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Parental Occupational Exposure to Benzene and the Risk of Childhood and Adolescent Acute Lymphoblastic Leukemia: a Population-Based Study

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ABSTRACT

Objectives Only a small number of studies have reported on the association of parental occupational exposure to benzene and risk of childhood and adolescent leukemias. We examined associations with acute lymphoblastic leukemia (ALL) in this population-based study in Denmark.

Methods Benzene was largely banned from Danish workplaces after 1975, thus this case-control study focused on the immediately prior years. Pediatric cancer cases (< age 20) were ascertained from the Danish Cancer Registry among children born 1968-1974, and controls were selected from population records. Paternal occupation within the 3 months preconception and maternal pregnancy occupation were identified from nationwide pension fund records. Blinded, we assigned benzene exposure using a job-exposure matrix that had been developed for the Danish population. Risk for ALL was estimated using conditional logistic regression. In an exploratory analysis, we also examined other cancers with at least 5 case parents exposed.

Results We identified 217 employed case fathers and 169 employed case mothers, of which 22 (10.1%) and 11 (6.5%), respectively, were exposed to benzene (vs. 6.7% and 2.9% of control fathers and mothers). Most exposed parents worked as machine or engine mechanics, or in the shoe industry. Maternal occupational exposure to benzene in pregnancy was related to increased risk of ALL in offspring (adjusted OR=2.28, 95% CI 1.17, 4.41), while paternal preconceptional benzene exposure was not as strongly associated (adjusted OR=1.40, 95% CI 0.88, 2.22).

Conclusions Our study supports an increased risk for ALL with parental occupational benzene exposure.

INTRODUCTION

Benzene has been encountered in a variety of occupational settings as an organic solvent and in engine exhaust originating from 1-5% levels in gasoline. The International Agency for Research on Cancer classified benzene as carcinogenic to humans (Group 1) based upon increased risk of acute myeloid leukemia in adults.[1] Childhood and adolescent acute lymphoblastic leukemia (ALL) has been studied less frequently, and results were mixed (OR range: mothers 0.5–2.6; fathers 0.8–2.0).[2-5] One study was population-based, using record-linkage of national registries,[5] while the other studies collected data from parental interviews. Most of these studies applied job-exposure matrices (JEMs) to assess exposure, while one relied on parental recall of chemicals encountered at work. As such, some previous findings may have been subject to recall bias or selective participation. Further, few studies had adequate specificity of exposure assessment to identify a potential effect from benzene independent of exposure to other chemicals; this is relevant given that persons exposed to benzene also may have high exposure to toluene and other agents. We sought to examine ALL risk from parental occupational exposure to benzene in a population-based study in which exposure was objectively estimated by expert assessment.

METHODS

As previously described,[6] we identified incident cases of ALL less than 20 years of age from the Danish Cancer Registry, then randomly selected controls among those matched by sex and age (25:1 matching rate) from the source population. Parental occupations during the perinatal period were identified from the Supplementary Pension Fund,[7] a compulsory supplement to the state pension for all employed persons age 18-66. The Supplementary Pension Fund records the start and end dates of all paid jobs along with the industry code, a 5-digit extended version of the

International Standard Industrial Classification of All Economic Activities. All information is maintained by the Supplementary Pension Fund even when businesses close or in the case of a person's death. Occupations with benzene exposure (ever/never exposed) were identified using the Danish version of the Nordic Occupational Cancer Study job-exposure matrix.[8] Because workplace benzene use began to drop prior to the first study year and our JEM assigned few workplace benzene exposures after 1975, we limited analyses to children born 1968-1974. Human subjects approvals for this study were received from the Danish Data Protection Board and the University of California, Los Angeles.

We excluded from the present analysis parents without records of employment (stay-at-home parents, students, and self-employed persons, whose records are not in the Pension Fund) during the perinatal period (23% of case fathers and 40% of case mothers). However, we conducted a sensitivity analysis to evaluate the effect of excluding these parents, in which we considered these parents as unexposed. Blinded to case-control status, we estimated risk of ALL from parental occupational exposure to benzene, examining fathers' exposures in the three months preconception and maternal exposures in pregnancy. Gestational age information was taken from the Medical Births Registry as previously described.[6] We did not estimate cancer risk from both parents being occupationally exposed to benzene, because this was extremely rare.

