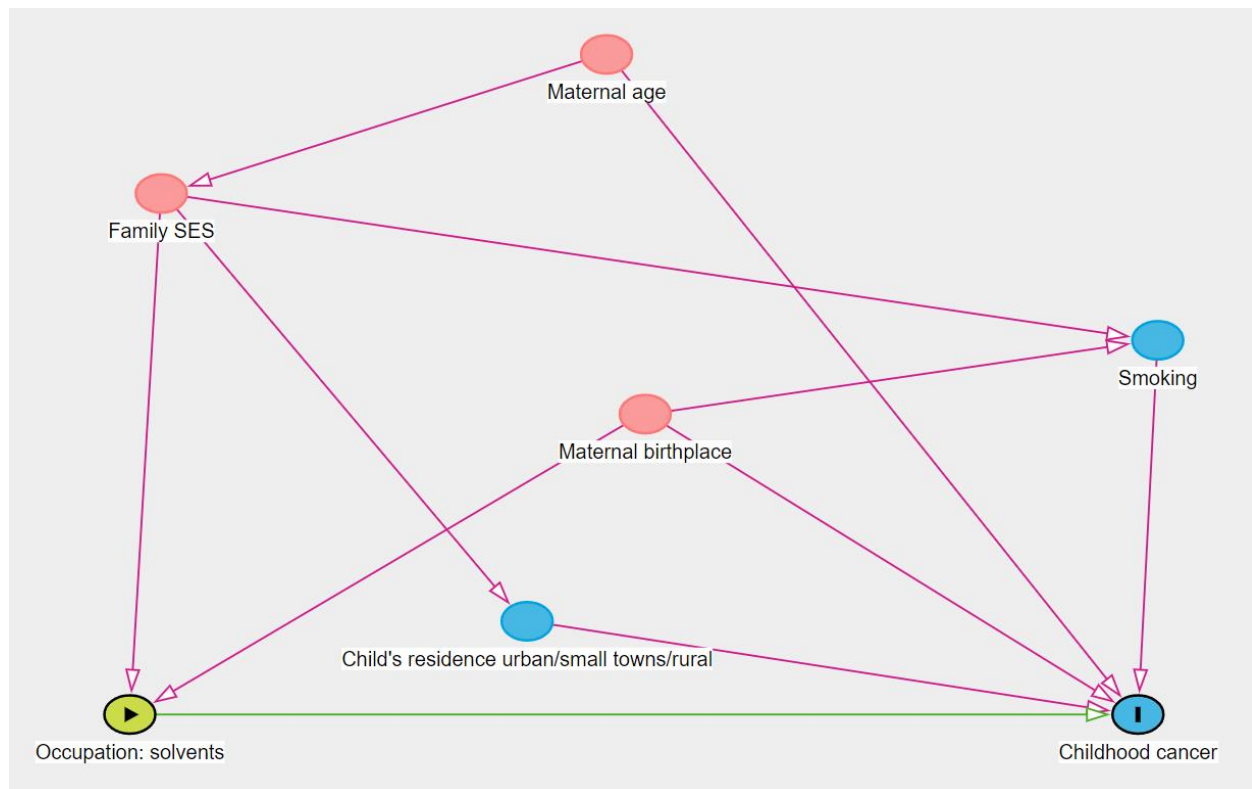
Note:

^a Odds ratios adjusted for maternal age, maternal race, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Figure S4-1. Directed acyclic graph for confounder selection



5 Paternal exposure to hydrocarbon solvents at workplace and cancer risk in offspring

5.1 Abstract

Background: According to the International Agency for Research on Cancer (IARC), hydrocarbons are known or suspected carcinogens. Our study aimed to estimate childhood cancer risks associated with paternal exposure to aromatic, aliphatic/alicyclic, chlorinated hydrocarbons, as well as the individual chemicals, trichloroethylene an IARC Group 1 carcinogen and the Group 2A carcinogens methylene chloride and 1,1,1-trichloroethane, and toluene.

Methods: For this population-based case-control study of Danish children (born 1968-2013) < 20 years of age 10,442 cancer cases diagnosed 1968-2016 were matched to 261,050 cancer-free controls (25:1 matching ratio by sex and birth date). Measures of paternal occupational exposure to hydrocarbons were generated by a job-exposure matrix to span the time 3 months prior to conception until the child's birthdate. We employed conditional logistic regression to estimate associations between hydrocarbons (any or high/low exposure) and offspring cancer risks adjusting for confounders.

Results: We found consistent associations for some hydrocarbon solvents and glioma, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), osteosarcoma, hepatoblastoma, and possibly retinoblastoma in children. The risk of glioma was highest in children of fathers highly exposed to chlorinated hydrocarbons (low exposure: adjusted Odds Ratio (aOR): 1.29; 95% Confidence Interval (CI): 0.91, 1.83; high exposure: aOR: 1.82; 95% CI: 1.18, 2.82), while AML risk was highest when fathers were exposed to aliphatic/alicyclic hydrocarbons (low: aOR:

1.13; 95% CI: 0.71, 1.80; high: aOR: 1.87; 95% CI: 1.24, 2.82). The risk of ALL was slightly increased with toluene exposure (low: aOR: 1.01; 95% CI: 0.82, 1.26; high: aOR: 1.23; 95% CI: 0.98, 1.54), and the risk of osteosarcoma increased with 1,1,1- trichloroethane exposure (low: aOR: 1.23; 95% CI: 0.63, 2.41; high: aOR: 2.29; 95% CI: 1.25, 4.18).

Conclusions: Our findings in Denmark suggest that paternal hydrocarbon exposure in preconception and pregnancy periods may increase the risk of certain childhood cancers in their offspring.

5.2 Introduction

Childhood cancer is the second leading cause of death among children in high-income countries,³⁹⁵ with incidence increasing over recent decades in Denmark.¹⁵ Although the etiology of childhood cancer remains largely unknown, it is suspected that paternal occupational exposure to chemicals prior to or during pregnancy can contribute to a higher risk of childhood cancer in the offspring.³⁴²

Genetic alterations in paternal germ cells caused by chemical exposures during the preconception period can be passed to the offspring.³⁹⁶ Alternatively, exposures during pregnancy brought home to expose the pregnant spouse may lead to altered fetal programming and permanent changes that affect the risk of childhood cancer.^{215, 336} Solvents including toluene, trichloroethylene (TCE), perchloroethylene (PCE), methylene chloride (DCM), and 1,1,1-trichloroethane (1,1,1-TCA) are widely used in industries such as petroleum refining, dry cleaning, printing, and metal degreasing.^{240, 333-335} TCE is classified as a Group 1 carcinogen, while PCE, 1,1,1-TCA and DCM are classified as Group 2A carcinogens by the International Agency for Research on Cancer (IARC).^{240, 333-335} Experimental studies showed toluene, PCE and TCE may contribute to germ cell mutations during spermatogenesis and DCM caused genotoxic effects on sperm cells.²⁰⁰⁻²⁰³ 1,1,1-TCA also exhibits mutagenicity in mouse models, although there is no information that mutations were observed in germ cells.²⁰³

Some epidemiologic studies have linked childhood cancer to paternal exposure to hydrocarbon groups as well as to individual hydrocarbons, but results were inconsistent. A moderate increase in the risk of acute lymphoblastic leukemia (ALL) was previously associated with paternal occupational exposure to aromatic hydrocarbons.^{93, 225} A two-fold increase in the

risk of ALL was associated with Latino fathers occupationally exposed to chlorinated hydrocarbons.⁹³ Nonetheless, several other studies of ALL and hydrocarbon solvents reported null associations or were underpowered.^{211, 225, 228, 343} Studies of other cancer types were often limited due to insufficient statistical power.^{231, 345, 397} One study reported a positive association between brain tumors and paternal occupational exposure to aromatic hydrocarbons.²⁰⁵

One challenge of previous investigations in addition to small sample sizes was that findings were based on retrospectively self-reported exposures. To overcome these limitations, we employed job exposure matrices (JEM) derived exposures to examine the risk of cancer in Danish children. Specifically, we examined associations of paternal exposure to four individual hydrocarbons (i.e., toluene, DCM, TCE, 1,1,1-TCA) and three major hydrocarbon subgroups (i.e., chlorinated, aliphatic/alicyclic, aromatic hydrocarbons) with childhood cancer. We had intended to examine PCE exposure as well, but this exposure was too rare in Denmark to be investigated for childhood cancers (3.8% of controls were exposed).

5.3 Methods

Data sources and study population

This population-based case-control study utilized database linkage. Data were taken from four Danish registries and linked via a unique personal identification number allocated to each resident: the Central Population Registry (established in 1968),³⁴⁷ the Danish Cancer Registry (established in 1942),³⁴⁸ the Supplementary Pension Fund (established in 1964),³⁴⁹ and the Danish Medical Birth Registry (computerized since 1973).³⁵⁰ Details on these registries were reported in previous publications.^{34, 351}

Our study includes all childhood cancer cases born from 1968 to 2013 and diagnosed from 1968 to 2016 in Denmark who were age 0-19 years at diagnosis. Childhood cancer cases were identified from the Danish Cancer Registry and classified based on the International Classification of Childhood Cancer, Version 1 until 2003 and Version 3 thereafter. The histologic subtypes of cancer were determined according to the International Classification of Diseases for Oncology, Version 1 until 2003 and Version 3 thereafter. We identified medulloblastoma using ICD-O coding defined by the Central Brain Tumor Registry of the United States.³⁵² Controls were individuals who were alive and free of cancer at the date of diagnosis of the corresponding case, randomly selected from the Central Population Registry, and matched to cases by birth date and sex (25:1 ratio). If 25 controls with the corresponding case's birthday could not be identified, we widened the search by 1 day (on either side), then 2 days, etc, until a sufficient number of controls were selected.

We obtained information on gestational factors from the Medical Birth Registry. Gestational age was not consistently available throughout the study period. When gestational age was missing, we used multiple imputation to estimate it, as described previously.³⁵³ Date of conception was calculated by subtracting the child's gestational age in days from their birth date.

Informed consent was not required for this registry-based study. Study approval was received from the Danish Data Protection Agency and the human subjects' protection boards at the University of California, Los Angeles, and the University of North Texas.

