Title
Parental occupational exposures and risk of childhood cancer

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Publication Date
2017

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Parental occupational exposures and risk of childhood cancer

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy in Epidemiology

by

Negar Omidakhsh

2017

ABSTRACT OF THE DISSERTATION

Parental occupational exposures and risk of childhood cancer

by

Negar Omidakhsh
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2017
Professor Beate R. Ritz, Chair

Childhood cancer remains the second most common cause of death in children living in the United States and Europe. Research to date has revealed little about the etiology of these diseases, and established risk factors are limited to certain rare genetic syndromes and polymorphisms, ionizing radiation, and congenital abnormalities. Parental occupational exposures have been associated with increased risk of some childhood cancers, including leukemia and brain tumors. However, studies on maternal exposures, and those that examine the rarer cancers, are largely lacking. For the present analyses, we utilized two datasets and examined associations between (1) parental occupational social contact and risk of hematopoietic, central nervous system (CNS) and bone cancers, (2) industry types and retinoblastoma and (3) exposure to harmful environmental agents and retinoblastoma.

Our first population-based case-control study utilized a linkage of four Danish data-registries, and included 4,112 cases and 411,200 age-matched controls. High occupational social contact, jobs that have regular contact with young children or the sick, was examined from (1) conception to birth and (2) birth to diagnosis. Acute lymphoblastic leukemia (ALL) and bone cancer were inversely associated with high maternal occupational social contact from conception to birth (OR: 0.82, 95% CI: 0.64-1.04) and birth to diagnosis (OR: 0.59, 95% CI: 0.39-0.91). Children of fathers with high occupational social contact from birth to diagnosis had an increased risk of bone cancers, particularly in rural areas (OR: 1.68, 95% CI: 1.07-2.64). Parental high social contact was associated with increased risk of astrocytoma, with strongest associations found in first born children (maternal contact: OR: 1.54, 95% CI: 1.02-2.32; paternal contact: OR: 1.82, 95% CI: 1.05-3.17).

Our second study utilized the same Danish dataset and examined the role of occupational industry type during two biologically relevant time periods (1) 90 days preconception to conception for fathers and (2) conception to birth for mothers and risk of retinoblastoma among offspring. Parents were grouped into major industry headings created from Danish industry codes, an extended version of the International Standard Industrial Classification of All Economic Activities. We observed increased risk of all retinoblastoma among fathers in the food and drink industry (OR: 2.27, 95% CI: 1.24-4.16) and those who sell groceries (OR: 3.56, 95% CI: 1.42-8.91). Bilateral disease was associated with paternal work in supermarkets (OR: 4.03, 95% CI: 1.52-10.71) and transportation on land (OR: 4.03, 95% CI: 1.52-10.71). For maternal occupation, we estimated an increased risk of all retinoblastoma for hospital workers or clinicians (OR: 2.05, 95% CI: 1.34-3.14).

In our final multicenter study on non-familial retinoblastoma, parents of 187 unilateral and 95 bilateral cases and 155 friend controls were interviewed by telephone. Exposure information was collected retroactively through a detailed occupational questionnaire which asked fathers to report every job held in the 10 years before conception, and mothers one month prior to and during the index pregnancy. We estimated elevated odds ratios for unilateral and bilateral retinoblastoma among offspring of fathers who were exposed to polycyclic aromatic hydrocarbons (PAHs) or paints in the 10 years prior to conception. However, only for exposure to paints did confidence limits exclude the null for bilateral disease (OR: 8.76, 95% CI: 1.32-58.09). Maternal prenatal exposure to at least one of the 9 agents was related to increased risk of unilateral disease in their children (OR: 5.25, 95% CI: 1.14-24.16).

Our results support the notion of a role of infections for some cancer types. Studies on the risk factors for retinoblastoma are rare and our results suggest that some parental occupational exposures may cause childhood retinoblastoma.

The dissertation of Negar Omidakhsh is approved.

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University of California, Los Angeles

2017

DEDICATION

For mom and dad, my greatest champions.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Acute lymphoblastic leukemia (ALL)

Acute myeloid leukemia (AML)

Age standardized annual incidence rate (ASR)

Central nervous system (CNS)

Children's Oncology Group (COG)

Confidence interval (CI)

Diethylstilbestrol (DES)

Human papillomavirus (HPV)

International Agency for Research on Cancer (IARC)

International Standard Industrial Classification for all Economic Activities (ISIC)

Non-Hodgkin lymphoma (NHL)

Odds ratio (OR)

Polycyclic aromatic hydrocarbons (PAH)

Retinoblastoma protein (pRB)

Sexually transmitted disease (STD)

Simian Virus 40 (SV40)

Socioeconomic status (SES)

Sulfur dioxide (SO_2)

Tumor suppressor retinoblastoma gene (RB1)

United States (US)

Volatile organic compounds (VOC)

ACKNOWLEDGEMENTS

I am so very grateful for the opportunity to safely and freely pursue higher education. I do not take for granted that many other women, equally capable and deserving, are not afforded this same privilege.

Dr. Beate Ritz, your mentorship has been valued and utilized in many aspects of my life, both professionally and personally. Thank you for holding me accountable to the highest ethical and academic standards. I have learned so much from you with regards to academic writing and the fundamentals of epidemiology, and I continue to be inspired by your enthusiasm and passion for this field.

I would also like to thank Dr. Julia Heck, this study's principle investigator, who played an integral role in the conception, analyses and writing of this dissertation, and who spent countless hours editing my work. My gratitude extends to my committee members, Drs. Niklas Krause, Wendie Robbins, Anne Coleman, and Ondine von Ehrenstein, whose expertise and guidance helped to shape this body of work.

I would like to thank the Research Training Program of the Southern California NIOSH Education and Research Center, as well as the Department of Epidemiology for their financial support.

In truth, this work was made possible because of the unwavering support of my husband, who has been the most equal partner and friend. These four years, you have put your own dreams on hold so that I could pursue mine. Without you, I would surely be lost. In that same respect, I must also thank my mother in law, who spent many-a-nights on my uncomfortable couch so that I could continue my studies while my children were lovingly looked after. You may never know

just how much that meant to me. And of course, to Sebastian and Evelina, who were born into this program. Any and all success will forever pale in comparison to the great honor it is to be your mother.

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Omidakhsh N, Ganguly A, Bunin GR, von Ehrenstein OS, Ritz B, Heck JE. Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group. *Am J Ophthalmol* 2017 doi: 10.1016/j.ajo.2017.01.016 [published Online First: 2017/01/31]

Omidakhsh N, Bunin GR, Ganguly A, Ritz B, Kennedy N, von Ehrenstein OS, Krause N, Heck JE. Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group. *Occupational and Environmental Medicine* 2017;Manuscript Submitted

Heck JE, Omidakhsh N, Azary S, Ritz B, von Ehrenstein OS, Bunin GR, Ganguly A. A case-control study of sporadic retinoblastoma in relation to maternal health conditions and reproductive factors: a report from the Children's Oncology group. *BMC Cancer* 2015;15:735. doi: 10.1186/s12885-015-1773-0 [published Online First: 2015/10/21]

1 Background

1.1 Childhood cancer: an overview

To date, childhood cancer remains the second most common cause of death in children living in the United States (US).[1] Each year it is estimated that over 15,000 children ages 0-19 will be diagnosed with cancer and approximately 2,300 deaths will result from disease.[1] Survival rates for some cancers, particularly retinoblastoma and leukemia which is upwards of about 85%, has vastly improved in recent decades; however, for others such as bone sarcomas and brain tumors, survival rates are much lower (at about 55% or less) and thousands of lives continue to be cut short. Unlike adult cancers, the total incidence of childhood cancer is relatively constant geographically (at approximately 1.0-2.5 per thousand); however, for specific subtypes there are clear variations in incidence between different regions of the world.[2] The most common of these malignancies in developed countries include leukemia, brain tumors, neuroblastoma, lymphomas and Wilms tumor.[3] Leukemia is the most common childhood cancer among predominantly white populations with an age standardized annual incidence rate (ASR) of 35-50 per million and its main subtype acute lymphoblastic leukemia (ALL), in particular, is the most common cancer among populations with high socioeconomic status (SES).[2] In the US, the incidence of ALL is nearly three times higher in white children ages 2 to 3 than in black children, further supporting the theory that socioeconomic characteristics are responsible for these discrepancies.[4] However, there is much debate on this topic as the rate of leukemias for Hispanic children in the US, who are among the most socioeconomically disadvantaged, is higher than for non-Hispanics (53.7 vs. 41.4 per million, respectively).[4] Moreover, a recent paper found that the incidence of ALL was negatively associated with socioeconomic position among Hispanics, but positively associated

for children of other ethnicities.[5] A comprehensive review on SES and childhood cancer stated that these associations vary according to time, place and study design, given that older studies (and those conducted in Europe with predominantly registry-based data) show positive associations between leukemia and SES whereas newer studies (and those conducted in North America, often through self-administered questionnaires in a case-control design) report an inverse association.[6] However, these studies report on different socioeconomic measures, possibly representing different risk factors, and thus may not be entirely comparable. In contrast, non-heritable retinoblastoma has a higher incidence in developing countries.[2] Lymphomas, and Burkitt's lymphoma in particular, are common in tropical regions of Africa and Papua New Guinea.[2]

1.2 Retinoblastoma: an overview

Retinoblastoma is the leading form of eye cancer affecting children in the US and worldwide with an incidence of 11.8 per million children aged 0-4 years in the US. [7] It results from an inactivation of both alleles of the *RB1* gene, a tumor suppressor gene located on chromosome 13, and produces a malignant tumor of the retina that can occur in one eye (unilaterally) or in both eyes (bilaterally) (Figure 1.1).[8] About 6-10% of these cases are due to inherited mutations, in which one mutated allele is inherited from a parent, and the second allele mutates sporadically.[9] In all other cases of disease, inactivation of both alleles occurs from sporadic mutations. When a child receives one defective *RB1* tumor suppressor gene preconception (either through an inherited or sporadic mutation in the parental germline), and one spontaneous mutation in the second allele post-conception, the result is bilateral retinoblastoma.[10] In approximately 85% of these cases, it is the father's allele in which this germ line mutation occurs.[11 12] When both mutations occur sporadically during pregnancy or early life,

the result is unilateral retinoblastoma. From 1974 to 2004 the approximate distribution of bilateral and unilateral retinoblastoma among US children aged 0-4 years was 27% and 73%, respectively.[7] Despite developing countries having higher overall incidence of retinoblastoma, the incidence of bilateral disease specifically varies little across regions. Thus this increase reflects a higher risk of developing unilateral disease, suggesting a role for infections or other environmental factors to cause mutations in utero or infancy.[2]

In Western countries, retinoblastoma is currently the most curable pediatric cancer.[13] There has been rapid advancement in the way of treatment for retinoblastoma in this last decade alone, with most patients in leading centers receiving ophthalmic artery chemosurgery and intravitreous chemotherapy, with the ability to save the eye, and survival rates being high, in even advanced cases.[13] The practice of enucleation, removal of all or part of the eye, is often abandoned for these more modern and less invasive practices.

1.3 Known prenatal risk factors

The etiology of childhood cancers remains unknown; however, most researchers agree that it results from a complex relationship between certain crucial exposures, modifying influences, inherited susceptibility and chance. With genetic factors estimated at explaining less than 10% of childhood cancer cases, new research is needed to uncover the etiology of disease.[14] Established causes of childhood cancers include exposure to ionizing radiation, chemotherapy drugs, diethylstilbestrol (DES) and parental smoking, all of which only explain a small number of cases.[15-20]

1.3.1 Ionizing radiation

Most researchers agree that the development of some childhood cancers can be attributed to ionizing radiation exposure, which acts directly on the DNA itself, during both pre- and post-conception.[19 21 22] The first report of this association was in the 1950s in Britain, when authors found a positive association between maternal abdominal X-ray exposure and childhood cancer.[20 23] Since then, most repeated case-control studies have confirmed this association[24-26] and a weighted average of the relative risks obtained from all published studies is 1.39 (95% CI: 1.33-1.45).[27] Results from cohort studies have been more inconsistent; however, authors often attribute this to the lack of statistical power in cohort studies.[28] Similarly, for paternal preconception radiation exposure, no reliable evidence exists to suggest a positive association with childhood cancer and specifically leukemia.[19] Two studies examined the association between ionizing radiation exposure in parents and the development of retinoblastoma, and both found that mothers and fathers who had high gonadal radiation exposure were at increased risk of having a child with sporadic bilateral retinoblastoma, although only the larger, more rigorous study was sufficiently powered.[29 30] Several studies have found elevated risks of brain and central nervous system (CNS) tumors among children exposed to diagnostic radiation during the prenatal period.[31-33]

1.3.2 Parental age

Some studies have reported an association between older parental age and increased risk of childhood cancer; however, in general, results are inconsistent, with the majority of research supporting a role for advanced maternal, rather than paternal, age.[34-37] The most widely accepted mechanism is through increased *de novo* mutations in the parental germ line cells and increased

chromosomal aberrations during maturation of germ cells, which increase the risk of cancer development in the offspring.[37] Physiologically, aging may also affect estrogen levels of the mother which could also induce cancer development among offspring.[10] The strongest association appears to be with maternal age and ALL. A pooled analysis utilizing data from the United States found that leukemia, lymphoma, CNS tumors, neuroblastoma, Wilms' tumors, bone tumors and soft tissue sarcomas were associated with advanced maternal age.[34] There also appears to be a link between high parental age and increased risk of retinoblastoma.[36 38-44] One study found paternal age to be a relevant risk factor only for sporadic bilateral, and not for unilateral, cases, providing more evidence that paternal germ line mutations play an important role in the development of bilateral disease.[41] In contrast, two studies found that only high maternal age resulted in an appreciable increase in the risk of retinoblastoma, which the authors attribute to changes in hormone levels that occur with age, which may increase cancer risk.[39 37] Therefore, although it seems clear that parental age plays an important role in the development of disease, results are mixed as to whether maternal, paternal or the age of both affects risk.

1.3.3 Smoking

Throughout the world, smoking is the leading cause of adult cancer and, if done during pregnancy, may be a risk factor for childhood cancer, as constituents of tabacco can cross the placenta.[45] Tabacco smoke can cause mutations in paternal germ cells and, in mice, has been shown to pass onto offspring, permanently altering their genomic makeup.[46] Sperm exposed to cigarette toxins was found to have an excess of DNA adducts, strand breaks and oxidative damage.[47 48] Animal studies have found spermatogonial stem cells to also be vulnerable to tobacco exposure.[46] Positive associations were seen for maternal smoking during pregnancy and bilateral retinoblastoma as well as some brain cancers.[30 49-51] A meta-analysis of 17 studies on

childhood brain tumors only found positive assocations with paternal smoking before pregnancy and risk of brain tumors.[52] The association between maternal smoking status and childhood cancers, particularly leukemia and ALL, is unclear, but most studies report a null or weak inverse association.[50 53-55] Given the relative toxicity of many chemical agents in tabacco, some fetus may develop birth defects and not survive to term, thus underestimating the true effect of smoking on childhood cancer.

1.4 Suspected risk factors

Other suspected risk factors that are less established include maternal alcohol consumption, chemical solvents such as formaldehyde and toluene, and infection.

1.4.1 Alcohol

Alcohol may impact the fetus through the transplacental transfer of ethanol[56] and some metabolites have been shown to interfere with DNA synthesis and repair, and may lead to DNA hypomethylation.[57] Maternal alcohol consumption has been positively associated with ALL in five studies[58-62] and negatively associated in two.[63 64] For acute myeloid leukemia (AML) the results are more consistent with almost all studies reporting a positive association with maternal alcohol consumption.[65] For paternal alcohol intake, results are equally mixed, though there is some evidence of a positive association with ALL with higher levels of alcohol consumption.[61 62 66 67] For brain tumors, two studies found a positive association with paternal lifetime consumption of "hard liquor" greater than 200 liters[68] and moderate intake of spirits in the year before pregnancy,[64] whereas several others on both maternal and paternal intake reported null findings.[69-73]

1.4.2 Toluene and formaldehyde

Toluene is a solvent widely used in paints, paint thinners, rubber and printing ink. In California, under proposition 65, toluene has been identified as one of 542 chemicals known to cause cancer, birth defects or reproductive harm. It is rapidly absorbed through the lungs and, like most organic solvents, has an affinity for lipid rich tissues and readily crosses the placental barrier.[74] Yet it is unclear what the mechanisms of action are for toluene.[75] Formaldehyde is a chemical compound found in consumer products (such as hair dyes and nail polishes), tobacco smoke, automobile exhaust, power plants and manufacturing facilities, and is considered a human carcinogen by the International Agency for Research on Cancer (IARC), the U.S. National Toxicology Program, the U.S. Environmental Protection Agency, and the Occupational Safety and Health Administration. Specifically, IARC has named formaldehyde a Group 1 carcinogen meaning "there is sufficient evidence in humans for the carcinogenicity of formaldehyde", with leukemia being one of the main cancers resulting from contact.[76] A recent study has shown that formaldehyde accumulates in the human placenta and crosses the fetal compartment.[77] An earlier study also found that formaldehyde crosses the placenta and enters fetal tissue, with concentrations higher in fetal organs, such as the brain and liver, than in maternal tissues.[78] Like toluene, the mechanisms of action for which formaldehyde induces an effect on reproductive development are not well understood, however, it has been proposed that it may act via genotoxicity, oxidative stress, disruption of the activity of proteins, enzymes and hormones important for the maturation of the male reproductive system, apoptosis and DNA methylation.[79] Aside from leukemia, few studies have examined the direct impact of formaldehyde exposure on childhood cancers. However, exposure to formaldehyde through

secondary sources, including air pollution, motor vehicle exhaust and tobacco have been associated with childhood brain tumors, retinoblastoma and germ cell tumors.[68 80 81]

1.4.3 Infection

Childhood infection, experienced either in utero or during early infancy, is a possible risk factor for several cancers, most notably leukemia, retinoblastoma and brain tumors. There are two well established hypotheses for the mechanisms in which infection could cause childhood cancer, originally developed to explain the increased rates of leukemia but which are now believed to be possible for all cancers. Greaves' 'delayed-infection' hypothesis suggests that individuals who have not been exposed to infections early in life are at an increased risk of developing cancer due to an inexperienced immune system that fails to adapt to later challenges.[82] Alternatively, Kinlen's 'population-mixing' hypothesis suggests that hematopoietic cancers have an infective origin and that evidence of this is in the higher than average rates of disease observed when rural populations undergo rapid urban-mixing (i.e. when men leave their rural towns to work in urban areas and, as such, are presumably exposed to greater numbers of infectious agents, which they then bring back home with them).[83] Cancers that have an established viral origin include Burkitt's lymphoma from a combination of Ebstein-Barr virus exposure and malarial infestation, Cervix cancer from human pappillomavirus (HPV), and liver cancer and hepatitis B virus.[84]

There is some evidence of a viral origin for childhood brain tumors. One European study reported an 11-fold increased risk (odds ratio [OR]: 10.6, 95% confidence interval [CI]: 1.1-503.2) in children whose mothers had a documented viral infection during pregnancy.[85] Likewise, other studies reported elevated risk of CNS tumors among children whose mothers had

influenza during pregnancy.[86 87] Animal studies have found viral RNA of influenza in the brains of infant mice who were exposed during gestation.[88] A meta-analysis found that Simian Virus 40 (SV40), shown to induce brain cancers in animal studies, was associated with brain tumors in children, including astrocytomas, glioblastomas and medulloblastomas.[89]

Some studies have suggested that factors that affect reproductive health play a role in the development of retinoblastoma, particularly infection with sexually transmitted diseases (STI) during pregnancy.[38 90-92] The earliest study found a protective effect for barrier contraceptives and retinoblastoma, but dismissed these results as chance findings.[30] Since then several studies have shown how barrier contraceptives reduce the risk of HPV and others have reported that HPV is associated with retinoblastoma risk.[93-96] Retinoblastoma is caused by a lack of functional retinoblastoma protein (pRB), which binds to and inactivates various transcription factors thus regulating cell cycle progression.[8 97] While the best known cause of the lack of functional pRB leading to retinoblastoma are mutations in the *RB1* gene, the HPV E7 protein can also cause pRB inactivation that results in disease without compromising the *RB1* gene.[98] Studies have found that between 4.5%-70% of all retinoblastoma tumor specimen contain various strains of HPV DNA.[38 95 96 99-101] In areas where HPV infection rates are low, the relationship between HPV and retinoblastoma appears to be less pronounced.[102]

Wilms' tumor, a childhood cancer affecting the kidney, has been inversely related to breastfeeding, which authors attribute to the protective effect of breastmilk on infectious diseases.[103] There is no established biological mechanism that explains the effect of breast-feeding on Wilms' tumor and currently the only established risk factors include rare genetic conditions and congenital anomalies.[1] Other possible risk factors for Wilms' tumor include high birth weight, maternal caffeine consumption and use of certain medications.[104-108]

1.5 Occupational exposures and childhood cancer

There is a clear rationale for investigating the relationship between various workplace exposures and childhood cancer. Currently, no well-established theory exists for the biological mechanisms through which parental occupational exposures may impact offspring cancer risk; however, during the preconception period, it is possible that occupational exposures to certain mutagens create germline mutations that pass on to children. In pregnancy, exposure to chemical agents could harm the fetus through transplacental crossover and, after birth, parents could bring home toxic substances or harmful pathogens from work that influence risk of disease through direct transmission of exposure residues.

Several authors have contended that American workers are spending more time at the work-place than their parents or grandparents did.[109 110] Furthermore, over the past half-century, there has been a sharp increase in the number of women working for pay followed by a decrease in the amount of time women stay home after childbirth.[111] In more recent decades, we have seen a steady increase in the number of hours spent on the job as well as a decline in union strength in the US, which has been an impediment to countering employer's demands to work longer hours in unsafe conditions with fewer breaks.[109] Education related inequality is largely responsible for disparities in the number of hours worked and income gained among different populations, implying that those with greatest occupational risk are also those who are most socioeconomically disadvantaged.[111]

1.5.1 Preconception

With regards to the preconception period, several chemical solvents have been found to cause alterations in male sperm, which could result in increased susceptibility to cancer among

offspring. This is especially likely for retinoblastoma where it is well documented that changes in the paternal genome contribute to development of disease.[12] Previous literature has shown that sperm are susceptible to environmental agents including lead, paint stripper and excessive heat; however, aside from infertility there is limited evidence on health outcomes that affect the offspring and result from these exposures.[112-114] One study found that toluene, a chemical found in paint and paint thinners, resulted in DNA damage in the sperm of rats.[115] Other occupational exposures, such as polycyclic aromatic hydrocarbons (PAHs) and ionizing radiation, have also been reported to impact the motility, viability and morphological abnormalities of male sperm.[116] [117] Exposure to PAHs was also found to alter the nucleotide excision and base excision repair mechanisms utilized to mend damaged sperm caused by chemical agents.[118] In one study, inhalation of sulfur dioxide (SO_2) caused internal damage to many cell systems including hepatic cells and alveolar cells, as well as the cerebral cortex and the mitochondria within cells.[119] In sperm cells, SO_2 exposure resulted in lipid peroxidation and changes to the antioxidative status in mice testicles, providing evidence that SO_2 is a toxin to both the reproductive and respiratory system of mammals and that exposure can cause oxidative damage to male sperm.[120] Despite the number of studies on the morphological effects of various chemical agents on male sperm, there are currently no environmental paternal teratogens or carcinogens that have been identified for many childhood cancers, including retinoblastoma, leukemia, brain tumors or bone cancers.

