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Occupational livestock or animal dust exposure and offspring cancer risk in Denmark, 1968-2016

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Abstract

Objective: To examine associations with occupational livestock or other animal dust exposure and offspring cancer risk.

Methods: In this population-based case-control study of Danish children aged <17 years old, 5,078 childhood cancer cases diagnosed 1968-2016 were matched to cancer-free controls by birth year and sex (n=123,228). Occupational livestock or animal dust exposure was identified using a job-exposure matrix. We employed multivariable conditional logistic regression models to estimate associations with offspring cancer for births 1968-2016 and 1989-2016, with the latter timeframe reflecting a period of presumed higher exposure due to changes in Danish farming practices. Sensitivity analyses considered place of birth (urban areas vs. rural areas and small towns).

Results: For births 1968-2016, paternal exposure from offspring birth to cancer diagnosis was associated with central nervous system tumors (adjusted odds ratio [OR]=1.30, 95% confidence interval [CI]=1.04-1.63) and germ cell tumors (OR=1.82, 95% CI=1.05-3.27), while maternal pregnancy exposure was associated with astrocytoma (OR=1.89, 95% CI=1.00-3.57). For births 1989-2016, paternal exposure from offspring birth to cancer

diagnosis was negatively associated with acute lymphoid leukemia (OR=0.58, 95% CI=0.33-1.00). For births in rural areas only, maternal exposure from offspring birth to cancer diagnosis was positively associated with acute myeloid leukemia (OR=2.16, 95% CI=1.09-4.29).

Conclusions: This study suggests that paternal occupational animal exposure is associated with offspring germ cell tumors, and maternal pregnancy exposure with astrocytomas. Our results are mixed with respect to leukemia subtypes.

Key words: childhood cancer; job-exposure matrix; leukemia; central nervous system tumor; germ cell tumor

Introduction

Few studies have assessed parental exposure to animals and childhood cancer risk, but there are suggestions that parental occupational animal exposure is positively associated with offspring brain tumors (Efird et al. 2003; Keegan et al. 2013; Kristensen et al. 1996; Olsen et al. 1991). Similarly, studies of parental/child farm residence and/or childhood animal contact have reported positive associations with childhood brain tumors (Christensen et al. 2012; Efird et al. 2003; Holly et al. 1998; Yeni-Komshian and Holly 2000). There have been fewer studies of parental occupational animal exposures that included rarer types of childhood cancer, e.g., germ cell tumors (Shu et al. 1995), retinoblastoma (Kristensen et al. 1996; MacCarthy et al. 2009; Olsen et al. 1991), lymphoma (Kristensen et al. 1996), and bone tumors (Hum et al. 1998; Kristensen et al. 1996; Magnani et al. 1989; Olsen et al. 1991; Valery et al. 2002).

Occupational animal contact is associated with increased risks for infection among exposed workers (Bosnjak et al. 2010; Lewis et al. 2008; Nielsen et al. 2013). Such infections may spread from animals to humans through direct contact or contact with animal dust, particles from animal waste (Nehme et al. 2008), or aerosols from animal activity (Cole et al. 2000). For mothers, infection during pregnancy can disrupt fetal development (Adams Waldorf and McAdams 2013) and is a suspected risk factor for some childhood cancers (Dickinson et al. 2002; Fear et al. 2001; Linos et al. 1998). For fathers, preconception infection or exposure to animal

dusts may lead to chronic systemic inflammation that alters DNA during spermatogenesis, potentially impacting offspring development *in utero* or after birth (Aitken et al. 2003; Aitken and Krausz 2001). For both parents, postnatal infection can spread to household contacts, including children (Nadimpalli et al. 2016); because some animal viruses have been shown to induce brain tumors in other animals (Copeland et al. 1975), infection in early childhood is a hypothesized risk factor for childhood brain tumors specifically. On the other hand, it has been suggested that exposure to common infections in early childhood primes the immune system and reduces subsequent risk for cancers like acute lymphoblastic leukemia (ALL) (Greaves 2006; Greaves and Alexander 1993).