Exposure assessment

Paternal occupational history information was extracted from the Supplementary Pension Fund Register. Participation in the Supplementary Pension Fund is mandatory for all salaried

employees in Denmark aged 18-66 years and working at least 9 hours per week (starting in 1978, individuals aged 16-17 years were additionally included). The system does not include students, unemployed (including stay-at-home parents), self-employed, or individuals born before April 1st, 1897.³⁴⁹ For each employment entry, the register keeps records of start/end dates, the company name, a unique company number, and the personal identification number. The Statistics Denmark Occupational Classification is a 5-digit extended version of the United Nation's 4-digit International Standard Industrial Classification of All Economic Activities.³⁵⁵ We identified industries with hydrocarbon exposure (i.e., chlorinated, aliphatic/alicyclic, aromatic hydrocarbons, toluene, TCE, DCM, 1,1,1-TCA), using the Danish version of the Nordic Occupational Cancer Study JEM.³⁵⁶ The JEMs employed in this study were adapted from templates of previously developed Finnish JEMs. The construction of JEMs for hydrocarbon groups were primarily based on expert assessments in 1968-1974, while the JEMs for individual hydrocarbons were constructed from estimated annual mean levels of exposure (ppm) based on workplace-based biomonitoring and ambient measurements in workplace environments since 1975.^{356, 357} Relying on both systems of exposure assessment resulted in some minor discrepancies when expert derived broader groupings did not include all measurement based individual chemicals. For example, workplaces with measured toluene may not have been considered exposed to aromatic hydrocarbons according to expert ratings, and workplaces with TCE, DCM or 1,1,1-TCA measurements may not have always been consistently rated as belonging to the larger category of chlorinated hydrocarbon exposure industries.

Using these JEMs, we previously investigated paternal occupations in specific industries where hydrocarbon exposures are common and reported on associations between central nervous

system (CNS) tumors and employment in painting and printing industries.^{208, 226, 398} Here we investigated hydrocarbons in the following groups: chlorinated, aliphatic/alicyclic, and aromatic hydrocarbons and the following individual solvents: toluene, TCE, DCM, and 1,1,1-TCA.

Spermatogenesis takes approximately 90 days.³⁹⁹ Paternal hydrocarbon exposures during the 3 months preconception were strongly correlated with those during the pregnancy periods (correlation coefficient: 0.90-0.91), thus the fathers remained within the same job for the two periods. We investigated paternal exposure from 3 months preconception to birth.⁴⁰⁰ We excluded children for whom there was no record of a paternal occupational history during this time.

Fathers were classified as exposed if they were employed in hydrocarbon-exposed industries. For each identified hydrocarbon-exposed industry, we calculated exposure intensity by multiplying the estimated exposure level by the exposure probability assigned for each hydrocarbon according to the JEM.³⁵⁶ Because linearity was violated for some associations indicated by Box-Tidwell tests, we stratified the exposure intensity by the median of all exposed control fathers. Industries with a period-specific exposure intensity above or equal to the median were classified as high exposure, while industries with a period specific exposure intensity below the median and above zero were classified as low exposure. Maternal exposure to hydrocarbon solvents in pregnancy were identified and classified, based on the same JEM and following the same approach.

Statistical analyses

Population characteristics were described, using frequencies (percentages) for categorical variables and means (standard deviations) for continuous variables. We calculated the

frequencies and percentages of fathers in our study employed in industries exposed to each hydrocarbon group.

Conditional logistic regression analyses with adjustment for confounders were performed to estimate the risk of childhood cancer associated with each of the paternal occupational exposures. We used binary (exposed/unexposed) measures in primary analyses but also compared high and low exposure to no exposure whenever statistical power allowed.

Based on previous research, we selected possible covariates for adjustment using a directed acyclic graph (**Figure S5-1**).^{205, 208, 358, 359} Information on parental and child factors as well as gestational factors were obtained from the Central Population Registry and the Medical Birth Registry. Paternal age (continuous), paternal birthplace (Denmark/Other Europe/North America/Asia/Africa/Other), and child's birthplace (urban/small town/rural residence) were selected for adjustment. Because maternal smoking is a suspected risk factor for childhood cancer,⁶¹ we also attempted to control for maternal smoking status (ever smoked vs. non-smoker). As maternal smoking was available for only half of the study period (1991+), we imputed maternal smoking status employing a predictive model for maternal smoking, using birthweight, birth year, and maternal socioeconomic status (SES) as a proxy for maternal education, parity, and maternal birthplace as a proxy for maternal race.³⁶⁰ Results remained largely unchanged when we adjusted for maternal smoking, hence this covariate was left out of our final models.

Sensitivity analyses

Some industries expose workers to multiple hydrocarbon solvents, and we are providing Pearson correlations for the 3 hydrocarbon groups and the 4 individual hydrocarbons. To address

potential confounding by co-exposure to other hydrocarbons, we identified industries only exposed to one hydrocarbon group. Sensitivity analyses were conducted in which we examined childhood cancer risk among fathers employed in industries only exposed to one of the hydrocarbon groups. We were not able to conduct similar sensitivity analyses for individual hydrocarbon solvents because these exposures generally overlapped.

Pearson correlations suggested that paternal and maternal hydrocarbon exposures were only weakly correlated (correlation coefficient: 0.09-0.12) in our study. Nevertheless, we conducted sensitivity analyses after excluding children born to mothers who were occupationally exposed to hydrocarbons to ensure that paternal results were not confounded by maternal exposures.

Finally, we conducted sensitivity analyses that included fathers with missing occupational history among the unexposed.

All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA). We only reported risk estimates when the number of exposed cases was ≥ 10 .

5.4 Results

Our study population consisted of 10,442 cases and 261,050 matched controls. Parental demographic characteristics as well as the child's characteristics (i.e., child's sex and birthplace) were similar in cases and controls (**Table 5-1**).

Fathers exposed to chlorinated hydrocarbons were commonly employed as painters, lacquerers, and floor layers (N = 2796, 25.5%), typographers (N = 2789, 25.4%), and laboratory assistants (N = 1893, 17.3%). For aliphatic/alicyclic hydrocarbons, exposed fathers were commonly employed as machine and engine mechanics (N = 15527, 53.9%), wooden surface

finishers (N = 4862, 16.9%), and typographers (N = 3255, 11.3%). Finally, those exposed to aromatic hydrocarbons were mostly employed as bench carpenters (N = 10223, 36.8%), or worked on maintenance crews and as supervisors (N = 5080, 18.3%), and typographers (N = 3255, 11.7%) (**Table S5-1**). Furthermore, fathers employed as laboratory assistants, metal plating and coating workers, and lithographers were only exposed to chlorinated hydrocarbons. Fathers employed as machine and engine mechanics, and wooden surface finishers were only exposed to aliphatic/alicyclic hydrocarbons. Fathers employed as service station attendants, bench carpenters, plastic product workers and maintenance crews and supervisors were only exposed to aromatic hydrocarbons.

All three hydrocarbon group exposures were moderately to highly correlated (**Table S5-2**, correlation coefficient: 0.44-0.60) and correlations were even stronger for the four individual hydrocarbon solvents (**Table S5-3**, correlation coefficient: 0.55-0.89).

Aliphatic/alicyclic hydrocarbons were associated with increased risks of hepatoblastoma (**Table 5-2**, aOR: 2.01; 95% CI: 0.96, 4.22), acute myeloid leukemia (AML, aOR: 1.46; 95% CI: 1.06, 2.01), and suggested for glioma (aOR: 1.17; 95% CI: 0.97, 1.42), osteosarcoma (aOR: 1.21; 95% CI: 0.74, 1.99), and ALL (aOR: 1.12; 95% CI: 0.95, 1.32). When we stratified by exposure intensity, the risk of AML was stronger when fathers were highly exposed (**Table S5-4 and Figure 5-1**, low: aOR: 1.13; 95% CI: 0.71, 1.80; high: aOR: 1.87; 95% CI: 1.24, 2.82) but a clear dose response was not seen for ALL and impossible to estimate for hepatoblastoma or osteosarcoma as they are too rare. Sensitivity analysis based on paternal exposure solely to aliphatic/alicyclic hydrocarbons (**Table S5-5**), estimates for glioma weakened but remained similar for ALL and AML and increased for osteosarcoma (aOR: 1.64; 95% CI: 0.98, 2.74).

Aromatic hydrocarbons were associated with increased risks of AML (**Table 5-2**, aOR: 1.34; 95% CI: 0.96, 1.87) and glioma (aOR: 1.25; 95% CI: 1.03, 1.51). When we stratified by exposure intensity, similar associations for estimated low and high exposures to aromatic hydrocarbons were seen with glioma (**Table S5-6 and Figure 5-1**, low: aOR: 1.22; 95% CI: 0.97, 1.53; high: aOR: 1.31; 95% CI: 0.95, 1.81) but not AML. In sensitivity analysis investigating exposure solely to aromatic hydrocarbon, effect estimates for glioma and AML remained similar (**Table S5-5**).

Chlorinated hydrocarbons were associated with an increased risk of glioma (**Table 5-2**, aOR: 1.46; 95% CI: 1.11, 1.92) and possibly also retinoblastoma (aOR: 1.59; 95% CI: 0.84, 3.00). When we stratified by exposure intensity, the risk of glioma was stronger when fathers were highly exposed (**Table S5-7 and Figure 5-1**, low: aOR: 1.29; 95% CI: 0.91, 1.83; high: aOR: 1.82; 95% CI: 1.18, 2.82). In sensitivity analysis investigating exposure only to chlorinated hydrocarbons (**Table S5-5**), the estimates for glioma increased.

Toluene, an aromatic hydrocarbon, was associated with increased risks of hepatoblastoma (aOR: 2.45; 95% CI: 1.23, 4.91), AML (**Table 5-3**, aOR: 1.46; 95% CI: 1.06, 2.00), and glioma (aOR: 1.20 95% CI: 0.99, 1.45) and associations were suggestive for ALL (aOR: 1.11; 95% CI: 0.95, 1.30). When we stratified by exposure intensity, the risk of ALL was stronger when fathers were highly exposed (**Table S5-8 and Figure 5-2**, low: aOR: 1.01; 95% CI: 0.82, 1.26; high: aOR: 1.23; 95% CI: 0.98, 1.54), while the risk of glioma was only increased among children of fathers with low exposure (low: aOR: 1.35; 95% CI: 1.07, 1.70; high: aOR: 1.02; 95% CI: 0.76, 1.36).

When examining individual chlorinated hydrocarbons, we found that DCM (**Table 5-3**, aOR: 1.19; 95% CI: 0.99, 1.42), TCE (aOR: 1.23; 95% CI: 1.03, 1.47), and 1,1,1-TCA (aOR: 1.19; 95% CI: 0.98, 1.45), were also positively associated with glioma. However, when we stratified by exposure intensity, the risk of glioma was only increased among children of fathers with low exposure (**Tables S5-9, S5-10, S5-11 and Figure 5-2**). Additionally, 1,1,1-TCA was positively associated with osteosarcoma (**Table 5-3**, aOR: 1.73; 95% CI: 1.10, 2.71) and the risk was most strongly increased when fathers were considered highly exposed (**Table 5-11 and Figure 5-2**, low: aOR: 1.23; 95% CI: 0.63, 2.41; high: aOR: 2.29; 95% CI: 1.25, 4.18).

None of the associations discussed above changed more than minimally when we excluded children with both parents exposed or when we re-classified fathers with missing occupational history as unexposed (**Tables S5-12, S5-13, S5-14, S5-15**).

5.5 Discussion

This nationwide registry-based case-control study found that paternal exposures to aromatic hydrocarbons in preconception and pregnancy periods increase risk of childhood glioma and newly suggests exposure-response relationships between certain hydrocarbon solvents and several other childhood cancers, specifically chlorinated hydrocarbons and glioma, aliphatic/alicyclic hydrocarbons and AML, toluene and ALL, and 1,1,1-TCA and osteosarcoma. Our findings add important new evidence to the literature on offspring cancer risk from paternal solvent exposures and highlight the need for regulatory measures to reduce workers' exposures to hydrocarbon solvents.