1.5.2 Pregnancy

There currently remain large gaps in the literature surrounding maternal occupational exposure in relation to childhood cancers, in particular, the rarer childhood cancers.[121] [122] Of the maternal occupational studies that do exist, most focus on exposure to ionizing radiation and chemical solvents.[123-125] Some studies have found an association between childhood cancer and

occupational or residential pesticide exposure during pregnancy.[126-130] Other occupational risk factors examined during the pregnancy period include exposure to motor-vehicles, electromagnetic fields, textile dust, engine exhaust and paints, though results were inconsistent across studies. [131-137] Some contaminants have been shown to cross the placenta in laboratory studies, including carcinogenic metals nickel and chromium, PAHs (found in paints, wood burning and vehicle exhaust), and acrylamide (used for producing grouts and soil stabilizers).[138-141]

1.5.3 After birth

A small number of studies have examined parental occupational exposures after birth and risk of childhood cancers. Of the few that exist, most investigate the role of infection, as some viruses have cancer-inducing properties.[100 142-146] Additionally, it is hypothesized that altered patterns of infection, which influence the strength of the immune system, in early childhood play a large role in the increased rates of leukemia in recent decades.[147] Studies that have examined this relationship have found factors such as daycare attendance, parity, birth order, vaccination history and population mixing to be inversely related to risk of leukemia.[148-150] Studies that explore vaccination in children have also found that those exposed to vaccinations early in life (particularly that of Haemophilis Influenza) experience reduced risk of leukemia, providing additional evidence that early immune stimulation may help moderate later response to new infections.[151 152] Two medical record studies found that having allergies was positively associated with leukemia, which is consistent with the hypothesis that both allergies and leukemia share the same risk factor of an immature immune system.[153 154] There is also some evidence that maternal and early childhood exposure to common viral infections may result in an increased risk of childhood brain tumors and, in particular, medulloblastoma and gliomas.[155-157] One study found

cytomegalovirus infection in over 90% of surgical brain specimens from glioblastoma multiforme tumors;[158] however, other laboratory studies were unable to report similar findings.[145 159 160]

1.6 Occupational social contact and infection

Certain occupations, and especially those with high social contact, may experience higher rates of infectious diseases. Studies have found that both age and occupation are important indicators of the social-mixing patterns and number of daily contacts individuals are exposed to[161] and, specifically, that children aged 0-4 have the greatest number of social contact hours as well as the greatest number of contacts.[162] Moreover, teachers, healthcare and service workers are exposed to more workplace contacts than the national average and have at least 50% more contact hours than those who are unemployed or retired, persons identified as having the lowest number of contacts.[162] Epidemiologic simulations have predicted that around 90% of infections originate from the 50% of the population with the highest transmission (or the highest number of social contact hours).[163] Studies have found that those exposed to animals and those in the medical or teaching professions have an increased risk of infections including hepatitis E, hepatitis C, tuberculosis and other respiratory infections.[164-168]

1.7 Comparison of work environments

For two studies, we utilize registry data from Denmark and report on associations between occupational exposures obtained through a government mandated registry and risk of childhood cancers. Working environments in Denmark are similar to those in the US. Both countries are highly developed with an abundance of jobs in the public and private sectors. Workplace health and safety practices have been put into place in both countries and, in general

terms, European safety standards tend to be similar or marginally more strict than those in the US.[169] Similar to America, Denmark has seen a substantial increase in the rate of female employment over the last 35 years, making it an ideal setting to examine maternal occupation exposures. Having access to employment records allows us to obtain a more realistic estimate of the proportion of women working now in Denmark (cited to be between 50-65%) as opposed to lower rates of female employment before the 1980's (ranging between 2-50%).[170-174] Compared to American women, of whom 59% were employed in 2009, 73% of Danish women were employed in 2007 making it the country with the 3rd highest rate of female employment among the European Union.[175 176]

1.8 Objective

In this report, we investigate the role of various occupational industries, hazardous chemicals and social contact as potential risk factors for the development of childhood retinoblastoma and hematopoietic, brain, and bone cancers. We examine all periods of susceptibility, specifically preconception, pregnancy, and birth to diagnosis, as a means to better understand the effect that these agents have in the timing and development of disease.

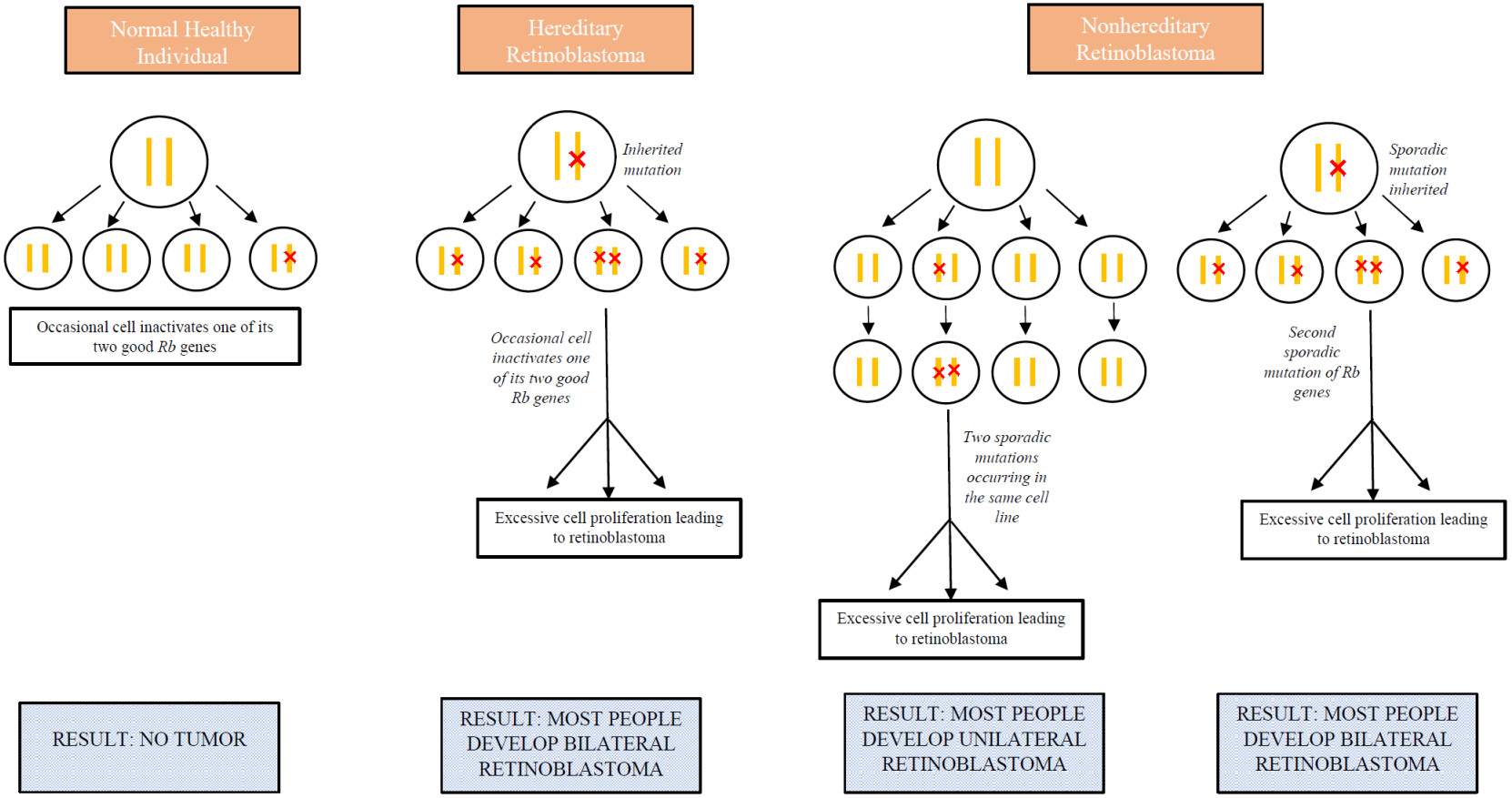

Figure 1.1 Genetic diagram of hereditary and nonhereditary retinoblastoma development

2 High parental occupational social contact and risk of childhood hematopoietic, brain and bone cancers.

2.1 Abstract

The etiology of childhood cancer is largely unknown, though some research suggests an infectious origin of hematopoietic, central nervous system (CNS) and bone cancers. We examined parental occupational social contact as a proxy for increased exposure to infectious agents and risk of childhood cancer. This population-based case-control study utilized a linkage of four Danish data-registries, and included 4,112 cases (<17 years, diagnosed from 1968-2012) and 411,200 age-matched controls. We examined the risks of leukemia, lymphoma, CNS and bone cancer related to high occupational social contact, jobs that have regular contact with young children or the sick, from (1) conception to birth and (2) birth to diagnosis. Acute lymphoblastic leukemia (ALL) and bone cancer were inversely associated with high maternal occupational social contact from conception to birth (OR: 0.82, 95% CI: 0.64-1.04) and birth to diagnosis (OR: 0.59, 95% CI: 0.39-0.91). Children of fathers with high occupational social contact from birth to diagnosis had an increased risk of bone cancers, particularly in rural areas (OR: 1.68, 95% CI: 1.07-2.64). Parental high social contact was associated with increased risk of astrocytoma, with strongest associations found in first born children (maternal contact: OR: 1.54, 95% CI: 1.02-2.32; paternal contact: OR: 1.82, 95% CI: 1.05-3.17). Our results support the notion of a role of infections for some cancer types.

2.2 Introduction

Childhood cancer remains the second most common cause of death in children living in the United States and Europe.[1 177] Research to date has revealed little about the etiology of these

diseases, and established risk factors are limited to certain rare genetic syndromes and polymorphisms, ionizing radiation, and congenital abnormalities.[178 179] Some studies have suggested that early exposure to infections, assessed using proxy measures such as birth order, daycare attendance or medical records, are possible risk factors for childhood hematopoietic or brain cancers.[82 150 180-183] High levels of parental social contact in certain jobs may be another way through which children during fetal development can be exposed to infectious agents, as these jobs often involve regular contact with young children or the ill. Few studies have examined occupational social contact as an indirect measure of infectious burden in relation to childhood cancer risks, with research mainly focusing on paternal exposures only.[184-188]

In recent years, two infectious hypotheses have gained momentum to help explain childhood leukemia incidence. Greaves' 'delayed-infection' hypothesis suggests that individuals who have not been exposed to infections early in life are more likely to develop cancer due to an abnormal immune response that fails to adapt to later challenges.[82] Alternatively, Kinlen's 'population-mixing' hypothesis suggests that the increased rates of hematopoietic cancers, and specifically acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), in recent decades are due to exposure to a single, and yet unidentified, infectious agent.[189] Kinlen postulated that the infectious agent causing leukemia is largely asymptomatic in the general population and that most infected individuals develop immunity. Thus, the spread of disease occurs not by those who show signs of illness but, rather, by the much larger number of infected individuals who show no clinical symptoms.[188] This theory is strengthened by the absence of a marked space-time clustering of leukemia in the general population, as compared to excesses of leukemia in rural populations that undergo rapid population mixing.[186 187]

Studies which have supported Greaves' hypothesis found leukemia to be inversely associated with increased exposure of infants and young children to common infections through daycare settings, higher parity and later birth order.[148-150] Thus, children who are diagnosed with leukemia tend to have fewer early childhood contacts with other children and infections, and may experience less immune system stimulation.[190] Studies by Kinlen have examined parental social contact by enlisting epidemiologists to grade jobs as either having low, medium, high or indeterminate social contact.[187] These studies have suggested that population-mixing, often resulting from men who leave their rural communities to work in urban areas and then return home, may have resulted in an excess of childhood leukemia cases.[83 187 189 191-193] As such, paternal occupational social contact was associated with risk of childhood leukemia in rural, but not urban, areas.[185-188] However, other studies were unable to corroborate these results for both hematopoietic and brain cancers.[184 194]

In most studies, high levels of occupational social contact was assigned to jobs that deal directly with young children or employment in the medical field,[186-188] occupations which are expected to expose its practitioners to infectious diseases.[144 164 195 196] Only two studies have been published who considered maternal occupational social contact, and both reported no difference in risk between high and low social contact jobs and hematopoietic cancers.[185 197] However, studies that examined childhood cancer risk by maternal job title, linked several maternal jobs known for high social contact (such as nurses, teachers and postal/communication workers) to increased risks of offspring hematopoietic, brain and bone cancers.[198-200] Although occupational social contact has not been specifically studied in relation to other childhood cancer types, maternal employment in the medical and dental field was related to Wilms tumor and maternal employment as a hairdresser was associated with neuroblastoma.[201 202]

During early childhood, contact with infectious agents can be influenced by parental work contacts, and may be particularly important for children who do not attend daycares or preschools or who do not have older siblings. We hypothesize that parents with high social contact jobs would likely expose their children to pathogenic agents in utero or during early life, resulting in ample opportunity to develop a strong immune response that decreases the risk for childhood hematopoietic, central nervous system (CNS) and bone cancers.

2.3 Methods

Data for this population-based case-control study was obtained from a linked database we created that combined data from four different Danish registries: The Central Population Registry,[203] the Danish Cancer Registry,[204] the Supplementary Pension Fund[205] and the Danish Medical Birth Registry.[206] The Danish Cancer Registry was used to ascertain cases (<17 years old) who were diagnosed between 1968-2012. Cases were classified according to the International Classification of Childhood Cancer (ICCC), version 1 until 2003 and version 3 thereafter. Tumor subtypes were identified using the International Classification of Diseases for Oncology (ICD-0), version 1 until 2003 and version 3 thereafter.[207 208] The Central Population Registry was used to ascertain 100 controls per case, all of whom were cancer-free at the time of diagnosis of the corresponding case. Controls with an equal probability of selection after matching by sex and year of birth were identified randomly from a population pool within the Central Population Registry in Denmark. To retrieve information on gestational characteristics and parental occupations, cases and controls had to have been born in Denmark to be eligible for the present study. Ethical approval for the current study was obtained from the University of California, Los Angeles institutional review board as well as from the Danish Data Protection

Agency, and informed consent requirements were waived as we performed secondary analyses of a registry-based dataset.

The Danish Supplementary Pension Fund, established in 1964, is mandated for all wage earners 18-66 years of age who are working at least 9 hours per week, and since 1978, for all wage earners 16-66 years of age. Information on students, individuals who are self-employed or persons born before April 1st, 1897 are not included in the Supplementary Pension Fund. This fund retains the employee's name along with information on the calendar period of employment and the name, address and a unique 8-digit identification number for each company. Occupations are categorized based on a five digit detailed version of the International Standard Industrial Classification of All Economic Activities (ISIC).[209 210] As membership in the Supplementary Pension Fund is mandatory and controlled by Danish authorities, the information is considered to be accurate and complete.[205] Validation studies of this and other Danish registries have reported low rates of misclassification of patient information and disease diagnoses.[204 206 211]

To identify the parents of cases and controls we utilized the Central Population Registry for births from 1968-1972. The Central Population Registry reports the legal guardian, but not necessarily the biological parent, of each child. After 1972, we could identify the biological mother from the Medical Birth Registry. Because most adoptions in Denmark are of foreign-born children,[212] and for our study we required that all study participants were born in Denmark, we expect that most parents in our dataset are biological parents. We conducted an analysis of 2014 data – that contains this information - to determine adoption rates and found that 99.4% were indeed biological parents.

For the period 1968-2012, we identified 5,721 cancer cases who were born in Denmark, and 572,100 controls. We excluded anyone born outside of Denmark (N=74) and those whose

parents did not have any occupational history information recorded during relevant time periods (N=27,658). Our analyses focused on cancers for which associations had been previously reported with occupational social contact, therefore cases were included if they were diagnosed with any hematopoietic, CNS or bone cancer.[184 186 194 199] In an exploratory analysis, we also examined the effects of parental social contact on some cancers for which a minimum of 150 total cases were available (retinoblastoma, specific brain cancer subtypes, neuroblastoma and Wilms tumor). Our final dataset consisted of 4,112 hematopoietic, CNS and bone cancer cases and 411,200 birth-year matched controls.

To distinguish between possible infections occurring in utero or in early life, we examined the association between occupational social contact and childhood cancer during two developmental periods in relation to mothers' and fathers' occupations: (1) conception to birth and (2) after birth to diagnosis. Date of conception was determined by subtracting child's gestational age in days from their birth date, details can be found in supplemental file 2.1.

Within each period of susceptibility, parents were categorized as either having very high, high, medium or low occupational social contact based on a job exposure matrix replicating previous work by Kinlen et al. (Supplemental table 2.1) which was updated for the Danish population based upon the advice of experts in Danish occupational health.[186] In short, these categories were defined as follows:

(A) Very high social contact: occupations in the health care industry and those involving a high level of contact with children and young or ill people (physicians, dentists, midwives, physiotherapists, elementary school teachers and daycare workers).

(B) High social contact: occupations in the transportation industry or the providers of services to many different type of people (e.g. drivers, pilots, hotel workers, real estate agents, non-elementary school teachers, and hairdressers).

(C) Medium and low social contact: low social contact was assigned to subjects with occupations in agriculture. Due to sample size restrictions, we merged this group with medium social contact, which comprised of all other occupations and formed the reference category.

Children of parents who had an indeterminate job for longer than 6 months at any point during the relevant periods of exposure or who were unemployed for the entire period of interest were excluded from the study. Most parents held more than one job during the relevant periods of interest. For these individuals, we assigned them to an exposure level based on the job they held, for any amount of time, with the highest exposure (very high > high > medium > low).

Analyses were conducted using conditional logistic regression and adjusted for maternal age (≤25, 26-30, 31-35, 36+ years) and urbanicity defined as urban or small town/rural residency according to the place of birth listed in the Danish Cancer Registry. Selection of potential confounders for adjustment was based on previous literature as well as exploring associations present in our data.[186] Variables also considered for inclusion in our adjusted model were number of previous pregnancies, number of previous live births, maternal smoking status and family socioeconomic status (SES), though most had large numbers of missing values (24%-78%). In sensitivity analyses adjusting for these additional variables, we found little difference in point estimates (<10% change) thus they were not retained in the models. Due to limited sample size for many cancer types, we combined very high and high social contact.

To avoid competing exposures due to non-occupational high social contact experienced in urban settings, we performed analyses that restricted to individuals living in small towns or rural areas only. Given that children with older siblings have higher exposure to infections at an earlier age,[180] we also conducted analyses restricted to first born children only. Whenever sample size allowed (N>5), we performed analyses that restricted to both rural households and first born children only. To determine whether including adopted children changed point estimates to an appreciable degree, we conducted sensitivity analyses that only examined data available after 1973, when the biological mother was clearly identified. We performed additional sensitivity analyses in the form of a trend test that assessed the effects of very high and high occupational social contact on childhood cancers separately to determine whether any dose-response pattern was present. We also performed analyses that excluded all individuals diagnosed before 1980, as the Danish population evolved from rural and mostly small towns to mostly urban during that time.[213] All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

2.4 Results

Cases and controls shared similar demographic characteristics with regard to parental age, family SES and residency type, although slightly more astrocytoma cases were female and fewer bone cancer cases had fathers 25 years of age or younger (Table 2.1).

Table 2.2 shows the risk of leukemia, CNS tumors and bone cancers associated with "very high and high parental occupational social contact", herein referred to as high social contact. Children of mothers who had high social contact jobs had a reduced risk of ALL (odds ratio [OR]: 0.82, 95% confidence interval [CI]: 0.64-1.04) and bone cancer (OR: 0.59, 95% CI: 0.39-0.93). However, we estimated a slightly increased risk of astrocytoma for children of

mothers who had high social contact jobs between birth and diagnosis (OR: 1.27, 95% CI: 0.99-1.64). For fathers, high social contact jobs from conception to birth was also associated with lower point estimates for leukemia (OR: 0.82, 95% CI: 0.65-1.03) but for bone cancer high social contact from birth to diagnosis related to increased risk (OR: 1.40, 95% CI: 0.96-2.04).

When we restricted to cases and controls living in rural areas, most odds ratios increased (Table 2.3). Specifically, for fathers having high social contact jobs from birth to diagnosis the estimated risk for bone cancer in children was increased (OR: 1.68, 95% CI: 1.07-2.64). We also estimated an increased risk of astrocytoma (OR: 1.40, 95% CI: 1.01-1.94) in children whose mothers had high social contact jobs from birth to diagnosis. Among first born children (Table 2.4), associations between high maternal occupational social contact and astrocytoma strengthened; paternal occupational social contact from conception to birth was also associated with astrocytoma (OR:1.82, 95% CI: 1.05-3.17). Among those living in rural areas and those who were first born, risk of astrocytoma was highest among children of fathers who had high social contact jobs from conception to birth (OR: 2.29, 95% CI: 1.12-4.69).

We did not find parental occupational social contact to be associated with lymphomas (Supplemental table 2.3). Among the other rare cancers we examined, we estimated increased risk for Wilms tumor (Supplemental table 2.4). In analyses that separated very high and high social contact, we observed a trend for leukemia ($P<0.05$) among fathers for very high and high social contact from conception to birth (very high OR: 0.44, 95% CI: 0.18-1.07 vs. high OR: 0.87, 95% CI: 0.69-1.10, Supplemental table 2.5). For other rare cancers we examined in an exploratory subanalysis, very high (but not high) social contact was associated with an increased risk of Wilms tumor (OR: 2.04, 95% CI: 0.98-4.23). Analyses restricting to children born after 1980 or those born after 1973 were similar to those presented here (data not shown).

2.5 Discussion

In the present study, using a large population-based sample and detailed historical employment information, we estimated a decreased risk of ALL and bone cancers and an increased risk of astrocytoma among the children of mothers with high social contact jobs. For the children of fathers with high occupational social contact, we also observed a similarly decreased risk of ALL, an increased risk of astrocytoma, but also an increased risk of bone cancers. This study is one of the first to examine maternal social contact and risk of childhood cancers and the sample size allowed us to examine some rarer cancer types and subtypes.

Incidence of leukemia has increased at about 1% per year throughout the last two decades in the United States,[214] suggesting that causal risk factors to disease have become more prevalent. Some authors have proposed that the increased rates of leukemia in developed countries are due to altered patterns of infection,[147] although other explanations include increasing parental age and changes in the racial/ethnic composition of the population.[35 215 216] We found that high parental occupational social contact between conception and birth related to an inverse association with childhood leukemia, signifying that perhaps the earliest exposures to infection in utero could stimulate the perinatal immune system. This is in line with findings from a meta-analysis compiling results from 15 studies on childcare attendance and risk of leukemia with a combined OR = 0.76 (95% C.I. 0.67-0.87).[190] A possible underlying explanation is the "two-hit model" of carcinogenesis asserting that susceptibility to leukemia likely begins in utero with an additional postnatal event required for the disease to manifest.[217] Support that the first hit occurs in utero is found through analyses of identical twins with concordant ALL that revealed identical breakpoints in *TEL-AML1* genes from the leukemia cells of both twins.[218 219] Further, for identical twin infant leukemia, it is thought that the concordance rate approaches 100%. [220]

However, for children 2-6 years of age, the concordance rate is around 5%, suggesting the need for some additional postnatal "hit".[220] Infection is thought to be largely responsible for promoting the second genetic hit through an underlying immune response. This theory is rooted in evolutionary biology,[221] which theorizes that the immune cell network with its complex responses evolved through an adaptation processes triggered by lethal infections promoting genetic dispositions that deal better with infections occurring in early life.[222 223] Accordingly, these exposures were essential for the early organization of an adequate immune response to future infectious agents. Therefore, increasing exposure to disease in utero or early life could stimulate modulation of the immune system, thus allowing it to adequately addresses and adapt to later challenges, in this case, one or more common infections responsible for indirectly promoting leukemia.[82]

An alternate theory, proposed by Kinlen, is that leukemia is the result of some specific infectious agent rather than an unusual reaction to infection.[83 189 191-193] Kinlen's studies took place in the rural U.K. when small towns were more geographically and socially isolated, while in contrast, studies in more recent years, or in more mixed populations such as the United States, have not shown this effect.[83 185 189] Similarly, several other large European population-based studies did not find high social contact to increase the risk of leukemia or its subtypes when examining data from urban populations.[187 188 194] If there is an infective agent responsible for leukemia, urban areas appear to be relatively resistant, possibly due to their higher population densities and, consequently, the absence of population-mixing. We did not observe increased risk of leukemia among children of parents with high social contact jobs in either urban or small town/rural areas, or among first born children. Restricting to the years between 1968-1980, when more Danes resided in rural small towns,[213] resulted in point estimates below 1 but wider

confidence intervals for ALL among mothers and fathers, which might suggest that early life infections are protective against leukemia, regardless of population density. Similar to ours, another study failed to find an association between high social contact and leukemia even after stratifying on urban and rural geographic area.[184] However, one study which examined both duration and contact level of paternal jobs reported a lower risk of ALL with increased duration of employment in a high social contact job in urban areas (OR: 0.79, 95% CI: 0.47-1.33) but an increased risk in rural areas (OR: 2.28, 95% CI: 0.76-6.85), yet confidence intervals were wide and included the null.

Our paper is among the first to report maternal exposure to high occupation social contact to be inversely associated with ALL. To our knowledge, only two other studies formally examined maternal occupational social contact and risk of leukemia and they report conflicting results, though neither had the power to stratify by urban/rural residency.[185 197] One additional study that utilized job titles to examine risk of childhood cancers found that assistant nurses were at an increased risk of having children diagnosed with leukemia.[199] Infections spread within families[224] and thus either maternal and paternal social contact should result in similar risks for childhood cancer. In most instances, our results for maternal and paternal agreed, except for bone cancers, where we estimated effects in opposite directions. Early studies, including one that also took place in Denmark and overlaps with our study population (children diagnosed between 1968-1984), found that both maternal and paternal occupations in teaching and healthcare were associated with a greater risk of childhood bone cancers, however neither study grouped jobs into social contact categories.[200 201] Another study reported excesses of bone cancer among offspring of women employed as postal or communication workers.[199] All published studies on

childhood bone cancer and parental occupations, including our own, are based on small sample sizes suggesting a need for pooled or meta-analyses to draw conclusions about this rare cancer.