In this registry and population-based case-control study of Danish children spanning several decades, we used a job-exposure matrix (JEM) to assess parental occupational livestock or animal dust exposure during different developmental periods ("exposure windows," i.e., three months preconception, pregnancy, offspring birth to cancer diagnosis), and estimated associations with offspring cancer risk.

Methods

This study was based on a linked database of all childhood cancers diagnosed in Denmark from 1968-2016, aged 0-19 at diagnosis. This database has been used for various epidemiologic studies of childhood cancer and includes data from the Danish Central Population Registry (data available 1968-2016) (Pedersen 2011), the Cancer Registry (1968-2016)

(Gjerstorff 2011), the Supplementary Pension Fund (1964-2014) (Hansen and Lassen 2011), and the Medical Birth Registry (1973-2016) (Knudsen and Olsen 1998). Linkage of these data sources was conducted using a unique personal identification number (PID) allocated to each resident in Denmark since 1968 by the Central Population Registry. The latter register keeps information on birth day, sex, place of birth, parents and siblings, and date of death or immigration.

For this study, childhood cancer cases were identified from the Cancer Registry and grouped according to the International Classification of Childhood Cancer (ICCC), Version 1 until 2003 and Version 3 thereafter; histologic subtypes of childhood cancer were identified using the International Classification of Diseases for Oncology (ICD-O), Version 1 until 2003 and Version 3 thereafter. Controls, free of cancer at the date of diagnosis of the corresponding case, were randomly selected from the Central Population Registry and matched to cases by birth year and sex.

Certain exclusion criteria were implemented for this study in particular. Because early life exposures should be more relevant for earlier diagnosed cancers, cases and their matched controls were excluded from our study population if the case was aged 17-19 years at diagnosis. Cases and controls were additionally excluded from our study population if they did not have any parental occupational history for the exposure windows of interest (for fathers, within three months preconception and from offspring birth to cancer diagnosis; for mothers, during pregnancy and from offspring birth to

cancer diagnosis), or if the case was a cancer type with fewer than five exposed cases throughout all four exposure windows.

The source of parental information varied by child's birth year, which has been described in detail elsewhere (Contreras et al. 2017). Information on maternal and gestational factors were obtained from the Medical Birth Registry. Date of conception was calculated using child's gestational age as listed in the Medical Births Registry (see Supplementary File 1 for details).

Parental occupational history was obtained from the files of the Supplementary Pension Fund, which has compulsory membership for all salaried employees in Denmark aged 18-66 years who work at least nine hours per week; in 1978, persons aged 16-17 were additionally included. Students, the self-employed, and those born before April 1st, 1897 are not covered by the Supplementary Pension Fund (Hansen and Lassen 2011). For each employment, this register keeps information on start/end dates, company name, a unique company number, and the PID. Company occupational activities are coded by Statistics Denmark using the Danish industry code, a five-digit extended version of the United Nation's four-digit International Standard Industrial Classification of All Economic Activities codes (United Nations. Statistical Office. 1968). For this study, occupations with animal dust exposure were identified using the Danish version of the Nordic Occupational Cancer Study JEM (Kauppinen et al. 2009), while occupations with livestock exposure were identified by an expert on Danish occupational health (J.H.). In order to avoid additional occupational

exposures (e.g., pesticides), occupations were only included if they specified work with livestock but not crops; however, not all competing exposures could be avoided during exposure assessment (e.g., insecticides may be used with animals). Parents were considered exposed if they had ever worked a job included in the JEM during the exposure window of interest.