Childhood glioma was positively associated with all hydrocarbon solvents we investigated. Although not specific to glioma, positive associations have previously been

reported for paternal exposure to aromatic hydrocarbons and childhood brain tumors.²⁰⁵ A study investigating paternal employment in painting industries with a mixture of exposures to aromatic and aliphatic hydrocarbons suggested an increased risk of childhood brain tumors in offspring.²⁰⁷ Our findings on glioma and both aromatic and aliphatic/alicyclic hydrocarbons may support these prior studies because glioma cases (N = 1032, 51.2%) account for more than half of the total number of CNS tumors in our study. No previous epidemiologic studies have linked the individual hydrocarbons we investigated to either childhood glioma or adult glioma.^{231, 333, 335, 401, 402} Experimental studies have found toluene, TCE and DCM were able to cause sperm DNA damage.²⁰⁰⁻²⁰³ Although we lacked the evidence in human, it is possible that paternal germline mutations caused by occupational hydrocarbon exposure predispose the children to a higher risk of glioma.⁴⁰³

Our findings also suggest that the risk of childhood AML increases with aromatic, aliphatic/alicyclic hydrocarbons, and toluene exposures. Prior studies of paternal aliphatic hydrocarbon exposure had mixed results,^{228, 343} and no studies investigated toluene specifically. Yet, occupational epidemiologic studies have reported increases in adult AML among organic solvent exposed workers,⁴⁰⁴ and including workers exposed to aromatic hydrocarbons a group to which toluene belongs.⁴⁰⁵ Although pediatric AML and adult AML differ in some critical genetic and epigenetic characteristics, they nevertheless share some common DNA mutations.⁴⁰⁶ Thus, similar mechanisms of leukemogenesis may exist in pediatric and adult AML.⁴⁰⁷

We observed a weak association between ALL and any paternal occupational exposure to toluene, as did a prior study.²¹¹ In addition, we observed a notably stronger increase in the risk of ALL associated with high paternal exposure to toluene. Toluene has been shown to induce germ

cell mutations during spermatogenesis in experimental studies.²⁰⁰ Several germline genetic mutations have been shown to increase the risk of leukemia including ALL.⁴⁰⁸

Our study is the first to report an increased risk of childhood hepatoblastoma with paternal occupational exposure to toluene in preconception and pregnancy periods. Previously, studies have reported that paternal exposures to paints or pigments which involved the use of toluene were associated with an increased risk of hepatoblastoma.^{82, 346}

Some of our results – especially subgroup analyses - may be generally affected by random errors due to small sample size or by potential live-birth bias if exposure to multiple or higher levels of hydrocarbons cause pregnancy loss. Previous studies have reported associations between exposure to high levels of solvents in industries such as dry cleaning, painting and increased risks of fetal loss, spontaneous abortion among occupationally exposed women.^{393, 394} Furthermore, it has been suggested that paternal occupational exposure to solvents in industries such as rubber manufacturing, refineries and painting might have increased the risk of fetal loss and spontaneous abortion.⁴⁰⁹⁻⁴¹¹ The industries investigated in these previous studies exposed workers to a mixture of hydrocarbons.

In this study, we avoided recall and selection bias by using nationwide and validated registers to identify occupational exposures and childhood cancer outcomes. The use of registry-recorded employment histories and JEMs allowed for more accurate and period-specific examination of occupational exposures. However, there are also limitations to a record linkage only study as non-differential exposure misclassification might occur because we solely relied on JEMs and employment records, possibly leading to a bias towards the null. We also were not able to assess exposure to any of the individual hydrocarbons due to limited sample size for such exposures as

most workers are exposed to several solvents. Thus, our findings for individual hydrocarbons should be interpreted with caution considering moderate to high correlation between all hydrocarbons and potential co-exposure confounding. Additionally, we were not able to assess self-employed individuals. It was reported the self-employment rate in Denmark over the past decade has been stable at about 8%.³⁵⁴

Our study is one of the few register-based studies investigating occupational exposure to various hydrocarbons and exposure intensities in relation to childhood cancer. Our results suggest that paternal occupational exposures to hydrocarbons between 3 months prior to conception until birth are likely to increase the risks of glioma, AML, ALL, osteosarcoma, and hepatoblastoma. This study further contributes to our knowledge base for occupational exposures as causes of cancer in offspring and encourages the further development of workplace safety measures.

5.6 Figures and tables

Table 5-1. Demographic and parental characteristics of population cases and controls, 1968-2016

Characteristics	Cases (N = 10442), N (%)	Controls (N = 261050), N (%)
Child's sex		
Male	5303 (50.8)	132575 (50.8)
Female	5139 (49.2)	128475 (49.2)
Child's birthplace		
Urban	3496 (33.5)	84946 (32.5)
Small towns	3358 (32.2)	85645 (32.8)
Rural	3588 (34.4)	90459 (34.7)
Paternal age, (Mean $\pm$ Standard Deviation)	30.4 $\pm$ 6.0	30.4 $\pm$ 5.9
Maternal age, (Mean $\pm$ Standard Deviation)	27.6 $\pm$ 5.1	27.6 $\pm$ 5.0
Paternal birthplace		
Denmark	9514 (91.1)	240222 (92.0)
Other Europe	333 (3.2)	7813 (3.0)
North America	33 (0.3)	526 (0.2)
Asia	106 (1.0)	2827 (1.1)
Africa	79 (0.8)	1795 (0.7)
Other	255 (2.4)	5923 (2.3)
Missing	122	1944
Maternal birthplace		
Denmark	9677 (92.7)	242389 (92.9)
Other Europe	325 (3.1)	7916 (3.0)
North America	24 (0.2)	458 (0.2)
Asia	121 (1.2)	3486 (1.3)
Africa	56 (0.5)	1335 (0.5)
Other	214 (2.1)	4889 (1.9)
Missing	25	577
Family socioeconomic status ^a		
1 (highest)	1042 (10.0)	26243 (10.1)
2	1360 (13.0)	34071 (13.1)
3	1574 (15.1)	40928 (15.7)
4	2773 (26.6)	69577 (26.7)
5 (lowest)	1572 (15.1)	39155 (15.0)
Missing	2121	51076
Maternal smoking status at the first prenatal visit ^b		
Smoker	1058 (10.1)	24976 (9.6)
Non-smoker	2942 (28.2)	75375 (28.9)

Missing	224	5249
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Note:

^a Missing data on family socioeconomic status increased over time due to changes in Danish tax law

^b Data for maternal smoking were only available for births from 1991 and onward

Table 5-2. Odds ratios and 95% confidence intervals for associations between paternal occupational exposure to 3 major hydrocarbon groups and offspring cancer risks, (N=228386)

Cancer types	Aliphatic/alicyclic hydrocarbons			Aromatic hydrocarbons			Chlorinated hydrocarbons		
	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	27670 (12.6)	Ref	Ref	26686 (12.2)	Ref	Ref	10532 (4.8)	Ref	Ref
ALL	178 (13.1)	1.11	1.12 (0.95, 1.32)	167 (12.3)	1.03	1.04 (0.88, 1.23)	63 (4.6)	0.99	0.99 (0.77, 1.28)
AML	47 (17.0)	1.44	1.46 (1.06, 2.01)	44 (15.9)	1.34	1.34 (0.96, 1.87)	17 (6.2)	1.34	1.39 (0.84, 2.31)
HL	40 (10.7)	0.85	0.88 (0.63, 1.23)	40 (10.7)	0.88	0.91 (0.65, 1.27)	17 (4.5)	0.99	0.96 (0.59, 1.58)
NHL	23 (9.2)	0.71	0.71 (0.46, 1.10)	32 (12.7)	1.16	1.17 (0.80, 1.71)	15 (6.0)	1.29	1.26 (0.74, 2.15)
Ependymoma	15 (11.1)	0.87	0.85 (0.49, 1.46)	16 (11.9)	0.97	0.97 (0.57, 1.65)	<10 ^b	***	***
Medulloblastoma	24 (11.8)	0.96	0.94 (0.61, 1.45)	24 (11.8)	1.05	1.05 (0.68, 1.62)	12 (5.9)	1.49	1.50 (0.82, 2.75)
Glioma	126 (14.4)	1.17	1.17 (0.97, 1.42)	129 (14.7)	1.25	1.25 (1.03, 1.51)	57 (6.5)	1.46	1.46 (1.11, 1.92)
Malignant bone tumors	41 (14.5)	1.22	1.22 (0.87, 1.71)	28 (9.9)	0.83	0.83 (0.56, 1.23)	12 (4.2)	0.91	0.92 (0.51, 1.65)
Osteosarcoma	19 (14.4)	1.21	1.21 (0.74, 1.99)	16 (12.1)	1.08	1.09 (0.64, 1.86)	<10 ^b	***	***
Ewing's sarcoma	18 (14.0)	1.22	1.22 (0.73, 2.03)	10 (7.8)	0.62	0.64 (0.33, 1.23)	<10 ^b	***	***
Rhabdomyosarcoma	20 (12.3)	0.97	0.98 (0.60, 1.57)	19 (11.7)	0.99	0.99 (0.61, 1.62)	<10 ^b	***	***
Germ cell tumors	47 (11.5)	0.86	0.86 (0.63, 1.17)	44 (10.7)	0.84	0.84 (0.61, 1.15)	16 (3.9)	0.81	0.81 (0.49, 1.35)
Teratoma	17 (10.4)	0.72	0.75 (0.45, 1.26)	18 (11.0)	0.81	0.83 (0.50, 1.36)	<10 ^b	***	***
Neuroblastoma	40 (12.3)	0.95	0.97 (0.69, 1.37)	41 (12.7)	1.06	1.09 (0.78, 1.52)	16 (4.9)	0.99	0.97 (0.58, 1.62)
Retinoblastoma	21 (14.0)	1.15	1.16 (0.72, 1.86)	19 (12.7)	1.03	1.04 (0.64, 1.71)	11 (7.3)	1.59	1.59 (0.84, 3.00)
Hepatoblastoma	10 (19.2)	2.05	2.01 (0.96, 4.22)	<10 ^b	***	***	<10 ^b	***	***
Wilms tumor	34 (13.1)	0.99	1.00 (0.69, 1.44)	35 (13.5)	1.08	1.08 (0.75, 1.56)	12 (4.6)	0.90	0.89 (0.49, 1.61)

Note:

^a Odds ratios adjusted for paternal age, paternal birthplace, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table 5-3. Odds ratios and 95% confidence intervals for associations between paternal occupational exposure to individual hydrocarbons and offspring cancer risks, (N=228386)