There is some evidence to suggest that maternal and early childhood exposure to common viral infections may result in an increased risk of childhood brain tumors, though few studies had the power to examine tumor subtypes.[155-157] Cytomegalovirus infection was associated with increased risk of both medulloblastoma and gliomas, including astrocytoma; however, atopic diseases such as asthma and hay fever have been shown to have an inverse association with gliomas, suggesting a role for certain immune responses in brain tumor etiology.[146 225 226] Most researchers believe that asthma and allergies favor a Th2 immune response, which is associated with the promotion of IgE and has greater anti-inflammatory properties, whereas infectious disease favors a Th1 response, primarily producing proinflammatory cytokine interferon gamma which, if excessive, can lead to uncontrolled tissue damage.[227] In the present study, increased risk of astrocytoma was observed among mothers with high occupational social contact from child's birth to diagnosis, with stronger associations being observed in analyses that stratified on rural residence status and first born children. This timing is consistent with evidence examining space-time clustering of astrocytoma that suggests infection occurring postnatally, as opposed to prenatally, being related to brain tumors.[156] Similar to our findings for fathers, one other study found that the risk of astrocytoma was slightly increased for children of fathers with high social contact occupations (crude OR: 1.16, 95% CI: 1.00-1.35); however, confidence intervals widened after adjustment for social class and authors did not report associations for maternal occupational social contact or examine different periods of susceptibility.[228] Another study on parental occupation found that mothers employed as nurses, whom we categorized as having very high social contact, had an increased risk of having a child

diagnosed with astrocytoma, based on a small number of case mothers working as nurses (N= 11, OR: 8.0, 95% C.I. 1.1-356.1).[198] About 32% of pilocytic (low-grade) astrocytoma cases have chromosomal abnormalities (gain of a whole chromosome), the majority occurring in patients over 15 years of age.[229] There is little evidence that astrocytoma results from DNA abnormalities or genetic mutations.[230 231] A study that reported finding human cytomegalovirus infection in over 90% of surgical brain specimens from glioblastoma multiforme tumors, rare in children,[158] remains controversial as other laboratory studies were unable to report similar findings.[145 159 160]

For the present study, we did not have access to information on childcare attendance, and childcare attendance is related to higher rates of infections in early childhood.[232] In Denmark, maternity and paternity leaves of 52 weeks are common since the passage of a 2002 law mandating this length. In the years 1989-2004, 2% of children were enrolled in a childcare facility before 3 months of age, 21% at 6 months of age, 53% at one year of age and 75% from 3-5 years of age.[233] Thus, infections due to parental occupational exposures should be most relevant for younger infants. Limitations of our study include the large number of missing values for potentially important covariates, including maternal smoking status. However, sensitivity analyses adjusting for this and other variables, when available, resulted in no difference in point estimates. Further, we created occupational social contact categories based on Kinlen's social contact matrix, but were unable to find validation studies to affirm the social contact levels for these jobs titles;[187] nonetheless, previous studies reported high rates of infectious diseases among the medical and teaching professions.[234 235]

In conclusion, our study reports a reduced risk of leukemia among children of parents with high occupational social contact between conception and birth and an increased risk of astrocytoma among children of parents with high occupational social contact. Further

mechanistic research is needed to uncover the potentially underlying biological relationships between occupational social contact and childhood cancers, and related risks for other rare pediatric cancers.

Table 2.1 Demographic characteristics of cases and controls

		Hematopoietic Cancers		Brain and Neural Cancers		
	All controls	**All Leukemia**	**ALL**	**CNS**	**Astrocytoma**	**Bone**
	N=411,200 (%)	**N=1672 (%)**	**N=1337**	**N=1494 (%)**	**N=499 (%)**	**N=241 (%)**
Sex of child						
Male	225500 (54.8)	910 (54.4)	753 (56.3)	800 (53.6)	237 (47.5)	127 (52.7)
Female	185700 (45.2)	762 (45.6)	584 (43.7)	694 (46.5)	262 (52.5)	114 (47.3)
Missing	0	0	0	0	0	0
Maternal age						
<=25	131210 (31.9)	482 (28.8)	375 (28.1)	484 (32.4)	169 (33.9)	70 (29.1)
26-30	154678 (37.6)	626 (37.4)	501 (37.5)	581 (38.9)	197 (39.5)	101 (41.9)
31-35	92510 (22.5)	395 (23.6)	317 (23.7)	316 (21.2)	99 (19.8)	46 (19.1)
36+	32720 (8.0)	169 (10.1)	144 (10.8)	113 (7.6)	34 (6.8)	24 (10.0)
Missing	82 (0.0)	0	0	0	0	0
Paternal age						
<=25	70071 (17.0)	258 (15.4)	188 (14.1)	254 (17.0)	82 (16.4)	26 (10.8)
26-30	140661 (34.2)	571 (34.2)	462 (34.6)	531 (35.5)	189 (37.9)	93 (38.6)
31-35	118541 (28.8)	478 (28.6)	391 (29.2)	426 (28.5)	131 (26.3)	75 (31.1)
36+	79329 (19.3)	354 (21.2)	290 (21.7)	269 (18.0)	93 (18.6)	46 (19.1)
Missing	2598 (0.6)	11 (0.7)	6 (0.5)	14 (1.0)	4 (0.8)	1 (0.4)
Family SES						
High	40417 (9.8)	150 (9.0)	121 (9.1)	150 (10.0)	49 (9.8)	22 (9.1)
Medium-high	52095 (12.7)	217 (13.0)	177 (13.2)	193 (12.9)	64 (12.8)	33 (13.7)
Medium	60268 (14.7)	232 (13.9)	190 (14.21)	227 (15.2)	89 (17.8)	46 (19.1)
Medium-low	105869 (25.8)	438 (26.2)	355 (26.6)	385 (25.8)	126 (25.3)	61 (25.3)
Low	54845 (13.3)	226 (13.5)	183 (13.7)	197 (13.2)	68 (13.6)	28 (11.6)
Missing	97706 (23.8)	409 (24.5)	311 (23.3)	342 (22.9)	103 (20.6)	51 (21.2)
Residence type						
Urban	133828 (32.6)	529 (31.6)	433 (32.4)	503 (33.7)	172 (34.5)	74 (30.7)
Small town	133811 (32.5)	540 (32.3)	428 (32.0)	484 (32.4)	154 (30.9)	77 (32.0)
Rural	143561 (34.9)	603 (36.1)	476 (35.6)	507 (33.9)	173 (34.7)	90 (37.3)
Missing	0	0	0	0	0	0

Table 2.2 Risk of leukemia, CNS tumors and bone cancers relative to parental occupational social contact at various times from conception to diagnosis

	All Controls (N=411200)	All Leukemia (N=1672) Average age at diagnosis: 5.5			ALL (N=1337) Average age at diagnosis: 5.6			CNS (N=1494) Average age at diagnosis: 7.2			Astrocytoma (N=499) Average age at diagnosis: 7.1			Bone (N=241) Average age at diagnosis: 10.6		
		N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)
Mother																
Conception to birth																
Very high & high	23682	98	0.9	0.90 (0.73-1.11)	73	0.82	0.82 (0.64-1.04)	87	0.91	0.90 (0.72-1.12)	32	1.06	1.05 (0.73-1.51)	12	0.79	0.76 (0.42-1.38)
Medium & low	254322	1147	ref	ref	933	ref	ref	1014	ref	ref	327	ref	ref	171	ref	ref
Birth to diagnosis																
Very high & high	47063	180	0.94	0.95 (0.81-1.11)	139	0.9	0.90 (0.75-1.07)	207	1.10	1.09 (0.94-1.27)	77	1.29	1.27 (0.99-1.64)	24	0.59	0.59 (0.39-0.91)
Medium & low	275698	1217	ref	ref	985	ref	ref	1062	ref	ref	354	ref	ref	186	ref	ref
Father																
Conception to birth																
Very high & high	21881	80	0.83	0.82 (0.65-1.03)	65	0.84	0.82 (0.64-1.06)	81	0.96	0.96 (0.77-1.21)	26	0.99	0.99 (0.66-1.48)	16	1.28	1.28 (0.75-2.14)
Medium & low	293946	1289	ref	ref	1036	ref	ref	1122	ref	ref	368	ref	ref	166	ref	ref
Birth to diagnosis																
Very high & high	37996	151	0.97	0.98 (0.82-1.16)	121	0.97	0.96 (0.80-1.17)	147	0.97	0.98 (0.82-1.16)	51	1.04	1.03 (0.77-1.39)	35	1.36	1.40 (0.96-2.04)
Medium & low	285775	1248	ref	ref	1000	ref	ref	1107	ref	ref	371	ref	ref	154	ref	ref

*Adjusted for maternal age and urban or small town/rural residence status

Table 2.3 Risk of leukemia, CNS tumors and bone cancers relative to parental occupational social contact at various times from conception to diagnosis among small town or rural cases and controls only

	All Controls (N=27737)	All Leukemia (N=1143) Average age at diagnosis: 5.5			ALL (N=904) Average age at diagnosis: 5.5			CNS (N=991) Average age at diagnosis: 7.2			Astrocytoma (N=327) Average age at diagnosis: 7.0			Bone (N=167) Average age at diagnosis: 10.4		
		N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)
Mother																
Conception to birth																
Very high & high	13588	57	0.89	0.89 (0.68-1.17)	44	0.87	0.87 (0.64-1.18)	51	0.96	0.96 (0.72-1.29)	18	1.05	1.05 (0.64-1.71)	8	0.94	0.93 (0.45-1.91)
Medium & low	174347	787	ref	ref	630	ref	ref	667	ref	ref	215	ref	ref	116	ref	ref
Birth to diagnosis																
Very high & high	27726	105	0.93	0.93 (0.76-1.14)	82	0.90	0.90 (0.71-1.14)	122	1.15	1.15 (0.95-1.40)	45	1.40	1.40 (1.01-1.94)	15	0.63	0.63 (0.37-1.08)
Medium & low	189965	849	ref	ref	677	ref	ref	708	ref	ref	231	ref	ref	126	ref	ref
Father																
Conception to birth																
Very high & high	11168	41	0.83	0.81 (0.59-1.11)	34	0.87	0.85 (0.60-1.20)	47	1.13	1.16 (0.86-1.56)	15	1.19	1.25 (0.73-2.11)	9	1.36	1.33 (0.67-2.65)
Medium & low	202574	898	ref	ref	708	ref	ref	748	ref	ref	241	ref	ref	116	ref	ref
Birth to diagnosis																
Very high & high	19738	84	1.05	1.04 (0.83-1.31)	69	1.08	1.07 (0.83-1.38)	84	1.1	1.12 (0.89-1.41)	29	1.17	1.19 (0.80-1.76)	24	1.7	1.68 (1.07-2.64)
Medium & low	197068	871	ref	ref	687	ref	ref	744	ref	ref	245	ref	ref	110	ref	ref

*Adjusted for maternal age

Table 2.4 Risk of leukemia, CNS tumors and bone cancers relative to parental occupational social contact at various times from conception to diagnosis among first born children only

	All Controls (N=120209)	All Leukemia (N=443) Average age at diagnosis: 6.1			ALL (N=367) Average age at diagnosis: 5.9			CNS (N=497) Average age at diagnosis: 7.4			Astrocytoma (N=175) Average age at diagnosis: 6.9			Bone (N=80) Average age at diagnosis: 11.0		
		N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)
Mother																
Conception to birth																
Very high & high	7796	28	0.9	0.91 (0.61-1.35)	22	0.84	0.84 (0.54-1.31)	37	1.16	1.18 (0.83-1.66)	12	1.14	1.13 (0.62-2.06)	4	0.73	0.71 (0.25-1.97)
Medium & low	83564	327	ref	ref	276	ref	ref	348	ref	ref	125	ref	ref	63	ref	ref
Birth to diagnosis																
Very high & high	15325	55	1.02	1.02 (0.77-1.37)	43	0.97	0.97 (0.70-1.35)	76	1.21	1.24 (0.96-1.60)	30	1.52	1.54 (1.02-2.32)	10	0.67	0.66 (0.34-1.29)
Medium & low	88425	336	ref	ref	281	ref	ref	360	ref	ref	124	ref	ref	66	ref	ref
Father																
Conception to birth																
Very high & high	5891	21	0.93	0.93 (0.59-1.45)	17	0.89	0.87 (0.53-1.44)	30	1.23	1.26 (0.86-1.85)	15	1.81	1.82 (1.05-3.17)	6	1.42	1.34 (0.56-3.20)
Medium & low	91340	342	ref	ref	285	ref	ref	373	ref	ref	128	ref	ref	63	ref	ref
Birth to diagnosis																
Very high & high	11681	44	1.06	1.06 (0.77-1.47)	36	1.04	1.04 (0.73-1.49)	50	0.97	1.0 (0.74-1.35)	19	1.12	1.12 (0.68-1.84)	10	0.91	0.93 (0.46-1.84)
Medium & low	88662	335	ref	ref	278	ref	ref	380	ref	ref	132	ref	ref	60	ref	ref

*Adjusted for maternal age and urban or small town/rural residence status

Supplemental table 2.1 Job exposure matrix of maternal and paternal jobs held for high and very high social contact

Job Type	Proportion of Cases N (%)			
	Mothers		Fathers	
	Conception to Birth N=240	Birth to Diagnosis N=505	Conception to Birth N=214	Birth to Diagnosis N=408
Very High Social Contact Jobs				
Elementary school teachers	18 (18.6%)	8 (32%)	37 (15.7)	13 (19.7)
Daycare and/or kindergarten workers	43 (44.3%)	3 (12%)	81 (34.5)	12 (18.2)
Other day-care institutions for children	13 (13.4%)	7 (28%)	39 (16.6)	17 (25.8)
Homes for children and young people	10 (10.3%)	55 (20%)	23 (9.8)	14 (21.2)
Practicing physicians	13 (13.4%)	2 (8%)	55 (23.4)	10 (15.2)
Practicing dentists	42 (16.6)	8 (2.8)	48 (8.5)	11 (1.8)
Practicing dental technicians	1 (0.4)	0	2 (0.4)	0
Maternity clinics and practicing midwives	0	0	2 (0.4)	0
Physiotherapy clinics and practicing physio therapists	1 (0.4)	0	4 (0.7)	1 (0.2)
High Social Contact Jobs				
Hotel or motel industry	31 (12.3)	26 (9.2)	82 (14.5)	41 (6.7)
Hostel workers	2 (0.8)	0	4 (0.7)	0
Other hotel business workers	5 (2.0)	6 (2.1)	16 (2.8)	16 (2.6)
Bus operation workers	4 (1.6)	17 (6.0)	9 (1.6)	54 (8.8)
Bus station workers	0	0	0	1 (0.2)
Sightseeing bus drivers	1 (0.4)	6 (2.1)	4 (0.71)	26 (4.2)
Taxi drivers	5 (2.0)	19 (6.7)	11 (1.9)	72 (11.7)
Scheduled air service and charter plane workers	20 (7.9)	35 (12.3)	25 (4.4)	43 (7.0)
Other air transportation workers	0	0	0	1 (0.2)
Auxiliary air transport businesses				
Airport workers	3 (1.2)	3 (1.1)	5 (0.9)	4 (0.7)
Other auxiliary air transport business workers	2 (0.8)	2 (0.7)	3 (0.5)	3 (0.5)
Real estate brokers and dealers	5 (2.0)	8 (2.8)	11 (1.9)	18 (2.9)
Police officers and judicial system employees	9 (3.6)	42 (14.8)	15 (2.7)	52 (8.4)
Institutions of higher educations	26 (10.3)	36 (12.7)	60 (10.6)	80 (13.0)
Academic high schools or prep schools	1 (0.4)	1 (0.4)	6 (1.1)	7 (1.1)
Other secondary schools	23 (9.1)	25 (8.8)	62 (11.0)	49 (7.9)
Trade schools for apprentices	12 (4.7)	23 (8.1)	45 (8.0)	61 (9.9)
Other trade schools	13 (5.14)	5 (1.8)	48 (8.5)	14 (2.3)
Special schools for the handicapped	0	1 (0.4)	3 (0.5)	3 (0.5)
Driving schools	0	0	0	2 (0.3)
Other instructional school workers	2 (0.8)	1 (0.4)	6 (1.1)	7 (1.1)
Private schools	15 (5.93)	8 (2.8)	46 (8.1)	22 (3.6)
Research institutions	6 (2.4)	11 (3.9)	17 (3.0)	27 (4.4)
Ladies' hairdresser or beauty parlor worker	22 (8.7)	0	27 (4.8)	2 (0.3)
Men's hairdresser	0	0	1 (0.2)	0
Unisex hairdresser	2 (0.8)	1 (0.4)	4 (0.7)	0

Supplemental table 2.2 Demographic characteristics of lymphoma cases and controls

		Lymphoma	
	All controls N=411,200 (%)	**NHL N= 179 (%)**	**Hodgkins N= 196 (%)**
Sex of child			
Male	225500 (54.8)	126 (70.4)	116 (59.2)
Female	185700 (45.2)	53 (29.6)	80 (40.8)
Missing	0	0	0
Maternal age			
<=25	131210 (31.9)	63 (35.2)	62 (31.6)
26-30	154678 (37.6)	61 (34.1)	71 (36.2)
31-35	92510 (22.5)	38 (21.2)	46 (23.5)
36+	32720 (8.0)	17 (9.5)	17 (8.7)
Missing	82 (0.0)	0	0
Paternal age			
<=25	70071 (17.0)	31 (17.3)	35 (17.9)
26-30	140661 (34.2)	64 (35.8)	63 (32.1)
31-35	118541 (28.8)	49 (27.4)	56 (28.6)
36+	79329 (19.3)	34 (19.0)	40 (20.4)
Missing	2598 (0.6)	1 (0.6)	2 (1.0)
Family SES			
High	40417 (9.8)	13 (7.3)	23 (11.7)
Medium-high	52095 (12.7)	23 (12.9)	20 (10.2)
Medium	60268 (14.7)	28 (15.6)	34 (17.4)
Medium-low	105869 (25.8)	52 (29.1)	57 (29.1)
Low	54845 (13.3)	23 (12.9)	22 (11.2)
Missing	97706 (23.8)	40 (22.4)	40 (20.4)
Residence type			
Urban	133828 (32.6)	70 (39.1)	84 (42.9)
Small town	133811 (32.5)	57 (31.8)	51 (26.0)
Rural	143561 (34.9)	52 (29.1)	61 (31.1)
Missing	0	0	0

Supplemental table 2.3 Risk of lymphoma cancer subtypes relative to parental occupational social contact at various times from conception to diagnosis

		NHL (N=179) Average age at diagnosis: 8.8			Hodgkin (N=196) Average age at diagnosis: 12.2		
	All Controls (N=411200)	**N Exposed**	**Crude OR**	**Adjusted* OR (95% CI)**	**N Exposed**	**Crude OR**	**Adjusted* OR (95% CI)**
Mother							
Conception to birth							
Very high & high	23682	11	1.09	1.04 (0.56-1.95)	8	0.72	0.68 (0.33-1.39)
Medium & low	254322	107	ref	ref	128	ref	ref
Birth to diagnosis							
Very high & high	47063	26	1.1	1.06 (0.69-1.63)	35	1.05	1.01 (0.69-1.47)
Medium & low	275698	124	ref	ref	140	ref	ref
Father							
Conception to birth							
Very high & high	21881	9	0.98	0.90 (0.46-1.79)	9	0.96	0.84 (0.42-1.66)
Medium & low	293946	127	ref	ref	138	ref	ref
Birth to diagnosis							
Very high & high	37996	24	1.29	1.23 (0.78-1.92)	27	1.18	1.05 (0.69-1.60)
Medium & low	285775	124	ref	ref	126	ref	ref

*Adjusted for maternal age and urban or small town/rural residence status

Supplemental table 2.4 Risk of other rare cancers relative to parental occupational social contact at various times from conception to diagnosis

	All Controls (N=564100)	Retinoblastoma (N=161) Average age at diagnosis: 1.7			Rhabdomyosarcoma (N=150) Average age at diagnosis: 5.7			Neuroblastoma (N=330) Average age at diagnosis: 2.8			Wilms (N=268) Average age at diagnosis: 3.6			Medulloblastoma (N= 231) Average age at diagnosis:		
		N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)
Mother																
Conception to birth																
Very high & high	32560	8	0.86	0.88 (0.43-1.83)	3	0.29	-	24	1.13	1.11 (0.72-1.69)	20	1.31	1.34 (0.83-2.14)	11	0.72	0.72 (0.39-1.34)
Medium & low	349731	101	ref	ref	113	ref	ref	221	ref	ref	163	ref	ref	167	ref	ref
Birth to diagnosis																
Very high & high	64599	9	0.86	0.89 (0.45-1.77)	16	0.88	0.87 (0.51-1.48)	33	1.24	1.22 (0.84-1.77)	24	1.01	1.02 (0.66-1.56)	24	0.88	0.89 (0.58-1.37)
Medium & low	376664	101	ref	ref	115	ref	ref	221	ref	ref	179	ref	ref	169	ref	ref
Father																
Conception to birth																
Very high & high	29985	3	0.30	-	9	1.02	1.01 (0.51-2.01)	19	1.01	0.97 (0.60-1.56)	17	1.15	1.18 (0.71-1.95)	19	1.45	1.48 (0.92-2.40)
Medium & low	404213	124	ref	ref	120	ref	ref	247	ref	ref	196	ref	ref	173	ref	ref
Birth to diagnosis																
Very high & high	52086	5	0.45	0.46 (0.19-1.14)	18	1.33	1.31 (0.78-2.17)	24	1.01	0.98 (0.64-1.50)	23	1.04	1.06 (0.68-1.64)	24	1.07	1.09 (0.70-1.69)
Medium & low	392141	127	ref	ref	111	ref	ref	247	ref	ref	210	ref	ref	171	ref	ref

*Adjusted for maternal age and urban or small town/rural residence status
- Adjusted estimates not performed for cancers with less than 5 exposed cases

Supplemental table 2.5 Risk of leukemia, CNS tumors and bone cancers relative to parental very high and high occupational social contact at various times from conception to diagnosis

		All Leukemia (N=1672)			ALL (N=1337)			CNS (N=1494)			Bone (N=241)		
		Average age at diagnosis: 5.5			Average age at diagnosis: 5.6			Average age at diagnosis: 7.2			Average age at diagnosis: 10.6		
	All Controls N=411200	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)	N Exposed	Crude OR	Adjusted* OR (95% CI)
Mother													
Conception to birth													
Very high	9050	36	0.89	0.89 (0.64-1.25)	22	0.67	0.67 (0.44-1.02)	36	1.00	0.98 (0.70-1.37)	6	0.96	0.97 (0.43-2.20)
High	14632	62	0.91	0.90 (0.70-1.17)	51	0.92	0.91 (0.68-1.21)	51	0.85	0.85 (0.64-1.13)	6	0.64	0.63 (0.28-1.43)
Medium & low	254322	1147	ref	ref	933	ref	ref	1014	ref	ref	171	ref	ref
Test for trend				P=0.08			P<0.05			P=0.21			P=0.51
Birth to diagnosis													
Very high	17751	68	0.95	0.96 (0.75-1.23)	53	0.90	0.91 (0.69-1.20)	76	1.07	1.05 (0.83-1.33)	10	0.66	0.66 (0.35-1.25)
High	29312	112	0.94	0.94 (0.77-1.14)	86	0.89	0.89 (0.71-1.11)	131	1.12	1.17 (0.93-1.34)	14	0.55	0.55 (0.32-0.95)
Medium & low	275698	1217	ref	ref	985	ref	ref	1062	ref	ref	186	ref	ref
Test for trend				P=0.08			P<0.05			P=0.35			P=0.11
Father													
Conception to birth													
Very high	2398	5	0.45	0.44 (0.18-1.07)	6	0.56	0.54 (0.22-1.20)	12	1.41	1.40 (0.78-2.48)	4	2.79	-
High	19483	75	0.88	0.87 (0.69-1.10)	60	0.88	0.86 (0.66-1.12)	69	0.91	0.91 (0.72-1.17)	12	1.08	1.07 (0.59-1.94)
Medium & low	293946	1289	ref	ref	1036	ref	ref	1122	ref	ref	166	ref	ref
Test for trend				P<0.05			P<0.05			P=0.35			N/A
Birth to diagnosis													
Very high	4984	15	0.72	0.72 (0.43-1.20)	9	0.53	0.52 (0.27-1.01)	17	0.84	0.84 (0.52-1.37)	6	1.89	1.99 (0.87-4.58)
High	33012	136	1.01	1.02 (0.85-1.22)	112	1.04	1.03 (0.85-1.26)	130	0.99	1.00 (0.83-1.20)	29	1.28	1.32 (0.88-1.98)
Medium & low	285775	1248	ref	ref	1000	ref	ref	1107	ref	ref	154	ref	ref
Test for trend				P<0.05			P<0.05			P=0.37			P=0.18

*Adjusted for maternal age and urban or small town/rural residence status
- Adjusted estimates not performed for cancers with less than 5 exposed cases

2.6 Supplemental file 2.1 Details of gestational age calculation

In the years 1968-1972, no gestational age variable was collected; therefore, children born during this period were assigned the average gestational age in the Danish population (40 weeks or 280 days). For the period 1973-1977, we had access to a categorical gestational age variable imputed in weeks and collected by midwives. Children born between 1978-1996 also had gestational age recorded in weeks. To transform this into a continuous variable, we assigned each child the midpoint value of their gestational age category. Children born after 1997 had a gestational age value recorded in days. For the 3.9% of children who had missing gestational age, multiple imputation was performed using birthweight, birth length, placental weight, child's sex, birth place, maternal smoking status, labor interventions or procedures, and presence of congenital malformations as predictors when available.

