Original article

Scand J Work Environ Health 2019;45(5):475-482

doi:10.5271/sjweh.3811

Risk of selected childhood cancers and parental employment in painting and printing industries: A register-based case−control study in Denmark 1968–2015

by Volk J, Heck JE, Schmiegelow K, Hansen J

This large nation-wide register-based study with objective exposure assessment found an increased risk of central nervous system (CNS) cancer in offspring whose mothers worked in both painting and printing industries. An increased risk of acute myeloid leukemia was found for fathers in both industries and of CNS cancers in offspring for fathers working in printing industries.

Affiliation: The Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark. julvol@cancer.dk

Key terms: cancer; case−control study; central nervous system cancer; childhood cancer; Danish Cancer Registry; leukemia; paint industry; painting; parental employment; parental occupation exposure; printing; printing industry; register study; register-based study; Supplementary Pension Fund

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/30838423

Scand J Work Environ Health. 2019;45(5):475–482. doi:10.5271/sjweh.3811

Risk of selected childhood cancers and parental employment in painting and printing industries: A register-based case–control study in Denmark 1968–2015

by Julie Volk, MD,[1] Julia E Heck, PhD,[2] Kjeld Schmiegelow, Dr Med Sci,[3] Johnni Hansen, PhD [1]

Volk J, Heck JE, Schmiegelow K, Hansen J. Risk of selected childhood cancers and parental employment in painting and printing industries: A register-based case–control study in Denmark 1968–2015. *Scand J Work Environ Health*. 2019;45(5):475–482. doi:10.5271/sjweh.3811

Objectives Parental exposures and offspring's risk of cancer have been studied with inconsistent results. We investigated parental employment in painting and printing industries and risk of childhood leukemia, central nervous system (CNS) cancers, and prenatal cancers (acute lymphoblastic leukemia, Wilms tumor, medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma).

Methods Using Danish registries, children aged ≤19 years diagnosed from 1968–2015 with leukemia (N=1999), CNS cancers (N=1111) or prenatal cancers (N=2704) were linked to parents and their employment history one year before birth to birth for fathers, and one year before birth to one year after for mothers. Twenty randomly selected controls per case were matched by age and sex. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using conditional logistic regression.

Results For fathers, we found increased risks for acute myeloid leukemia (AML) consistent in painting (OR 2.26, 95% CI 1.07–4.80) and printing industries (OR 2.43, 95% CI 0.94–6.23) and these industries combined (OR 2.10, 95% CI 1.14–3.87). For mothers, increased risks of CNS cancers were found for painting industries (OR 2.34, 95% CI 1.10–4.95) and painting and printing combined (OR 1.97, 95% CI 1.08–3.64). For fathers working in combined industries, the OR for CNS was increased (OR 1.54, 95% CI 1.02–2.31), most prominently in printing industries (OR 2.09, 95% CI 1.17–3.75).

Conclusion We observed increased risks of CNS tumors in offspring after parental employment in painting and printing industries. Children of fathers employed in painting and printing industries had a two-fold increase in AML.

Key terms central nervous system cancer; Danish Cancer Registry; leukemia; paint industry; parental occupation exposure; register-based study; register study; Supplementary Pension Fund.

The incidence of childhood cancer is increasing worldwide (1). Leukemia and central nervous system (CNS) tumors are the most common childhood cancers and some of the leading causes of death among children in the western world (2). Survivors face increased morbidity and mortality into adulthood (3) and causes remain almost unknown. Occupational exposure to several chemicals and complex mixtures are well-documented causes of cancer in adults, and parental exposure to potential carcinogens may contribute to several different types of childhood cancer (4). The potential impact of maternal exposure might occur either preconceptionally, during gestation, or after birth either through mutations to the gametes, direct or indirect exposure of the womb, or direct transmission of substances to the child (5). Research also suggests that paternal preconceptional environmental exposures could affect the offspring's risk of childhood cancer through epigenetic influences on sperm (6).

Exposures encountered in painting and printing industries are somewhat similar, and the International Agency for Research on Cancer (IARC) have classified them as group 1 and group 2B, respectively (7, 8).

In 2007, the IARC found positive associations between maternal exposure to painting and childhood leukemia, but this was based on a few studies (7). Fur-

1 Danish Cancer Society Research Centre, Copenhagen, Denmark.
2 UCLA Fielding School of Public Health, Department of Epidemiology, Los Angeles, CA, USA.
3 University Hospital Rigshospitalet, Department of Pediatrics and Adolescent Medicine, Copenhagen, Denmark.