Cancer types	Toluene			Methylene chloride			Trichloroethylene			1,1,1-Trichloroethane		
	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	29091 (13.2)	Ref	Ref	33212 (15.1)	Ref	Ref	33722 (15.4)	Ref	Ref	26249 (12.0)	Ref	Ref
ALL	185 (13.6)	1.10	1.11 (0.95, 1.30)	187 (13.8)	0.93	0.93 (0.80, 1.09)	197 (14.5)	0.97	0.97 (0.83, 1.13)	162 (11.9)	1.04	1.04 (0.88, 1.23)
AML	49 (17.8)	1.44	1.46 (1.06, 2.00)	44 (15.9)	1.08	1.11 (0.80, 1.54)	43 (15.6)	1.03	1.05 (0.76, 1.47)	32 (11.6)	0.99	0.99 (0.68, 1.45)
HL	41 (11.0)	0.81	0.84 (0.61, 1.17)	44 (11.8)	0.74	0.75 (0.54, 1.03)	49 (13.1)	0.82	0.83 (0.61, 1.12)	36 (9.6)	0.76	0.78 (0.55, 1.10)
NHL	24 (9.6)	0.71	0.71 (0.46, 1.09)	31 (12.4)	0.80	0.79 (0.54, 1.16)	33 (13.1)	0.86	0.85 (0.59, 1.24)	23 (9.2)	0.74	0.73 (0.47, 1.13)
Ependymoma	15 (11.1)	0.82	0.8 (0.46, 1.38)	22 (16.3)	1.13	1.12 (0.70, 1.79)	22 (16.3)	1.09	1.08 (0.68, 1.72)	17 (12.6)	1.11	1.09 (0.65, 1.83)
Medulloblastoma	25 (12.3)	0.94	0.91 (0.60, 1.40)	24 (11.8)	0.80	0.79 (0.51, 1.21)	26 (12.7)	0.86	0.85 (0.56, 1.30)	20 (9.8)	0.83	0.82 (0.51, 1.31)
Glioma	136 (15.5)	1.20	1.20 (0.99, 1.45)	150 (17.1)	1.19	1.19 (0.99, 1.42)	121 (13.8)	1.23	1.23 (1.03, 1.47)	157 (17.9)	1.19	1.19 (0.98, 1.45)
Malignant bone tumors	44 (15.5)	1.22	1.23 (0.88, 1.71)	44 (15.5)	1.06	1.07 (0.77, 1.48)	48 (17.0)	1.14	1.15 (0.83, 1.57)	42 (14.8)	1.30	1.31 (0.93, 1.83)
Osteosarcoma	22 (16.7)	1.32	1.32 (0.82, 2.11)	24 (18.2)	1.30	1.29 (0.82, 2.03)	24 (18.2)	1.27	1.26 (0.80, 1.98)	25 (18.9)	1.73	1.73 (1.10, 2.71)
Ewing's sarcoma	18 (14.0)	1.13	1.13 (0.68, 1.89)	17 (13.2)	0.90	0.90 (0.54, 1.52)	19 (14.7)	0.99	1.00 (0.60, 1.64)	13 (10.1)	0.88	0.89 (0.49, 1.59)
Rhabdomyosarcoma	21 (12.9)	0.96	0.96 (0.60, 1.54)	19 (11.7)	0.80	0.78 (0.48, 1.28)	17 (10.4)	0.68	0.67 (0.40, 1.12)	13 (8.0)	0.65	0.64 (0.36, 1.14)
Germ cell tumors	52 (12.7)	0.91	0.92 (0.68, 1.23)	59 (14.4)	0.89	0.90 (0.68, 1.19)	54 (13.2)	0.82	0.82 (0.61, 1.09)	41 (10.0)	0.80	0.79 (0.57, 1.10)
Teratoma	17 (10.4)	0.69	0.72 (0.43, 1.19)	20 (12.3)	0.73	0.74 (0.46, 1.20)	11 (6.7)	0.66	0.67 (0.41, 1.10)	18 (11.0)	0.52	0.54 (0.29, 1.00)
Neuroblastoma	45 (13.9)	1.04	1.07 (0.77, 1.48)	43 (13.3)	0.84	0.85 (0.61, 1.18)	43 (13.3)	0.80	0.81 (0.58, 1.12)	32 (9.9)	0.77	0.78 (0.53, 1.12)
Retinoblastoma	23 (15.3)	1.21	1.22 (0.77, 1.92)	23 (15.3)	1.07	1.07 (0.68, 1.68)	27 (18.0)	1.21	1.21 (0.79, 1.85)	23 (15.3)	1.36	1.36 (0.86, 2.14)
Hepatoblastoma	12 (23.1)	2.46	2.45 (1.23, 4.91)	11 (21.2)	1.75	1.83 (0.90, 3.73)	10 (19.2)	1.53	1.54 (0.74, 3.22)	<10 ^b	***	***
Wilms tumor	35 (13.5)	0.99	1.00 (0.69, 1.43)	41 (15.8)	1.00	1.00 (0.71, 1.41)	44 (16.9)	1.07	1.08 (0.77, 1.50)	35 (13.5)	1.11	1.13 (0.79, 1.63)

Note:

^a Odds ratios adjusted for paternal age, paternal birthplace, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Figure 5-1. Plots show adjusted log odds and corresponding 95% confidence intervals (CIs; error bars) of childhood cancer subtypes associated with higher and lower paternal occupational exposure to hydrocarbon groups. Corresponding odds ratios and confidence intervals are available in Table S5-4, S5-6, S5-7. Odds ratios were not estimated when only less than 10 exposed cases were available for the analysis.

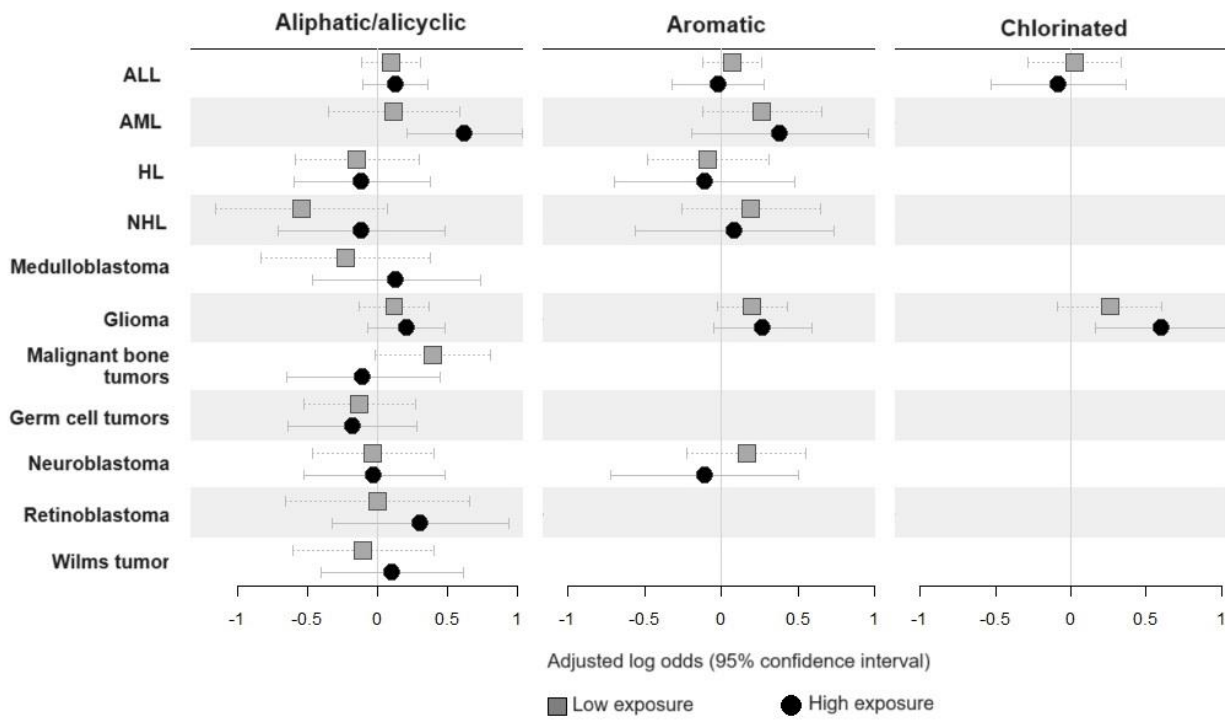
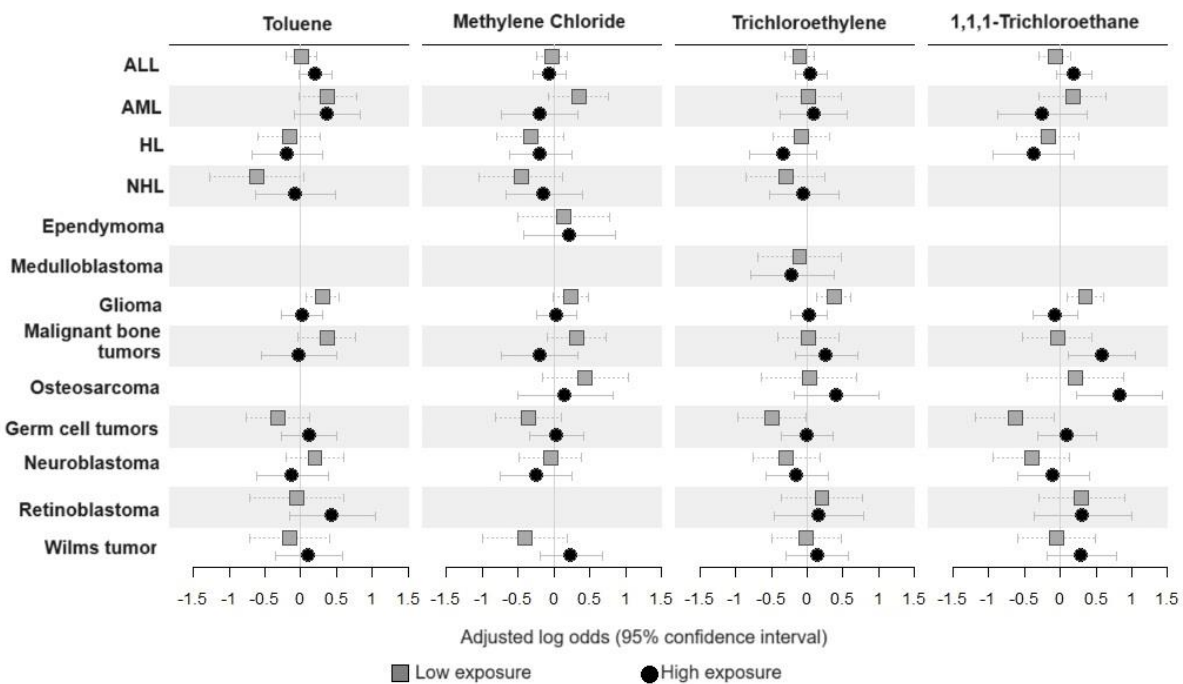


Figure 5-2. Plots show adjusted log odds and corresponding 95% confidence intervals (CIs; error bars) of childhood cancer subtypes associated with higher and lower paternal occupational exposure to individual hydrocarbons. Corresponding odds ratios and confidence intervals are available in Table S5-8, S5-9, S5-10, S5-11. Odds ratios were not estimated when only less than 10 exposed cases were available for the analysis.