We estimated odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression with adjustment for parental ages and socioeconomic status. Inclusion of parental age in models was based on the literature as well as associations seen in our data.[6] We additionally considered adjustment for socioeconomic status because it was related to the exposure. We were

not able to adjust for maternal smoking because it was not collected during the time period of interest; however a recent study of Danish children, based on the same national registries, did not report any increased risk of ALL from smoking.[9] Further, adjustment for socioeconomic status will also partly adjust for smoking. We additionally examined associations after the exclusion of children with Down syndrome.

Because benzene was highly correlated with toluene [1] we could not easily determine whether any observed associations with benzene might also have been due to toluene. As such we separately examined the risk of ALL from occupational toluene exposure during the time period immediately after benzene use was largely phased out (1975-1984).

In an exploratory analysis we also examined other cancer types with at least 5 exposed cases. There were 6 (8.6%) exposed astrocytoma case fathers, 10 (10.9%) exposed fathers of germ cell tumor cases, and 5 (22.7%) exposed case fathers of a rare leukemia subtype, acute undifferentiated leukemia/acute leukemia not otherwise specified [NOS; International Classification of Diseases for Oncology (ICD-O-1) code 98013]. All analyses were done using SAS (Cary, NC).

RESULTS

We observed excesses of ALL for maternal exposure to benzene in pregnancy (Table 1). With regards to paternal preconception exposure, ORs were elevated with wide confidence intervals. The parents in our study exposed to benzene were most often employed as machine and engine mechanics, with smaller numbers employed in laboratory settings, in the shoe industry, or in

Table 1. Parental Occupational Exposure to Benzene and Risk of Childhood Acute Lymphoblastic Leukemia Among Children born 1968-1974					
	N Exposed/total cases	**N Exposed/total controls**	**Crude OR**	**Adjusted OR[a] (95% CI)**	**Adjusted OR[b] (95% CI)**
Father's occupations in 3 months preconception					
Any occupation with benzene exposure	22/217 (10.1%)	400/5233 (6.7%)	1.42 (0.89, 2.24)	1.42 (0.90, 2.25)	1.40 (0.88, 2.22)
Mother's occupations during pregnancy					
Any occupation with benzene exposure	11/169 (6.5%)	112/3905 (2.9%)	2.28 (1.18, 4.39)	2.31 (1.19, 4.63)	2.28 (1.17, 4.41)

a. Adjusted for maternal and paternal age

b. Adjusted for maternal and paternal age and family socioeconomic status

OR, Odds Ratio; CI, Confidence Interval.

other manufacturing (Supplementary Table 1). The exclusion of children with Down syndrome did not change results appreciably (Supplementary Table 2). When we considered parents without employment records as unexposed to benzene and included them in analyses, results did not change (Supplementary Table 3).

In examining the association of exposure to toluene between 1975-1984 and risk of ALL, we did not observe associations between ALL and paternal preconception toluene exposure (Supplementary Table 4; adjusted OR=1.14, 95% CI 0.78, 1.68) nor maternal pregnancy toluene exposure (adjusted OR=0.57, 95% CI 0.23, 1.41).

Paternal benzene exposure was not clearly related to astrocytoma (Supplementary Table 5; adjusted OR=1.29, 95% CI 0.54, 3.06), germ cell tumors (adjusted OR=1.37, 95% CI 0.69, 2.71), but was related to acute undifferentiated leukemia/acute leukemia NOS (adjusted OR=6.11, 95% CI 1.81, 20.61).

DISCUSSION

In this population-based study in which parental occupational benzene exposure was assessed via job-exposure matrix, we observed increases in ALL with maternal exposure to benzene in pregnancy. In Denmark and internationally, the proportion of benzene in gasoline has dropped considerably over the last decades, with current European Union regulations limiting benzene to less than 1% of gasoline.[1] In Denmark, its use as a solvent in other occupational settings was phased out by the mid-1970s. Workplace exposures are expected to have been considerably more widespread in the 1950's and 1960's, prior to the study period.[1]

Our results are in line with most other studies on maternal [2 3 5] and paternal[3-5] occupational benzene and ALL which showed increased effect estimates for the pregnancy period and preconception. Of the studies that examined maternal exposures, most relied on parental interview [2-4] while one utilized parental occupation as listed on census records and linked to cancer registry data.[5] Point estimates were elevated across most studies, although confidence intervals were often wide due to small numbers of exposed parents. Not all studies showed increases in risk, but results may have been influenced by the use of proxy respondents (usually the mother

reporting on father's exposures), moderate participation rates, or unequal socioeconomic distributions between case and control groups.