Correspondence to: Julie Volk, The Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark. [E-mail: julvol@cancer.dk]

ther, positive associations between parental exposure to benzene, which has previously been a solvent or pollutant in some paints prior to the 1980s, has recently been associated with childhood acute myeloid leukemia (AML) (9). Somewhat inconsistent associations have been reported between occupation as a painter and in printing processes and childhood CNS cancers (4, 10–15). Thus, the small number of studies and inconsistent findings suggest further studies are warranted.

In epidemiologic studies, it is methodologically difficult to retrospectively assess prenatal occupational exposures in parents. A major common limitation in most existing studies of parental exposures and childhood cancer is the potential for recall bias when collecting exposure information after diagnosis and using proxy-informants, eg, mothers reporting on father's exposure. Further, most studies have focused on paternal occupational exposure, but increasingly maternal exposures are being studied. The aim of this study is to examine whether perinatal paternal and maternal employment in painting or printing industries, as well as the two industries combined, is associated with childhood leukemia, CNS tumors, and prenatal cancers by using reliable nationwide register-based employment data.

Methods

Cases ascertainment and control selection

In total, 8011 children with cancer, including leukemia (N=1999), CNS cancers (N=1111) and prenatal cancers (N=2704) were identified in the Danish Cancer Registry. Prenatal cancers covered several cancers thought to have originated prenatally [ie, acute lymphoblastic leukemia, Wilms tumor (nephroblastoma), medulloblastoma, neuroblastoma, retinoblastoma, and hepatoblastoma] (16, 17). Founded in 1942, the Danish Cancer Registry contains information on name, sex, date of birth, and date of diagnosis. It also holds information on topography and morphology based on the original notification forms using a conversion system from a Danish modification of International Classification of Diseases, Revision 7 (ICD-7) before 1978, a converted edition of ICD-7 to ICD-10 until 2004, and subsequently ICD-10 afterward (18). Further, the International Classification of Childhood Cancer (ICCC-1 and ICCC-3) also classified morphology and topography.

Children aged ≤19 years and diagnosed with cancer between 1968 and 2015 were included in the study, with the requirement that they were born in Denmark in order to have access to birth-related information and parental employment history around the time of birth. Information on place of birth was retrieved from the Civil Registration System, established in 1968, thus initiating the study period, by using the unique personal 10-digit identifier (CPR number) given to all permanent residents of Denmark. Information in this registry is kept regardless of changes to the individual's status (eg, death or emigration) providing a registry of very high quality (19). From this register, 20 controls per case were randomly chosen and matched on age and sex, who were free of cancer at the time of diagnosis of the index child.

Parental employment history

Family relationships can be ascertained by using the CPR number in the Civil Registration System and through record linkages, thus we were able to identify parents of both cases and controls. However, fathers of 0.65% of cases and 0.51% of controls could not be identified.

Information on paternal and maternal employment history was gathered by linkage to the Supplementary Pension Fund Register (in Danish: Arbejdsmarkedets Tillægspension, ATP), founded in 1964, which keeps records of mandatory pension contributions for all employees in Denmark aged 18–66 years; from 1978 also aged 16–17 years (20). This register keeps information on the name and CPR number of the employee as well as start and end dates of each employment. Information is preserved even in the event of closure of a company, retirement, emigration or death of employees. Each employer is identified through a unique 8-digit company number.

Each company is assigned an industry code (in Danish: Danmarks Statistiks Erhvervsgrupperingskode, DSE) that, until 1993, is a 5-digit Danish extension of UN International Standard Industrial Classification (ISIC) of all economic activities, revision 2, based on the economically most important activities of the company. A Danish 6-digit extension (in Danish: Dansk Branchekode, DB) of the four-digit European Union NACE classification was used from 2003–2007 and subsequently a revised version, DB-07, was introduced (20). All industry codes were transferred back to the original version, namely, DSE-77.