Frequencies and percentages were calculated to describe study population characteristics by case/control status. Detailed information on other covariates in relation to specific cancer types has been previously reported in this population (Contreras et al. 2017). Multivariable conditional logistic regression analyses were used to estimate associations with parental occupational livestock or animal dust exposure during each exposure window (i.e., three months preconception, pregnancy, offspring birth to cancer diagnosis) and childhood cancer in offspring. We identified potential confounders from previous studies (Christensen et al. 2012; Holly et al. 1998; Kristensen et al. 1996), i.e., parental age, birth year, and child sex, but we only considered parental age a confounder in this analysis. We also considered adjustment for other covariates, including parity (0, 1, or ≥2) and maternal smoking status (ever vs. never), but adjustment for these factors did not change point estimates by more than 10%. Therefore, final models adjusted for parental age only (maternal age for maternal exposures and paternal age for paternal exposures). In order to address the impact of more intense livestock farming exposures over time, we conducted subgroup analyses limited to births after 1988 to capture changes in Danish livestock

farming practices. During this time, legal changes allowed farmers to increase the size of their landholdings (Prosterman and Hanstad 1999), which allowed for larger herd sizes. Because larger herd sizes are predictive of persistent infection within herds (Agger and Paul 2014; Ersboll et al. 2010; Paul et al. 2012), our analysis of births 1989-2016 is intended to assesses a period with presumably higher exposure and higher risk for infection among exposed workers. We additionally conducted sensitivity analyses for births 1968-2016 stratified by child's birthplace (urban areas vs. rural areas and small towns), as the occupational exposures of interest were hypothesized to be concentrated in more rural areas. Information on childhood residence or child's residence at time of diagnosis was not available. We also conducted sensitivity analyses that did not stratify by either parent or exposure window; analyses that only stratified by exposure window (for which paternal exposures during three months preconception were combined with maternal exposures during pregnancy); and analyses that only stratified by parent. For all analyses, if the number of exposed cases was less than five, risk estimates were not provided and the exposed number was denoted as "<5" to comply with ethics and privacy rules.

All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The study population consisted of 5,078 childhood cancer cases aged 0-16 years old, and 123,228 sex and birth year-matched controls.

Demographic and gestational characteristics were similar among cases and controls (Table 1).

Parents were frequently employed in the same occupation throughout the entire study period (Table 2); Pearson correlation analyses revealed a moderate correlation between exposure windows of interest among mothers and fathers, respectively (maternal: r^2=0.59; paternal: r^2=0.66).

For CNS tumors, we observed a positive association with paternal occupational exposure to livestock or animal dust from offspring birth to cancer diagnosis for births 1968-2016 (Table 3), while maternal occupational exposure from offspring birth to cancer diagnosis was negatively associated with all CNS tumors for births 1989-2016 only, a period of presumed higher exposure to livestock or animal dust (Table 4). In sensitivity analyses, paternal exposure from offspring birth to cancer diagnosis was positively associated with CNS tumors for children born in rural areas or small towns (OR=1.26, 95% CI=0.98-1.63; Supplementary Table 1), while maternal exposure from offspring birth to cancer diagnosis was negatively associated (OR=0.66, 95% CI=0.43-1.01; Supplementary Table 2). For astrocytoma, maternal exposure during pregnancy was positively associated with offspring cancer for births 1968-2016 and 1989-2016 (Table 4).

For ALL, we observed a negative association with paternal exposure from offspring birth to cancer diagnosis for births 1989-2016 only (Table 3). For acute myeloid leukemia (AML), we observed a positive association with maternal exposure from offspring birth to cancer diagnosis for births 1968-

2016 (Table 4); an association of similar strength was detected for births 1989-2016, but the number of exposed cases was halved and the estimate was imprecise. For children born in rural areas or small towns, maternal exposure from offspring birth to cancer diagnosis was also positively associated with AML (OR=2.16, 95% CI=1.09-4.29; Supplementary Table 2).