3 Parental occupation and risk of childhood retinoblastoma in Denmark

3.1 Abstract

Retinoblastoma is the most common primary intraocular tumor affecting children. Here, we examine the role of parental occupational exposures and risk of retinoblastoma among offspring. Our population-based case-control study linked data from four Danish registries and included all cases of retinoblastoma diagnosed in Danish children (<17 years) between 1968-2012. Detailed occupational history of parents were obtained from Denmark's Supplementary Pension Fund, a government registry recording the calendar period of employment that is mandated for all wage earners 16-66 years of age, during two biologically relevant time periods (1) 90 days preconception to conception for fathers and (2) conception to birth for mothers. Parents were grouped into major industry headings created from Danish industry codes, an extended version of the International Standard Industrial Classification of All Economic Activities. We performed conditional logistic regression analyses on 143 cases and 14,300 age and sex-matched controls, adjusting for parental age and urban or small town/rural residency status when possible. We observed increased risk of all retinoblastoma among fathers in the food and drink industry (OR: 2.27, 95% CI: 1.24-4.16) and those who sell groceries (OR: 3.56, 95% CI: 1.42-8.91). Bilateral disease was associated with paternal work in supermarkets (OR: 4.03, 95% CI: 1.52-10.71) and transportation on land (OR: 4.03, 95% CI: 1.52-10.71). For maternal occupation, we estimated an increased risk of all retinoblastoma for hospital workers or clinicians (OR: 2.05, 95% CI: 1.34-3.14). Studies on the risk factors for retinoblastoma are rare and our results suggest that some parental occupational exposures may cause childhood cancer.

3.2 Introduction

Retinoblastoma is the most common form of childhood eye cancer worldwide with approximately 9,000 new cases diagnosed annually.[236] Most cases (63%) are diagnosed in infancy before age 2 and 95% by age 5.[237] It manifests in the infant retina as a result of mutations in both alleles of the tumor suppressor retinoblastoma gene (*RB1*).[8] A widely accepted two-hit hypothesis was proposed by Knudson, i.e. suggesting that retinoblastoma is caused by two mutational events.[10] The timing of these events is related to laterality of the disease. For bilateral retinoblastoma (affecting both eyes), which accounts for approximately 40% of all retinoblastoma cases,[9] disease can result from inheriting one mutated allele from the parent through the germinal cells (the first "hit"), and then acquiring a second mutation or hit sporadically post conception that results in tumorigenesis. This accounts for approximately 30% of all bilateral cases. The other 70% of bilateral cases are due to a de novo mutation that occurs before conception in germinal cells; which, in approximately 85% of these cases, occur in the father's allele, followed by another mutation occurring sporadically post conception.[11 12] Unilateral disease most often occurs as a result of two somatic mutations that occur sporadically in the same retinal cell in utero or very early life, although a small number (10-15%) of cases arise from inherited mutations.[10]

There are variations in disease incidence across countries, with some parts of South America and Southeast Asia having higher than average incidence rates.[3] Among European countries, the rates of retinoblastoma are higher in Denmark (age standardized rate [ASR] = 6.0 per 100,000) than in Southern and Eastern European nations (ASR ranging from 2.0- 4.0) .[238] Several studies have examined the association between parental occupation and retinoblastoma with inconclusive results.[123 239 240] Paternal work in agriculture or as a pesticide applicator has

been examined as a risk factor for retinoblastoma or among childhood eye cancers (of which retinoblastoma accounts for over 90%);[241-245] however, only two of these studies found positive associations.[239 246] These positive associations are further supported by findings of increased retinoblastoma risk when parents use insecticides in the homes.[30 127] Other occupational studies have reported increased risk of retinoblastoma among children of fathers who are electrical workers,[247] exposed to paints,[248] or employed in the metal industry.[123 240] A report of a risk increase among fathers employed as television or radio repairmen, possibly due to occupational radiation exposure,[22] was not corroborated in two other studies.[239 240] We previously reported for the first time on maternal occupational exposures; specifically, we found that exposures to chemical agents including volatile organic compounds, paints and pesticides were associated with unilateral disease.[248] There is a need for more studies that investigate parental occupational exposures. Here, we examine associations between paternal occupations 3 months preconception to conception and maternal occupations from conception to birth and retinoblastoma risk in the offspring.

3.3 Methods

The present population-based case-control study utilized data from a linked database that included all childhood cancer cases born from 1968-2008 and diagnosed from1968-2012 in Denmark. To be eligible all cases and controls had to be born in Denmark, to allow us to retrieve information on gestational characteristics and parental occupations at birth. Data was taken from four Danish Registries: The Central Population Registry[203] (data available 1968-2012), the Danish Cancer Registry[204] (1968-2012), the Supplementary Pension Fund[205] (1964-2012) and the Danish Medical Birth Registry[206] (1973-2012). Details concerning these registries, as well as the disease and occupational classification methods used, can be found on page 19. Briefly, the

Danish Cancer Registry was used to ascertain cases diagnosed between 1968-2012 and the Central Population Registry was used to ascertain 100 age (by year of birth) and sex-matched controls per case. Data on all jobs held for both parents, available from 1964 onward, was obtained from the Danish Supplementary Pension Fund. Ethics approval for the current study was obtained by the University of California, Los Angeles institutional review board as well as the Danish Data Protection Agency.

As the Central Population Registry contains information on the legal guardian, as opposed to the biological parent, of each child, we used the Medical Birth Registry to identify the biological mother after 1972, when that information was available. For births before 1972, we relied upon the Central Population Registry to identify the parents; however we expected most legal guardians to be biological parents as all participants were born in Denmark, and most adoptions in Denmark are of foreign-born children.[212] We analyzed 2014 data - which contained this information – and found that 99.4% of registered legal guardians in our data were the biological parents.

Our dataset contained a total of 5,721 childhood cancer cases, of all cancer types, and 572,100 corresponding controls. We identified 161 cases of retinoblastoma using the International Classification of Childhood Cancer (ICCC), version 1 until 2003 and version 3 thereafter. We further excluded parents who did not have any occupational history information during relevant time periods (N=27,658). Our final analysis included all retinoblastoma cases for which we had occupational history of at least one parent (N_{total}=146, $N_{fathers}$=123, $N_{mothers}$=110) and their corresponding controls (N_{total}=14,600, $N_{fathers}$=12,300, $N_{mothers}$=11,000).

Given that spermatogenesis spans approximately 90 days,[249] there is a small window for environmental toxins to cause alterations to sperm. This suggests a role of paternal 3 months

preconception and maternal pregnancy exposures as potential risk factors in the development of bilateral and unilateral retinoblastoma, respectively. Hence, we examined parental occupations during two time periods from (1) 3 months preconception to conception for fathers and (2) conception to birth for mothers.[10] Date of conception was determined by subtracting the child's gestational age in days from their birth date, details can be found in Supplemental file 2.1 on page 40. The Statistics Denmark Occupational Classification codes are a 5-digit extended version of the UN's 4-digit International Standard Industrial Classification (ISIC) of All Economic Activities, and contain the same hierarchical structure but with greater detail within industry subgroups. We categorized occupations into 22 industry types based on the major headings within the Danish classification codes. These included occupations previously identified as increasing risk such as agriculture and electrical work,[246 247] as well as broader categories such as manufacturing, transportation and warehouse storage, and human health care and social work. Within the 22 main industries, we identified specific job types and performed subgroup analyses when sample size allowed.

Selection of variables as possible covariates was identified from previous research.[239 36 43 248 250] We performed conditional logistic regression analyses that adjusted for parental age (≤25, 26-30, 31-35, 36+) and urban or small town/rural residency, taken from the place of birth listed in the Danish Cancer Registry. In addition to these variables, we attempted to adjust for maternal smoking status, family socioeconomic status (SES) and parental place of birth (Denmark versus elsewhere) as a crude measure of ethnicity. However, due to changes to the model of <10% for the years that these variables were available, as well as large numbers of missing values (upwards of 75%), we did not include these variables in our final analyses.

As fathers could bring home toxic chemicals from work on their clothing, thereby exposing their wife and child (transplacentally),[251] we performed sensitivity analyses that explored whether paternal occupation from conception to birth was associated with retinoblastoma. Several studies have found an association between parental age and retinoblastoma;[36 38-44 248] therefore, we also performed sensitivity analyses that stratified on older (>30 years) maternal and paternal age. To avoid competing exposures due to pollution experienced in urban settings, we did sensitivity analyses that restricted to individuals living in rural areas only. We also examined paternal jobs held in the one year prior to conception so as to compare our results with one other study that examined paternal occupational exposures occurring in the one year preconception period.[239] All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3.4 Results

Case mothers were slightly younger (≤25 years) than control mothers (36% vs. 31%, Table 3.1) and in our control group a higher proportion of families were in the high and medium SES categories, whereas a larger percentage of case families had medium-low SES (36% vs. 25%), although it should be noted that larger proportions of SES data were missing in the latter years of the study (66% missing from 2000-2012). There were no considerable differences in paternal age or urban or small town/rural residence type among case and control families.

For childhood bilateral/all retinoblastomas and paternal work in various industries from 3 months preconception to conception, adjusted models with a sufficient number of exposed cases showed elevated point estimates for all main industry types except the wholesale retail trade,

which was null, and public administration and defense, which had a point estimate below one for all retinoblastomas (Odds Ratio [OR]: 0.23, 95% Confidence Interval [CI]: 0.10-0.57, Table 3.2).

Paternal work in the manufacturing industry was associated with an increased risk of childhood retinoblastoma (OR: 1.60, 95% CI: 1.12-2.30); those working in the food and drink industry having the strongest association (OR: 2.27, 95% CI: 1.12-2.30). The most common occupation among case fathers in this industry was hog slaughtering and meat preparation (N=7). Elevated point estimates were also observed for children born to fathers in the iron and metal industry (OR: 1.40, 95% CI: 0.89-2.20).

Though the larger category of wholesale and retail trade showed no association for all retinoblastomas, we observed an increased risk for bilateral disease (OR: 2.27, 95% CI: 1.03-5.02) as well as among children whose fathers worked in a subgroup of this trade, selling food products and groceries (OR: 3.56, 95% CI: 1.42-8.91), and bilateral disease was associated with paternal preconception employment in general retail stores (OR: 3.46, 95% CI: 1.27-9.43), which included department, hardware and sporting goods stores, as well as bicycle and automobile dealerships. Fathers who worked in jobs that required transportation on land, including taxi drivers, those employed in carrier businesses or for railroads, were also at increased risk of having a child with bilateral retinoblastoma (OR: 4.03, 95% CI: 1.52-10.71).

Mothers who worked in human health care or social work had an increased risk of disease (OR: 1.89, 95% CI: 1.26-2.86), as did mothers in “other service activities”, which included jobs in religious societies and institutions (N=3), employer and wage-earner associations (N=1) and hairdressers (N=1) (Table 3.3). Within the human health care and social work industry, we observed the highest risk of disease among children whose mothers worked in hospitals or as health care practitioners (OR: 2.05, 95% CI: 1.34-3.14). We similarly observed

elevated point estimates for unilateral retinoblastoma among mothers working in human health and social work; however, confidence intervals were wide.

All case fathers, except one, held the same job during the year and the 3 months preconception period. Similarly, fathers continued to work in the same jobs from conception to birth. In analyses that restricted to older fathers (age 31 years or older), we found point estimates to increase by up to 50%, though confidence intervals widened due to small cell counts. We did not observe differences greater than 10% in our sensitivity analyses that stratified by high (>30 years) maternal age or that restricted to a subgroup of our population born after 1972, for which we had information on the biological mother. In analyses that stratified to rural residence type, we observed differences in risk (>10%) of all retinoblastoma for fathers working in professional, scientific and technical activities (OR: 1.63, 95% CI: 0.65-4.09) and for mothers working in human health and social work (OR: 2.27, 95% CI: 1.40-3.69, Supplementary table 3.1),

3.5 Discussion

We found several parental occupations to be associated with risk of childhood retinoblastoma. In particular, our study findings suggest an increased risk of all retinoblastoma among children whose fathers worked in manufacturing up to three months preconception, and especially among those working in animal slaughtering. When examining bilateral disease only, we observed similar or stronger positive associations within all main industry types, which is consistent with the proposed underlying mechanisms of disease that suggest development of bilateral retinoblastoma due to paternal germline mutations occurring during preconception. Maternal work in the human health care or social work industry between conception and birth was associated with all retinoblastoma. Our point estimates for unilateral retinoblastoma aligned

closely with those for all retinoblastoma, though confidence intervals were wider due to fewer numbers of exposed cases within industry groups.

The most likely biological mechanism to explain how paternal preconception exposures could induce childhood cancers, and specifically retinoblastoma given the role of de novo mutations in germline cells,[12] is through exposure to toxicants that cause alterations to sperm. Previous literature has shown sperm to be susceptible to chemicals such as lead and paint stripper; however, most research examines sperm count and motility, as opposed to DNA damage, and does not report on the resulting health outcomes of offspring.[112-114] For bilateral retinoblastoma, which most often results from somatic mutations that occur preconceptionally in male germline cells, we found associations with paternal employment in supermarkets and transportation. Individuals in the transportation industry can be exposed to numerous combustion related air toxicants including polycyclic aromatic hydrocarbons and carbon monoxide, which have been associated with retinoblastoma and damage to the human retina.[248 252] Previous studies have reported an increased risk of bilateral retinoblastoma,[80 81] as well as all retinoblastomas,[253] with exposure to air pollution. However, these studies reported on exposures during pregnancy and not the preconception period.

The manufacturing industry is large and comprises of occupations with an array of potential risk factors. Overall, we found all industry subtypes to be associated with higher risks of retinoblastoma, with the greatest increase seen among fathers working in the food and drink industry. We were unable to find other studies on retinoblastoma risk among children of fathers in the food industry, or more specifically in hog slaughtering and meat preparation; however, one study examined paternal occupational exposure to animals and risk of either heritable or non-heritable retinoblastoma but reported no association.[123] Other childhood cancer types have been

associated with fathers who work with animals[200 228] and in food manufacturing.[247] Raw animal carcasses can be infected with cancer-causing viruses, including bovine leukemia virus that cause lymphosarcoma in cattle and bovine papilloma viruses that cause bladder cancer and meningiomas in cattle.[143 254 255] Slaughterhouse workers have exceptionally high exposure to these viruses; however, it is not known whether these viral agents can also cause cancer in humans or alter sperm, though they have been shown to infect and transform healthy human cells to cancerous cells *in vitro*.[142 256] These workers are also exposed to certain chemical nitrates and nitrites in high concentrations,[257] as well as endotoxin.[258] We were only able to find studies that examined health outcomes associated with oral exposure to nitrates and nitrites (often found in meat products for consumption); one of which reports an increased risk of retinoblastoma among children whose fathers had one or more servings of cured meats per day.[259] Though there is a large body of research regarding the high morbidity and mortality rates among animal slaughter workers,[260-266] we could not find studies on the impacts to children they fathered. In the USA, 8 of the 10 lowest paid jobs are in the food industry, indicating a possible role for socioeconomic differences,[267] however, in analyses that adjusted for SES point estimates did not differ by more than 10% for any industry, including food, and other studies have not shown a convincing role for socioeconomic status in retinoblastoma incidence. [38 268]

Paternal work in wholesale and retail trades was not associated with retinoblastoma; however, risk of all retinoblastomas for children whose fathers sold groceries and bilateral disease for fathers working in general retail stores were increased. These associations may be due to fathers' exposure to raw meat or pesticide residues in food; however, we did not observe increased risk of disease among agricultural workers, though this could be due to the small number of exposed cases (N=4). One previous study found an association between

retinoblastoma and paternal work in the shoe and leather industry,[247] but we were unable to estimate this association due to small numbers of parents in this job category (N=1). Within the construction industry, fathers whose occupations involved the construction of roads and buildings, including bricklayers, carpenters, painters, plumbers and electricians, were at increased risk of having a child diagnosed with retinoblastoma. Thus, this finding may somewhat support previous studies finding increases in retinoblastoma risk among offspring of parents exposed to paints,[239] polycyclic aromatic hydrocarbons[248] (often found in paints) as well as work as electrical repairmen.[22] Similarly, elevated point estimates were observed for fathers who worked in the iron and metal industry. Paternal work in the metal industry[240] and exposure to non-welding metals[239] has been previously identified as a risk factor for retinoblastoma. Although specific metals of concern have not been identified, nickel and hexavalent chromium have carcinogenic properties,[269 270] and have been associated with reproductive toxicity, subfertility, malformations and birth defects.[271] Rats injected with nickel developed retinoblastoma in an experimental study.[272] Further, atmospheric nickel exposure during pregnancy was associated with retinoblastoma.[253]

Lower risk of childhood retinoblastoma was associated with paternal preconception work in public administration and defense. Fathers in this category were all employed in public administration and may have lacked all chemical exposures or have led healthier lifestyles due to lower levels of occupational stress.[273] In one study in Denmark, persons employed as managers or professionals had higher levels of self-assessed general health than those working in blue collar or manufacturing occupations.[274] A healthy diet consisting of fruit and vitamin intake has also been inversely associated with retinoblastoma.[259 275-277]

We observed an increased risk of childhood retinoblastoma among children whose mothers worked in the human health care and social work industry between conception to birth. Our subgroup analyses revealed highest point estimates for mothers who worked inside hospitals or as practitioners. To our knowledge, only one study examined associations between work in health care and risk of retinoblastoma, and it also reported an increased risk of heritable retinoblastoma among fathers who worked in health care; however, confidence intervals included one (OR:1.38, 95% CI: 0.50-3.94).[123] This study did not examine maternal occupation nor did it find similar results for non-heritable (unilateral) disease (OR: 0.42, 95% CI: 0.12-1.27). The literature on parental work in the healthcare industry in relation to childhood cancers is mixed, with the majority reporting increased risks.[122 133 198 200 247] Hospital workers may have higher rates of exposure to ionizing radiation,[278] which has been previously associated with retinoblastoma.[29 30] These workers also may have higher exposure to infectious diseases and to night shift work, which may increase cancer risk. Our positive findings on occupational health care exposure and retinoblastoma, coupled with the relatively large number of exposed cases in this group and the consistency with previous studies examining paternal exposure in the health care industry, indicates the need for further investigation into the risk factors associated with childhood cancer among these professionals.

In this study, we explored the relationship between various occupational exposures and retinoblastoma during two clinically relevant time periods. We also differentiated between laterality of disease, an important indicator for which parent and time period of exposure is most relevant to disease onset. One limitation is the large numbers of missing values for several potential confounders, including parental smoking status and socioeconomic status, though adjusting for these variables when available did not change point estimates by more than 10%.

Only a handful of studies have investigated parental occupation and risk of retinoblastoma, often with sample sizes too small to draw conclusions for the rarer exposures. Likely due to the rarity of this disease, published studies have typically not been able to assess dose-response effects and most often measure exposures held in the year or 10 years before pregnancy, or occupations held at birth. Nonetheless, jobs do not generally change much across the brief period of preconception or pregnancy, though identifying exposures experienced within a shorter window of disease susceptibility can eliminate the problem of competing exposures. If mothers in our study started their maternity leave before the birth of their child, they may not have been exposed during the entirety of their pregnancy. Currently, women in Denmark are entitled to take four weeks off before the child is born.[279] Working conditions in Denmark, and particularly those that are physically demanding and involve long hours or shift work, have been positively associated with increased sick leave during pregnancy,[280] possibly indicating that the highest risk women are going on maternity leave earlier and thus experience lower levels of exposure. If this is true, then our point estimates for retinoblastoma associated with maternal occupational exposures may be an underestimate of the true effects.

Our population-based study utilized detailed historical employment records and found an increased risk of all retinoblastoma among children whose fathers had exposures to livestock or meat processing and of bilateral disease among those working in the transportation industry. We also estimated an increased risk for children of mothers working in hospitals or as health care practitioners. Due to the rarity of this disease, there is a need for further research on occupational risk factors related to retinoblastoma, particularly for mothers.

Table 3.1 Demographic characteristics among retinoblastoma cases and corresponding controls who had at least one parent with valid occupational data

	All Cases N= 146 (%)	**Unilateral Cases N=87 (%)**	**Bilateral Cases N=34 (%)**	**All controls N=14600 (%)**
Sex of child				
Male	84 (57.5)	50 (57.5)	20 (58.8)	8400 (57.5)
Female	62 (42.5)	37 (42.5)	14 (41.2)	6200 (42.5)
Missing	0	0	0	0
Maternal age				
≤25	53 (36.3)	33 (37.9)	11 (32.4)	4540 (31.1)
26-30	53 (36.3)	32 (36.8)	15 (44.1)	5520 (37.8)
31-35	30 (20.6)	15 (17.2)	6 (17.7)	3362 (23.0)
36+	10 (6.9)	7 (8.1)	2 (5.9)	1177 (8.1)
Missing	0	0	0	1 (0.0)
Paternal age				
≤25	23 (15.8)	14 (16.1)	3 (8.8)	2432 (16.7)
26-30	52 (35.6)	32 (37.8)	16 (47.1)	4938 (33.8)
31-35	45 (30.8)	26 (29.9)	9 (26.5)	4187 (28.7)
36+	26 (17.8)	15 (17.2)	6 (17.7)	2951 (20.2)
Missing	0	0	0	92 (0.6)
Family SES				
High	11 (7.5)	5 (5.8)	13 (38.2)	1365 (9.4)
Medium-high	19 (13.0)	14 (16.1)	1 (2.9)	1928 (13.2)
Medium	12 (8.2)	6 (6.9)	3 (8.8)	2099 (14.4)
Medium-low	52 (35.6)	30 (34.5)	3 (8.8)	3607 (24.7)
Low	15 (10.3)	10 (11.5)	10 (29.4)	1863 (12.8)
Missing	37 (25.3)	22 (25.3)	4 (11.8)	3738 (25.6)
Residence type				
Urban	45 (30.8)	27 (31.0)	7 (20.6)	4778 (32.7)
Small town	48 (32.9)	26 (29.9)	15 (44.1)	4816 (33.0)
Rural	53 (36.3)	34 (39.1)	12 (35.3)	5006 (34.3)
Missing	0	0	0	0

Table 3.2 Association between retinoblastoma and paternal employment in various industries from three months preconception to conception

			All Retinoblastoma		Bilateral Retinoblastoma		
	Exposed Controls (N=12300)	**Exposed Cases (N=123)**	**Crude OR**	**Adjusted OR (95% CI)**	**Exposed Cases (N=34)**	**Crude OR**	**Adjusted OR (95% CI)**
Industry type							
Agriculture, forestry, and fishing	363	4	0.96	-	0	NA	NA
Mining and quarrying	20	0	NA	NA	0	NA	NA
Manufacturing	3068	48	1.61	1.60 (1.12-2.30)	10	1.42	1.34 (0.62-2.90)
Food and drink industry	487	12	2.29	2.27 (1.24-4.16)	1	0.81	-
Paper and graphics industry	266	5	1.71	1.73 (0.70-4.28)	1	1.61	-
Iron and metal industry	1520	23	1.41	1.40 (0.89-2.20)	6	1.70	1.62 (0.65-4.01)
Electricity, gas, steam and air conditioning supply	78	1	1.15	-	1	8.30	-
Water supply, sewerage, etc.	119	1	0.74	-	0	NA	NA
Construction	1349	18	1.20	1.19 (0.72-1.96)	3	0.81	-
Contractors	473	4	0.74	-	0	NA	NA
Construction of roads and buildings	805	14	1.58	1.53 (0.87-2.68)	3	1.42	-
Wholesale and retail trade	1683	19	0.98	0.98 (0.60-1.60)	9	2.33	2.27 (1.03-5.02)
Food products and grocceries	121	5	3.70	3.56 (1.42-8.91)	1	3.16	-
Raw materials and machines	659	5	0.65	0.64 (0.26-1.57)	3	1.62	-
General retail stores	622	8	1.12	1.08 (0.52-2.22)	5	3.48	3.46 (1.27-9.43)
Repair of motor vehicles	111	0	NA	NA	0	NA	NA
Transportation and storage	875	12	1.24	1.24 (0.68-2.25)	5	2.49	2.50 (0.95-6.63)
Transportation on land	574	8	1.24	1.22 (0.60-2.51)	5	4.21	4.03 (1.52-10.71)
Accommodation and food service activities	188	0	NA	NA	0	NA	NA
Information and communication	223	2	0.76	-	0	NA	NA
Financial and insurance activities	373	4	0.93	-	0	NA	NA
Real estate activities	53	1	1.90	-	0	NA	NA
Professional, scientific and technical activities	457	6	1.15	1.16 (0.51-2.66)	2	1.43	-
Administrative and support service activities	232	0	NA	NA	0	NA	NA
Public admin and defense, compulsory social security	1697	5	0.23	0.23 (0.10-0.57)	0	NA	NA
Education	238	1	0.37	-	0	NA	NA
Human health and social work activities	464	8	1.57	1.60 (0.77-3.31)	2	1.77	
Arts, entertainment and recreation	101	0	NA	NA	0	NA	NA
Other service activities	138	2	1.26	-	0	NA	NA
Activities of households as employers	3	0	NA	NA	0	NA	NA
Activities of extraterritorial organizations and bodies	4	0	NA	NA	0	NA	NA