An expert on the working environment industry evaluated all codes, and employment was separated into painting and printing industries as classified by the DSE coding system. Painting industries included automobile paintings (95133), paint and varnish manufacture (35210), industrial painting (38196), building and home painting (50150), and paint and wallpaper shops (62131). Printing industries and corresponding to the DSE-77 code included various printing occupations (34220, 34221, 34222, 34223, 34224 and 34229). We examined parental employment in painting and printing industries separately and together. In order to capture the biologically relevant periods of preconception and the postnatal period when breastfeeding would occur, employment history for mothers were restricted to one year before and one year after birth. For fathers, the study period of interest was restricted to one year before birth to represent the period of spermatogenesis (21). Study subjects of parents without any employment during the time period of interest were excluded in order to reduce selection bias by making cases and controls more socio-economically comparable, ie, all employed. Results from initial analyses where non-working parents where included in the analyses did, however, only marginally change final results. After exclusion of mothers, 1643 (23.2%) leukemia cases, 905 (13.0%) cases of CNS cancer, and 2218 (35.0%) mothers of prenatal cancers remained in the study. The same exclusion criteria left 1736 (23.1%) fathers of leukemia cases, 956 (12.7%) fathers of CNS cancer cases, and 2362 (35.0%) fathers of prenatal cancers for analysis.

Covariates

Selection of covariates was based upon the literature (22–26) as well as our observations of associations in our data and included information on socioeconomic status (SES) at the family level, parental age at birth of index child, birth order and parity, and maternal smoking status. This information was obtained from the Civil Registration System apart from maternal smoking status, which was obtained from the Medical Birth Registry. This computerized registry was established in 1973, and midwives gathered information until 1996 when hospitals took over. This registry has undergone a major revision, which is why the accessibility of variables has changed over time (27).

SES was based on the highest level of education for either parent from the last known job title, taken from the latest available income tax form, and was categorized into six groups corresponding to the definition by the Danish Institute of Social Sciences. This categorization included academics or executive managers reflecting highest status group, higher education of intermediate duration, higher education of shorter duration, skilled work, unskilled work, and unknown (28).

Categories for covariates were defined as follows: parental age at birth of index child (≤25, 26–28, 29–33, ≥34 years), birth order (first, second, third or later), parity (1, 2, ≥3). Maternal smoking status was dichotomized from more detailed information (ever, never).

Statistical analyses

We used conditional logistic regression to estimate relative risks using odds ratios (OR) and their corresponding 95% confidence interval (95% CI) for paternal and maternal data separately. We considered adjustment for SES at the family level, parental age at birth of index child, birth order, and parity. The inclusion of these variables changed estimates by <10% and was therefore left out of final models.

Sensitivity analysis was performed for maternal smoking status as this variable was not available for the entire study period. Further, we examined the associations of parental employment from 1968–1980 compared to 1981–2015 to see whether the former period carried an increased risk due to different components of paints, dyes, and pigments in that period (7).

Stata version 14.2 (Stata Corp, College Station, TX, USA) was used for statistical analyses.

The Danish Data Protection Agency approved this study (No. 2008-41-2639, 2014-41-3174). No personal consent was needed as only register-based information was used.

Results

A larger proportion of children with cancer were boys than girls. Mothers of children with leukemia tended to have fewer children than mothers of healthy children. Fewer fathers of children with CNS cancer were in the oldest age category, while mothers of children with CNS cancer tended to be younger, and less likely to have unknown smoking status. Compared to control children, children with CNS cancer were more likely to be firstborn (table 1).

Offspring of fathers employed in painting and printing industries (combined analysis) had a twofold increased risk for AML (table 2). Further, similar-sized OR were observed when employment in painting and printing industries were separated (table 3).

We observed no increased risk for leukemia but did find a significant twofold increased relative risk for CNS in children of mothers employed in combined painting and printing industries (table 2).

A significantly increased relative risk of CNS cancers in offspring was seen for fathers in the combined industries (table 2) and for the subgroup employed in the printing industries (table 3).

Regarding CNS cancers, we found an increased relative risk of CNS for mothers working in painting industries, while an analysis was not feasible for printing industries due to the low number of exposed cases (table 3).

Analyses of cancers with a prenatal origin were not associated with increased relative risk for either parent (table 3).

In sensitivity analyses, results showed maternal smoking status was not associated with higher risk of

Table 1. Characteristics of the population.