For retinoblastoma, we observed an association with maternal exposure during pregnancy for births 1968-2016 (Table 4). In sensitivity analyses, increased risks for retinoblastoma were observed with paternal exposure during three months preconception for children born in rural areas or small towns (OR=2.57, 95% CI=1.01-6.53; Supplementary Table 1); with any parental livestock or animal dust exposure during any exposure window (OR=1.96, 95% CI=1.04-3.69; Supplementary Table 3); and with paternal exposure during three months preconception and/or maternal exposure during pregnancy (OR=2.25, 95% CI=1.15-4.38; Supplementary Table 4).

For germ cell tumors, we observed an association with paternal exposure from offspring birth to cancer diagnosis for births 1968-2016 (Table 3). In sensitivity analyses, increased risks for germ cell tumors were observed with paternal exposure from offspring birth to cancer diagnosis for children born in rural areas or small towns (OR=1.89, 95% CI=1.02-3.49; Supplementary Table 1) and with any paternal exposure (OR=1.82, 95% CI=1.05-3.14); Supplementary Table 5).

Rhabdomyosarcoma was associated with paternal exposure from offspring birth to cancer diagnosis for births 1989-2016 only (Table 3), and

for children born in rural areas or small towns (OR=2.07, 95% CI=0.99-4.32; Supplementary Table 1). For births 1968-2016, bone tumors were associated with paternal exposure within three months preconception (Table 3).

Discussion

This study suggests that parental occupational livestock or animal dust exposure is associated with increased risks for offspring germ cell tumor and astrocytoma. For CNS tumors and leukemias, our findings were conflicting as both positive and negative associations were observed with parental exposure, either overall or in sensitivity analyses. For rarer childhood cancers, such as retinoblastoma, rhabdomyosarcoma, and bone tumors, our study is among the first to suggest parental animal contact as a risk factor. Earlier studies of parental animal exposure and childhood cancer mostly examined maternal farm residence with data collection and exposure assessment relying mainly on questionnaires, which may have been affected by recall bias (Christensen et al. 2012; Efird et al. 2003; Holly et al. 1998; Yeni-Komshian and Holly 2000). Few other studies have used registry-based occupational information to assess parental animal exposures in relation to childhood cancer risk (Keegan et al. 2012; Keegan et al. 2013; Kristensen et al. 1996; Olsen et al. 1991), but our study is novel in its use of a JEM to assess occupational exposure to livestock or animal dust specifically.

Our study is the first to estimate an association with paternal animal exposure and childhood germ cell tumors. One previous case-control study of 105 childhood germ cell tumor cases did not observe associations with

paternal (OR=1.3, 95% CI=0.6-3.0) or maternal (OR=0.9, 95% CI=0.4-2.2) occupational farm animal contact (Shu et al. 1995). All associations we observed were with paternal exposure from offspring birth to cancer diagnosis and the strength of association was similar across sensitivity analyses. Notably, all but one of the 14 exposed germ cell tumor cases were born in a rural area or small town. Though imprecise, the association with exposure from offspring birth to cancer diagnosis and germ cell tumors was strongest when assessing births 1989-2016 (presumably a time of higher exposure). This suggests that either exposure residues brought home from work may be responsible for risk increases, or infection resulting from paternal occupational animal exposure (either direct contact or contact with animal dusts, manure, meat, etc.) that spreads through household contacts (Nadimpalli et al. 2016). However, no epidemiologic studies have currently implicated infection in the etiology of childhood germ cell tumors (Hall et al. 2017; Shu et al. 1995). Established risk factors for childhood germ cell tumors are limited to cryptorchidism, Asian/Pacific Islander race/ethnicity, and the presence of congenital anomalies (Hall et al. 2017); yet, none of 14 exposed germ cell tumor cases here were diagnosed with congenital anomalies at birth. While some evidence suggests risk factors differ by major histologic subtype in young children (yolk sac tumor and teratoma) (Hall et al. 2019; Hall et al. 2017), we did not have the case sample size to investigate this.