5.7 Supplementary materials

Table S5-1. Prevalence of industry employment with the exposure to hydrocarbons among the exposed fathers

Hydrocarbon group	Industry	N	%
Chlorinated hydrocarbon			
Total exposed N = 10973	Painters, lacquerers and floor layers	2796	25.5
	Typographers	2789	25.4
	Laboratory assistants	1893	17.3
	Distillers, Cookers and furnacemen (chemical processes)	1270	11.6
	Metal plating and coating work	622	5.7
	Lithographers	473	4.3
	Rubber products workers	391	3.6
	Occupation in graphics, etc	273	2.5
	Refinery workers, other occupations in the chemical industry	139	1.3
	Footwear workers, etc	136	1.2
	Leather cutters for footwear	53	0.5
	Laundry workers	52	0.5
	Lasters and sole fitters, etc	44	0.4
	Shoe sewers	32	0.3
	Chemists	10	0.1
Aliphatic/alicyclic hydrocarbon			
Total exposed N = 28806	Machine and engine mechanics	15527	53.9
	Wooden surface finishers	4862	16.9
	Typographers	3255	11.3
	Painters, lacquerers and floor layers	2738	9.5
	Distillers, Cookers and furnacemen (chemical processes)	1273	4.4
	Rubber products workers	378	1.3
	Occupation in graphics, etc	272	0.9
	Footwear workers, etc	136	0.5
	Refinery workers, other occupations in the chemical industry	141	0.5
	Upholsterers	46	0.2
	Leather cutters for footwear	53	0.2
	Lasters and sole fitters, etc	44	0.2
	Laundry workers	52	0.2
	Shoe sewers	29	0.1
Aromatic hydrocarbon	Bench carpenters	10223	36.8

Total exposed N =
27760

Maintenance crews and supervisors	5080	18.3
Typographers	3255	11.7
Painters, lacquerers and floor layers	2731	9.8
Plastic product workers	1949	7
Chemists	1544	5.6
Distillers, Cookers and furnacemen (chemical processes)	1269	4.6
Service station attendants	561	2
Rubber products workers	379	1.4
Occupation in graphics, etc	272	1
Footwear workers, etc	136	0.5
Refinery workers, other occupations in the chemical industry	137	0.5
Upholsterers	46	0.2
Leather cutters for footwear	53	0.2
Lasters and sole fitters, etc	44	0.2
Laundry workers	50	0.2
Shoe sewers	31	0.1

Table S5-2. Correlation coefficients between 3 hydrocarbon groups

	Chlorinated hydrocarbon	Aromatic hydrocarbon	Aliphatic/alicyclic hydrocarbon
Chlorinated hydrocarbon	1		
Aromatic hydrocarbon	0.55	1	
Aliphatic/alicyclic hydrocarbon	0.44	0.60	1

Table S5-3. Correlation coefficients between individual hydrocarbons

	Methylene Chloride	Toluene	1,1,1- Trichloroethane	Trichloroethylene
Methylene Chloride	1			
Toluene	0.71	1		
1,1,1- Trichloroethane	0.74	0.55	1	
Trichloroethylene	0.89	0.67	0.85	1

Table S5-4. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low aliphatic/acyclic hydrocarbon exposure to the unexposed fathers, ^a (N=228386)

Cancer types		Aliphatic/acyclic hydrocarbon		
		Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	15495 (7.1)	Ref	Ref
	High intensity	12175 (5.5)	Ref	Ref
ALL	Low intensity	99 (7.3)	1.10	1.11 (0.90, 1.36)
	High intensity	79 (5.8)	1.13	1.14 (0.90, 1.44)
AML	Low intensity	20 (7.2)	1.11	1.13 (0.71, 1.80)
	High intensity	27 (9.8)	1.86	1.87 (1.24, 2.82)
HL	Low intensity	22 (5.9)	0.83	0.87 (0.56, 1.34)
	High intensity	18 (4.8)	0.87	0.90 (0.55, 1.45)
NHL	Low intensity	11 (4.4)	0.58	0.58 (0.32, 1.08)
	High intensity	12 (4.8)	0.88	0.89 (0.49, 1.61)
Medulloblastoma	Low intensity	12 (5.9)	0.83	0.80 (0.44, 1.45)
	High intensity	12 (5.9)	1.16	1.15 (0.63, 2.08)
Glioma	Low intensity	69 (7.9)	1.13	1.13 (0.88, 1.45)
	High intensity	57 (6.5)	1.24	1.23 (0.94, 1.63)
Malignant bone tumors	Low intensity	27 (9.5)	1.49	1.49 (0.99, 2.24)
	High intensity	14 (4.9)	0.90	0.90 (0.52, 1.56)
Germ cell tumors	Low intensity	27 (6.6)	0.88	0.88 (0.59, 1.31)
	High intensity	20 (4.9)	0.83	0.84 (0.53, 1.32)
Neuroblastoma	Low intensity	23 (7.1)	0.95	0.97 (0.63, 1.50)

Retinoblastoma	High intensity	17 (5.2)	0.97	0.98 (0.59, 1.62)
	Low intensity	10 (6.7)	1.00	1.00 (0.52, 1.93)
Wilms tumor	High intensity	11 (7.3)	1.34	1.36 (0.72, 2.56)
	Low intensity	17 (6.5)	0.90	0.90 (0.55, 1.50)
	High intensity	17 (6.5)	1.12	1.11 (0.67, 1.84)

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-5. Odds ratios and 95% confidence intervals examining fathers exposed to one hydrocarbon group only and the associations with offspring cancer risks, (N=228386)

Cancer types	Aliphatic/alicyclic hydrocarbons only			Aromatic hydrocarbons only			Chlorinated hydrocarbons only		
	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	19733 (9.0)	Ref	Ref	19921 (9.1)	Ref	Ref	4167 (1.9)	Ref	Ref
ALL	130 (9.6)	1.14	1.16 (0.96, 1.39)	126 (9.3)	1.03	1.04 (0.86, 1.26)	21 (1.5)	0.81	0.81 (0.52, 1.25)
AML	34 (12.3)	1.43	1.43 (0.99, 2.07)	33 (12.0)	1.31	1.28 (0.88, 1.87)	<10 ^b	***	***
HL	28 (7.5)	0.82	0.87 (0.59, 1.29)	31 (8.3)	0.91	0.96 (0.66, 1.39)	<10 ^b	***	***
NHL	12 (4.8)	0.51	0.52 (0.29, 0.93)	23 (9.2)	1.13	1.16 (0.75, 1.80)	<10	***	***
Ependymoma	11 (8.1)	0.90	0.87 (0.46, 1.63)	13 (9.6)	1.07	1.02 (0.57, 1.84)	<10 ^b	***	***
Medulloblastoma	17 (8.3)	0.91	0.88 (0.53, 1.47)	19 (9.3)	1.09	1.08 (0.67, 1.76)	<10 ^b	***	***
Glioma	86 (9.8)	1.09	1.09 (0.87, 1.37)	94 (10.7)	1.19	1.19 (0.96, 1.49)	26 (3.0)	1.71	1.71 (1.14, 2.56)
Malignant bone tumors	33 (11.7)	1.38	1.38 (0.95, 2.01)	20 (7.1)	0.80	0.80 (0.50, 1.26)	<10 ^b	***	***
Osteosarcoma	18 (13.6)	1.62	1.64 (0.98, 2.74)	15 (11.4)	1.40	1.43 (0.82, 2.49)	<10 ^b	***	***
Ewing's sarcoma	12 (9.3)	1.17	1.18 (0.64, 2.16)	<10 ^b	***	***	<10 ^b	***	***
Rhabdomyosarcoma	15 (9.2)	1.02	1.03 (0.60, 1.78)	14 (8.6)	0.97	0.98 (0.56, 1.72)	<10 ^b	***	***
Germ cell tumors	35 (8.5)	0.89	0.89 (0.63, 1.27)	34 (8.3)	0.87	0.87 (0.61, 1.25)	<10 ^b	***	***
Teratoma	11 (6.7)	0.66	0.70 (0.37, 1.30)	14 (8.6)	0.87	0.89 (0.51, 1.56)	<10 ^b	***	***
Neuroblastoma	28 (8.6)	0.94	0.97 (0.65, 1.45)	35 (10.8)	1.23	1.28 (0.89, 1.83)	11 (3.4)	1.69	1.62 (0.87, 3.02)
Retinoblastoma	13 (8.7)	1.00	1.01 (0.56, 1.80)	11 (7.3)	0.79	0.80 (0.43, 1.50)	<10 ^b	***	***
Hepatoblastoma	<10 ^b	***	***	<10 ^b	***	***	<10 ^b	***	***
Wilms tumor	24 (9.2)	1.00	1.01 (0.66, 1.55)	27 (10.4)	1.13	1.15 (0.76, 1.73)	<10 ^b	***	***

Note:

^a Odds ratios adjusted for paternal age, paternal race, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-6. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low aromatic hydrocarbon exposure to the unexposed fathers, ^a (N=228386)

Cancer types		Cases, N (%)	Aromatic hydrocarbon	
			Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	18477 (8.4)	Ref	Ref
	High intensity	8209 (3.7)	Ref	Ref
ALL	Low intensity	120 (8.8)	1.06	1.07 (0.88, 1.30)
	High intensity	47 (3.5)	0.97	0.98 (0.73, 1.32)
AML	Low intensity	31 (11.2)	1.33	1.30 (0.88, 1.91)
	High intensity	13 (4.7)	1.38	1.47 (0.82, 2.61)
HL	Low intensity	28 (7.5)	0.87	0.92 (0.62, 1.36)
	High intensity	12 (3.2)	0.91	0.90 (0.50, 1.62)
NHL	Low intensity	22 (8.8)	1.18	1.21 (0.77, 1.90)
	High intensity	10 (4.0)	1.12	1.09 (0.57, 2.09)
Glioma	Low intensity	88 (10.0)	1.22	1.22 (0.97, 1.53)
	High intensity	41 (4.7)	1.32	1.31 (0.95, 1.81)
Neuroblastoma	Low intensity	30 (9.3)	1.13	1.18 (0.80, 1.73)
	High intensity	11 (3.4)	0.91	0.90 (0.49, 1.66)

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-7. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low chlorinated hydrocarbon exposure to the unexposed fathers, ^a (N=228386)

Cancer types		Cases, N (%)	Chlorinated hydrocarbon	
			Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	7138 (3.3)	Ref	Ref
	High intensity	3394 (1.5)	Ref	Ref
ALL	Low intensity	43 (3.2)	1.02	1.03 (0.75, 1.40)
	High intensity	20 (1.5)	0.93	0.92 (0.59, 1.45)
Glioma	Low intensity	35 (4.0)	1.30	1.29 (0.91, 1.83)
	High intensity	22 (2.5)	1.82	1.82 (1.18, 2.82)