	Leukemia				Central nervous system cancers			
	Mothers		Fathers		Mothers		Fathers	
	Cases N=1643	Controls N=29 835	Cases N=1736	Controls N=32 846	Cases N=905	Controls N=16 744	Cases N=956	Controls N=18 401
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Child's sex								
Male	901 (54.8)	16 608 (55.7)	957 (55.1)	18 153 (55.3)	483 (53.4)	8834 (52.8)	507 (53.0)	9735 (52.9)
Female	742 (45.2)	13 227 (44.3)	779 (44.9)	14 693 (44.7)	422 (46.6)	7910 (47.2)	449 (47.0)	8666 (47.1)
Birth order								
First	787 (47.9)	14 056 (47.1)	779 (44.9)	14 636 (44.5)	448 (49.5)	7910 (47.2)	450 (47.0)	8262 (44.9)
Second	602 (36.6)	11 044 (37.0)	659 (38.0)	12 498 (38.1)	333 (36.8)	6293 (37.6)	356 (37.4)	7049 (38.3)
Third or later	254 (15.5)	4735 (15.9)	298 (17.1)	5712 (17.4)	124 (13.7)	2541 (15.2)	150 (15.7)	3090 (16.8)
Family socioeconomic status								
Academics	147 (8.9)	2888 (9.7)	147 (8.5)	3170 (9.7)	100 (11.0)	1665 (9.9)	99 (10.4)	1768 (9.6)
Middle education	225 (13.7)	4181 (14.0)	229 (13.2)	4195 (12.8)	123 (13.6)	2515 (15.0)	121 (12.7)	2509 (13.6)
Shorter education	209 (12.7)	4052 (13.6)	209 (12.1)	4144 (12.6)	146 (16.1)	2590 (15.5)	148 (15.4)	2615 (14.2)
Skilled	421 (25.6)	7211 (24.2)	451 (26.1)	8221 (25.1)	228 (25.2)	4490 (26.8)	251 (26.2)	5099 (27.7)
Unskilled	199 (12.1)	3492 (11.7)	237 (13.6)	4219 (12.8)	102 (11.3)	2065 (12.3)	120 (12.6)	2556 (13.9)
Unknown	442 (26.9)	8011 (26.9)	463 (26.6)	8897 (27.0)	206 (22.8)	3419 (20.4)	217 (22.7)	3854 (20.9)
Parental age (years) at birth of the index child								
≤25	385 (23.4)	7507 (25.2)	216 (12.4)	4486 (13.7)	263 (29.1)	4619 (27.6)	146 (15.3)	2674 (14.5)
26–28	391 (23.8)	6952 (23.3)	331 (19.1)	6217 (18.9)	238 (26.3)	3993 (23.8)	197 (20.7)	3737 (20.3)
29–33	550 (33.5)	9983 (33.5)	618 (35.6)	11 523 (35.1)	265 (29.3)	5410 (32.3)	356 (37.2)	6563 (35.7)
≥34	317 (19.3)	5393 (18.1)	571 (32.9)	10 620 (32.3)	139 (15.4)	2722 (16.3)	257 (26.8)	5427 (29.5)
Child's birthplace								
Urban	514 (31.3)	9814 (32.9)	551 (31.8)	10 832 (33.0)	311 (34.4)	5388 (32.2)	320 (33.6)	5946 (32.3)
Small town	517 (31.5)	9259 (31.0)	547 (31.6)	10 542 (32.1)	278 (30.7)	5446 (32.5)	300 (31.5)	6142 (33.4)
Rural	612 (37.2)	10 762 (36.1)	638 (36.6)	11 472 (34.9)	316 (34.9)	5910 (35.3)	336 (34.9)	6313 (34.3)
Number of children								
1	360 (21.9)	6188 (20.7)			185 (20.4)	3066 (18.3)		
2	832 (50.6)	14 976 (50.2)			448 (49.5)	8601 (51.4)		
≥3	451 (27.4)	8671 (29.1)			272 (30.1)	5077 (30.3)		

Table 2. Odds ratios (OR) for offspring of mothers and fathers with employment in painting and printing industries.

	Mothers		Fathers	
	Exposed cases/ controls	OR (95% CI)	Exposed cases/ controls	OR (95% CI)
Leukemia	16/308	0.96 (0.58–1.61)	36/671	1.03 (0.73–1.45)
Acute lymphoblastic leukemia	12/246	0.89 (0.49–1.60)	19/513	0.70 (0.44–1.12)
Acute myeloid leukemia	* [a]		12/110	2.10 (1.14–3.87)
Central nervous system cancer	12/116	1.97 (1.08–3.61)	26/343	1.54 (1.02–2.31)
Astrocytoma	6/67	1.79 (0.76–4.17)	13/191	1.38 (0.78–2.46)
Medulloblastoma	* [a]		7/78	1.63 (0.74–3.56)
Prenatal cancer [b]	19/391	0.89 (0.56–1.41)	43/893	0.92 (0.67–1.25)

[a] N<5

[b] Cancer types with a prenatal origin: ALL, medulloblastoma, hepatoblastoma, retinoblastoma, nephroblastoma and neuroblastoma.

childhood leukemia or CNS cancers. Further, we found that employment from 1968–1980 was not associated with higher relative risk of childhood leukemia or CNS cancer compared to employment from 1980–2015 (table 4), with similar point estimates and overlapping CI.