*Adjusted for paternal age and urban or small town/rural residence status

- Adjusted estimates not provided for exposures with less than 5 exposed cases

Table 3.3 Association between retinoblastoma and maternal employment in various industries from conception to birth

			All Retinoblastoma		Unilateral Retinoblastoma		
	Exposed Controls (N=11000)	**Exposed Cases (N=110)**	**Crude OR**	**Adjusted OR (95% CI)**	**Exposed Cases (N=87)**	**Crude OR**	**Adjusted OR (95% CI)**
Industry type							
Agriculture, forestry, and fishing	91	1	1.02	-	1	1.76	-
Mining and quarrying	5	0	NA	NA	0	NA	NA
Manufacturing	1523	15	0.89	0.83 (0.48-1.45)	9	0.85	0.81 (0.40-1.65)
Electricity, gas, steam and air conditioning supply	30	0	NA	NA	0	NA	NA
Water supply, sewerage, etc.	109	1	0.87	-	1	1.70	-
Construction	128	0	NA	NA	0	NA	NA
Wholesale and retail trade	1258	18	1.42	1.33 (0.79-2.23)	10	1.26	1.18 (0.59-2.34)
Repair of motor vehicles	5	0	NA	NA	0	NA	NA
Transportation and storage	242	1	0.40	-	1	0.68	-
Accommodation and food service activities	245	2	0.76	-	1	0.68	-
Information and communication	179	3	1.61	-	3	2.70	-
Financial and insurance activities	484	4	0.83	-	2	0.66	-
Real estate activities	56	1	1.68	-	1	2.93	-
Professional, scientific and technical activities	347	3	0.85	-	2	0.93	-
Administrative and support service activities	154	0	NA	NA	0	NA	NA
Public admin and defense, compulsory social security	3512	38	1.03	1.05 (0.71-1.57)	24	1.08	1.11 (0.67-1.84)
Education	311	1	0.29	-	1	0.51	-
Human health and social work activities	2130	35	1.79	1.89 (1.26-2.86)	16	1.24	1.31 (0.73-2.32)
Hospital and practitioner work	1723	31	1.93	2.05 (1.34-3.14)	15	1.43	1.52 (0.84-2.74)
Arts, entertainment and recreation	77	0	NA	NA	0	NA	NA
Other service activities	220	5	2.35	2.32 (0.93-5.79)	3	2.45	-
Activities of households as employers	2	0	NA	NA	0	NA	NA
Activities of extraterritorial organizations and bodies	3	0	NA	NA	0	NA	NA

*Adjusted for maternal age and urban or small town/rural residence status

- Adjusted estimates not provided for exposures with less than 5 exposed cases

Supplemental table 3.1 Association between all retinoblastoma and parental occupation at various developmental periods among small town or rural cases and controls only

	Fathers Preconception to Conception				Mothers Conception to Birth			
	Exposed Controls (N=6400)	**Exposed Cases (N=64)**	**Crude OR**	**Adjusted OR (95% CI)**	**Exposed Controls (N=6400)**	**Exposed Cases (N=64)**	**Crude OR**	**Adjusted OR (95% CI)**
Industry type								
Agriculture, forestry, and fishing	376	3	0.72	-	77	1	1.09	-
Mining and quarrying	21	0	NA	NA	4	0	NA	NA
Manufacturing	2507	37	1.65	1.65 (1.08-2.52)	1297	11	0.79	0.74 (0.39-1.43)
Electricity, gas, steam and air conditioning supply	57	1	1.90	-	24	0	NA	NA
Water supply, sewerage, etc.	60	1	1.21	-	71	0	NA	NA
Construction	1121	15	1.27	1.28 (0.73-2.24)	99	0	NA	NA
Wholesale and retail trade	1279	13	0.91	0.91 (0.51-1.65)	967	12	1.37	1.30 (0.69-2.43)
Repair of motor vehicles	95	0	NA	NA	4	0	NA	NA
Transportation and storage	620	8	1.16	-	149	1	0.67	-
Accommodation and food service activities	115	0	NA	NA	177	2	1.02	-
Information and communication	146	2	1.32	-	101	2	2.06	-
Financial and insurance activities	235	2	0.81	-	331	3	0.97	-
Real estate activities	38	0	NA	NA	37	1	2.78	-
Professional, scientific and technical activities	273	5	1.63	1.63 (0.65-4.09)	230	1	0.45	-
Administrative and support service activities	144	0	NA	NA	83	0	NA	NA
Public admin and defense, compulsory social security	1171	3	0.21	-	2700	28	1.03	1.06 (0.66-1.70)
Education	129	1	0.82	-	186	1	0.49	-
Human health and social work activities	271	5	1.69	1.66 (0.66-4.15)	1471	27	2.17	2.27 (1.40-3.69)
Arts, entertainment and recreation	40	0	NA	NA	30	0	NA	NA
Other service activities	89	0	NA	NA	151	2	1.33	-
Activities of households as employers	1	0	NA	NA	1	0	NA	NA
Activities of extraterritorial organizations and bodies	4	0	NA	NA	3	0	NA	NA

*Adjusted for paternal age

- Adjusted estimates not provided for exposures with less than 5 exposed cases

4 Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group

4.1 Abstract

We examined associations between parental occupational chemical exposures up to 10 years prior to conception and the risk of sporadic retinoblastoma among offspring. In our multicenter study on non-familial retinoblastoma, parents of 187 unilateral and 95 bilateral cases and 155 friend controls were interviewed by telephone. Exposure information was collected retroactively through a detailed occupational questionnaire which asked fathers to report every job held in the 10 years before conception, and mothers one month prior to and during the index pregnancy. An industrial hygienist reviewed all occupational data and assigned an overall exposure score to each job indicating presence of 9 hazardous agents. We estimated elevated odds ratios for unilateral and bilateral retinoblastoma among offspring of fathers who were exposed to polycyclic aromatic hydrocarbons (PAHs) or paints in the 10 years prior to conception. However, only for exposure to paints did confidence limits exclude the null for bilateral disease (OR: 8.76, 95% CI: 1.32-58.09). Maternal prenatal exposure to at least one of the 9 agents was related to increased risk of unilateral disease in their children (OR: 5.25, 95% CI: 1.14-24.16). Fathers exposed to at least one of the 9 agents and who were ≥30 years of age or had a family income ≥$75,000 were at increased risk of having a child diagnosed with bilateral (OR: 6.59, 95% CI: 1.34-32.42) or unilateral (OR: 4.64, 95% CI: 1.17-18.47) retinoblastoma. Our results suggest a role for several hazardous occupational exposures in the development of childhood retinoblastoma.

4.2 Introduction

Retinoblastoma is the leading eye cancer affecting children worldwide with an incidence of 11.8 per million children aged 0-4 years in the United States.[7] It results from an inactivation of both alleles of the *RB1* gene, a tumor suppressor gene located on chromosome 13, and produces a malignant tumor of the retina that can occur in one eye (unilaterally) or in both eyes (bilaterally).[8] Given that retinoblastoma is diagnosed very early in life, the economic cost and social burden associated with this disease is substantial. In most cases, this tumor results in partial or complete vision loss.[281] [282]

About 6-10% of retinoblastoma cases are due to inherited mutations, in which one mutated allele is inherited from a parent with the mutation in their germline, and the second mutated allele is sporadic.[9] In all other cases, inactivation of both alleles occurs from sporadic mutations. Within sporadic cases of retinoblastoma, approximately 30% have one *de novo* allele mutation occurring before conception in the parental germline cells or very early on in embryonic development, and one mutation occurring after conception. In the majority (>85%) of these cases, it is the father's allele in which this germline mutation occurs.[11] [12] These cases typically present bilaterally and given the role of the paternal germline cells, the father's exposures before conception are of particular interest. Alternatively, in approximately 60% of cases, retinoblastoma results from two somatic mutations of the *RB1* gene occurring after conception and leads to unilateral disease. These somatic changes occur during pregnancy or very early in life, and thus maternal or early childhood exposures are likely the most relevant risk factors. Mutations occurring in germline cells (most often leading to bilateral retinoblastoma) result in heritable disease as children can now pass these mutation on to their own offspring.

Few studies have examined risk factors for sporadic retinoblastoma. Some suggest that paternal work activities, including those in agriculture, metal-working and painting, are associated with sporadic cases.[29 123 239 240] Maternal occupation has been studied far less and only one study attempted to estimate the risk of sporadic retinoblastoma associated with maternal occupational exposures, however, due to the small number of exposed women no estimates were reported.[240]

We examined associations between paternal occupational exposures experienced up to 10 years prior to the index pregnancy and maternal exposures experienced in the one month prior to and during pregnancy, and the risk of sporadic bilateral and unilateral retinoblastoma in children.

4.3 Methods

4.3.1 Subject recruitment

We recruited unilateral and bilateral sporadic retinoblastoma cases that were diagnosed at Wills Eye Hospital in Philadelphia or at a US or Canadian institution that is a member of the Children's Oncology Group (COG) (which includes over 200 medical centers) between June 1, 2006 and June 30, 2012. Detailed methods on participant eligibility and recruitment were previously published.[49] Briefly, study approval was obtained by each participating COG institution, Wills Eye Institute, the University of Pennsylvania and the University of California, Los Angeles. After initial approval by a physician to contact a patient, eligibility included residing in the continental U.S., Alaska, or Canada, having at least one parent who spoke English or Spanish, and having at least one biological parent available to participate in the study. Children conceived with a donor egg or sperm could participate. Eligible cases had biological samples taken and analyzed to ensure that their *RB1* mutation occurred sporadically and was not

inherited from either parent or mosaic. Trained personnel, who could not be blinded to the case/control status of participants, conducted interviews by phone. Written consent was obtained for blood and saliva sample collection and verbal consent was collected during telephone interviews.

Researchers initially attempted a population-based recruitment strategy for controls using birth certificates; however, this method proved unsuccessful due to low response rates. Therefore, case families were asked to nominate an age-matched control that was the child's friend or relative and under 15 years of age. For unilateral cases, mothers could not be biologically related to the female adult from the selected control family and for bilateral cases, fathers could not be biologically related to the male adult. Investigators examined the list of potential controls given by each case family and attempted to recruit the child who was closest in age to the matched case. In some instances, the researchers accepted controls that were either not age matched or who were biological relatives (N= 12, 7.8%). Proxy interviews were conducted for 13 (3%) maternal and 66 (16%) paternal interviews, and typically the proxy was the other parent.

At the end of recruitment, 282 cases of sporadic retinoblastoma (187 unilateral and 95 bilateral) and 155 friend controls had completed the interview.

4.3.2 Exposure assessment

The occupational questionnaire asked each father to recall every job held in the ten years prior to conception by job title; including part time, full time and seasonal jobs. For each job, the fathers were asked to recall the number of hours they worked per week and how many months out of the year they worked. Exposure related questions were open-ended and asked:

"What did [employer] make or what services did they provide?"

"What were your main activities or duties as a [job title] at [employer]?"

"What kinds of chemicals or materials, if any, did you handle, not including standard office materials?"

"What kinds of tools and equipment, if any, did you use, not including computers or standard office equipment?"

The same questionnaire was administered to mothers, however, only jobs held in the month before and during pregnancy of the index child were considered in the analyses as exposures during this time period are thought to be most relevant to the development of disease.

Parental occupational agents of interest were the same as in a previous study of paternal occupational exposures and sporadic bilateral retinoblastoma[239] and included pesticides, welding fumes, non-welding metals, sulfur dioxide (SO_2), polycyclic aromatic hydrocarbons (PAH), ionizing radiation, paints, chlorinated and non-chlorinated volatile organic compounds (VOCs) and non-paint VOCs. These agents have previously been associated with risk for childhood cancers.[22 123 239 241 247 283-286]

A trained industrial hygienist, who was blinded to case status, reviewed all occupational data and assigned exposure ratings for exposure probability (1=<50%; 2=50%-80%; 3=>80%), intensity (1=low; 2=moderate; 3=high) and frequency (1=once per week or less; 2=some part of most days; 3=most of the time) for each job held. Based on these subscores, a final (overall) score was given for each hazardous exposure derived from her judgement (1=low/no exposure; 2=moderate exposure; 3=high exposure).

All analyses used the overall scores, categorizing subjects as 'exposed' if they were assigned a rating of 2 (moderate) or higher. Both broad (10 years) and narrow (6 months prior to

conception) time windows for the exposure scores were examined, as the etiologically important time window for the effect of paternal exposures and risk of childhood cancers is unknown. Both a maximum exposure score ('any-prior' exposure) and a time-weighted average score were calculated for each agent of interest. Time-weighted averages were derived by multiplying the number of hours at each job by the overall exposure score for that job, and dividing it by the total number of hours worked in the time-window of interest (10 years or 6 months):

$$Time\ weighted\ average: \frac{\sum number\ of\ hours\ at\ a\ job * \ job\ exposure\ score}{Total\ number\ of\ hours\ worked}$$

The number of hours worked at each job was calculated by multiplying hours worked per week by number of weeks worked per year by number of years worked. This assumes that the assigned exposures occurred uniformly throughout the duration of each job. For these time-weighted averages, an exposure score ≥1.5 was considered the threshold for calling someone exposed to the particular agent of interest. An additional sensitivity analysis was conducted utilizing a score of ≥2 as the threshold for being exposed so as to maintain consistency with analyses that utilized maximum exposure scores.

Since cases were age-matched to controls, we implicitly controlled for age in our unconditional analyses. Given that several studies have linked paternal age to increased risk of retinoblastoma,[36 38-40] and that this relationship may not necessarily be linear, we included categories of paternal age *a priori* as a covariate in adjusted models (<25, 25-29, 30-34, 35-39, 40+ years). Other variables that altered effect estimates by more than 10% were included in our adjusted models, i.e., smoking status (never smoked; smoked in the year before pregnancy; smoked, but not in the year before pregnancy), race/ethnicity (White, non-Hispanic; Black, non-Hispanic; Hispanic; other), income (<$25,00; $25,000-$49,999; $50,000-$99,999; ≥$100,000)

and educational attainment (less than high school; high school; post high school training or some college; college graduate; graduate level or professional school). We previously observed these factors to be associated with retinoblastoma risk in our studies,[29 239] and smoking, race/ethnicity and education have been controlled for also in previous studies of retinoblastoma and parental occupational exposures.[29 239 240 287] To mitigate the effects of possible over adjustment due to socioeconomic status (SES), a sensitivity analysis was conducted utilizing a minimally adjusted model that only included paternal age and smoking status.

We attempted to use both conditional and unconditional logistic regression to evaluate the risk of retinoblastoma. However, due to small cell counts in most occupational exposure categories, only results of the unconditional analyses are presented. We report odds ratios (ORs) and 95% confidence intervals (CIs) for both adjusted and unadjusted models.

Risks for unilateral and bilateral retinoblastoma related to paternal occupational exposure to each agent were examined for the periods 6 months and 10 years prior to conception. We also conducted analyses stratified by fathers age (<30 years versus ≥30) so as to ensure there was a long enough work history for each father to capture relevant exposures, and also by household income (<$75,000 versus ≥$75,000) to attempt to account for SES differences between cases and controls. Due to the small numbers in some exposure groups, in these analyses we used "any" paternal hazardous occupational exposure as the exposure variable.

Though 75% of women worked in the month before or during pregnancy, few were exposed to one of the 9 hazardous agents we evaluated (N= 16, 4%). Therefore, we were limited to assessing any type of chemical exposure only, including occupational pesticide, paint, non-chlorinated and non-paint VOCs, PAH or ionizing radiation exposure. No women were exposed to welding fumes, non-welding metals, chlorinated VOCs or SO_2.

Regression models relied on different reference groups i.e. those exposed to a specific agent of interest vs. those unexposed to the agent of interest. However, we also conducted sensitivity analyses examining unilateral and bilateral retinoblastoma comparing each agent of interest with a single common reference group of subjects unexposed to all agents of interest. Both maximum exposure values and time-weighted exposure values were assessed in each analysis.

4.4 Results

Father's age was similar on average for cases and controls. Control parents were more likely to be white non-Hispanic, never smokers, and to have graduate level or professional school education (Table 4.1). Families of cases, especially the bilateral type, were more likely to have annual incomes of less than $25,000.

In the 10 years prior to conception of the index pregnancy, the average number of jobs held by case and control fathers was 2.9 (standard deviation of 1.6 and 1.5, respectively). Table 4.2 displays the prevalence of paternal occupational exposures for cases (unilateral and bilateral) and controls as well as the related risk of disease among children. Due to small cell counts (of less than five exposed cases or controls), we were limited to performing unadjusted analyses only for certain exposures: non-welding related metal exposures, SO_2 (unilateral), ionizing radiation (unilateral), paint, and non-chlorinated VOCs (bilateral). For unilateral cases, we were unable to examine associations for welding fumes and for chlorinated VOCs while for bilateral cases we were unable to examine welding fumes, SO_2, ionizing radiation and chlorinated VOCs separately.

Children of fathers who had any hazardous exposure in the 10 years prior to conception had an elevated risk of both unilateral and bilateral retinoblastoma. For unilateral cases, increased risks were estimated for children whose fathers were exposed to PAH and paints, but confidence intervals were wide due to small numbers. Exposure to pesticides, PAH and paints were also associated with increased risk of bilateral disease, however, only for exposure to paints did confidence limits exclude 1 (OR: 8.76, 95% C.I. 1.32-58.09).

When stratifying by paternal age, the association between any exposure and bilateral disease was positive, albeit relatively weak, in younger fathers (under 30 years of age), but among fathers who were 30 years or older risk was increased (adjusted OR: 6.59, 95% C.I. 1.34-32.4) (Table 4.3). Similarly, children of fathers who were exposed to any hazardous agent and in a higher income bracket (≥$75,000) were at increased risk of having a child diagnosed with unilateral disease in both crude and adjusted models (OR: 4.64, 95% C.I. 1.17-18.5 and OR: 3.16, 95% CI: 0.57-17.66, respectively). Of note, paternal age and family income were only weakly correlated (r=0.3).

Results did not change when we utilized maximum exposure values rather than time-weighted averages, though confidence intervals were wider (results not shown). Effect estimates did not change by more than 20% for any variable when we performed analyses adjusting only for paternal age and smoking status. A separate analysis comparing exposed fathers to a single reference group of fathers who were unexposed to all agents of interest revealed no difference in unilateral estimates and slightly higher point estimates for bilateral retinoblastoma, particularly for pesticide exposure (adjusted OR: 1.82, 95% C.I. 0.64-5.19). Analyses that targeted paternal exposures 6 months prior to the index pregnancy only, were only able to examine pesticides, PAHs or ‘any’ hazardous occupational exposure due to the small number of exposed fathers, and

associations between exposure and risk of unilateral or bilateral retinoblastoma were near the null with wide confidence intervals for all exposures except PAH (OR: 1.37, 95% CI: 0.32-5.81).

For mothers with occupational exposures to pesticides, paints, VOCs, PAH or ionizing radiation in the 6 months before conception or during pregnancy we estimated increased risks of having a child with unilateral disease (OR: 5.25, 95% C.I. 1.14-24.2) (Table 4.4). For bilateral retinoblastoma, point estimates were elevated; however, due to the small number of exposed cases (N=2) these results were generally less stable (OR: 3.03, 95% C.I. 0.31-29.9).

4.5 Discussion

Our study indicated that several paternal occupational exposures may elevate the risks for both unilateral and bilateral retinoblastoma. The risk of sporadic unilateral retinoblastoma increased with paternal exposure to PAH and paints and the risk of sporadic bilateral retinoblastoma increased with paternal exposure to PAH, paints and pesticides in the 10 years prior to conception; however, only for exposure to paints confidence limits excluded 1. Maternal occupational exposure to any of the agents (pesticides, paints, VOCs, PAH or ionizing radiation) was associated with increased risk of having a child diagnosed with unilateral disease. Although our study is among the largest to examine parental occupational exposure and retinoblastoma risk, particularly for unilateral cases, given the rarity of disease we were limited to presenting results of unadjusted analyses only for many occupational exposures.

Currently, the biological mechanisms through which paternal occupational exposures may impact offspring cancer risk, including retinoblastoma, are not well understood. One proposed theory is that fathers expose women with toxic chemicals from work on their skin or clothing, thereby exposing the child (transplacentally).[251] However, it is unknown how high a

dose is needed for the toxic agent to affect the woman and fetus through these means. A more plausible mechanism is that paternal exposure to toxicants results in alterations to the father's sperm, which could result in increased susceptibility to cancer among offspring. This is especially likely for retinoblastoma where it is well documented that specific genetic changes in the paternal germline contribute to risk of disease.[12] Previous literature has shown that sperm are susceptible to environmental agents including lead, paint strippers and excessive heat; however, aside from infertility there is limited evidence that these exposures affect the offspring.[112-114] One study reported that toluene, a solvent found in paint and paint thinners, results in DNA damage in the sperm of rats.[115] Another study found PAHs to impact the motility and viability and result in morphological abnormalities of male sperm.[117] Exposure to PAHs was also found to alter the nucleotide excision and base excision repair mechanisms utilized to mend damaged sperm caused by chemical agents.[118]

Only one study found paternal employment-related pesticide exposure in both the 10 years and one year prior to conception to be associated with offspring sporadic bilateral retinoblastoma (OR: 1.64, 95% C.I. 1.08-2.50 and OR: 2.12, 95% C.I. 1.25-3.61, respectively).[239] The study also found that higher levels of pesticide exposure (compared with moderate or none) relate to higher risks of bilateral disease. Several other studies, which examined both occupational and residential pesticide use by parents and risk of retinoblastoma, showed no association.[123 241-243 288] However, these studies had limitations particularly in that they obtained all occupational data from birth or death records only, and thus did not have access to information such as the specific agents that parents were exposed to at work, employment dates or number of jobs held.[123 240 288] Furthermore, most studies, while sufficiently powered to assess exposure-disease relationships among all cancer types, did not have enough data to be

informative when performing subgroup analyses specifically for retinoblastoma or "all childhood eye cancer" (of which retinoblastoma accounts for over 90%), with the total number of cases ranging from 2 to 16.[241-243 288] Most of the abovementioned studies were unable to examine the effects of maternal or paternal exposures separately, nor were they able to distinguish between heritability or laterality of disease, therefore the findings are not directly comparable to ours.

The present study found paternal occupational exposures in the 10 years prior to index pregnancy to be associated with retinoblastoma risk, however, elevated risks were not seen for exposures in the year before pregnancy, with the exception of PAH, as effect estimates were all near one with wide confidence intervals. Although spermatogenesis spans approximately 90 days, we hypothesize that longer periods of relevant exposure could lead to genetic germline mutations eventually causing disease due to cumulative damage.[289] Long term exposure to cigarette smoke, which emits PAHs, has been previously shown to affect both the genomic and epigenomic components of sperm, which may be associated with developmental defects in the offspring.[290] Another study found that paternal exposures longer than 90 days preconception resulted in increased risk of sporadic retinoblastoma, although this study examined non-occupational medical radiation exposure.[29] These authors suggested that these exposures may have caused mutations to occur in stem cell spermatogonia cells, which persist throughout reproductive life.[29] Additionally, our sample only included a small number of exposed fathers (ranging from n=3 to n=28); therefore, additional studies with larger sample sizes are needed before reliable conclusions can be drawn.

