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Parental occupation and risk of childhood retinoblastoma in Denmark

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Abstract

Objective: Retinoblastoma is the most common primary intraocular tumor affecting children. We examine the role of parental occupational exposures and risk of retinoblastoma among offspring.

Methods: Our population-based case-control study linked data from four nationwide Danish registries and included all cases of retinoblastoma diagnosed in Danish children (<5 years, n=144) between 1975–2014. We focused on two biologically relevant time periods: 90 days preconception to conception for fathers; conception to birth for mothers. Parents were grouped into major industry headings created from Danish industry codes.

Results: We observed increased risk of all retinoblastoma for children of fathers in the food and drink industry and iron and metal industry. Bilateral disease was associated with paternal work in manufacturing and land transportation.

Conclusion: Our results suggest that some occupational exposures may increase the risk of childhood sporadic retinoblastoma.

Keywords

retinoblastoma; childhood cancer; occupational exposures; parental exposures

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Ethics approval: 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 study did not include any primary data collection, but rather utilized anonymized registry data, patient consent was not required.

Conflict of interest: None declared.

Introduction

Retinoblastoma is the most common form of childhood eye cancer worldwide with approximately 9,000 new cases diagnosed annually (1). Most cases (63%) are diagnosed in infancy before age 2 and 95% by age 5 (2). It manifests in the infant retina as a result of mutations in the tumor suppressor retinoblastoma gene (*RB1*) (3). A widely accepted two-hit hypothesis was proposed by Knudson, i.e. suggesting that retinoblastoma is caused by two mutational events (4). 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 (5), 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 (6, 7). Unilateral disease is autosomal dominant and most often occurs as a result of a mutation that occurs sporadically in a retinal cell in utero or very early life, although a small number (10–15%) of cases arise from an inherited mutation (4).

There are variations in disease incidence across countries, with some parts of South America and Southeast Asia having higher than average incidence rates (8). 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) (9). Several studies have examined the association between parental occupation and retinoblastoma with inconclusive results (10–12). 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%) (13–17); however, only two of these studies found positive associations (10, 18). These positive associations are further supported by findings of increased retinoblastoma risk when parents use insecticides in their homes (19, 20). Other occupational studies have reported increased risk of retinoblastoma among children of fathers who are electrical workers (21), exposed to paints (22), or employed in the metal industry (11, 12). A report of a risk increase among fathers employed as television or radio repairmen, possibly due to occupational radiation exposure (23), was not corroborated in two other studies (10, 11). 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 (22). There is a need for more studies that investigate parental occupational exposures. Here, we examine associations for retinoblastoma risk in the offspring based on nationwide register data, for paternal occupations from 3 months preconception to conception and maternal occupations from conception to birth.

Methods

The present population-based case-control study utilized a linked database that includes all childhood cancer cases born from 1968–2013 and diagnosed from 1968–2016 in Denmark.

To be eligible, all cases and controls had to be born in Denmark; this allows us to retrieve information on gestational characteristics and parental occupations before birth. Data were taken from four Danish Registries that were linked by unique identifiers: The Central Population Registry (24) (data available 1968–2016), the Danish Cancer Registry (25) (1968–2016), the Supplementary Pension Fund (26) (1964–2013) and the Danish Medical Birth Registry (27) (1973–2013). Details concerning these registries, as well as the disease and occupational classification methods we used, were reported in more detail in previous publications (28, 29). Briefly, the Danish Cancer Registry was used to ascertain cases diagnosed between 1968–2016 and the Central Population Register was used to ascertain 25 age (by exact date of birth) and sex-matched controls per case. If 25 controls with the exact case birthday could not be identified, we widened the search by one day (on either side), then two days, then three days… etc., until all controls were selected. Data on all jobs held for both parents, available from 1964 onward, were obtained from the database of the Danish Supplementary Pension Fund. All information could be linked due to the existence of a unique personal identifier applied to all residents since 1968. 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 Register 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, the first time such information was available. For births before 1972, we relied upon the Central Population Registry to identify parents. We expect most legal guardians to be biological parents as all participants were born in Denmark, and most adoptions in Denmark are of foreign-born children (30).