For covariates used in analyses, we did not find that these factors changed results in crude compared to adjusted analysis.

Discussion

We conducted a nationwide nested case–control study of childhood leukemia and CNS cancers in relation to parental employment in painting and printing industries, using objective register-based data showing that both paternal and maternal employment in these industries increased the risk of CNS tumors. Further, fathers had a two-fold increased risk of AML after employment in both painting and printing industries, but no increased risk was observed in the offspring of mothers working in these industries. While our sample size was limited for specific cancer subtypes, our study was among the first to rely upon prospectively collected employment records, with a study design that included population-based controls and thus was not subject to recall biases or selective participation.

Around half of all childhood cancers are suggested as having emerged in utero (16), and our finding may be related to epigenetic changes, which are suggested as a potential underlying biological mechanism for certain childhood cancers (29). These proposed mechanisms may differ for mothers and fathers. Over a lifetime, maternal exposures can accumulate in the fixed number of ova present at birth. Exposures can be transferred

Table 3. Odds ratios (OR) for offspring of mothers and fathers with employment in painting versus printing industries.

	Mothers				Fathers			
	Painting industries		Printing industries		Painting industries		Printing industries	
	Exposed cases / controls	OR (95% CI)	Exposed cases / controls	OR (95% CI)	Exposed cases / controls	OR (95% CI)	Exposed cases / controls	OR (95% CI)
Leukemia	9/156	1.05 (0.53–2.08)	7/153	0.83 (0.39–1.79)	29/416	1.34 (0.91–1.96)	8/255	0.60 (0.29–1.21)
Acute lymphoblastic leukemia	6/128	0.83 (0.36–1.89)	6/119	0.92 (0.40–2.10)	17/325	1.00 (0.61–1.64)	* [a]	
Acute myeloid leukemia	* [a]		* [a]		8/69	2.26 (1.07–4.80)	5/41	2.43 (0.94–6.23)
Central nervous system cancer	8/59	2.34 (1.10–4.95)	* [a]		13/219	1.20 (0.68–2.12)	13/124	2.09 (1.17–3.75)
Astrocytoma	* [a]		* [a]		7/120	1.20 (0.55–2.60)	6/71	1.64 (0.70–3.83)
Prenatal cancer [b]	12/205	1.03 (0.57–1.86)	7/187	0.69 (0.32–1.47)	30/546	1.05 (0.72–1.52)	13/347	0.72 (0.41–1.25)

[a] N<5.

[b] Cancer types with a prenatal origin: ALL, medulloblastoma, hepatoblastoma, retinoblastoma, nephroblastoma and neuroblastoma.

Table 4. Odds ratios (OR) for offspring born before and after 1980 of mothers and fathers with employment in painting and printing industries.

	Mothers				Fathers			
	Born before 1980		Born after 1980		Born before 1980		Born after 1980	
	Exposed cases / controls	OR (95% CI)	Exposed cases / controls	OR (95% CI)	Exposed cases / controls	OR (95% CI)	Exposed cases / controls	OR (95% CI)
Leukemia	7/100	1.15 (0.53–2.52)	9/208	0.83 (0.42–1.64)	16/278	1.05 (0.63–1.75)	20/393	1.01 (0.64–1.59)
Central nervous system cancer	* [a]		9/86	1.96 (0.97–3.93)	12/146	1.65 (0.90–3.01)	14/ 197	1.45 (0.83–2.52)

[a] N<5.

directly to the child through the placenta, or via lactation (30). For fathers, genetic changes are thought to be transferred in the sperm, and morphological changes in sperm have been seen after use of paint stripper, but not paint, but whether this has a clinical impact on the offspring is not yet known (31). Thus, preconceptional exposure could be a plausible biological mechanism. As prenatal cancers were not associated with increased risks in our study, perhaps postnatal exposure is of more relevance, but extension of the study period for fathers to also include one year after birth led to minor changes to most results.