The preconception and pregnancy periods are plausibly relevant time periods to examine the influence of parental exposures. ALL is likely initiated in utero, as shown by studies of neonatal dried blood spots which have identified ALL-related leukocyte chromosomal translocations in children who later developed leukemia.[10] Benzene metabolites induce genomic instability and a variety of chromosomal aberrations,[1] thus it is feasible that they could cause the characteristic translocations seen in ALL.

We did not attempt to assess narrower time periods of exposure (e.g. trimesters) since few parents changed jobs during pregnancy. In the 1970s, maternity leave in Denmark officially began eight weeks prior to the expected due date, although in practice it could have started earlier if the mother's health concerns necessitated it. Thus, the maternal benzene exposures that we estimated would have occurred primarily in the first and second trimesters. Although benzene metabolites can be transferred in breast milk, exposure level would have likely dropped after birth during maternity leave and because in the late 1960's and early 1970's, half of all Danish mothers stayed home with their small children.[11] Families would have had other sources of benzene exposure due to traffic exhaust and because European Union directives restricting benzene concentration in toys did not occur until 1982 (Directive 82/806/EEC).

Advantages of this study include the record-based, population-based design with the inclusion of all cancer cases born and diagnosed in Denmark during the time period of interest, thus without selection bias. We used a validated job-exposure matrix to assess exposures. Our reliance on employment records with the start and end dates of each position meant our study was not subject to recall bias. A limitation of our study is that the use of a job-exposure matrix will inherently introduce non-differential misclassification of exposure, which may bias results towards the null. The small numbers of exposed parents preluded us examining dose-response in results.

In sum, we observed increases in ALL risk among children whose parents were occupationally exposed to benzene. Given evidence of a linear association between ambient benzene exposure and childhood and adolescent leukemia,[12] it is justified to reduce occupational benzene exposures.

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Contributorship

JEH conceived, designed the presented work, and drafted the article. JH acquired and linked data. DH and ZAC performed the data analysis and interpretation. JH, JO, BR provided critical revision comments of the article. All authors reviewed results, commented on the manuscript, and approved of the final version to be published.

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Competing interests

The authors report no conflicts of interest.

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Supplementary Table 1. Parental Occupations with Benzene Exposure as Determined by Job-Exposure Matrix

	Job Code	ALL (N)	Controls (N)
Father's occupation in the 3 months preconception			
Chemists	35119	1	6
Laboratory assistants	83245	0	7
Service station attendants	62213	1	13
Upholsterers	33202	0	0
Leather cutters for footwear	61164 62158 62159 95110	0	1
Shoe sewers	95110 32401 32409	1	2
Lasters and sole fitters	32310 32330 32401 32402 32409 61164	1	4
Footwear workers	32401 32409	1	1
Machine and engine mechanics	38210 38220 38231 38232 38241 38242 38243 38249 38251 38280 38290 38291 38293 38294 38298 38299 38413 38431 61180 61181 61182 61183 61184 61185 61189	17	285
Painters, lacquerers and floor layers	35210 38196 39097 50150 50191 95133	2	82
Printers	34221 34222 34223	0	0
Occupations in graphics	34223 34299 38520	0	0
Cookers and furnacemen (chemical processes)	35119	1	6
Refinery workers, other occupations in the chemical industry	31151	0	3
Rubber products workers	35590	1	2
Laundry workers	95200	0	0
Mother's occupations during pregnancy			
Chemists	35119	0	1
Laboratory assistants	83245	0	4
Service station attendants	62213	0	3
Upholsterers	33202	0	1
Leather cutters for footwear	61164 62158 62159 95110	1	5
Shoe sewers	95110 32401 32409	2	13
Lasters and sole fitters	32310 32330 32401 32402 32409 61164	2	19
Footwear workers	32401 32409	2	13

Machine and engine mechanics	38210 38220 38231 38232 38241 38242 38243 38249 38251 38280 38290 38291 38293 38294 38298 38299 38413 38431 61180 61181 61182 61183 61184 61185 61189	7	66
Painters, lacquerers and floor layers	35210 38196 39097 50150 50191 95133	1	7
Printers	34221 34222 34223	0	0
Occupations in graphics	34223 34299 38520	0	0
Cookers and furnacemen (chemical processes)	35119	0	1
Refinery workers, other occupations in the chemical industry	31151	0	0
Rubber products workers	35590	0	6
Laundry workers	95200	0	0