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia

Table S5-8. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low toluene exposure to the unexposed fathers, ^a (N=228386)

Cancer types		Cases, N (%)	Toluene Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	16314 (7.4)	Ref	Ref
	High intensity	12777 (5.8)	Ref	Ref
ALL	Low intensity	96 (7.1)	1.00	1.01 (0.82, 1.26)
	High intensity	89 (6.6)	1.22	1.23 (0.98, 1.54)
AML	Low intensity	28 (10.1)	1.48	1.46 (0.97, 2.20)
	High intensity	21 (7.6)	1.39	1.45 (0.91, 2.30)
HL	Low intensity	24 (6.4)	0.79	0.85 (0.55, 1.30)
	High intensity	17 (4.5)	0.83	0.83 (0.51, 1.38)
NHL	Low intensity	10 (4.0)	0.53	0.54 (0.28, 1.03)
	High intensity	14 (5.6)	0.94	0.93 (0.53, 1.62)
Glioma	Low intensity	84 (9.6)	1.34	1.35 (1.07, 1.70)
	High intensity	52 (5.9)	1.03	1.02 (0.76, 1.36)
Malignant bone tumors	Low intensity	28 (9.9)	1.43	1.44 (0.96, 2.16)
	High intensity	16 (5.7)	0.98	0.98 (0.58, 1.65)
Germ cell tumors	Low intensity	22 (5.4)	0.73	0.73 (0.47, 1.14)
	High intensity	30 (7.3)	1.12	1.13 (0.77, 1.66)
Neuroblastoma	Low intensity	28 (8.6)	1.17	1.22 (0.82, 1.82)
	High intensity	17 (5.2)	0.89	0.89 (0.54, 1.47)
Retinoblastoma	Low intensity	10 (6.7)	0.94	0.94 (0.49, 1.82)
	High intensity	13 (8.7)	1.55	1.56 (0.86, 2.84)

Wilms tumor	Low intensity	14 (5.4)	0.85	0.86 (0.49, 1.49)
	High intensity	21 (8.1)	1.13	1.12 (0.70, 1.78)

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-9. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low methylene chloride exposure to the unexposed fathers, ^a (N=228386)

		Methylene chloride		
Cancer types		Cases, N (%)	Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	16299 (7.5)	Ref	Ref
	High intensity	14524 (6.7)	Ref	Ref
ALL	Low intensity	97 (7.2)	0.97	0.98 (0.79, 1.21)
	High intensity	83 (6.2)	0.94	0.94 (0.75, 1.18)
AML	Low intensity	26 (9.5)	1.39	1.41 (0.92, 2.14)
	High intensity	15 (5.5)	0.79	0.82 (0.48, 1.39)
HL	Low intensity	20 (5.4)	0.69	0.72 (0.45, 1.14)
	High intensity	22 (5.9)	0.84	0.83 (0.53, 1.28)
NHL	Low intensity	12 (4.9)	0.62	0.63 (0.35, 1.13)
	High intensity	15 (6.1)	0.89	0.87 (0.51, 1.49)
Ependymoma	Low intensity	11 (8.1)	1.18	1.15 (0.61, 2.18)
	High intensity	11 (8.1)	1.25	1.25 (0.66, 2.36)
Glioma	Low intensity	78 (9.0)	1.26	1.26 (0.99, 1.61)
	High intensity	58 (6.7)	1.05	1.04 (0.79, 1.37)
Malignant bone tumors	Low intensity	27 (9.6)	1.37	1.37 (0.91, 2.07)
	High intensity	15 (5.3)	0.81	0.82 (0.48, 1.39)
Osteosarcoma	Low intensity	13 (9.9)	1.56	1.55 (0.85, 2.81)
	High intensity	10 (7.6)	1.18	1.17 (0.60, 2.28)
Germ cell tumors	Low intensity	21 (5.2)	0.69	0.70 (0.44, 1.09)
	High intensity	31 (7.7)	1.04	1.04 (0.71, 1.52)

Neuroblastoma	Low intensity	24 (7.5)	0.93	0.95 (0.62, 1.46)
	High intensity	17 (5.3)	0.78	
Wilms tumor	Low intensity	12 (4.7)	0.67	0.67 (0.37, 1.21)
	High intensity	24 (9.4)	1.27	

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-10. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low trichloroethylene exposure to the unexposed fathers, ^a (N=228386)

Cancer types		Cases, N (%)	Trichloroethylene	
			Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	17518 (8.0)	Ref	Ref
	High intensity	16204 (7.4)	Ref	Ref
ALL	Low intensity	101 (7.4)	0.90	0.90 (0.73, 1.11)
	High intensity	96 (7.1)	1.05	1.06 (0.85, 1.31)
AML	Low intensity	22 (8.0)	1.01	1.02 (0.65, 1.61)
	High intensity	21 (7.6)	1.06	1.10 (0.69, 1.75)
HL	Low intensity	29 (7.8)	0.90	0.92 (0.62, 1.36)
	High intensity	20 (5.3)	0.72	0.72 (0.45, 1.15)
NHL	Low intensity	14 (5.6)	0.75	0.74 (0.43, 1.30)
	High intensity	19 (7.6)	0.97	0.96 (0.59, 1.57)
Medulloblastoma	Low intensity	13 (6.4)	0.89	0.90 (0.50, 1.62)
	High intensity	13 (6.4)	0.84	0.81 (0.45, 1.45)
Glioma	Low intensity	88 (10.0)	1.45	1.45 (1.15, 1.83)
	High intensity	69 (7.9)	1.03	1.03 (0.80, 1.33)
Malignant bone tumors	Low intensity	24 (8.5)	1.01	1.02 (0.66, 1.57)
	High intensity	24 (8.5)	1.31	1.31 (0.84, 2.03)
Osteosarcoma	Low intensity	10 (7.6)	1.04	1.03 (0.53, 2.01)
	High intensity	14 (10.6)	1.51	1.51 (0.84, 2.72)
Germ cell tumors	Low intensity	19 (4.6)	0.61	0.61 (0.38, 0.99)
	High intensity	35 (8.5)	1.00	1.00 (0.70, 1.43)
Neuroblastoma	Low intensity	20 (6.2)	0.74	0.75 (0.47, 1.19)
	High intensity	23 (7.1)	0.87	0.87 (0.56, 1.35)
Retinoblastoma	Low intensity	15 (10.0)	1.22	1.23 (0.70, 2.15)
	High intensity	12 (8.0)	1.18	1.18 (0.64, 2.20)
Wilms tumor	Low intensity	19 (7.3)	0.98	0.99 (0.61, 1.62)
	High intensity	25 (9.6)	1.15	1.16 (0.75, 1.79)

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia;

AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-11. Odds ratios and 95% confidence intervals for offspring cancer risks, comparing fathers with high/low 1,1,1-trichloroethane exposure to the unexposed fathers, ^a (N=228386)

		1,1,1-Trichloroethane		
Cancer types		Exposed cases, N (%)	Crude OR	Adjusted OR (95% CI) ^b
Controls	Low intensity	14847 (6.8)	Ref	Ref
	High intensity	11250 (5.1)	Ref	Ref
ALL	Low intensity	88 (6.5)	0.92	0.93 (0.74, 1.16)
	High intensity	73 (5.4)	1.21	1.22 (0.95, 1.56)
AML	Low intensity	21 (7.6)	1.18	1.19 (0.74, 1.89)
	High intensity	11 (4.0)	0.76	0.78 (0.42, 1.45)
HL	Low intensity	23 (6.1)	0.82	0.84 (0.55, 1.31)
	High intensity	13 (3.5)	0.69	0.69 (0.39, 1.22)
Glioma	Low intensity	73 (8.3)	1.42	1.42 (1.10, 1.83)
	High intensity	46 (5.3)	0.93	0.93 (0.68, 1.27)
Malignant bone tumors	Low intensity	19 (6.7)	0.95	0.96 (0.59, 1.56)
	High intensity	22 (7.8)	1.80	1.79 (1.13, 2.86)
Osteosarcoma	Low intensity	10 (7.6)	1.24	1.23 (0.63, 2.41)
	High intensity	14 (10.7)	2.26	2.29 (1.25, 4.18)
Germ cell tumors	Low intensity	14 (3.4)	0.52	0.53 (0.30, 0.91)
	High intensity	27 (6.6)	1.11	1.10 (0.73, 1.66)
Neuroblastoma	Low intensity	15 (4.6)	0.65	0.67 (0.39, 1.13)
	High intensity	17 (5.2)	0.91	0.91 (0.55, 1.52)
Retinoblastoma	Low intensity	13 (8.7)	1.34	1.35 (0.74, 2.45)
	High intensity	10 (6.7)	1.37	1.37 (0.70, 2.71)

Wilms tumor	Low intensity	15 (5.8)	0.94	0.95 (0.55, 1.64)
	High intensity	20 (7.7)		1.35 (0.83, 2.18)

Note:

^a Only cancer types with ≥ 10 exposed cases in low and high categories were reported

^b Odds ratios adjusted for paternal age, paternal race, and child's birthplace

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma

Table S5-12. Sensitivity analysis for the associations with hydrocarbon groups, excluding children with both parents exposed to hydrocarbons

Cancer types	Aliphatic/alicyclic hydrocarbon ^a			Aromatic hydrocarbon ^b			Chlorinated hydrocarbon ^c		
	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^d	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^d	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^d
Controls	17739 (8.5)	Ref	Ref	17330 (8.2)	Ref	Ref	6819 (3.2)	Ref	Ref
ALL	120 (9.2)	1.19	1.20 (0.99, 1.46)	115 (8.8)	1.10	1.11 (0.91, 1.34)	46 (3.4)	1.14	1.14 (0.85, 1.55)
AML	36 (13.6)	1.70	1.70 (1.19, 2.45)	33 (12.5)	1.52	1.51 (1.04, 2.20)	10 (3.7)	1.17	1.22 (0.64, 2.33)
HL	20 (5.6)	0.64	0.66 (0.42, 1.05)	25 (7.0)	0.84	0.86 (0.57, 1.29)	<10 ^e	***	***
NHL	15 (6.2)	0.75	0.76 (0.44, 1.28)	20 (8.4)	1.17	1.18 (0.74, 1.88)	<10 ^e	***	***
Ependymoma	12 (9.1)	1.04	1.01 (0.55, 1.86)	12 (9.2)	1.09	1.06 (0.58, 1.95)	<10 ^e	***	***
Medulloblastoma	15 (7.7)	0.88	0.86 (0.50, 1.47)	17 (8.6)	1.10	1.09 (0.66, 1.82)	<10 ^e	***	***
Glioma	84 (10.1)	1.21	1.21 (0.96, 1.52)	94 (11.2)	1.38	1.38 (1.10, 1.72)	39 (4.5)	1.54	1.54 (1.10, 2.14)
Malignant bone tumors	27 (10.0)	1.23	1.23 (0.82, 1.84)	18 (6.6)	0.78	0.78 (0.48, 1.27)	<10 ^e	***	***
Osteosarcoma	12 (9.6)	1.19	1.17 (0.64, 2.16)	10 (7.9)	1.01	1.02 (0.53, 1.98)	<10 ^e	***	***
Ewing's sarcoma	12 (9.8)	1.30	1.29 (0.70, 2.37)	<10 ^e	***	***	<10 ^e	***	***
Rhabdomyosarcoma	13 (8.3)	1.00	1.01 (0.57, 1.81)	10 (6.5)	0.83	0.84 (0.44, 1.62)	<10 ^e	***	***
Germ cell tumors	33 (8.3)	0.93	0.93 (0.65, 1.34)	31 (7.8)	0.90	0.91 (0.62, 1.32)	12 (3.0)	0.92	0.92 (0.51, 1.65)
Teratoma	<10 ^e	***	***	12 (7.6)	0.84	0.86 (0.47, 1.57)	<10 ^e	***	***
Neuroblastoma	29 (9.3)	1.07	1.09 (0.74, 1.61)	33 (10.4)	1.27	1.29 (0.89, 1.87)	13 (4.0)	1.16	1.12 (0.63, 1.98)
Retinoblastoma	15 (10.4)	1.23	1.22 (0.71, 2.11)	15 (10.3)	1.23	1.23 (0.71, 2.12)	<10 ^e	***	***
Wilms tumor	21 (8.5)	0.96	0.96 (0.61, 1.52)	22 (8.9)	1.06	1.07 (0.68, 1.68)	10 (3.9)	1.16	1.13 (0.59, 2.17)