Paternal employment as a painter and risk of childhood AML was investigated in Bailey et al's meta- and pooled analysis (32) and a subsequent study (33), neither of which supported our positive association. For CNS cancers, the largest available study investigating risk used proportional mortality rate in offspring of fathers employed as painters. The study used information from death records to assess exposure and did not find a positive association (34). The use of death certificates may introduce bias in part because survival rates were lower during the study period than current rates. Yet, several smaller studies, where exposure was established mainly by interviews, often found increased OR and wide CI due to the small number of exposed cases (10, 14, 35–38). For printing industries, the largest study of 103 exposed fathers did not find an increased risk (13), and several smaller studies demonstrated inconsistent results (10, 12, 15, 36, 38). Two of the studies have grouped several hydrocarbon-related occupations (36, 38) and risk estimates are thus not restricted to occupation in our selected industries, which might obscure a possible positive effect. While interview-based studies may contain more detailed information on exposure than register-based studies, these studies may be subject to selective participation.

In opposition to the IARC's evaluation on maternal employment as a painter, we did not find an increased relative risk of leukemia cancers in offspring. However, the evaluation was based on four studies investigating maternal exposure, including one study on household painting. One study did not mention the number of exposed cases, while the remaining three included 53–160 exposed case mothers. To our knowledge, no studies have had a sufficient number of exposed cases to conduct analyses of the potential effects of maternal employment as a painter in relation to CNS cancers. This may be explained by the lower frequency of women of the childbearing age in the workforce in many other countries and of women working in this industry in particular. Since the 1960s, Danish women have had a high rate of employment, and, in 2015, 70.1% of women worked outside the home (39) with around 1% employed in the industries of interest in this study. This represents among the higher female employment rates internationally.

Parental leave in Denmark, and therefore exposure time, changed across the study period, which might have induced exposure misclassification. Additionally, job adjustment or absence due to working conditions not being acceptable during pregnancy or pregnancy-related sickness could also influence exposure encountered during pregnancy; for example, a mother who was not physically able to paint might be assigned a different job task during her pregnancy, however, this would not change her job industry, and therefore she would still be listed as a painter and thereby exposed in our study. No registries directly record what proportion of mothers are reassigned during pregnancy, but estimates vary from 35 to 48% (38). Hence, during the later study period (2002 and onwards) maternal early postnatal exposure would have been rare; however, excluding the postnatal period changed risk estimates only minimally. Thus, the maternal exposures that we examined were likely to represent first and second trimester and possibly early third trimester exposures; this is also presumably the most vulnerable period for the fetus due to the timing of organogenesis. For fathers, we expect the biologically important period to be preconception. Since paternity leave is of short duration, we do not expect this to have affected our results.

Both industries involve complex exposures to several chemicals, including in particular volatile organic solvents, pigments and dyes, which makes separating between specific exposures impossible (7, 8). Parental exposure to volatile organic solvents has previously been associated with childhood leukemia and CNS cancers (40, 41). Moreover, household exposure to paints has previously been shown to be associated with specific cytogenic subtypes of *all* children (42). Thus, many different components could potentially impact relative risk estimates.

Further, we initially created two exposure periods to reflect changes in exposure before 1980 compared to after. Yet only minor changes in risk estimates were found, and further exploration of potential changes was not feasible due to the relatively few exposed cases and controls. Identification of individual tasks performed was not possible using register-based data.

Despite including all nationwide cases over a 47-year period, limitations of this study also include the relatively low number of exposed cases due to the disease being rare. Even though employment rates remained stable throughout the period, a relatively small proportion of parents were employed in these industries. Additionally, not all potential confounding factors were available for study for the entire study period. Further, our study used pension fund records to determine exposure thereby eliminating recall bias, but possibly introducing misclassification bias as a uniform exposure at the industrial level is assumed. Also, as industry codes are used for exposure classification, a few white-collar workers might be misclassified as exposed to paints and printing. This may have led to an underestimation of potential effects of parental employment in relation to the selected childhood cancers. We did not compare exposed cases to other blue-collar workers not exposed to solvents as controls, as this could have introduced unpredictable confounding from unknown exposures potentially associated with childhood cancer, eg, dusts, air pollution, social contacts, pesticides, etc.

Major strengths of the study are use of national register-based data and the objective and prospective assessment of employment history (20), thereby eliminating participation and recall bias. In addition, the registries used have a high degree of completeness and are generally of high quality (18–20, 27). The personal identifier allows correct linkages between the registers and excludes counting the same case more than once, and further secures access to various potential confounders.

Concluding remarks

Our results showed an increased risk for CNS cancers in offspring of mothers and fathers employed in painting as well as painting and printing industries. For fathers, also a positive association was present between AML and employment in both painting and printing industries. In contrast to the IARC's evaluation on maternal employment as a painter, we did not find an increased relative risk of leukemia cancers in offspring.

Conflicts of interest

None declared.