Previous studies have described non-familial unilateral retinoblastoma incidence with two post-conception hits to the *RB1* gene, implying that maternal exposures during pregnancy (when these mutations occur) are important potential risk factors.[291] Only 18 mothers in our

study were determined to have any chemical or physical exposures in the month before or during pregnancy and we thus had to group all occupational exposures together. Despite small numbers, we estimated increased risks for unilateral disease among exposed mothers, which is consistent with the postulated etiology of disease. A recent case-control study of retinoblastoma found that a greater proportion of mothers in farming occupations had a child with retinoblastoma compared with controls (71% vs. 32%).[246] A previous study examining the risk of sporadic heritable and non-heritable retinoblastoma from maternal occupations faced similar restrictions as few mothers held jobs with hazardous exposures.[240] For non-occupational exposures, one study reporting on household pesticide use found the risk for non-heritable unilateral retinoblastoma to be increased among mothers who were exposed to insect or garden sprays during pregnancy, although confidence intervals were wide (OR, 2.7; CI, 0.6-15.6).[30] Similarly, we recently reported an increased risk of unilateral disease associated with parental use of home insecticides as well as home use of professional lawn or landscape services.[127] Two studies examined the association between ionizing radiation exposure in parents and the development of retinoblastoma in offspring, and both found that mothers who had high gonadal radiation exposure were at increased risk of having a child with sporadic bilateral retinoblastoma, although only the larger, more rigorous study was sufficiently powered.[29 30]

Stratifying on paternal age and family income suggested stronger associations among older fathers and higher family income and risk of bilateral and unilateral disease, respectively. Several other studies have reported a link between parental age and increased risk of retinoblastoma.[36 38-44] Only one of these studies was population based and determined that the mean age of fathers was higher among children with sporadic retinoblastoma (33.7 years) than children in the general population (32.5 years), although whether this marginal increase in age

truly reflects a difference in risk is unclear.[42] Reproductive age may influence the risk of childhood cancer through increased mutations in the paternal germ line cells and increased chromosomal aberrations during maturation of maternal germ cells, which increase the risk of cancer development in the offspring.[37] Higher family income may be a proxy for more hours worked (including overtime hours) which, in turn, could increase the level of chemical exposure and, subsequently, the risk of disease.

Our study is among the largest to examine maternal and paternal occupational exposures specifically associated with sporadic retinoblastoma. As with all interview based case-control studies, recall bias is a possibility. However, most occupations tend to be recalled quite accurately[292] and we anticipate that errors in recall would be non-differential among cases and controls as we asked about their jobs and not specific potentially hazardous agents. An additional limitation of our study is the possibility of overmatching due to the use of friend controls. Friend controls may have been more similar to cases on many factors that relate to SES, race and education. Indeed, a previous analysis from the first stage of this study found that for demographic characteristics (race/ethnicity, education, income and paternal age) there appeared to be a greater number of concordant case-control sets than would be expected.[287] However, when reviewing potential exposures of interest (including smoking and multivitamin use), the number of concordant pairs was similar to what would be expected by chance, as determined by comparing the observed concordance to simulated data that randomly permutated the controls' demographic factors and exposures.[287] This suggests that utilizing friend controls may not have resulted in overmatching for several exposures of interest, yet it may provide cases and controls that are more closely matched on possible covariates, reducing confounding bias. Over adjustment due to SES is possible given that our SES variables (education and income) may be

mediators on the pathway between exposure and disease. It has also been argued that adjusting for SES may underestimate true effect estimates.[293] To account for these concerns, we performed a minimally adjusted model that included age and smoking status and found only slight differences in point estimates.

Our occupational questionnaire did not ask specifically about occupational radiation exposure, despite it being a known risk factor for retinoblastoma.[29] However, we expect that subjects exposed to radiation are aware of this occupational hazard and that reporting is similar among parents of cases and controls. We were unable to conduct conditional regression analyses as many cases did not have a matched control.

The limited number of studies on parental occupational exposures, particularly maternal exposures, and retinoblastoma risk suggests that our results ideally should be confirmed in larger populations. However, this will be difficult since the disease is very rare. Our study supports the notion that parental occupational exposures are preventable risk factors for the development of sporadic bilateral and unilateral retinoblastoma.

Table 4.1 Demographic characteristics of cases (unilateral and bilateral) and controls[1]

	Controls (%)	Unilateral RB (%)	Bilateral RB (%)
	N=155	**N=187**	**N=95**
Father's Race			
White non-Hispanic	104 (67.1)	96 (51.3)	59 (62.1)
African American/Black non-Hispanic	7 (4.5)	12 (6.4)	5 (5.2)
Hispanic	22 (14.2)	34 (18.2)	16 (16.8)
Other	9 (5.8)	25 (13.4)	11 (11.6)
Father's age at child's birth			
<25	11 (7.1)	16 (8.6)	7 (7.4)
25-29	40 (25.8)	35 (18.7)	19 (20.0)
30-34	47 (30.3)	53 (28.3)	29 (30.5)
35-39	32 (20.6)	42 (22.5)	22 (23.2)
40+	13 (8.4)	20 (10.7)	13 (13.7)
Father's smoking status			
Never smoked	94 (60.6)	91 (48.7)	57 (60.0)
Smoked in year before pregnancy	31 (20.0)	52 (27.8)	27 (28.4)
Smoked, but not in year before pregnancy	18 (11.6)	24 (12.8)	7 (7.3)
Household income			
< $25,000	11 (7.1)	20 (10.7)	15 (15.8)
$25,000 - $49,000	27 (17.4)	43 (23.0)	18 (18.9)
$50,000 - $99,000	57 (36.8)	53 (28.3)	28 (29.5)
≥ $100,000	40 (25.8)	40 (21.4)	24 (25.3)
Father's Education			
Less than high school	7 (4.5)	13 (7.0)	11 (11.6)
High school	20 (12.9)	31 (16.6)	19 (20.0)
Post high school training or some college	24 (15.5)	39 (20.9)	14 (14.7)
College graduate	53 (34.2)	63 (33.7)	31 (32.6)
Graduate level or professional school	39 (25.2)	21 (11.2)	16 (16.8)

[1]Due to missing data, not all columns add to 100%

Table 4.2 Risk of unilateral and bilateral retinoblastoma among children whose fathers were exposed to various occupational exposures in the 10 years prior to conception, based on time-weighted average exposure values[1]

	Unilateral				Bilateral			
Occupational Exposure	**Exposed Cases (N=187)**	**Exposed Controls (N=155)**	**Crude OR (95% CI)***	**Adjusted OR (95% CI)****	**Exposed Cases (N=95)**	**Exposed Controls (N=155)**	**Crude OR (95% CI)***	**Adjusted OR (95% CI)****
Any hazardous exposure[2]	32	23	1.30 (0.71, 2.38)	1.33 (0.63, 2.79)	21	23	2.01 (0.96, 4.21)	2.45 (0.92, 6.51)
Pesticide	22	20	0.95 (0.49, 1.84)	0.99 (0.45, 2.20)	15	20	1.27 (0.58, 2.79)	1.46 (0.52, 4.10)
Welding Fumes	2	0	-	-	2	0	-	-
Non Welding Metals	4	5	0.83 (0.21, 3.25)	~	1	5	0.51 (0.05, 5.39)	~
SO_2	4	4	0.81 (0.20, 3.40)	~	0	4	-	-
PAH	15	9	1.49 (0.62, 3.56)	1.34 (0.48, 3.72)	7	9	1.58 (0.51, 4.91)	1.51 (0.36, 6.38)
Ionizing Radiation	2	2	0.69 (0.10, 5.05)	~	0	2	-	-
Paint	5	2	2.52 (0.47, 13.57)	~	5	2	8.76 (1.32, 58.09)	~
Chlorinated VOCs	3	0	-	-	0	0	-	-
Non Chlorinated VOCs	5	5	1.01 (0.28, 3.64)	1.30 (0.28, 6.05)	2	5	1.01 (0.19, 6.43)	~

[1]Utilizing different reference groups for each exposure (those unexposed to chemical of interest only).

[2]Occupational exposure to one or more of the following agents: pesticides, welding fumes, non-welding metals, SO_2, PAH, ionizing radiation, paint, chlorinated VOCs and non-chlorinated VOCs

*Adjusted for child's age at interview

**Adjusted for father's race, age, smoking status, income and education

~Insufficient number of exposed cases/controls for providing adjusted estimates

Table 4.3 Risk of unilateral and bilateral retinoblastoma relative to any paternal hazardous occupational exposure in the 10 years prior to conception, stratified by age and education

	Exposed Cases	Exposed Controls	Crude OR (95% CI)*	Adjusted OR (95% CI)
Exposure to any chemical and <30 years of age**				
	(N=50)	**(N=51)**		
Unilateral	13	13	1.02 (0.42, 2.51)	1.89 (0.47, 7.57)
	(N=27)	**(N=51)**		
Bilateral	7	13	1.06 (0.36, 3.16)	1.12 (0.22, 5.59)
Exposure to any chemical and ≥30 years of age**				
	(N=111)	**(N=92)**		
Unilateral	19	10	1.78 (0.76, 4.14)	1.32 (0.48, 3.61)
	(N=63)	**(N=92)**		
Bilateral	14	10	4.56 (1.44, 14.5)	6.59 (1.34, 32.4)
Exposure to any chemical and income <$75,000 ***				
	(N=94)	(N=72)		
Unilateral	22	16	1.04 (0.50, 2.20)	0.82 (0.34, 2.00)
Bilateral	(N=51)	(N=72)	2.14 (0.89, 5.16)	2.17 (0.73, 6.47)
	18	16		
Exposure to any chemical and income ≥$75,000***				
	(N=58)	**(N=63)**		
Unilateral	10	3	4.64 (1.17, 18.47)	3.16 (0.57, 17.66)
	(N=33)	**(N=63)**		
Bilateral	2	3	4.88 (0.53, 45.25)	6.16 (0.18, 209.3)

*Adjusted for child's age at interview
**Adjusted for father's race, smoking status, income and education
***Adjusted for father's race, age, smoking status and education

Table 4.4 Risk of unilateral and bilateral retinoblastoma among children whose mothers had occupational pesticide, paint, VOC, PAH or ionizing radiation exposure in the one month before conception or during pregnancy

Disease	**Exposed Cases**	**Exposed Controls**	**Crude OR***
	(N=187)	**(N=155)**	
Unilateral	12	2	5.25 (1.14, 24.2)
	(N=95)	**(N=155)**	
Bilateral	2	2	3.03 (0.31, 29.9)

*Adjusted for child's age at interview

5 Conclusion

Here, we report several positive associations between occupational exposures and childhood cancer. For retinoblastoma, our results support the theory that paternal preconception exposures can influence risk of bilateral disease. Paternal occupational exposures found to have the greatest association with bilateral disease included paints, animal slaughter and land transportation. We investigate maternal occupational exposures during pregnancy and similarly report increased risk of retinoblastoma, particularly unilateral disease. Our findings for both bilateral and unilateral retinoblastoma are in line with the proposed biological mechanisms of disease that suggest disease laterality is influenced, in part, by the timing of exposures. Our results also indicate a possible role for infections in the etiology of childhood cancers and, specifically, a positive association with brain tumors and a negative association with hematopoietic cancers.

Given that childhood cancer is diagnosed very early in life, the economic cost and social burden associated with this disease is substantial. For the most common childhood eye cancer, retinoblastoma, the average cost of chemotherapy is $253,000 over the course of nine cycles, the cost of enucleation (removal of the infected eye and part of the optic nerve) is $48,000 and the cost of treatment with Melphalan (a chemotherapy drug) ranges from $40,000 to $360,000.[294] The majority of these children develop partial or complete vision loss, resulting in increased health care costs well beyond cancer remission. Most children in cancer remission will live with disability for the entirety of their life, affecting their productivity, emotional and mental health, and limiting the types of jobs they can hold. For other childhood cancers, the cost on the American health care system is considerable. Data shows that in 2005 there were over 100,000 hospital stays resulting from childhood cancer cases, costing approximately $1.7 billion.[295] A

substantial amount of stress is also experienced by parents and family members. Children who do survive continue to strain the health care system due to diminished health status and increased risk of chronic disease compared to the general population.[296]

Even so, results from our analyses must be interpreted with caution. As previously mentioned, childhood cancer results from an amalgamation of hereditary, epigenetic, environmental and chance factors that work in unison to cause disease; therefore, isolating a single causal agent is difficult. Our results suggest that some chemical exposures may increase risk of childhood cancers; however, parents who work with one chemical are often exposed to a mixture of chemicals, of which the biological effects are largely unknown. The workplace also contains other occupational hazards, not related to chemical exposure, that can contribute to adverse fetal outcomes including cancer; these include excessive manual labor and psychological stress. Moreover, factors that we were unable to measure, including workplace ventilation, use of safety equipment and protective clothing, or disposal/storage methods of toxic material may contribute to the level of exposure within the workplace and, consequently, risk of disease. As such, larger prospective studies are needed, though for rarer cancers this can be difficult to achieve. Despite these shortcomings, our findings are important and support the notion that exposures in the workplace influence not only our health, but also the health of our offspring. Policy makers and governmental bodies should continue striving towards improved working conditions that support mental well-being and physical health, as well as minimize exposure to harmful chemicals.

6 References

1. Ries LA, Smith MA, Gurney JG, et al. Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995. Bethesda, MD: National Cancer Institute, 1999.
2. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull* 1996;52(4):682-703. [published Online First: 1996/10/01]
3. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol* 2017 doi: 10.1016/s1470-2045(17)30186-9 [published Online First: 2017/04/16]
4. Li J, Thompson TD, Miller JW, et al. Cancer incidence among children and adolescents in the United States, 2001-2003. *Pediatrics* 2008;121(6):e1470-7. doi: 10.1542/peds.2007-2964 [published Online First: 2008/06/04]
5. Wang L, Gomez SL, Yasui Y. Racial and Ethnic Differences in Socioeconomic Position and Risk of Childhood Acute Lymphoblastic Leukemia. *Am J Epidemiol* 2017:1-9. doi: 10.1093/aje/kww164 [published Online First: 2017/04/04]
6. Poole C, Greenland S, Luetters C, et al. Socioeconomic status and childhood leukaemia: a review. *Int J Epidemiol* 2006;35(2):370-84. doi: 10.1093/ije/dyi248 [published Online First: 2005/11/26]
7. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. *Br J Ophthalmol* 2009;93(1):21-3. doi: 10.1136/bjo.2008.138750 [published Online First: 2008/07/16]

8. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature* 1986;323(6089):643-6. doi: 10.1038/323643a0 [published Online First: 1986/10/16]

9. Leiderman YI, Kiss S, Mukai S. Molecular genetics of RB1--the retinoblastoma gene. *Semin Ophthalmol* 2007;22(4):247-54. doi: 10.1080/08820530701745165 [published Online First: 2007/12/22]

10. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68(4):820-3. [published Online First: 1971/04/01]

11. Dryja TP, Morrow JF, Rapaport JM. Quantification of the paternal allele bias for new germline mutations in the retinoblastoma gene. *Hum Genet* 1997;100(3-4):446-9. [published Online First: 1997/09/01]

12. Zhu XP, Dunn JM, Phillips RA, et al. Preferential germline mutation of the paternal allele in retinoblastoma. *Nature* 1989;340(6231):312-3. doi: 10.1038/340312a0 [published Online First: 1989/07/27]

13. Abramson DH, Shields CL, Munier FL, et al. Treatment of Retinoblastoma in 2015: Agreement and Disagreement. *JAMA Ophthalmol* 2015;133(11):1341-7. doi: 10.1001/jamaophthalmol.2015.3108 [published Online First: 2015/09/18]

14. Strahm B, Malkin D. Hereditary cancer predisposition in children: Genetic basis and clinical implications. *Int J Cancer* 2006;119(9):2001-06.

15. Secretan B, Straif K, Baan R, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *The lancet oncology* 2009;10(11):1033-4.

16. Little J. Epidemiology of Childhood Cancer. Lyon: IARC, 1999.

17. Linet MS, Devesa SS. Descriptive epidemiology of childhood leukaemia. *Br J Cancer* 1991;63(3):424-9.

18. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *The New England journal of medicine* 1971;284(15):878-81. doi: 10.1056/nejm197104222841604 [published Online First: 1971/04/15]

19. Wakeford R. The risk of childhood cancer from intrauterine and preconceptional exposure to ionizing radiation. *Environ Health Perspect* 1995;103(11):1018-25. [published Online First: 1995/11/01]

20. Giles D, Hewitt D, Stewart A, et al. Malignant disease in childhood and diagnostic irradiation in utero. *Lancet* 1956;271(6940):447. [published Online First: 1956/09/01]

21. Nussbaum RH, Kohnlein W. Inconsistencies and open questions regarding low-dose health effects of ionizing radiation. *Environ Health Perspect* 1994;102(8):656-67. [published Online First: 1994/08/01]

22. Hicks N, Zack M, Caldwell GG, et al. Childhood cancer and occupational radiation exposure in parents. *Cancer* 1984;53(8):1637-43. [published Online First: 1984/04/15]

23. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. *Br Med J* 1958;1(5086):1495-508. [published Online First: 1958/06/28]

24. Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancers. *Lancet* 1970;1(7658):1185-8. [published Online First: 1970/06/06]

25. Monson R, MacMahon B. Prenatal x-ray exposure and cancer in children. Radiation carcinogenesis: epidemiology and biological significance1984.

26. Macmahon B. Prenatal x-ray exposure and childhood cancer. *Journal of the National Cancer Institute* 1962;28:1173-91. [published Online First: 1962/05/01]

27. Bithell J. Epidemiological studies of children irradiated in utero. Low dose radiation: biological bases of risk assessment1989.

28. Radiation UNSCotEoA. Sources and effects of ionizing radiation: sources: United Nations Publications 2000.

29. Bunin GR, Felice MA, Davidson W, et al. Medical radiation exposure and risk of retinoblastoma resulting from new germline RB1 mutation. *Int J Cancer* 2011;128(10):2393-404. doi: 10.1002/ijc.25565 [published Online First: 2010/07/22]

30. Bunin GR, Meadows AT, Emanuel BS, et al. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. *Cancer Res* 1989;49(20):5730-5. [published Online First: 1989/10/15]

31. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 1997;70:130-9. doi: 10.1259/bjr.70.830.9135438 [published Online First: 1997/02/01]

32. Harvey EB, Boice JD, Jr., Honeyman M, et al. Prenatal x-ray exposure and childhood cancer in twins. *N Engl J Med* 1985;312(9):541-5. doi: 10.1056/nejm198502283120903 [published Online First: 1985/02/28]

33. Rodvall Y, Pershagen G, Hrubec Z, et al. Prenatal X-ray exposure and childhood cancer in Swedish twins. *Int J Cancer* 1990;46(3):362-5. [published Online First: 1990/09/15]

34. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology* 2009;20(4):475-83. doi: 10.1097/EDE.0b013e3181a5a332 [published Online First: 2009/04/18]

35. Sergentanis TN, Thomopoulos TP, Gialamas SP, et al. Risk for childhood leukemia associated with maternal and paternal age. *Eur J Epidemiol* 2015;30(12):1229-61. doi: 10.1007/s10654-015-0089-3 [published Online First: 2015/11/06]

36. Dockerty JD, Draper G, Vincent T, et al. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol* 2001;30(6):1428-37. [published Online First: 2002/02/01]

37. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol* 2006;35(6):1495-503. doi: 10.1093/ije/dyl177 [published Online First: 2006/09/30]

38. Heck JE, Lombardi CA, Meyers TJ, et al. Perinatal characteristics and retinoblastoma. *Cancer Causes Control* 2012;23(9):1567-75. doi: 10.1007/s10552-012-0034-7 [published Online First: 2012/07/31]

39. Saremi L, Imani S, Rostaminia M, et al. Parental age-related risk of retinoblastoma in Iranian children. *Asian Pac J Cancer Prev* 2014;15(6):2847-50. [published Online First: 2014/04/26]

40. Mills MB, Hudgins L, Balise RR, et al. Mutation risk associated with paternal and maternal age in a cohort of retinoblastoma survivors. *Hum Genet* 2012;131(7):1115-22. doi: 10.1007/s00439-011-1126-2 [published Online First: 2011/12/29]

41. Sivakumaran TA, Ghose S, Kumar H, et al. Parental age in Indian patients with sporadic hereditary retinoblastoma. *Ophthalmic Epidemiol* 2000;7(4):285-91. [published Online First: 2001/03/23]

42. DerKinderen DJ, Koten JW, Tan KE, et al. Parental age in sporadic hereditary retinoblastoma. *Am J Ophthalmol* 1990;110(6):605-9. [published Online First: 1990/12/15]

43. Moll AC, Imhof SM, Kuik DJ, et al. High parental age is associated with sporadic hereditary retinoblastoma: the Dutch retinoblastoma register 1862-1994. *Hum Genet* 1996;98(1):109-12. [published Online First: 1996/07/01]

44. Matsunaga E, Minoda K, Sasaki MS. Parental age and seasonal variation in the births of children with sporadic retinoblastoma: a mutation-epidemiologic study. *Hum Genet* 1990;84(2):155-8. [published Online First: 1990/01/01]

45. Jauniaux E, Burton GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. *Early Hum Dev* 2007;83(11):699-706. doi: 10.1016/j.earlhumdev.2007.07.016 [published Online First: 2007/09/29]

46. Yauk CL, Berndt ML, Williams A, et al. Mainstream tobacco smoke causes paternal germ-line DNA mutation. *Cancer Res* 2007;67(11):5103-6. doi: 10.1158/0008-5472.can-07-0279 [published Online First: 2007/06/05]

47. DeMarini DM. Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. *Mutation research* 2004;567(2-3):447-74. doi: 10.1016/j.mrrev.2004.02.001 [published Online First: 2004/12/02]

48. Potts RJ, Newbury CJ, Smith G, et al. Sperm chromatin damage associated with male smoking. *Mutation research* 1999;423(1-2):103-11. [published Online First: 1999/02/25]

49. Azary S, Ganguly A, Bunin GR, et al. Sporadic Retinoblastoma and Parental Smoking and Alcohol Consumption before and after Conception: A Report from the Children's

Oncology Group. *PloS one* 2016;11(3):e0151728. doi: 10.1371/journal.pone.0151728 [published Online First: 2016/03/19]

50. Heck JE, Contreras ZA, Park AS, et al. Smoking in pregnancy and risk of cancer among young children: A population-based study. *Int J Cancer* 2016;139(3):613-6. doi: 10.1002/ijc.30111 [published Online First: 2016/03/27]
51. Brooks DR, Mucci LA, Hatch EE, et al. Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. *Cancer Causes Control* 2004;15(10):997-1005. [published Online First: 2005/04/02]
52. Huang Y, Huang J, Lan H, et al. A meta-analysis of parental smoking and the risk of childhood brain tumors. *PloS one* 2014;9(7):e102910. doi: 10.1371/journal.pone.0102910 [published Online First: 2014/07/25]
53. Milne E, Greenop KR, Scott RJ, et al. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. *Am J Epidemiol* 2012;175(1):43-53. doi: 10.1093/aje/kwr275 [published Online First: 2011/12/07]
54. Chang JS. Parental smoking and childhood leukemia. *Methods Mol Biol* 2009;472:103-37. doi: 10.1007/978-1-60327-492-0_5 [published Online First: 2008/12/25]
55. Momen NC, Olsen J, Gissler M, et al. Exposure to maternal smoking during pregnancy and risk of childhood cancer: a study using the Danish national registers. *Cancer Causes Control* 2016;27(3):341-9. doi: 10.1007/s10552-015-0707-0 [published Online First: 2015/12/23]
56. IARC. Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum* 2010;96:3-1383. [published Online First: 2010/01/01]

57. Poschl G, Stickel F, Wang XD, et al. Alcohol and cancer: genetic and nutritional aspects. *Proc Nutr Soc* 2004;63(1):65-71. doi: 10.1079/pns2003323 [published Online First: 2004/04/09]

58. Rudant J, Menegaux F, Leverger G, et al. Childhood hematopoietic malignancies and parental use of tobacco and alcohol: the ESCALE study (SFCE). *Cancer Causes Control* 2008;19(10):1277-90. doi: 10.1007/s10552-008-9199-5 [published Online First: 2008/07/12]

59. Menegaux F, Ripert M, Hemon D, et al. Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. *Paediatr Perinat Epidemiol* 2007;21(4):293-9. doi: 10.1111/j.1365-3016.2007.00824.x [published Online First: 2007/06/15]

60. Menegaux F, Steffen C, Bellec S, et al. Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect Prev* 2005;29(6):487-93. doi: 10.1016/j.cdp.2005.06.008 [published Online First: 2005/11/18]

61. Shu XO, Ross JA, Pendergrass TW, et al. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. *Journal of the National Cancer Institute* 1996;88(1):24-31. [published Online First: 1996/01/03]

62. MacArthur AC, McBride ML, Spinelli JJ, et al. Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. *Cancer Causes Control* 2008;19(3):283-95. doi: 10.1007/s10552-007-9091-8 [published Online First: 2008/02/20]

63. Alexander FE, Patheal SL, Biondi A, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res* 2001;61(6):2542-6. [published Online First: 2001/04/06]

64. Milne E, Greenop KR, Scott RJ, et al. Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors. *Cancer Causes Control* 2013;24(2):391-402. doi: 10.1007/s10552-012-0125-5 [published Online First: 2012/12/19]

65. Latino-Martel P, Chan DS, Druesne-Pecollo N, et al. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2010;19(5):1238-60. doi: 10.1158/1055-9965.epi-09-1110 [published Online First: 2010/05/08]

66. Cocco P, Rapallo M, Targhetta R, et al. Analysis of risk factors in a cluster of childhood acute lymphoblastic leukemia. *Arch Environ Health* 1996;51(3):242-4. doi: 10.1080/00039896.1996.9936022 [published Online First: 1996/05/01]

67. Infante-Rivard C, Krajinovic M, Labuda D, et al. Childhood acute lymphoblastic leukemia associated with parental alcohol consumption and polymorphisms of carcinogen-metabolizing genes. *Epidemiology* 2002;13(3):277-81. [published Online First: 2002/04/20]

68. Hu J, Mao Y, Ugnat AM. Parental cigarette smoking, hard liquor consumption and the risk of childhood brain tumors--a case-control study in northeast China. *Acta Oncol* 2000;39(8):979-84. [published Online First: 2001/02/24]

69. Kuijten RR, Bunin GR, Nass CC, et al. Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. *Cancer Res* 1990;50(9):2608-12. [published Online First: 1990/05/01]

70. Preston-Martin S, Yu MC, Benton B, et al. N-Nitroso compounds and childhood brain tumors: a case-control study. *Cancer Res* 1982;42(12):5240-5. [published Online First: 1982/12/01]

71. Bunin GR, Buckley JD, Boesel CP, et al. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biomarkers Prev* 1994;3(3):197-204. [published Online First: 1994/04/01]

72. Schuz J, Kaletsch U, Kaatsch P, et al. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol* 2001;36(2):274-82. doi: 10.1002/1096-911x(20010201)36:2<274::aid-mpo1065>3.0.co;2-d [published Online First: 2001/07/17]

73. Cordier S, Iglesias MJ, Le Goaster C, et al. Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer* 1994;59(6):776-82. [published Online First: 1994/12/15]

74. Bukowski JA. Review of the epidemiological evidence relating toluene to reproductive outcomes. *Regulatory toxicology and pharmacology : RTP* 2001;33(2):147-56. doi: 10.1006/rtph.2000.1448 [published Online First: 2001/05/15]

75. Hannigan JH, Bowen SE. Reproductive toxicology and teratology of abused toluene. *Systems biology in reproductive medicine* 2010;56(2):184-200. doi: 10.3109/19396360903377195 [published Online First: 2010/04/10]

76. WHO. Occupational exposures of hairdressers and barbers and personal use of hair colourants;some hair dyes, cosmetic colourants, industrail dyestuffs and aromatic amines.