ALL, Acute Lymphoblastic Leukemia

Supplementary Table 2. Parental Occupational Exposure to Benzene and Risk of Childhood ALL Among Children born 1968-1974, after exclusion of children with Down syndrome

	N Exposed/total cases	N Exposed/total controls	Crude OR	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Father's occupations in 3 months preconception					
Any occupation with benzene exposure	21/214 (9.8%)	400/5231 (7.7%)	1.37 (0.86, 2.19)	1.37 (0.86, 2.19)	1.36 (0.85, 2.17)
Mother's occupations during pregnancy					
Any occupation with benzene exposure	11/167 (6.6%)	112/3903 (2.9%)	2.28 (1.18, 4.39)	2.30 (1.19, 4.46)	2.27 (1.17, 4.41)

a. Adjusted for maternal and paternal age
b. Adjusted for maternal and paternal age and family socioeconomic status

OR, Odds Ratio; CI, Confidence Interval; ALL, Acute Lymphoblastic Leukemia.

Supplementary Table 3. Parental Occupational Exposure to Benzene and Risk of Childhood ALL Among Children born 1968-1974, including unemployed parents among the unexposed

	N Exposed/total cases	N Exposed/total controls	Crude OR	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Father's occupations in 3 months preconception					
Any occupation with benzene exposure	22/282 (7.8%)	400/7050 (5.7%)	1.41 (0.90, 2.20)	1.43 (0.91, 2.23)	1.41 (0.90, 2.21)
Mother's occupations during pregnancy					
Any occupation with benzene exposure	11/282 (3.9%)	112/7050 (1.6%)	2.53 (1.34, 4.77)	2.59 (1.37, 4.89)	2.55 (1.35, 4.81)

a. Adjusted for maternal and paternal age
b. Adjusted for maternal and paternal age and family socioeconomic status
OR, Odds Ratio; CI, Confidence Interval; ALL, Acute Lymphoblastic Leukemia.

Supplementary Table 4. Parental Occupational Exposure to Toluene and Risk of Acute Lymphoblastic Leukemia, among Children born 1975-1984

	N Exposed/total cases	N Exposed/total matched controls	Crude OR	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Father's exposure in 3 months preconception					
Any occupation with toluene exposure	33/273 (12.1%)	706/6497 (10.9%)	1.13 (0.78, 1.65)	1.14 (0.78, 1.67)	1.14 (0.78, 1.68)
Maternal exposure in pregnancy					
Any occupation with toluene exposure	5/244 (2.1%)	207/5845 (3.5%)	0.56 (0.23, 1.39)	0.58 (0.23, 1.42)	0.57 (0.23, 1.41)

a. Adjusted for maternal and paternal age

b. Adjusted for maternal and paternal age and family socioeconomic status

OR, Odds Ratio; CI, Confidence Interval; ALL, Acute Lymphoblastic Leukemia.

Supplementary Table 5. Paternal Occupational Exposure to Benzene and Risk of non-ALL Childhood Cancers, among Children born 1968-1974

	N Exposed/total cases	N Exposed/total matched controls	Crude OR	Adjusted OR[a] (95% CI)	Adjusted OR[B] (95% CI)
Father's occupational exposure in 3 months preconception					
Acute undifferentiated leukemia/Acute leukemia NOS (ICD-O-1 code 98013)	5/22 (22.7%)	33/575 (5.7%)	5.70 (1.84, 17.68)	5.77 (1.83, 18.17)	6.11 (1.81, 20.61)
Astrocytoma	6/70 (8.6%)	139/1874 (7.4%)	1.21 (0.51, 2.84)	1.22 (0.52, 2.89)	1.29 (0.54, 3.06)
Germ cell tumors	10/92 (10.9%)	158/2101 (7.5%)	1.42 (0.72, 2.79)	1.43 (0.73, 2.81)	1.37 (0.69, 2.71)

a. Adjusted for maternal and paternal age

b. Adjusted for maternal and paternal age and family socioeconomic status

OR, Odds Ratio; CI, Confidence Interval; ALL, Acute Lymphoblastic Leukemia.