References

1. Steliarova-Foucher E, Colombet M, Ries LA, Moreno F, Dolya A, Bray F et al.; IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol 2017 Jun;18(6):719–31. https://doi.org/10.1016/S1470-2045(17)30186-9.

2. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev 2010 Jun;36(4):277–85. https://doi.org/10.1016/j.ctrv.2010.02.003.

3. Galligan AJ. Childhood Cancer Survivorship and Long-Term Outcomes. Adv Pediatr 2017 Aug;64(1):133–69. https://doi.org/10.1016/j.yapd.2017.03.014.

4. Colt JS, Blair A. Parental occupational exposures and risk of childhood cancer. Environ Health Perspect 1998 Jun;106 Suppl 3:909–25.

5. Anderson LM, Diwan BA, Fear NT, Roman E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 2000 Jun;108 Suppl 3:573–94.

6. Braun JM, Messerlian C, Hauser R. Fathers Matter: Why

It's Time to Consider the Impact of Paternal Environmental Exposures on Children's Health. Curr Epidemiol Rep 2017 Mar;4(1):46–55. https://doi.org/10.1007/s40471-017-0098-8.

7. Painting, firefighting, and shiftwork. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. 2010;98:9–764.

8. Printing processes and printing inks, carbon black and some nitro compounds. Lyon, France, 10-17 October 1995. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. 1996;65:33–495.

9. Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L et al.; International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of benzene. Lancet Oncol 2017 Dec;18(12):1574–5. https://doi.org/10.1016/S1470-2045(17)30832-X.

10. McKinney PA, Fear NT, Stockton D; UK Childhood Cancer Study Investigators. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. Occup Environ Med 2003 Dec;60(12):901–9. https://doi.org/10.1136/oem.60.12.901.

11. Greenop KR, Peters S, Fritschi L, Glass DC, Ashton LJ, Bailey HD et al. Exposure to household painting and floor treatments, and parental occupational paint exposure and risk of childhood brain tumors: results from an Australian case-control study. Cancer Causes Control 2014 Mar;25(3):283–91. https://doi.org/10.1007/s10552-013-0330-x.

12. Cordier S, Lefeuvre B, Filippini G, Peris-Bonet R, Farinotti M, Lovicu G et al. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). Cancer Causes Control 1997 Sep;8(5):688–97. https://doi.org/10.1023/A:1018419118841.

13. Keegan TJ, Bunch KJ, Vincent TJ, King JC, O'Neill KA, Kendall GM 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 May;108(9):1907–14. https://doi.org/10.1038/bjc.2013.171.

14. Feychting M, Plato N, Nise G, Ahlbom A. Paternal occupational exposures and childhood cancer. Environ Health Perspect 2001 Feb;109(2):193–6. https://doi.org/10.1289/ehp.01109193.

15. Kuijten RR, Bunin GR, Nass CC, Meadows AT. Parental occupation and childhood astrocytoma: results of a case-control study. Cancer Res 1992 Feb;52(4):782–6.

16. Marshall GM, Carter DR, Cheung BB, Liu T, Mateos MK, Meyerowitz JG et al. The prenatal origins of cancer. Nat Rev Cancer 2014 Apr;14(4):277–89. https://doi.org/10.1038/nrc3679.

17. von Schweinitz D. Neonatal liver tumours. Semin Neonatol 2003 Oct;8(5):403–10. https://doi.org/10.1016/S1084-2756(03)00092-7.

18. Gjerstorff ML. The Danish cancer registry. Scand J Public Health 2011 Jul;39(7 Suppl):42–5. https://doi.org/10.1177/1403494810393562.

19. Pedersen CB, Gøtzsche H, Møller JØ, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006 Nov;53(4):441–9.

20. Hansen J, Lassen CF. The supplementary pension fund register. Scand J Public Health 2011 Jul;39(7 Suppl):99–102. https://doi.org/10.1177/1403494810394716.

21. Wilcox AJ. Fertility and Pregnancy An Epidemiologic Perspective: Oxford University Press; 2010.

22. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. Cancer Epidemiol 2017 Aug;49:202–15. https://doi.org/10.1016/j.canep.2017.06.010.

23. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 2001 Dec;30(6):1428–37. https://doi.org/10.1093/ije/30.6.1428.

24. Schüz J, Luta G, Erdmann F, Ferro G, Bautz A, Simony SB et al. Birth order and risk of childhood cancer in the Danish birth cohort of 1973-2010. Cancer Causes Control 2015 Nov;26(11):1575–82. https://doi.org/10.1007/s10552-015-0651-z.