Note:

^a The number indicates the study population excluding children of mothers who were also exposed to aromatic hydrocarbon

^b The number indicates the study population excluding children of mothers who were also exposed to aliphatic/alicyclic hydrocarbon

^c The number indicates the study population excluding children of mothers who were also exposed to chlorinated hydrocarbon

^d Odds ratios adjusted for paternal age, paternal birthplace, and child's birthplace

^e Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-13. Sensitivity analysis for the associations with individual hydrocarbons, excluding children with both parents exposed to hydrocarbons

Cancer types	Toluene ^a			Methylene chloride ^b			Trichloroethylene ^c			1,1,1-Trichloroethane ^d		
	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^e	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^e	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^e	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^e
Controls	18550 (8.9)	Ref	Ref	20712 (10.0)	Ref	Ref	21140 (10.2)	Ref	Ref	16920 (8.0)	Ref	Ref
ALL	123 (9.5)	1.17	1.19 (0.98, 1.44)	118 (9.2)	0.95	0.96 (0.79, 1.16)	122 (9.5)	0.96	0.97 (0.80, 1.17)	102 (7.9)	1.01	1.02 (0.83, 1.25)
AML	39 (14.7)	1.76	1.76 (1.24, 2.50)	34 (12.8)	1.33	1.34 (0.93, 1.94)	31 (11.7)	1.16	1.17 (0.80, 1.71)	24 (9.0)	1.13	1.12 (0.73, 1.72)
HL	20 (5.7)	0.60	0.62 (0.39, 0.98)	21 (6.0)	0.57	0.58 (0.37, 0.90)	27 (7.7)	0.73	0.73 (0.49, 1.09)	21 (5.8)	0.71	0.72 (0.46, 1.13)
NHL	15 (6.2)	0.73	0.73 (0.43, 1.24)	19 (7.9)	0.82	0.82 (0.51, 1.32)	22 (9.2)	0.95	0.95 (0.61, 1.49)	15 (6.2)	0.78	0.77 (0.46, 1.32)
Ependymoma	12 (9.1)	1.00	0.97 (0.53, 1.78)	16 (12.4)	1.27	1.25 (0.73, 2.14)	16 (12.4)	1.23	1.21 (0.71, 2.06)	13 (9.9)	1.26	1.23 (0.69, 2.22)
Medulloblastoma	16 (8.2)	0.88	0.86 (0.51, 1.45)	15 (7.7)	0.78	0.77 (0.45, 1.31)	17 (8.7)	0.88	0.86 (0.52, 1.43)	14 (7.1)	0.88	0.87 (0.50, 1.52)
Glioma	90 (10.8)	1.24	1.24 (0.99, 1.55)	97 (11.8)	1.22	1.21 (0.98, 1.51)	105 (12.7)	1.29	1.29 (1.05, 1.59)	84 (10.0)	1.26	1.26 (1.00, 1.59)
Malignant bone tumors	28 (10.5)	1.21	1.21 (0.81, 1.80)	29 (10.8)	1.10	1.11 (0.75, 1.64)	32 (12)	1.19	1.19 (0.82, 1.74)	29 (10.7)	1.39	1.39 (0.94, 2.07)
Osteosarcoma	13 (10.6)	1.23	1.22 (0.67, 2.19)	16 (12.9)	1.35	1.33 (0.78, 2.28)	15 (12.2)	1.22	1.21 (0.70, 2.10)	16 (13.0)	1.72	1.71 (1.00, 2.94)
Ewing's sarcoma	12 (9.8)	1.20	1.19 (0.65, 2.19)	10 (8.2)	0.86	0.86 (0.44, 1.65)	13 (10.6)	1.10	1.09 (0.61, 1.96)	10 (7.9)	1.07	1.07 (0.55, 2.06)
Rhabdomyosarcoma	14 (9.0)	1.02	1.03 (0.59, 1.81)	14 (8.9)	0.89	0.88 (0.50, 1.54)	13 (8.2)	0.80	0.80 (0.45, 1.43)	11 (6.8)	0.82	0.82 (0.44, 1.52)
Germ cell tumors	38 (9.6)	1.02	1.03 (0.73, 1.45)	40 (10.2)	0.96	0.96 (0.69, 1.35)	35 (9.0)	0.84	0.83 (0.59, 1.19)	29 (7.3)	0.87	0.87 (0.59, 1.27)
Neuroblastoma	32 (10.3)	1.15	1.17 (0.81, 1.71)	29 (9.4)	0.88	0.88 (0.60, 1.30)	27 (8.8)	0.79	0.8 (0.53, 1.19)	20 (6.4)	0.75	0.76 (0.48, 1.21)
Retinoblastoma	17 (11.8)	1.38	1.38 (0.82, 2.31)	15 (10.6)	1.08	1.07 (0.62, 1.85)	17 (12.1)	1.19	1.18 (0.70, 1.98)	15 (10.6)	1.41	1.40 (0.81, 2.43)
Hepatoblastoma	10 (20.0)	2.92	2.88 (1.35, 6.14)	<10 ^f	***	***	<10 ^f	***	***	<10 ^f	***	***
Wilms tumor	22 (8.9)	0.97	0.97 (0.62, 1.52)	25 (10.2)	0.99	0.99 (0.65, 1.51)	27 (11.1)	1.07	1.08 (0.72, 1.63)	21 (8.5)	1.06	1.08 (0.68, 1.70)

Note:

^a The number indicates the study population excluding children of mothers who were also exposed to toluene

^b The number indicates the study population excluding children of mothers who were also exposed to methylene chloride

^c The number indicates the study population excluding children of mothers who were also exposed to trichloroethylene

^d The number indicates the study population excluding children of mothers who were also exposed to 1,1,1-trichloroethane

^e Odds ratios adjusted for paternal age, paternal birthplace, and child's birthplace

^f Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-14. Classifying fathers missing occupational history from 3 months prior to conception until birth as the unexposed: odds ratios and 95% confidence intervals for associations between paternal occupational exposure to 3 major hydrocarbon groups and offspring cancer risks, (N=271492)

Cancer types	Aliphatic/alicyclic hydrocarbons			Aromatic hydrocarbons			Chlorinated hydrocarbons		
	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a	Exposed, N (%)	Crude OR	Adjusted OR (95% CI) ^a
Controls	27670 (10.6)	Ref	Ref	26686 (10.2)	Ref	Ref	10532 (4.0)	Ref	Ref
ALL	178 (13.1)	1.14	1.16 (0.99, 1.36)	167 (12.3)	1.06	1.08 (0.91, 1.27)	63 (4.6)	1.02	1.03 (0.79, 1.33)
AML	47 (17.0)	1.47	1.47 (1.07, 2.02)	44 (15.9)	1.37	1.36 (0.98, 1.89)	17 (6.2)	1.37	1.42 (0.86, 2.34)
HL	40 (10.7)	0.81	0.85 (0.61, 1.18)	40 (10.7)	0.85	0.88 (0.63, 1.22)	17 (4.5)	0.95	0.93 (0.57, 1.53)
NHL	23 (9.2)	0.73	0.73 (0.47, 1.13)	32 (12.7)	1.18	1.19 (0.82, 1.74)	15 (6.0)	1.32	1.29 (0.76, 2.20)
Ependymoma	15 (11.1)	0.87	0.86 (0.50, 1.48)	16 (11.9)	0.97	0.95 (0.56, 1.61)	<10 ^b	***	***
Medulloblastoma	24 (11.8)	1.03	1.01 (0.65, 1.56)	24 (11.8)	1.12	1.11 (0.72, 1.72)	12 (5.9)	1.58	1.60 (0.88, 2.91)
Glioma	126 (14.4)	1.18	1.19 (0.98, 1.44)	129 (14.7)	1.26	1.27 (1.05, 1.53)	57 (6.5)	1.47	1.47 (1.12, 1.94)
Malignant bone tumors	41 (14.5)	1.15	1.15 (0.83, 1.61)	28 (9.9)	0.79	0.79 (0.53, 1.17)	12 (4.2)	0.87	0.88 (0.49, 1.58)
Osteosarcoma	19 (14.4)	1.11	1.10 (0.67, 1.79)	16 (12.1)	0.99	0.99 (0.58, 1.67)	<10 ^b	***	***
Ewing's sarcoma	18 (14.0)	1.17	1.19 (0.72, 1.97)	10 (7.8)	0.61	0.63 (0.33, 1.20)	<10 ^b	***	***
Rhabdomyosarcoma	20 (12.3)	1.02	1.01 (0.63, 1.63)	19 (11.7)	1.04	1.03 (0.64, 1.68)	<10 ^b	***	***
Germ cell tumors	47 (11.5)	0.86	0.88 (0.64, 1.19)	44 (10.7)	0.84	0.85 (0.62, 1.17)	16 (3.9)	0.82	0.83 (0.50, 1.37)
Teratoma	17 (10.4)	0.75	0.78 (0.47, 1.30)	18 (11.0)	0.84	0.86 (0.53, 1.42)	<10 ^b	***	***
Neuroblastoma	40 (12.3)	1.01	1.04 (0.74, 1.45)	41 (12.7)	1.12	1.15 (0.83, 1.61)	16 (4.9)	1.05	1.03 (0.62, 1.73)
Retinoblastoma	21 (14.0)	1.14	1.16 (0.73, 1.84)	19 (12.7)	1.02	1.05 (0.64, 1.70)	11 (7.3)	1.56	1.55 (0.82, 2.90)
Hepatoblastoma	10 (19.2)	1.97	2.00 (0.97, 4.10)	<10 ^b	***	***	<10 ^b	***	***
Wilms tumor	34 (13.1)	1.07	1.06 (0.74, 1.53)	35 (13.5)	1.15	1.15 (0.80, 1.65)	12 (4.6)	0.96	0.95 (0.53, 1.72)