In: (IARC) IAfRoC, ed. Monographos on the evaluation of carcinogenic risks to humans 1993.

77. Pidoux G, Gerbaud P, Guibourdenche J, et al. Formaldehyde Crosses the Human Placenta and Affects Human Trophoblast Differentiation and Hormonal Functions. *PloS one* 2015;10(7):e0133506. doi: 10.1371/journal.pone.0133506 [published Online First: 2015/07/18]

78. Thrasher JD, Kilburn KH. Embryo toxicity and teratogenicity of formaldehyde. *Archives of environmental health* 2001;56(4):300-11. doi: 10.1080/00039890109604460 [published Online First: 2001/09/27]

79. Duong A, Steinmaus C, McHale CM, et al. Reproductive and developmental toxicity of formaldehyde: a systematic review. *Mutation research* 2011;728(3):118-38. doi: 10.1016/j.mrrev.2011.07.003 [published Online First: 2011/07/27]

80. Heck JE, Wu J, Lombardi C, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. *Environmental health perspectives* 2013;121(11-12):1385-91. doi: 10.1289/ehp.1306761 [published Online First: 2013/09/12]

81. Ghosh JK, Heck JE, Cockburn M, et al. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. *Am J Epidemiol* 2013;178(8):1233-9. doi: 10.1093/aje/kwt129 [published Online First: 2013/08/31]

82. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nature reviews* 2006;6(3):193-203.

83. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet (London, England)* 1988;2(8624):1323-7. [published Online First: 1988/12/10]

84. Kinlen L. Infections and immune factors in cancer: the role of epidemiology. *Oncogene* 2004;23(38):6341-8. doi: 10.1038/sj.onc.1207898 [published Online First: 2004/08/24]

85. Fear NT, Roman E, Ansell P, et al. Malignant neoplasms of the brain during childhood: the role of prenatal and neonatal factors (United Kingdom). *Cancer Causes Control* 2001;12(5):443-9. [published Online First: 2001/09/08]

86. Linos A, Kardara M, Kosmidis H, et al. Reported influenza in pregnancy and childhood tumour. *Eur J Epidemiol* 1998;14(5):471-5. [published Online First: 1998/09/23]

87. Dickinson HO, Nyari TA, Parker L. Childhood solid tumours in relation to infections in the community in Cumbria during pregnancy and around the time of birth. *Br J Cancer* 2002;87(7):746-50. doi: 10.1038/sj.bjc.6600530 [published Online First: 2002/09/17]

88. Aronsson F, Lannebo C, Paucar M, et al. Persistence of viral RNA in the brain of offspring to mice infected with influenza A/WSN/33 virus during pregnancy. *J Neurovirol* 2002;8(4):353-7. doi: 10.1080/13550280290100480 [published Online First: 2002/08/06]

89. Vilchez RA, Butel JS. SV40 in human brain cancers and non-Hodgkin's lymphoma. *Oncogene* 2003;22(33):5164-72. doi: 10.1038/sj.onc.1206547 [published Online First: 2003/08/12]

90. Cardy AH, Little J, McKean-Cowdin R, et al. Maternal medication use and the risk of brain tumors in the offspring: the SEARCH international case-control study. *Int J Cancer* 2006;118(5):1302-8. doi: 10.1002/ijc.21482 [published Online First: 2005/09/15]

91. Kwan ML, Metayer C, Crouse V, et al. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. *Am J Epidemiol* 2007;165(1):27-35. doi: 10.1093/aje/kwj336 [published Online First: 2006/10/13]

92. Ross JA, Xie Y, Davies SM, et al. Prescription medication use during pregnancy and risk of infant leukemia (United States). *Cancer Causes Control* 2003;14(5):447-51. [published Online First: 2003/08/30]

93. Hankins C, Coutlee F, Lapointe N, et al. Prevalence of risk factors associated with human papillomavirus infection in women living with HIV. Canadian Women's HIV Study Group. *CMAJ* 1999;160(2):185-91. [published Online First: 1999/02/10]

94. Slattery ML, Overall JC, Jr., Abbott TM, et al. Sexual activity, contraception, genital infections, and cervical cancer: support for a sexually transmitted disease hypothesis. *Am J Epidemiol* 1989;130(2):248-58. [published Online First: 1989/08/01]

95. Orjuela M, Castaneda VP, Ridaura C, et al. Presence of human papilloma virus in tumor tissue from children with retinoblastoma: an alternative mechanism for tumor development. *Clin Cancer Res* 2000;6(10):4010-6. [published Online First: 2000/10/29]

96. Palazzi MA, Yunes JA, Cardinalli IA, et al. Detection of oncogenic human papillomavirus in sporadic retinoblastoma. *Acta Ophthalmol Scand* 2003;81(4):396-8. [published Online First: 2003/07/16]

97. Helin K, Harlow E, Fattaey A. Inhibition of E2F-1 transactivation by direct binding of the retinoblastoma protein. *Mol Cell Biol* 1993;13(10):6501-8. [published Online First: 1993/10/01]

98. Dyson N, Howley PM, Munger K, et al. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 1989;243(4893):934-7. [published Online First: 1989/02/17]

99. Antoneli CB, Ribeiro KB, Sredni ST, et al. Low prevalence of HPV in Brazilian children with retinoblastoma. *J Med Virol* 2011;83(1):115-8. doi: 10.1002/jmv.21925 [published Online First: 2010/11/26]

100. Mohan A, Venkatesan N, Kandalam M, et al. Detection of human papillomavirus DNA in retinoblastoma samples: a preliminary study. *J Pediatr Hematol Oncol* 2009;31(1):8-13. doi: 10.1097/MPH.0b013e31818b373b [published Online First: 2009/01/07]

101. Shetty OA, Naresh KN, Banavali SD, et al. Evidence for the presence of high risk human papillomavirus in retinoblastoma tissue from nonfamilial retinoblastoma in developing countries. *Pediatr Blood Cancer* 2012;58(2):185-90. doi: 10.1002/pbc.23346 [published Online First: 2011/10/25]

102. Ryoo NK, Kim JE, Choung HK, et al. Human papilloma virus in retinoblastoma tissues from Korean patients. *Korean J Ophthalmol* 2013;27(5):368-71. doi: 10.3341/kjo.2013.27.5.368 [published Online First: 2013/10/02]

103. Saddlemire S, Olshan AF, Daniels JL, et al. Breast-feeding and Wilms tumor: a report from the Children's Oncology Group. *Cancer Causes Control* 2006;17(5):687-93. doi: 10.1007/s10552-005-0508-y [published Online First: 2006/04/25]

104. Heuch JM, Heuch I, Kvale G. Birth characteristics and risk of Wilms' tumour: a nationwide prospective study in Norway. *Br J Cancer* 1996;74(7):1148-51. [published Online First: 1996/10/01]

105. Bunin GR, Kramer S, Marrero O, et al. Gestational risk factors for Wilms' tumor: results of a case-control study. *Cancer Res* 1987;47(11):2972-7. [published Online First: 1987/06/01]

106. Schuz J, Kaletsch U, Meinert R, et al. High-birth weight and other risk factors for Wilms tumour: results of a population-based case-control study. *Eur J Pediatr* 2001;160(6):333-8. [published Online First: 2001/06/26]

107. Leisenring WM, Breslow NE, Evans IE, et al. Increased birth weights of National Wilms' Tumor Study patients suggest a growth factor excess. *Cancer Res* 1994;54(17):4680-3. [published Online First: 1994/09/01]

108. Smulevich VB, Solionova LG, Belyakova SV. Parental occupation and other factors and cancer risk in children: I. Study methodology and non-occupational factors. *Int J Cancer* 1999;83(6):712-7. [published Online First: 1999/12/22]

109. Schor J. The overworked American: The unexpected decline of leisure: Basic books 2008.

110. Bond JT, Galinsky E, Swanberg JE. The National Study of the Changing Workforce, 1997. No. 2: ERIC 1997.

111. Bianchi SM. Changing families, changing workplaces. *Future Child* 2011;21(2):15-36. [published Online First: 2011/10/22]

112. Vaziri MH, Sadighi Gilani MA, Kavousi A, et al. The Relationship between Occupation and Semen Quality. *International journal of fertility & sterility* 2011;5(2):66-71. [published Online First: 2011/07/01]

113. Chia SE, Ong CN, Lee ST, et al. Study of the effects of occupation and industry on sperm quality. *Annals of the Academy of Medicine, Singapore* 1994;23(5):645-9. [published Online First: 1994/09/01]

114. Cherry N, Povey AC, McNamee R, et al. Occupation exposures and sperm morphology: a case-referent analysis of a multi-centre study. *Occupational and environmental medicine*

2014;71(9):598-604. doi: 10.1136/oemed-2013-101996 [published Online First: 2014/05/23]

115. Nakai N, Murata M, Nagahama M, et al. Oxidative DNA damage induced by toluene is involved in its male reproductive toxicity. *Free radical research* 2003;37(1):69-76. [published Online First: 2003/03/26]

116. Kumar D, Salian SR, Kalthur G, et al. Semen abnormalities, sperm DNA damage and global hypermethylation in health workers occupationally exposed to ionizing radiation. *PloS one* 2013;8(7):e69927. doi: 10.1371/journal.pone.0069927 [published Online First: 2013/08/08]

117. Jeng HA, Yu L. Alteration of sperm quality and hormone levels by polycyclic aromatic hydrocarbons on airborne particulate particles. *Journal of environmental science and health Part A, Toxic/hazardous substances & environmental engineering* 2008;43(7):675-81. doi: 10.1080/10934520801959815 [published Online First: 2008/04/30]

118. Ji G, Gu A, Zhou Y, et al. Interactions between exposure to environmental polycyclic aromatic hydrocarbons and DNA repair gene polymorphisms on bulky DNA adducts in human sperm. *PloS one* 2010;5(10) doi: 10.1371/journal.pone.0013145 [published Online First: 2010/10/20]

119. Meng Z, Liu Y. Cell morphological ultrastructural changes in various organs from mice exposed by inhalation to sulfur dioxide. *Inhalation toxicology* 2007;19(6-7):543-51. doi: 10.1080/08958370701271373 [published Online First: 2007/05/15]

120. Meng Z, Bai W. Oxidation damage of sulfur dioxide on testicles of mice. *Environmental research* 2004;96(3):298-304. doi: 10.1016/j.envres.2004.04.008 [published Online First: 2004/09/15]

121. Colt JS, Blair A. Parental occupational exposures & risk of childhood cancer. *Environ Health Perspect* 1998;106:909-25.

122. Savitz DA, Chen JH. Parental occupation and childhood cancer: review of epidemiologic studies. *Environ Health Perspect* 1990;88:325-37. [published Online First: 1990/08/01]

123. MacCarthy A, Bunch KJ, Fear NT, et al. Paternal occupation and retinoblastoma: a case-control study based on data for Great Britain 1962-1999. *Occupational and environmental medicine* 2009;66(10):644-9. doi: 10.1136/oem.2007.037218 [published Online First: 2009/09/23]

124. Sung TI, Wang JD, Chen PC. Increased risk of cancer in the offspring of female electronics workers. *Reproductive toxicology (Elmsford, NY)* 2008;25(1):115-9.

125. Johnson KJ, Alexander BH, Doody MM, et al. Childhood cancer in the offspring born in 1921-1984 to US radiologic technologists. *Br J Cancer* 2008;99(3):545-50.

126. Kumar A, Vashist M, Rathee R. Maternal factors and risk of childhood leukemia. *Asian Pac J Cancer Prev* 2014;15(2):781-4. [published Online First: 2014/02/27]

127. Omidakhsh N, Ganguly A, Bunin GR, et al. Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group. *Am J Ophthalmol* 2017 doi: 10.1016/j.ajo.2017.01.016 [published Online First: 2017/01/31]

128. Vinson F, Merhi M, Baldi I, et al. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. *Occup Environ Med* 2011;68(9):694-702. doi: 10.1136/oemed-2011-100082 [published Online First: 2011/05/25]

129. Greenop KR, Peters S, Bailey HD, et al. Exposure to pesticides and the risk of childhood brain tumors. *Cancer causes & control : CCC* 2013;24(7):1269-78. doi: 10.1007/s10552-013-0205-1 [published Online First: 2013/04/06]

130. Bailey HD, Fritschi L, Infante-Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. *Int J Cancer* 2014;135(9):2157-72. doi: 10.1002/ijc.28854 [published Online First: 2014/04/05]

131. Bailey HD, Fritschi L, Metayer C, et al. Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control* 2014;25(10):1351-67. doi: 10.1007/s10552-014-0441-z [published Online First: 2014/08/05]

132. Peters S, Glass DC, Reid A, et al. Parental occupational exposure to engine exhausts and childhood brain tumors. *Int J Cancer* 2013;132(12):2975-9. doi: 10.1002/ijc.27972 [published Online First: 2012/11/28]

133. McKinney PA, Fear NT, Stockton D. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. *Occup Environ Med* 2003;60(12):901-9. [published Online First: 2003/11/25]

134. Cordier S, Mandereau L, Preston-Martin S, et al. Parental occupations and childhood brain tumors: results of an international case-control study. *Cancer Causes Control* 2001;12(9):865-74. [published Online First: 2001/11/21]

135. Infante-Rivard C. Electromagnetic field exposure during pregnancy and childhood leukaemia. *Lancet* 1995;346(8968):177. [published Online First: 1995/07/15]

136. Sorahan T, Hamilton L, Gardiner K, et al. Maternal occupational exposure to electromagnetic fields before, during, and after pregnancy in relation to risks of childhood cancers: findings from the Oxford Survey of Childhood Cancers, 1953-1981 deaths. *American journal of industrial medicine* 1999;35(4):348-57. [published Online First: 1999/03/23]

137. Hemminki K, Saloniemi I, Salonen T, et al. Childhood cancer and parental occupation in Finland. *Journal of epidemiology and community health* 1981;35(1):11-5. [published Online First: 1981/03/01]

138. Al-Saleh I, Alsabbahen A, Shinwari N, et al. Polycyclic aromatic hydrocarbons (PAHs) as determinants of various anthropometric measures of birth outcome. *Sci Total Environ* 2013;444:565-78. doi: 10.1016/j.scitotenv.2012.12.021 [published Online First: 2013/01/15]

139. Serafim A, Company R, Lopes B, et al. Assessment of essential and nonessential metals and different metal exposure biomarkers in the human placenta in a population from the south of Portugal. *J Toxicol Environ Health A* 2012;75(13-15):867-77. doi: 10.1080/15287394.2012.690704 [published Online First: 2012/07/14]

140. Dearfield KL, Abernathy CO, Ottley MS, et al. Acrylamide: its metabolism, developmental and reproductive effects, genotoxicity, and carcinogenicity. *Mutation research* 1988;195(1):45-77. [published Online First: 1988/01/01]

141. Leonard A, Gerber GB, Jacquet P. Carcinogenicity, mutagenicity and teratogenicity of nickel. *Mutation research* 1981;87(1):1-15. [published Online First: 1981/07/01]

142. Buehring GC, Shen HM, Jensen HM, et al. Bovine leukemia virus DNA in human breast tissue. *Emerg Infect Dis* 2014;20(5):772-82. doi: 10.3201/eid2005.131298 [published Online First: 2014/04/23]

143. Frie MC, Coussens PM. Bovine leukemia virus: a major silent threat to proper immune responses in cattle. *Vet Immunol Immunopathol* 2015;163(3-4):103-14. doi: 10.1016/j.vetimm.2014.11.014 [published Online First: 2015/01/03]

144. Adler SP. Cytomegalovirus and child day care. Evidence for an increased infection rate among day-care workers. *The New England journal of medicine* 1989;321(19):1290-6. doi: 10.1056/nejm198911093211903 [published Online First: 1989/11/09]

145. Lawler SE. Cytomegalovirus and glioblastoma; controversies and opportunities. *Journal of neuro-oncology* 2015;123(3):465-71. doi: 10.1007/s11060-015-1734-0 [published Online First: 2015/02/16]

146. Dey M, Ahmed AU, Lesniak MS. Cytomegalovirus and glioma: putting the cart before the horse. *J Neurol Neurosurg Psychiatry* 2015;86(2):191-9. doi: 10.1136/jnnp-2014-307727 [published Online First: 2014/06/08]

147. Wiemels J. Perspectives on the causes of childhood leukemia. *Chemico-biological interactions* 2012;196(3):59-67. doi: 10.1016/j.cbi.2012.01.007 [published Online First: 2012/02/14]

148. Cardwell CR, McKinney PA, Patterson CC, et al. Infections in early life and childhood leukaemia risk: a UK case-control study of general practitioner records. *Br J Cancer* 2008;99(9):1529-33. doi: 10.1038/sj.bjc.6604696 [published Online First: 2008/10/02]

149. Simpson J, Smith A, Ansell P, et al. Childhood leukaemia and infectious exposure: a report from the United Kingdom Childhood Cancer Study (UKCCS). *European journal of*

cancer (Oxford, England : 1990) 2007;43(16):2396-403. doi: 10.1016/j.ejca.2007.07.027 [published Online First: 2007/09/11]

150. Gilham C, Peto J, Simpson J, et al. Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. *BMJ (Clinical research ed)* 2005;330(7503):1294. doi: 10.1136/bmj.38428.521042.8F [published Online First: 2005/04/26]

151. Groves F, Sinha D, Auvinen A. Haemophilus influenzae type b vaccine formulation and risk of childhood leukaemia. *Br J Cancer* 2002;87(5):511-2. doi: 10.1038/sj.bjc.6600489 [published Online First: 2002/08/22]

152. Ma X, Does MB, Metayer C, et al. Vaccination history and risk of childhood leukaemia. *Int J Epidemiol* 2005;34(5):1100-9. doi: 10.1093/ije/dyi113 [published Online First: 2005/06/14]

153. Chang JS, Tsai YW, Tsai CR, et al. Allergy and risk of childhood acute lymphoblastic leukemia: a population-based and record-based study. *Am J Epidemiol* 2012;176(11):970-8. doi: 10.1093/aje/kws263 [published Online First: 2012/11/23]

154. Spector L, Groves F, DeStefano F, et al. Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. *European journal of cancer (Oxford, England : 1990)* 2004;40(4):579-84. doi: 10.1016/j.ejca.2003.08.024 [published Online First: 2004/02/14]

155. McKinney PA. Central nervous system tumours in children: epidemiology and risk factors. *Bioelectromagnetics* 2005;Suppl 7:S60-8. doi: 10.1002/bem.20149 [published Online First: 2005/09/06]

156. McNally RJ, Cairns DP, Eden OB, et al. An infectious aetiology for childhood brain tumours? Evidence from space-time clustering and seasonality analyses. *Br J Cancer* 2002;86(7):1070-7. doi: 10.1038/sj.bjc.6600228 [published Online First: 2002/04/16]

157. Shaw AK, Li P, Infante-Rivard C. Early infection and risk of childhood brain tumors (Canada). *Cancer Causes Control* 2006;17(10):1267-74. doi: 10.1007/s10552-006-0066-y [published Online First: 2006/11/18]

158. dos Santos CJ, Stangherlin LM, Figueiredo EG, et al. High prevalence of HCMV and viral load in tumor tissues and peripheral blood of glioblastoma multiforme patients. *J Med Virol* 2014;86(11):1953-61. doi: 10.1002/jmv.23820 [published Online First: 2013/11/01]

159. Tang KW, Hellstrand K, Larsson E. Absence of cytomegalovirus in high-coverage DNA sequencing of human glioblastoma multiforme. *Int J Cancer* 2015;136(4):977-81. doi: 10.1002/ijc.29042 [published Online First: 2014/06/26]

160. Yamashita Y, Ito Y, Isomura H, et al. Lack of presence of the human cytomegalovirus in human glioblastoma. *Mod Pathol* 2014;27(7):922-9. doi: 10.1038/modpathol.2013.219 [published Online First: 2013/12/18]

161. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med* 2008;5(3):e74. doi: 10.1371/journal.pmed.0050074 [published Online First: 2008/03/28]

162. Danon L, Read JM, House TA, et al. Social encounter networks: characterizing Great Britain. *Proc Biol Sci* 2013;280(1765):20131037. doi: 10.1098/rspb.2013.1037 [published Online First: 2013/06/28]

163. Danon L, House TA, Read JM, et al. Social encounter networks: collective properties and disease transmission. *J R Soc Interface* 2012;9(76):2826-33. doi: 10.1098/rsif.2012.0357 [published Online First: 2012/06/22]

164. Macintyre CR, Seale H, Yang P, et al. Quantifying the risk of respiratory infection in healthcare workers performing high-risk procedures. *Epidemiol Infect* 2014;142(9):1802-8. doi: 10.1017/s095026881300304x [published Online First: 2013/12/07]

165. Claassens MM, van Schalkwyk C, du Toit E, et al. Tuberculosis in healthcare workers and infection control measures at primary healthcare facilities in South Africa. *PloS one* 2013;8(10):e76272. doi: 10.1371/journal.pone.0076272 [published Online First: 2013/10/08]

166. De Schryver A, De Schrijver K, Francois G, et al. Hepatitis E virus infection: an emerging occupational risk? *Occup Med (Lond)* 2015;65(8):667-72. doi: 10.1093/occmed/kqv154 [published Online First: 2015/10/11]

167. Pozzetto B, Memmi M, Garraud O, et al. Health care-associated hepatitis C virus infection. *World J Gastroenterol* 2014;20(46):17265-78. doi: 10.3748/wjg.v20.i46.17265 [published Online First: 2014/12/18]

168. Michelin A, Henderson DK. Infection control guidelines for prevention of health care-associated transmission of hepatitis B and C viruses. *Clin Liver Dis* 2010;14(1):119-36; ix-x. doi: 10.1016/j.cld.2009.11.005 [published Online First: 2010/02/04]

169. Block RN, Berg P, Roberts K. Comparsing and quantifying labor standards in the United States and European Union. 13th World congress of the International Industrial Relations Association. Berlin, 1993.

170. Olsen JH, Jensen OM. Occupation and risk of cancer in Denmark. *Scandinavian journal of work, environment & health* 1987;13 Suppl 1:1-91.

171. Johnson CC, Spitz MR. Childhood nervous system tumours: an assessment of risk associated with paternal occupations involving use, repair or manufacture of electrical and electronic equipment. *Int J Epidemiol* 1989;18(4):756-62.

172. Kwa SL, Fine LJ. The association between parental occupation and childhood malignancy. *J Occup Med* 1980;22(12):792-4.

173. McKinney PA, Fear NT, Stockton D. Parental occupation at periconception. *OEM* 2003;60(12):901-9.

174. Cordier S, Mandereau L, Preston-Martin S, et al. Parental occupations and childhood brain tumors. *Cancer Causes Control* 2001;12(9):865-74.