From our dataset, we identified 159 cases of retinoblastoma using the International Classification of Childhood Cancer (ICCC), version 1 until 2003 and version 3 thereafter. We excluded case and control parents who did not have any occupational history information during relevant periods (N=390). Our final analysis included all retinoblastoma cases for which we had occupational history of at least one parent (N_{total}=144, $N_{fathers}$=119, $N_{mothers}$=115) and their corresponding controls (N_{total}=3600, $N_{fathers}$=2841, $N_{mothers}$=2596). All cases of retinoblastoma were diagnosed between 1975 and 2014, and under 5 years of age.

Given that spermatogenesis spans approximately 90 days (31), there is a small window for environmental toxins to cause alterations to sperm. This suggests a role for paternal exposures 3 months preconception and for 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 (4). 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 1). 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 (18, 21), 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 possible covariates was guided by previous research (10, 32–35). We performed conditional logistic regression analyses adjusting for parental age (≤25, 26–30, 31–35, 36+) and urban or small town/rural residency according to place of birth listed in the Central Population Register. 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, the addition of these variables did not change our estimates substantially and were thus excluded from our final analyses.

As fathers could bring home toxic chemicals from work on their clothing, thereby exposing their wife and child (transplacentally) (36), 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 (32, 33, 35, 37–42); 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 (10). All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Case mothers were slightly younger (≤25 years) than control mothers (36% vs. 31%, Table 1). There were no considerable differences in paternal age, family SES or urban vs. rural residence 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 construction, which was null, and public administration and defense, which had a point estimate below one for all retinoblastomas (Odds Ratio [OR]: 0.31, 95% Confidence Interval [CI]: 0.14–0.68, Table 2).

Paternal work in the manufacturing industry was associated with an increased risk of all childhood retinoblastoma (OR: 1.90, 95% CI: 1.30–2.77) as well as bilateral retinoblastoma (OR: 2.14, 95% CI: 1.09, 4.21); with those working in the food and drink industry having the strongest association (OR: 2.18, 95% CI: 1.13–4.21). Given the small number of retinoblastoma cases, the number of fathers in any single industry were small; the most common occupation among case fathers in this industry was animal slaughtering(N=6) (Supplementary Table 1). Increased risk of retinoblastoma was also observed for children

born to fathers in the iron and metal industry (OR: 1.63, 95% CI: 1.02–2.59). Fathers who worked in jobs that involved transportation on land, including taxi drivers (n=2), those employed in carrier businesses (n=2) or for railroads (n=2), were also at increased risk of having a child with bilateral retinoblastoma (OR: 3.50, 95% CI: 1.24–9.86).

Maternal job associations are presented in Table 3. The numbers of exposed mothers were too small to make meaningful conclusions. However, mothers who worked in “other service activities”, which included jobs in religious societies and institutions (N=3), employer and wage-earner associations (N=2) and hairdressers (N=1) had elevated point estimates for all retinoblastoma (OR: 2.14, 95% CI: 0.89, 5.15) (Table 3).

All case fathers, except one, held the same job during the entire year and the 3 months preconception period. Similarly, fathers continued to work in the same jobs from conception to birth. As a result, we observed no changes in point estimates for these sensitivity analyses. In analyses that restricted to older fathers and mothers (>30 years), we found point estimates elevated by approximately 50% compared to all fathers or mothers combined, though confidence intervals widened due to small cell counts (Supplementary Table 2, Supplementary Table 3, respectively). Our effect estimates were similar when restricting to rural residency for both fathers (Supplementary Table 4) and mothers (Supplementary Table 5).