25. Momen NC, Olsen J, Gissler M, Li J. Exposure to maternal smoking during pregnancy and risk of childhood cancer: a study using the Danish national registers. Cancer Causes Control 2016 Mar;27(3):341–9.

26. Huang Y, Huang J, Lan H, Zhao G, Huang C. A meta-analysis of parental smoking and the risk of childhood brain tumors. PLoS One 2014 Jul;9(7):e102910. https://doi.org/10.1371/journal.pone.0102910.

27. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998 Jun;45(3):320–3.

28. Hansen EJ. Socialgrupper i Danmark Socialforskningsinstituttet [Social groups in Denmark]. Copenhagen: The Danish National Institute of Social Research; 1984.

29. Burgio E, Piscitelli P, Colao A. Environmental Carcinogenesis and Transgenerational Transmission of Carcinogenic Risk: From Genetics to Epigenetics. Int J Environ Res Public Health 2018 Aug;15(8):E1791. https://doi.org/10.3390/ijerph15081791.

30. Madhavan ND, Naidu KA. Polycyclic aromatic hydrocarbons in placenta, maternal blood, umbilical cord blood and milk of Indian women. Hum Exp Toxicol 1995 Jun;14(6):503–6. https://doi.org/10.1177/096032719501400607.

31. Cherry N, Povey AC, McNamee R, Moore H, Baillie H, Clyma JA et al.; participating centres of CHAPS-UK. Occupation exposures and sperm morphology: a case-referent analysis of a multi-centre study. Occup Environ Med 2014 Sep;71(9):598–604. https://doi.org/10.1136/oemed-2013-101996.

32. Bailey HD, Fritschi L, Metayer C, Infante-Rivard C, Magnani C, Petridou E et al. Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International

Scan

Consortium. Cancer Causes Control 2014 Oct;25(10):1351–67. https://doi.org/10.1007/s10552-014-0441-z.

33. Metayer C, Scelo G, Kang AY, Gunier RB, Reinier K, Lea S et al. A task-based assessment of parental occupational exposure to organic solvents and other compounds and the risk of childhood leukemia in California. Environ Res 2016 Nov;151:174–83. https://doi.org/10.1016/j.envres.2016.06.047.

34. Sanders BM, White GC, Draper GJ. Occupations of fathers of children dying from neoplasms. J Epidemiol Community Health 1981 Dec;35(4):245–50. https://doi.org/10.1136/jech.35.4.245.

35. Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H. Childhood cancer and parental occupation in Finland. J Epidemiol Community Health 1981 Mar;35(1):11–5. https://doi.org/10.1136/jech.35.1.11.

36. Hakulinen T, Salonen T, Teppo L. Cancer in the offspring of fathers in hydrocarbon-related occupations. Br J Prev Soc Med 1976 Jun;30(2):138–40.

37. Cordier S, Mandereau L, Preston-Martin S, Little J, Lubin F, Mueller B et al. Parental occupations and childhood brain tumors: results of an international case-control study. Cancer Causes Control 2001 Nov;12(9):865–74. https://doi.org/10.1023/A:1012277703631.

38. Johnson CC, Annegers JF, Frankowski RF, Spitz MR, Buffler PA. Childhood nervous system tumors--an evaluation of the association with paternal occupational exposure to hydrocarbons. Am J Epidemiol 1987 Oct;126(4):605–13. https://doi.org/10.1093/oxfordjournals.aje.a114700.

39. Kvinder og mænd i 100 år - fra lige valgret mod ligestilling [Women and men in 100 years – from equal votes towards gender equality]. Available from: http://www.dst.dk/Site/Dst/Udgivelser/GetPubFile.aspx?id=22699&sid=kvind. Danmarks Statistik; 2015

40. Infante-Rivard C, Siemiatycki J, Lakhani R, Nadon L. Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect 2005 Jun;113(6):787–92. https://doi.org/10.1289/ehp.7707.

41. Peters S, Glass DC, Greenop KR, Armstrong BK, Kirby M, Milne E et al. Childhood brain tumours: associations with parental occupational exposure to solvents. Br J Cancer 2014 Aug;111(5):998–1003. https://doi.org/10.1038/bjc.2014.358.

42. Scélo G, Metayer C, Zhang L, Wiemels JL, Aldrich MC, Selvin S et al. Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. Environ Health Perspect 2009 Jan;117(1):133–9. https://doi.org/10.1289/ehp.11927.

Received for publication: 11 December 2018