175. Europe in figures - Eurostat yearbook 2009. Luxembourg: Eurostat, 2010.

176. US Department of Labor. Quick stats on women workers. Washington, DC: US Department of Labor, 2009.

177. Steliarova-Foucher E, Stiller C, Colombet M, et al. Registration of childhood cancer: Moving towards pan-European coverage? *European journal of cancer (Oxford, England : 1990)* 2015;51(9):1064-79. doi: 10.1016/j.ejca.2015.03.009 [published Online First: 2015/04/23]

178. IARC. Personal habits and indoor combustions. Volume 100 E. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 2012;100(Pt E):1-538. [published Online First: 2012/12/01]

179. Stiller CA. Epidemiology and genetics of childhood cancer. *Oncogene* 2004;23(38):6429-44. doi: 10.1038/sj.onc.1207717 [published Online First: 2004/08/24]

180. Greaves MF. Commentary: Birth order and risk of childhood acute lymphoblastic leukaemia (ALL). *Int J Epidemiol* 2001;30(6):1438-9. [published Online First: 2002/02/01]

181. Perrillat F, Clavel J, Auclerc MF, et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. *Br J Cancer* 2002;86(7):1064-9. doi: 10.1038/sj.bjc.6600091 [published Online First: 2002/04/16]

182. Maia Rda R, Wunsch Filho V. Infection and childhood leukemia: review of evidence. *Rev Saude Publica* 2013;47(6):1172-85. [published Online First: 2014/03/15]

183. Andersen TV, Schmidt LS, Poulsen AH, et al. Patterns of exposure to infectious diseases and social contacts in early life and risk of brain tumours in children and adolescents: an International Case-Control Study (CEFALO). *Br J Cancer* 2013;108(11):2346-53. doi: 10.1038/bjc.2013.201 [published Online First: 2013/05/09]

184. Fear NT, Simpson J, Roman E. Childhood cancer and social contact: paternal occupation. *Cancer Causes Control* 2005;16(9):1091-7.

185. Chang JS, Metayer C, Fear NT, et al. Parental social contact in the work place and the risk of childhood acute lymphoblastic leukaemia. *Br J Cancer* 2007;97(9):1315-21.

186. Kinlen L, Jiang J, Hemminki K. A case-control study of childhood leukaemia and paternal occupational contact level in rural Sweden. *Br J Cancer* 2002;86(5):732-7.

187. Kinlen LJ. High-contact paternal occupations, infection and childhood leukaemia: five studies of unusual population-mixing of adults. *Br J Cancer* 1997;76(12):1539-45.

188. Kinlen LJ, Bramald S. Paternal occupational contact level and childhood leukaemia in rural Scotland: a case-control study. *Br J Cancer* 2001;84(7):1002-7.

189. Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 1995;71(1):1-5.

190. Urayama KY, Buffler PA, Gallagher ER, et al. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. *Int J Epidemiol* 2010;39(3):718-32. doi: 10.1093/ije/dyp378 [published Online First: 2010/01/30]

191. Kinlen LJ, Clarke K, Hudson C. Evidence from population mixing in British New Towns 1946-85 of an infective basis for childhood leukaemia. *Lancet (London, England)* 1990;336(8715):577-82. [published Online First: 1990/09/08]

192. Kinlen LJ, O'Brien F, Clarke K, et al. Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site. *BMJ (Clinical research ed)* 1993;306(6880):743-8. [published Online First: 1993/03/20]

193. Kinlen LJ, Hudson C. Childhood leukaemia and poliomyelitis in relation to military encampments in England and Wales in the period of national military service, 1950-63. *BMJ (Clinical research ed)* 1991;303(6814):1357-62. [published Online First: 1991/11/30]

194. Fear NT, Roman E, Reeves G, et al. Are the children of fathers whose jobs involve contact with many people at an increased risk of leukaemia? *Occupational and environmental medicine* 1999;56(7):438-42.

195. Chin TL, MacGowan AP, Jacobson SK, et al. Viral infections in pregnancy: advice for healthcare workers. *J Hosp Infect* 2014;87(1):11-24. doi: 10.1016/j.jhin.2013.12.011 [published Online First: 2014/04/29]

196. Haskins R, Kotch J. Day care and illness: evidence, cost, and public policy. *Pediatrics* 1986;77(6 Pt 2):951-82. [published Online First: 1986/06/01]

197. Roman E, Watson A, Bull D, et al. Leukaemia risk and social contact in children aged 0-4 years in southern England. *J Epidemiol Community Health* 1994;48(6):601-2. [published Online First: 1994/12/01]

198. Kuijten RR, Bunin GR, Nass CC, et al. Parental occupation and childhood astrocytoma: results of a case-control study. *Cancer Res* 1992;52(4):782-6.

199. Mutanen P, Hemminki K. Childhood cancer and parental occupation in the Swedish Family-Cancer Database. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 2001;43(11):952-8.

200. Hum L, Kreiger N, Finkelstein MM. The relationship between parental occupation and bone cancer risk in offspring. *Int J Epidemiol* 1998;27(5):766-71.

201. Olsen JH, de Nully Brown P, Schulgen G, et al. Parental employment at time of conception and risk of cancer in offspring. *European journal of cancer (Oxford, England : 1990)* 1991;27(8):958-65. [published Online First: 1991/01/01]

202. Olshan AF, De Roos AJ, Teschke K, et al. Neuroblastoma and parental occupation. *Cancer Causes Control* 1999;10(6):539-49. [published Online First: 2000/01/05]

203. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(7 Suppl):22-5. doi: 10.1177/1403494810387965 [published Online First: 2011/08/04]

204. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011;39(7 Suppl):42-5. doi: 10.1177/1403494810393562 [published Online First: 2011/08/04]

205. Hansen J, Lassen CF. The Supplementary Pension Fund Register. *Scand J Public Health* 2011;39(7 Suppl):99-102. doi: 10.1177/1403494810394716 [published Online First: 2011/08/04]

206. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45(3):320-3. [published Online First: 1998/07/24]

207. World Health Organization. International statistical classification of diseases and related health problems. 10th revision, 2nd edition. ed. Geneva: World Health Organization 2004.

208. Fritz AG. International classification of diseases for oncology : ICD-O. 3rd ed. Geneva: World Health Organization 2000.

209. United Nations. Statistical Office. Dept. of International Economic and Social Affairs. International standard industrial classification of all economic activities. New York: United Nations 1968.

210. Hansen J, Lassen CF. The Supplementary Pension Fund Registry. *Scand J Public Health* 2010;In press

211. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90. doi: 10.2147/clep.s91125 [published Online First: 2015/11/26]

212. Petersen L, Sorensen TI. The Danish Adoption Register. *Scand J Public Health* 2011;39(7 Suppl):83-6. doi: 10.1177/1403494810394714 [published Online First: 2011/08/04]

213. Jensen-Butler C. Rural Industrialisation in Denmark and the Role of Public Policy. *Urban Studies* 1992;29(6):881-904.

214. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). *Cancer* 2008;112(2):416-32. doi: 10.1002/cncr.23169 [published Online First: 2007/12/13]

215. Nabhan C, Aschebrook-Kilfoy B, Chiu BC, et al. The impact of race, ethnicity, age and sex on clinical outcome in chronic lymphocytic leukemia: a comprehensive Surveillance, Epidemiology, and End Results analysis in the modern era. *Leuk Lymphoma* 2014;55(12):2778-84. doi: 10.3109/10428194.2014.898758 [published Online First: 2014/03/05]

216. Urayama KY, Manabe A. Genomic evaluations of childhood acute lymphoblastic leukemia susceptibility across race/ethnicities. *Rinsho Ketsueki* 2014;55(10):2242-8. [published Online First: 2014/10/10]

217. Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. *European journal of cancer (Oxford, England : 1990)* 1999;35(14):1941-53. [published Online First: 2000/03/11]

218. Ford AM, Ridge SA, Cabrera ME, et al. In utero rearrangements in the trithorax-related oncogene in infant leukaemias. *Nature* 1993;363(6427):358-60. doi: 10.1038/363358a0 [published Online First: 1993/05/27]

219. Wiemels JL, Ford AM, Van Wering ER, et al. Protracted and variable latency of acute lymphoblastic leukemia after TEL-AML1 gene fusion in utero. *Blood* 1999;94(3):1057-62. [published Online First: 1999/07/27]

220. Greaves M. Childhood leukaemia. *BMJ (Clinical research ed)* 2002;324(7332):283-7. [published Online First: 2002/02/02]

221. Greaves MF. Aetiology of acute leukaemia. *Lancet (London, England)* 1997;349(9048):344-9. [published Online First: 1997/02/01]

222. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;1(1):69-75. doi: 10.1038/35095579 [published Online First: 2002/03/22]

223. Dunne DW, Cooke A. A worm's eye view of the immune system: consequences for evolution of human autoimmune disease. *Nat Rev Immunol* 2005;5(5):420-6. doi: 10.1038/nri1601 [published Online First: 2005/05/03]

224. Ma J, van den Driessche P, Willeboordse FH. Effective degree household network disease model. *J Math Biol* 2013;66(1-2):75-94. doi: 10.1007/s00285-011-0502-9 [published Online First: 2012/01/19]

225. Bartek J, Jr., Fornara O, Merchut-Maya JM, et al. Replication stress, DNA damage signalling, and cytomegalovirus infection in human medulloblastomas. *Mol Oncol* 2017 doi: 10.1002/1878-0261.12061 [published Online First: 2017/04/07]

226. Linos E, Raine T, Alonso A, et al. Atopy and risk of brain tumors: a meta-analysis. *Journal of the National Cancer Institute* 2007;99(20):1544-50. doi: 10.1093/jnci/djm170 [published Online First: 2007/10/11]

227. Berger A. Th1 and Th2 responses: what are they? *BMJ* 2000;321(7258):424. [published Online First: 2000/08/11]

228. Keegan TJ, Bunch KJ, Vincent TJ, et al. Case-control study of paternal occupation and social class with risk of childhood central nervous system tumours in Great Britain, 1962-2006. *Br J Cancer* 2013;108(9):1907-14. doi: 10.1038/bjc.2013.171 [published Online First: 2013/04/25]

229. Jones DT, Ichimura K, Liu L, et al. Genomic analysis of pilocytic astrocytomas at 0.97 Mb resolution shows an increasing tendency toward chromosomal copy number change with age. *J Neuropathol Exp Neurol* 2006;65(11):1049-58. doi: 10.1097/01.jnen.0000240465.33628.87 [published Online First: 2006/11/07]

230. Watanabe T, Nobusawa S, Kleihues P, et al. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathol* 2009;174(4):1149-53. doi: 10.2353/ajpath.2009.080958 [published Online First: 2009/02/28]

231. Marko NF, Weil RJ. The molecular biology of WHO grade I astrocytomas. *Neuro Oncol* 2012;14(12):1424-31. doi: 10.1093/neuonc/nos257 [published Online First: 2012/10/24]

232. de Hoog ML, Venekamp RP, van der Ent CK, et al. Impact of early daycare on healthcare resource use related to upper respiratory tract infections during childhood: prospective WHISTLER cohort study. *BMC Med* 2014;12:107. doi: 10.1186/1741-7015-12-107 [published Online First: 2014/06/27]

233. Kamper-Jorgensen M, Wohlfahrt J, Simonsen J, et al. The Childcare Database: a valuable register linkage. *Scand J Public Health* 2007;35(3):323-9. doi: 10.1080/14034940601072356 [published Online First: 2007/05/29]

234. McKenna MT, Hutton M, Cauthen G, et al. The association between occupation and tuberculosis. A population-based survey. *Am J Respir Crit Care Med* 1996;154(3 Pt 1):587-93. doi: 10.1164/ajrccm.154.3.8810591 [published Online First: 1996/09/01]

235. Pass RF, Hutto C, Lyon MD, et al. Increased rate of cytomegalovirus infection among day care center workers. *Pediatr Infect Dis J* 1990;9(7):465-70. [published Online First: 1990/07/01]

236. Kivela T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009;93(9):1129-31. doi: 10.1136/bjo.2008.150292 [published Online First: 2009/08/26]

237. Wong JR, Tucker MA, Kleinerman RA, et al. Retinoblastoma incidence patterns in the US Surveillance, Epidemiology, and End Results program. *JAMA ophthalmology* 2014;132(4):478-83.

238. Parkin D, Kramarova E, Draper G, et al. International incidence of childhood cancer(Volume II). *IARC scientific publications* 1998

239. Abdolahi A, van Wijngaarden E, McClean MD, et al. A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. *Occupational and environmental medicine* 2013;70(6):372-9. doi: 10.1136/oemed-2012-101062 [published Online First: 2013/03/19]

240. Bunin GR, Petrakova A, Meadows AT, et al. Occupations of parents of children with retinoblastoma: a report from the Children's Cancer Study Group. *Cancer Res* 1990;50(22):7129-33. [published Online First: 1990/11/15]

241. Kristensen P, Andersen A, Irgens LM, et al. Cancer in offspring of parents engaged in agricultural activities in Norway. *International Journal of Cancer* 1996;65(1):39-50.

242. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect* 2004;112(5):631-5. [published Online First: 2004/04/06]

243. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. *Occupational and environmental medicine* 2003;60(10):798-801. [published Online First: 2003/09/25]

244. Fear NT, Roman E, Reeves G, et al. Childhood cancer and paternal employment in agriculture. *British Journal of Cancer* 1998;77(5):825-9.

245. Pearce MS, Hammal DM, Dorak MT, et al. Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case-control study from the North of England. *Archives of environmental & occupational health* 2006;61(3):138-44.

246. Yang YQ, Li J, Yuan HF. Epidemiology and risk factors of retinoblastoma in Chongqing area. *Int J Ophthalmol* 2016;9(7):984-8. doi: 10.18240/ijo.2016.07.08 [published Online First: 2016/08/09]

247. Mutanen P, Hemminki K. Childhood cancer and parental occupation in the Swedish Family-Cancer Database. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 2001;43(11):952-8.

248. Omidakhsh N, Bunin GR, Ganguly A, et al. Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group. *Occupational and Environmental Medicine* 2017;Manuscript Submitted

249. Clermont Y. Kinetics of spermatogenesis in mammals: seminiferous epithelium cycle and spermatogonial renewal. *Physiol Rev* 1972;52(1):198-236. [published Online First: 1972/01/01]

250. Heck JE, Omidakhsh N, Azary S, et al. A case-control study of sporadic retinoblastoma in relation to maternal health conditions and reproductive factors: a report from the Children's Oncology group. *BMC Cancer* 2015;15:735. doi: 10.1186/s12885-015-1773-0 [published Online First: 2015/10/21]

251. Knishkowy B, Baker EL. Transmission of occupational disease to family contacts. *American journal of industrial medicine* 1986;9(6):543-50. [published Online First: 1986/01/01]

252. Kelley JS, Sophocleus GJ. Retinal hemorrhages in subacute carbon monoxide poisoning. Exposures in homes with blocked furnace flues. *JAMA* 1978;239(15):1515-7. [published Online First: 1978/04/14]

253. Heck JE, Park AS, Qiu J, et al. Retinoblastoma and ambient exposure to air toxics in the perinatal period. *J Expo Sci Environ Epidemiol* 2015;25(2):182-6. doi: 10.1038/jes.2013.84 [published Online First: 2013/11/28]

254. Campo MS. Papillomas and cancer in cattle. *Cancer Surv* 1987;6(1):39-54. [published Online First: 1987/01/01]

255. Lancaster WD, Olson C. Animal papillomaviruses. *Microbiol Rev* 1982;46(2):191-207. [published Online First: 1982/06/01]

256. Aida Y, Murakami H, Takahashi M, et al. Mechanisms of pathogenesis induced by bovine leukemia virus as a model for human T-cell leukemia virus. *Front Microbiol* 2013;4:328. doi: 10.3389/fmicb.2013.00328 [published Online First: 2013/11/23]

257. Codrin R, Dumbrava Dan P, Carmen R. EXPOSURE TO NITRATES - PROFESSIONAL HAZARD OR WORK ACCIDENT IN FOOD INDUSTRY WORKERS. CASE REPORT OF A COLLECTIVE INTOXICATION *Analele Universităţii din Oradea, Fascicula Protecţia Mediului* 2016;27

258. Hagmar L, Schütz A, Hallberg T, et al. Health effects of exposure to endotoxins and organic dust in poultry slaughter-house workers. *Int Arch Occup Environ Health* 1990;62(2):159-64.

259. Bunin GR, Tseng M, Li Y, et al. Parental diet and risk of retinoblastoma resulting from new germline RB1 mutation. *Environ Mol Mutagen* 2012;53(6):451-61. doi: 10.1002/em.21705 [published Online First: 2012/06/26]

260. Johnson ES, Ndetan H, Lo KM. Cancer mortality in poultry slaughtering/processing plant workers belonging to a union pension fund. *Environmental research* 2010;110(6):588-94. doi: 10.1016/j.envres.2010.05.010 [published Online First: 2010/06/15]

261. Johnson ES. Cancer mortality in workers employed in cattle, pigs, and sheep slaughtering and processing plants. *Environ Int* 2011;37(5):950-9. doi: 10.1016/j.envint.2011.03.014 [published Online First: 2011/04/19]

262. Johnson ES, Ndetan H. Non-cancer mortality in poultry slaughtering/processing plant workers belonging to a union pension fund. *Environ Int* 2011;37(2):322-7. doi: 10.1016/j.envint.2010.09.007 [published Online First: 2010/11/16]

263. Newman KL, Leon JS, Newman LS. Estimating Occupational Illness, Injury, and Mortality in Food Production in the United States: A Farm-to-Table Analysis. *J Occup Environ Med* 2015;57(7):718-25. doi: 10.1097/jom.0000000000000476 [published Online First: 2015/05/15]

264. Felini M, Preacely N, Shah N, et al. A case-cohort study of lung cancer in poultry and control workers: occupational findings. *Occup Environ Med* 2012;69(3):191-7. doi: 10.1136/oemed-2011-100310 [published Online First: 2011/10/19]

265. Metayer C, Johnson ES, Rice JC. Nested case-control study of tumors of the hemopoietic and lymphatic systems among workers in the meat industry. *Am J Epidemiol* 1998;147(8):727-38. [published Online First: 1998/04/29]

266. Netto GF, Johnson ES. Mortality in workers in poultry slaughtering/processing plants: the Missouri poultry cohort study. *Occup Environ Med* 2003;60(10):784-8. [published Online First: 2003/09/25]

267. Statistics BoL. Employment and wages for the highest and lowest paying occupations, May 2012. Available at: https://www.bls.gov/oes/2012/may/high_low_paying.htm. Published 2013. Accessed April 26, 2014. 2013

268. de Camargo B, de Oliveira Ferreira JM, de Souza Reis R, et al. Socioeconomic status and the incidence of non-central nervous system childhood embryonic tumours in Brazil. *BMC Cancer* 2011;11:160. doi: 10.1186/1471-2407-11-160 [published Online First: 2011/05/07]

269. Proctor DM, Suh M, Campleman SL, et al. Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. *Toxicology* 2014;325:160-79. doi: 10.1016/j.tox.2014.08.009 [published Online First: 2014/09/02]

270. Zambelli B, Ciurli S. Nickel and human health. *Met Ions Life Sci* 2013;13:321-57. doi: 10.1007/978-94-007-7500-8_10 [published Online First: 2014/01/29]

271. Apostoli P, Catalani S. Metal ions affecting reproduction and development. *Met Ions Life Sci* 2011;8:263-303. [published Online First: 2011/04/09]

272. Albert DM, Gonder JR, Papale J, et al. Induction of ocular neoplasms in Fischer rats by intraocular injection of nickel subsulfide. *Invest Ophthalmol Vis Sci* 1982;22(6):768-82. [published Online First: 1982/06/01]

273. Johnson S, Cooper C, Cartwright S, et al. The experience of work-related stress across occupations. *Journal of managerial psychology* 2005;20(2):178-87.

274. Datta Gupta N, Kristensen N. Work environment satisfaction and employee health: panel evidence from Denmark, France and Spain, 1994-2001. *Eur J Health Econ* 2008;9(1):51-61. doi: 10.1007/s10198-007-0037-6 [published Online First: 2007/02/14]

275. Lombardi C, Ganguly A, Bunin GR, et al. Maternal diet during pregnancy and unilateral retinoblastoma. *Cancer Causes Control* 2015;26(3):387-97. doi: 10.1007/s10552-014-0514-z [published Online First: 2014/12/30]

276. Bunin GR, Li Y, Ganguly A, et al. Parental nutrient intake and risk of retinoblastoma resulting from new germline RB1 mutation. *Cancer Causes Control* 2013;24(2):343-55. doi: 10.1007/s10552-012-0120-x [published Online First: 2012/12/12]

277. Orjuela MA, Titievsky L, Liu X, et al. Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. *Cancer Epidemiol Biomarkers Prev* 2005;14(6):1433-40. doi: 10.1158/1055-9965.epi-04-0427 [published Online First: 2005/06/09]

278. Venneri L, Rossi F, Botto N, et al. Cancer risk from professional exposure in staff working in cardiac catheterization laboratory: insights from the National Research Council's Biological Effects of Ionizing Radiation VII Report. *Am Heart J* 2009;157(1):118-24. doi: 10.1016/j.ahj.2008.08.009 [published Online First: 2008/12/17]

279. Rostgaard T, Christoffersen MN, Weise H. Parental leave in Denmark: na 1999.

280. Hansen ML, Thulstrup AM, Juhl M, et al. Occupational exposures and sick leave during pregnancy: results from a Danish cohort study. *Scand J Work Environ Health* 2015;41(4):397-406. doi: 10.5271/sjweh.3507 [published Online First: 2015/06/06]

281. Bonanomi MT, Almeida MT, Cristofani LM, et al. Retinoblastoma: a three-year-study at a Brazilian medical school hospital. *Clinics (Sao Paulo)* 2009;64(5):427-34. [published Online First: 2009/06/03]

282. Kaste SC, Chen G, Fontanesi J, et al. Orbital development in long-term survivors of retinoblastoma. *J Clin Oncol* 1997;15(3):1183-9. [published Online First: 1997/03/01]

283. Bonde JP, Olsen JH, Hansen KS. Adverse pregnancy outcome and childhood malignancy with reference to paternal welding exposure. *Scand J Work Environ Health* 1992;18(3):169-77. [published Online First: 1992/06/01]

284. Kristensen P, Andersen A. A cohort study on cancer incidence in offspring of male printing workers. *Epidemiology* 1992;3(1):6-10. [published Online First: 1992/01/01]

285. O'Leary LM, Hicks AM, Peters JM, et al. Parental occupational exposures and risk of childhood cancer: a review. *American journal of industrial medicine* 1991;20(1):17-35. [published Online First: 1991/01/01]

286. Pan SY, Ugnat AM, Mao Y. Occupational risk factors for brain cancer in Canada. *J Occup Environ Med* 2005;47(7):704-17. [published Online First: 2005/07/13]

287. Bunin GR, Vardhanabhuti S, Lin A, et al. Practical and analytical aspects of using friend controls in case-control studies: experience from a case-control study of childhood cancer. *Paediatr Perinat Epidemiol* 2011;25(5):402-12. doi: 10.1111/j.1365-3016.2011.01210.x [published Online First: 2011/08/09]

288. Fear NT, Roman E, Reeves G, et al. Childhood cancer and paternal employment in agriculture: the role of pesticides. *Br J Cancer* 1998;77(5):825-9. [published Online First: 1998/03/26]

289. Knowles JF. Long-term irradiation of a marine fish, the plaice Pleuronectes platessa: an assessment of the effects on size and composition of the testes and of possible genotoxic changes in peripheral erythrocytes. *Int J Radiat Biol* 1999;75(6):773-82. [published Online First: 2001/02/07]

290. Esakky P, Moley KH. Paternal smoking and germ cell death: A mechanistic link to the effects of cigarette smoke on spermatogenesis and possible long-term sequelae in offspring. *Mol Cell Endocrinol* 2016;435:85-93. doi: 10.1016/j.mce.2016.07.015 [published Online First: 2016/07/18]

291. Little MP, Kleinerman RA, Stiller CA, et al. Analysis of retinoblastoma age incidence data using a fully stochastic cancer model. *International journal of cancer Journal international du cancer* 2012;130(3):631-40. doi: 10.1002/ijc.26039 [published Online First: 2011/03/10]

292. Basso O, Olsen J, Bisanti L, et al. The performance of several indicators in detecting recall bias. European Study Group on Infertility and Subfecundity. *Epidemiology* 1997;8(3):269-74. [published Online First: 1997/05/01]

293. Tuchsen F, Hannerz H, Jensen MV, et al. Socioeconomic status, occupation, and risk of hospitalisation due to coxarthrosis in Denmark 1981-99. *Ann Rheum Dis* 2003;62(11):1100-5. [published Online First: 2003/10/30]

294. Aziz HA, Lasenna CE, Vigoda M, et al. Retinoblastoma treatment burden and economic cost: impact of age at diagnosis and selection of primary therapy. *Clinical ophthalmology (Auckland, NZ)* 2012;6:1601-6. doi: 10.2147/opth.s33094 [published Online First: 2012/10/12]

295. Merrill CT, Nagamine M, Hambrick MM. Pediatric hospital stays for cancer, 2005. Washington, DC: AHRQ, 2007.

296. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *The New England journal of medicine* 2006;355(15):1572-82.