Discussion

When we evaluated the most common industrial occupations, we found several to be associated with increased risk of childhood retinoblastoma. In particular, our study findings suggest an increased risk of retinoblastoma among children whose fathers worked in manufacturing during the sensitive three months preconception period, especially those working in animal slaughtering. When examining bilateral disease only, we observed similar or stronger positive associations within all main industry types that had associations with all retinoblastomas, which is consistent with the proposed underlying disease mechanisms that suggest development of bilateral retinoblastoma due to paternal germline mutations occurring during preconception. Maternal work in the industries we included between conception and birth was not strongly associated with childhood retinoblastoma. Our point estimates for unilateral retinoblastoma aligned closely with those for all retinoblastoma.

The most likely biological mechanism for how paternal preconception exposures could induce childhood cancers, and specifically retinoblastoma, given the role of de novo mutations in germline cells (6), is through exposure to toxicants that cause alterations to sperm. The epidemiologic 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 (43–45). For bilateral retinoblastoma, which most often results from somatic mutations that occur preconceptionally in male germline cells, we found associations with paternal employment in retail and transportation. Interestingly, half of the fathers working in retail were employed in automobile and motorcycle shops (Supplementary Table 5). 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 in epidemiologic studies (32, 46). Previous studies have reported an increased risk of bilateral retinoblastoma (47, 48), as well as all retinoblastomas (49), with exposure to air pollution. However, these studies reported exclusively on maternal exposures during pregnancy and did not have data on paternal exposures during the preconception period.

The manufacturing industry is diverse and includes occupations with an array of potential risk factors. We found all industry subtypes within manufacturing to be associated with higher risks of retinoblastoma, with the greatest increase seen among fathers working in the food and drink industry, specifically slaughtering. We were unable to find other studies on retinoblastoma risk among children of fathers in the food industry, or more specifically in animal 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 (12). In a separate analysis, our group reported an increased risk of all retinoblastoma among children of mothers who were exposed to animal dust (OR: 2.67; 95% CI: 1.01–7.03) (50). Other childhood cancer types, including bone cancer and cancers of the central nervous system, have been associated with fathers who work with animals (51, 52) and in food manufacturing (21).

The odds of retinoblastoma (all and bilateral) were elevated for paternal employment in general retail stores. One previous study found an association specifically between retinoblastoma and paternal work in the shoe and leather industry (21); however, the largest group of men in our study were employed in automobile and motorcycle shops, indicating a possible role of car exhaust pollutants.

Several studies have reported findings for specific occupational agents with retinoblastoma. Elevated risk of retinoblastoma among offspring of parents exposed to paints (10), polycyclic aromatic hydrocarbons (32), metals (10) has been found, as well as fathers employed as electrical repairmen (23) and in the metal industry (11). While specific metals have not been identified in these studies, suspected agents may include nickel, cadmium, beryllium and hexavalent chromium as these are recognized as human carcinogens (64, 65), and have been associated with reproductive toxicity, subfertility, malformations and birth defects (66). Further, rats injected with nickel developed retinoblastoma in an experimental study (67) and atmospheric nickel exposure during pregnancy was associated with retinoblastoma in humans (49).

Several associations with retinoblastoma were found for paternal industry and work categories with low probable risk for exposure to toxic agents. Specifically, we found a lower odds of retinoblastoma among fathers working in public administration and defense during the preconception period. We hypothesize that fathers in this category may have less occupational chemical exposure than other jobs or led healthier lifestyles due to higher socioeconomic status (68). In Denmark, persons employed as managers or professionals self-reported higher levels of general health than those working in blue collar or manufacturing occupations (69). A healthy diet consisting of fruit and vitamin intake has been inversely associated with retinoblastoma (61, 70–72). It also is possible that fathers

employed in jobs other than public administration included jobs with greater potential for exposure to toxic agents, resulting in the odds ratio below null.