While all CNS tumors were inversely associated with maternal exposure from offspring birth to cancer diagnosis, astrocytoma was positively associated with maternal pregnancy exposure, and the association strengthened when assessing births 1989-2016. These findings corroborate one previous analysis which reported a weakly positive association with offspring astroglial tumors and maternal on-farm animal exposure during pregnancy (adjusted OR=1.4, 95% CI=0.92-2.1) (Efird et al. 2003). To the best of our knowledge, there is only one additional study that stratified by brain tumor subtypes, which detected inverse associations with parental animal exposures and childhood gliomas (Christensen et al. 2012). In Denmark, occupational animal exposure is associated with an increased risk for infection (Bosnjak et al. 2010; Lewis et al. 2008; Nielsen et al. 2013), and infection during pregnancy is a suspected risk factor for offspring brain tumors (Dickinson et al. 2002; Fear et al. 2001; Linos et al. 1998). Some viruses (e.g., JC polyomavirus) are found in pediatric and adult CNS tumor subtypes with various frequencies (Saddawi-Konefka and Crawford 2010). However, most studies have reported a high viral presence in glial tumors and low to no presence in medulloblastomas (Del Valle et al. 2001; Eftimov et al. 2016; Kim et al. 2002), suggesting some agents may be more relevant to the etiology of certain brain tumor subtypes than others. We did not have sufficient sample size to estimate associations with maternal pregnancy exposure and offspring medulloblastoma.

We observed mixed trends with respect to offspring CNS tumors. We estimated a positive association with paternal exposure from offspring birth to cancer diagnosis and CNS tumors in offspring, corroborating a previous study that detected an increased risk for CNS tumors in the offspring of fathers occupationally exposed to animals (OR=1.40, 95% CI=1.01-1.94) (Keegan et al. 2013). Similarly, a Danish record-based analysis of parental occupation around conception revealed an increased risk for CNS tumors in the offspring of fathers employed as butchers (OR=7.0) (Olsen et al. 1991); while some data from our study overlaps with the former, only cases born 1968-1984 were included in the older study. On the other hand, our findings do not corroborate past studies that reported positive associations with maternal exposure to animals and CNS or brain tumors in offspring (Efird et al. 2003; Holly et al. 1998; Kristensen et al. 1996; Yeni-Komshian and Holly 2000), but our negative association with exposure from offspring birth to cancer diagnosis is similar to one case-control study which detected inverse associations with early life exposure to specific animals (sheep, goats, and birds) and childhood brain tumors (Christensen et al. 2012). We observed this decreased risk when examining births 1989-2016 and births in rural areas and small towns only. For overall CNS tumor risk, our results are inconsistent for exposure from offspring birth to cancer diagnosis as positive associations were observed with paternal exposure and negative associations with maternal exposure. It is unclear why this occurred, but chance could be one explanation.

Our results were also mixed with respect to parental exposure and offspring leukemia subtypes. For births 1989-2016, we detected an inverse association with paternal exposure from offspring birth to cancer diagnosis and ALL risk, which is consistent with previous studies that found negative associations with early exposure to infectious diseases and childhood ALL (Jourdan-Da Silva et al. 2004; Rudant et al. 2010). These findings are compatible with the delayed infection hypothesis, which suggests that exposure to common infections in early life primes the immune system and reduces risk for ALL, specifically c-ALL (Greaves 2006). In this study, we were unable to examine c-ALL because this subtype information is not available in the Danish Cancer Registry. For offspring AML, we detected positive associations with maternal exposure from offspring birth to cancer diagnosis, both overall and when limiting to births in rural areas. While a recent study pooling birth cohort data, including data from Denmark, detected a positive association with paternal occupational animal contact exposure and AML (exposed n=3; hazard ratio=3.89, 95% CI=1.18-12.90), small numbers did not allow for the same analysis of maternal exposure (Patel et al. 2019). To our knowledge, no other studies have implicated parental animal contact or early life infections in the etiology of childhood AML.