Note:

^a Odds ratios adjusted for paternal age, paternal birthplace, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Table S5-15. Classifying fathers missing occupational history from 3 months prior to conception until birth as the unexposed: odds ratios and 95% confidence intervals for associations between paternal occupational exposure to individual hydrocarbons and offspring cancer risks, (N=271492)

Cancer types	Exposed, N (%)	Toluene		Exposed, N (%)	Methylene chloride		Exposed, N (%)	Trichloroethylene		Exposed, N (%)	1,1,1-Trichloroethane	
		Crude OR	Adjusted OR (95% CI) ^a		Crude OR	Adjusted OR (95% CI) ^a		Crude OR	Adjusted OR (95% CI) ^a		Crude OR	Adjusted OR (95% CI) ^a
Controls	29091 (11.1)	Ref	Ref	33212 (12.7)	Ref	Ref	33722 (12.9)	Ref	Ref	26249 (10.1)	Ref	Ref
ALL	185 (13.6)	1.13	1.14 (0.98, 1.34)	187 (13.8)	0.96	0.97 (0.83, 1.13)	197 (14.5)	1.00	1.01 (0.87, 1.17)	162 (11.9)	1.07	1.08 (0.91, 1.28)
AML	49 (17.8)	1.46	1.46 (1.07, 2.00)	44 (15.9)	1.11	1.12 (0.81, 1.55)	43 (15.6)	1.06	1.07 (0.77, 1.48)	32 (11.6)	1.01	1.01 (0.70, 1.47)
HL	41 (11.0)	0.78	0.81 (0.58, 1.12)	44 (11.8)	0.71	0.72 (0.53, 0.99)	49 (13.1)	0.79	0.80 (0.59, 1.08)	36 (9.6)	0.74	0.75 (0.53, 1.07)
NHL	24 (9.6)	0.73	0.73 (0.48, 1.12)	31 (12.4)	0.82	0.81 (0.56, 1.19)	33 (13.1)	0.88	0.88 (0.61, 1.27)	23 (9.2)	0.76	0.75 (0.49, 1.16)
Ependymoma	15 (11.1)	0.82	0.81 (0.47, 1.39)	22 (16.3)	1.12	1.12 (0.71, 1.78)	22 (16.3)	1.09	1.09 (0.69, 1.72)	17 (12.6)	1.10	1.10 (0.66, 1.83)
Medulloblastoma	25 (12.3)	1.00	0.98 (0.64, 1.51)	24 (11.8)	0.85	0.85 (0.55, 1.30)	26 (12.7)	0.92	0.92 (0.61, 1.39)	20 (9.8)	0.89	0.88 (0.55, 1.41)
Glioma	136 (15.5)	1.21	1.22 (1.01, 1.46)	150 (17.1)	1.20	1.20 (1.01, 1.44)	121 (13.8)	1.24	1.24 (1.04, 1.48)	157 (17.9)	1.20	1.21 (0.99, 1.47)
Malignant bone tumors	44 (15.5)	1.15	1.16 (0.84, 1.61)	44 (15.5)	1.01	1.02 (0.74, 1.40)	48 (17.0)	1.08	1.08 (0.79, 1.48)	42 (14.8)	1.22	1.23 (0.89, 1.72)
Osteosarcoma	22 (16.7)	1.20	1.19 (0.75, 1.89)	24 (18.2)	1.18	1.17 (0.75, 1.82)	24 (18.2)	1.15	1.14 (0.73, 1.77)	25 (18.9)	1.56	1.54 (0.99, 2.39)
Ewing's sarcoma	18 (14.0)	1.08	1.11 (0.67, 1.83)	17 (13.2)	0.87	0.89 (0.53, 1.48)	19 (14.7)	0.95	0.98 (0.60, 1.60)	13 (10.1)	0.85	0.88 (0.49, 1.56)
Rhabdomyosarcoma	21 (12.9)	1.01	1.00 (0.63, 1.59)	19 (11.7)	0.84	0.82 (0.51, 1.34)	17 (10.4)	0.72	0.70 (0.42, 1.17)	13 (8.0)	0.68	0.67 (0.38, 1.19)
Germ cell tumors	52 (12.7)	0.92	0.93 (0.69, 1.25)	59 (14.4)	0.90	0.91 (0.69, 1.21)	54 (13.2)	0.83	0.83 (0.63, 1.11)	41 (10.0)	0.81	0.81 (0.58, 1.12)
Teratoma	17 (10.4)	0.72	0.74 (0.45, 1.24)	20 (12.3)	0.76	0.78 (0.49, 1.25)	11 (6.7)	0.69	0.71 (0.43, 1.16)	18 (11.0)	0.55	0.56 (0.30, 1.04)
Neuroblastoma	45 (13.9)	1.11	1.14 (0.82, 1.56)	43 (13.3)	0.90	0.91 (0.66, 1.25)	43 (13.3)	0.86	0.87 (0.63, 1.20)	32 (9.9)	0.82	0.83 (0.57, 1.20)
Retinoblastoma	23 (15.3)	1.19	1.21 (0.77, 1.90)	23 (15.3)	1.05	1.07 (0.68, 1.67)	27 (18.0)	1.19	1.20 (0.79, 1.83)	23 (15.3)	1.33	1.35 (0.86, 2.12)

Hepatoblastoma	12 (23.1)	2.34	2.41 (1.23, 4.72)	11 (21.2)	1.68	1.80 (0.91, 3.59)	10 (19.2)	1.48	1.55 (0.76, 3.17)	<10 ^b	***	***
Wilms tumor	35 (13.5)	1.06	1.06 (0.74, 1.52)	41 (15.8)	1.07	1.07 (0.76, 1.50)	44 (16.9)	1.15	1.15 (0.83, 1.60)	35 (13.5)	1.19	1.20 (0.84, 1.73)

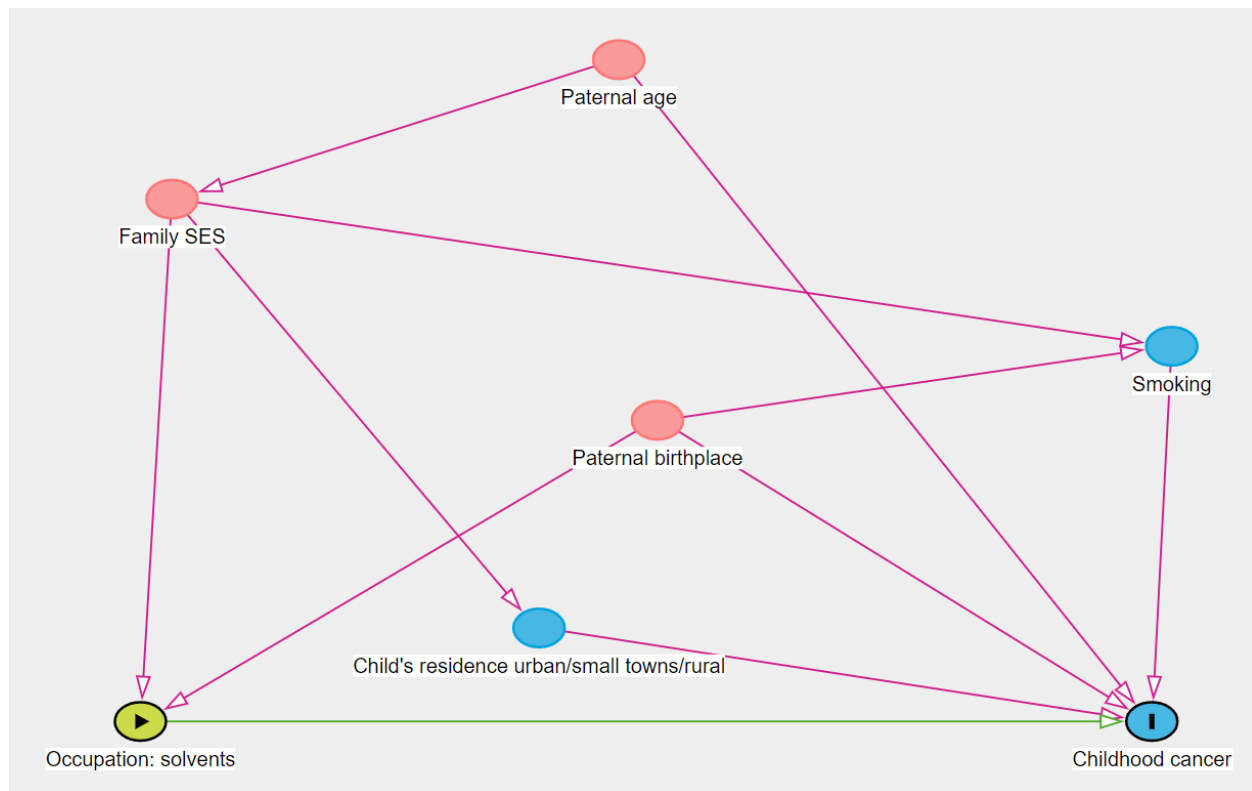
Note:

^a Odds ratios adjusted for paternal age, paternal birthplace, and child's birthplace

^b Due to small sample size (N<10), results were omitted

Abbreviations: OR, odds ratio; CI: confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma

Figure S5-1. Directed acyclic graph for confounder selection



6 Public health relevance

In this dissertation, we report on the associations between various environmental toxics and the risk of childhood cancer. Our findings enrich the current understanding of the role of environmental exposures in the etiology of childhood cancer. It is also important to note the public health relevance of our findings, particularly the steps that can be taken to contribute to the prevention of childhood cancer.

We found that neonatal exposures to PFOS and PFOA as identified in dried blood spots were associated with an increased risk of retinoblastoma. Although PFOS and PFOA have been phased out in the US, PFAS are still not regulated in drinking water in the US and maximum contaminant levels for PFAS have not been established yet in California.⁴¹²

In addition, we used the number of well counts as a proxy for OGD-related air pollution and revealed that maternal exposure to any well and inactive wells within 1km, 1-3km and 3km of residential address in pregnancy was associated with increased risks of various types of childhood cancer. Our study supports the California legislation which prohibits new or reworked oil and gas wells within 1km of residences and suggests 3km distance threshold could be considered for prevention of childhood cancer.¹⁸⁷ In addition to active wells, we emphasize the importance of appropriately plugging and regulating inactive oil and gas wells within 3km of residences.

Lastly, we identified that several hydrocarbon solvents were associated with increased risks of various types of childhood cancer. Our findings add to a growing body of literature regarding parental occupational exposures and the risk of childhood cancer, where many studies

face similar limitations including small sample sizes, unmeasured factors such as protective clothing and workplace ventilation which may affect the level of exposure at workplace, and lack of a prospective study design. Nevertheless, our findings support that workplace hazards could possibly influence the health of our future generations and inform policymakers to regulate and minimize the exposure of harmful chemicals at workplace and to build a safer work environment.

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