A strength of our study is the exploration of parental occupation on retinoblastoma in offspring using two clinically relevant periods (preconception, pregnancy). We evaluated risk of retinoblastoma by laterality, an important indicator for which parent and period of exposure is most relevant for disease onset. A limitation of our study is missing values for several potential confounders, including parental smoking status and socioeconomic status. When we restricted to individuals with complete covariate data (e.g. smoking, socioeconomic status) the results were similar. Importantly, our study included pediatric cases of retinoblastoma that spanned nearly 4 decades (earliest diagnosis: 1975, latest diagnosis: 2014). Parental exposures within a single industry can change drastically within this time frame, particularly with the advancement of personal protective equipment, efforts to improve ventilation, and increased knowledge regarding potential chemical hazards. Given the rarity of disease, and thus the limited number of retinoblastoma cases in our dataset, we were required to utilize the entire timeframe in order to ensure sufficient statistical power. As a result, our study may overestimate the risk of retinoblastoma in certain industries that have made efforts to limit or eliminate their exposure to hazardous agents. Our small sample of cases prevented us from performing additional sensitivity analyses that restricted to older maternal and paternal age (i.e., only 2 cases had either a mother or father over age 40 at child's birth). There is a need for larger, registry-based, studies, that aim to examine the association between parental occupation and childhood retinoblastoma among parents age 40 and older.

Only a handful of studies have investigated parental occupation and risk of retinoblastoma, often with sample sizes too small to draw conclusions for rarer exposures. Further, published studies have typically not reported dose-response effects or exposures held in the year or 10 years before pregnancy, or occupations held at birth. We found that jobs are relatively stable across the preconception and pregnancy windows and our focus on a short window of disease susceptibility diminishes the concern of competing exposures. However, as a result, we were unable to explore differences in disease susceptibility related to varying exposure periods (one year preconception to conception vs. 90 days preconception to conception). Other strengths of this study included the objectively recorded and exact employment history, a nationwide population-based study design and the ability to examine risk of retinoblastoma across two unique periods (preconception to conception, conception to birth).

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 (73). Physically demanding working conditions in Denmark, and particularly those that involve long hours or shift work, have been positively associated with increased sick leave during pregnancy (74), possibly indicating that the highest risk women are going on maternity leave earlier and subsequently experience lower levels of exposure. If this is true, then our point estimates for retinoblastoma associated with maternal occupational exposures may underestimate true effects.

Using detailed historical employment records in a population-based design, we found an increased risk of retinoblastoma (all cases) among children whose fathers had a history of employment in the livestock or meat processing industry during the preconception window. When we evaluated bilateral retinoblastoma, we found elevated risk among fathers who worked in transportation, iron and metal, and retail industries. We did not have information on the specific agents that may explain these associations. Additional research is needed to explore the reasons for these potential associations of retinoblastoma with parental occupational exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

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

	All Cases N= 144 (%)	Unilateral Cases N=94 (%)	Bilateral Cases N=45 (%)	All controls N=3600 (%)
Sex of child				
Male	83 (57.6)	52 (55.3)	28 (62.2)	2075 (57.6)
Female	61 (42.4)	42 (44.7)	17 (37.8)	1525 (42.4)
Missing	0	0	0	0
Maternal age				
<=25	52 (36.1)	33 (35.1)	15 (33.3)	1108 (30.7)
26–30	50 (34.7)	34 (36.2)	16 (35.6)	1342 (37.3)
31–35	30 (20.8)	19 (20.2)	10 (22.2)	860 (23.9)
36+	12 (8.3)	8 (8.5)	4 (8.9)	290 (8.1)
Missing	0	0	0	0
Paternal age				
<=25	22 (15.3)	14 (14.9)	5 (11.1)	576 (16.0)
26–30	52 (36.1)	34 (36.2)	18 (40.0)	1224 (34.0)
31–35	43 (29.9)	29 (30.9)	13 (28.9)	1044 (29.0)
36+	27 (18.8)	17 (18.1)	9 (20.0)	741 (20.6)
Missing	0	0	0	15 (0.4)
Family SES				
High	11 (7.6)	9 (9.6)	1 (2.2)	353 (9.8)
Medium-high	24 (16.7)	17 (18.1)	6 (13.3)	406 (11.3)
Medium	14 (9.7)	9 (9.6)	3 (6.7)	510 (14.2)
Medium-low	40 (27.8)	27 (28.7)	13 (28.9)	790 (21.9)
Low	20 (13.9)	11 (11.7)	8 (17.8)	516 (14.3)
Missing	35 (24.3)	21 (22.3)	14 (31.1)	1025 (28.5)
Residence type				
Urban	45 (31.3)	32 (34.0)	11 (24.4)	1195 (33.2)
Rural	99 (68.8)	62 (66.0)	34 (75.6)	2405 (66.8)
Missing	0	0	0	0