Though based on a small number of exposed cases, we estimated positive associations for retinoblastoma with parental exposure during any exposure window and with maternal exposure during pregnancy and/or paternal exposure within three months preconception. This contrasts with

one previous study that assessed paternal occupation animal exposure and offspring retinoblastoma (MacCarthy et al. 2009). However, one Danish study detected a positive association with retinoblastoma, maternal occupation as a nurse (OR=3.3), and paternal occupation as a physician (OR=10.2) (Olsen et al. 1991), which may support a role for viral exposures, but both estimates were based on fewer than five exposed cases. We also detected positive associations, though imprecise, for paternal exposure and rhabdomyosarcoma. No other studies have identified paternal animal contact as a potential risk factor for this rare cancer.

This study was limited by the small number of childhood cancer cases, which resulted in imprecise estimates and the inability to stratify by subtype in some instances. Additionally, for some birth years (1968-1972), we were unable to determine whether parents were biological parents, though this is unlikely to vary by case status (Contreras et al. 2017). We also lacked information on some childhood cancer risk factors, such as paternal smoking and family history of cancer. This study's strengths include the utilization of a JEM for refined exposure assessment, which allowed us to assess occupations with specific exposure to livestock or animal dust. Previous studies relied on cruder and often self-reported exposure, combining all farming jobs or using farm residence as an indicator for exposure (Christensen et al. 2012; Efird et al. 2003; Holly et al. 1998; Yeni-Komshian and Holly 2000); these approaches inherently include additional exposures, e.g. pesticides, that may contribute to cancer development in children (Chen

et al. 2015). While the occupations included in our JEM were selected such that they are not likely to include concomitant exposures, the possibility of residual confounding by such exposures (e.g., insecticides) still exists. Our JEM also included a variety of occupations with different human-animal interactions (e.g., veterinarians vs. butchers), but we were unable to assess the differential impact of meeting living animals over handling meat, fur, etc. due to the small number of exposures within individual job categories. Self-employed livestock farmers could not be assessed because they are not covered by the Supplementary Pension Fund; however, self-employment is extremely rare in Denmark. It is possible that the parents of some cases or controls had additional self-employment that involved livestock or animal dust exposure, but we do not expect this to bias results. This study's record-based nature prevented recall and selection bias due to self-selection.

Overall, our findings suggest that parental occupational exposure to livestock or animal dust may be implicated in the etiology of some childhood cancers, potentially due to infection during pregnancy or after birth. Additional epidemiologic and mechanistic research is needed to further elucidate the relation between these exposures and childhood cancer, with an emphasis on identifying specific hazardous and preventable agents.

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Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Danish Data Protection Agency and the human subjects' protection board at the University of California, Los Angeles, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent: Because this was a record-based study, informed consent was not required.

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

Characteristic	Cases (N=5078)		Controls (N=123,228)	
	N	%	N	%
Child's sex				
Male	2751	54.2	66,764	54.2
Female	2327	45.8	56,464	45.8
Child's birthplace				
Urban	1702	33.5	40,664	33.0
Rural/Small towns	3376	66.5	82,564	67.0
Maternal age (years)				
≤ 25	1677	33.0	42,188	34.2
26-30	1911	37.6	45,426	36.9
31-35	1077	21.2	26,453	21.5
≥ 36	413	8.1	9161	7.4
Paternal age (years)				
≤ 25	908	18.0	23,703	19.3
26-30	1838	36.4	42,816	34.9
31-35	1360	27.0	33,811	27.6
≥ 36	941	18.6	22,391	18.3
Missing (father unknown)	31		507	
Family socioeconomic status[a]				
High	490	12.6	12,063	12.7
Medium-high	681	17.5	15,928	16.8
Medium	718	18.4	17,784	18.7
Medium-low	1266	32.5	31,050	32.7

Low	750	19.0	18,079	19.1
Missing	1183		28,324	
Parity				
0	2207	43.5	53,553	43.5
1	1910	37.6	46,394	37.6
2+	961	18.9	23,281	18.9
Data available for births 1991+				
Maternal smoking status				
Smoker	515	23.6	12,339	23.1
Non-smoker	1669	76.4	41,080	76.9
Missing	1103		2495	

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

Table 2. Prevalence of occupations included in the livestock/animal dust job-exposure matrix, stratified by parent, exposure period of interest, and case/control status, 1968-2016.