Table 2.

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

		All Retinoblastoma			Bilateral Retinoblastoma		
	Exposed Controls (N=2841)	Exposed Cases (N=119)	Crude OR	Adjusted OR (95% CI)	Exposed Cases (N=45)	Crude OR	Adjusted OR (95% CI)
Industry type							
Manufacturing	723	48	1.89	1.90 (1.30, 2.77)	16	2.23	2.14 (1.09, 4.21)
Food and drink industry	117	11	2.19	2.18 (1.13, 4.21)	<5	-	-
Paper and graphics industry	67	6	2.19	2.22 (0.94, 5.25)	<5	-	-
Iron and metal industry	373	24	1.64	1.63 (1.02, 2.59)	9	2.19	2.13 (0.97, 4.68)
Construction	339	15	0.98	0.97 (0.56, 1.69)	5	1.12	1.10 (0.42, 2.93)
Construction of roads and buildings	212	11	1.15	1.14 (0.61, 2.16)	<5	-	-
Wholesale and retail trade	437	20	1.06	1.06 (0.65, 1.74)	10	1.87	1.85 (0.86, 3.97)
General retail stores	171	10	1.43	1.44 (0.74, 2.80)	7	3.38	3.39 (1.43, 8.04)
Transportation and storage	206	10	1.11	1.11 (0.57, 2.16)	5	2.22	2.34 (0.84, 6.50)
Transportation on land	140	6	0.97	0.97 (0.42, 2.25)	5	3.46	3.50 (1.24, 9.86)
Professional, scientific and technical activities	101	5	1.18	1.18 (0.47, 2.99)	<5	-	-
Public admin and defense, compulsory social security	448	7	0.31	0.31 (0.14, 0.68)	<5	-	-
Human health and social work activities	98	5	1.26	1.28 (0.50, 3.24)	<5	-	-

*Adjusted for paternal age and urban/rural residence status

-Estimates not provided for exposures with less than 5 exposed cases

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Table 3.

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

		All Retinoblastoma			Unilateral Retinoblastoma		
	Exposed Controls (N=2596)	**Exposed Cases (N=115)**	**Crude OR**	**Adjusted OR (95% CI)**	**Exposed Cases (N=94)**	**Crude OR**	**Adjusted OR (95% CI)**
Industry type							
Manufacturing	379	14	0.84	0.80 (0.45, 1.43)	10	0.95	0.93 (0.47, 1.85)
Wholesale and retail trade	302	16	1.21	1.16 (0.67, 1.99)	10	1.21	1.19 (0.60, 2.37)
Public admin and defense, compulsory social security	927	41	0.97	0.99 (0.66, 1.47)	28	1.07	1.10 (0.67, 1.79)
Human health and social work activities	498	24	1.07	1.13 (0.71, 1.81)	14	0.93	0.95 (0.52, 1.74)
Hospital and practitioner work	388	19	1.09	1.16 (0.70, 1.94)	12	1.04	1.07 (0.56, 2.03)
Other service activities	64	6	2.16	2.14 (0.89, 5.15)	<5	-	-

*Adjusted for maternal age and urban/rural residence status

-Estimates not provided for exposures with less than 5 exposed cases