	Paternal exposure window								Maternal exposure window							
	Three months preconception				Offspring birth to cancer diagnosis				Pregnancy				Offspring birth to cancer diagnosis			
	Controls (N=99,849)		Cases (N=4219)		Controls (N=112,404)		Cases (N=4735)		Controls (N=88,787)		Cases (N=3914)		Controls (N=104,404)		Cases (N=4508)	
Occupation title	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
All occupations in job-exposure matrix	2265	2.2	11	2.6	4128	3.6	19	4.1	111		4		234		9	
Stud-farms	6	7	<5	1	20	7	8	8	5	1.26	9	1.25	4	2.25	2	2.04
Farming, livestock	449	0.0	21	0.0	919	0.0	48	0.0	<5	0.00	-		14	0.01	< 5	0.02
Hog slaughtering	1234	0.4	53	0.5	2184	0.8	96	1.0	133	0.15	5	0.13	318	0.30	1 4	0.31
Meat-product/canning plants	251	1.2	13	1.2	580	1.9	29	2.0	373	0.42	1 4	0.36	741	0.71	2 4	0.53
Cattle slaughterhouses	58	0.2	<5	0.3	152	0.5	7	0.6	139	0.16	< 5	0.05	361	0.35	7	0.16
Gut-cleaning plants	82	6	<5	5	150	4	7	5	5	0.01	-		24	0.02	-	
Poultry slaughterhouses	111	0.0	7	0.0	260	0.1	<5	0.0	58	0.07	< 5	0.05	108	0.10	8	0.18
Other meat preparation	26	0.1	<5	0.1	68	0.2	14	0.3	173	0.19	8	0.20	403	0.39	2 0	0.44
Furriers	7	1	<5	9	15	3	5	0	26	0.03	-		59	0.06	< 5	0.04
Fur preparation	<5	0.0		2		0.0		0.1			< 5	0.10			< 5	0.09
Meat products, poultry, game	146	0.0	-	0	23	0.0	-	1	21	0.02	< 5	0.10	47	0.05	< 5	0.09
Butcher shops, delicatessens	126	0.1	8	2	389	0.1	19	0.4	<5	0.00	< 5	0.03	28	0.03	< 5	0.02
Veterinarians	48	0.1	<5	0.1	239	0.2	<5	0.3	55	0.06	< 5	0.03	140	0.13	< 5	0.04
		3		9		1		0	191	0.22	1	0.28	429	0.41	1 9	0.42
		0.0		0.0		0.0		0.0			<				<	
		5		7		8		4	76	0.09	5	0.10	130	0.12	5	0.09

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for paternal occupational exposure to livestock or animal dust and offspring cancer risk, stratified by birth years of interest and exposure window.

Cancer type	Births 1968-2016								Births 1989-2016							
	Three months preconception				Offspring birth to cancer diagnosis				Three months preconception				Offspring birth to cancer diagnosis			
	N	**%**	**OR[a]**	**OR[b] (95% CI)**	**N**	**%**	**OR[a]**	**OR[b] (95% CI)**	**N**	**%**	**OR[a]**	**OR[b] (95% CI)**	**N**	**%**	**OR[a]**	**OR[b] (95% CI)**
Controls	2265	2.27			4128	3.67			1225	2.41			1996	3.52		
Leukemias	32	2.08	**0.90**	0.91 (0.64-1.31)	57	3.29	**0.95**	0.97 (0.74-1.27)	13	1.65	**0.67**	0.69 (0.39-1.20)	20	2.27	**0.69**	0.71 (0.45-1.11)
ALL	24	1.97	**0.84**	0.86 (0.57-1.29)	41	3.00	**0.88**	0.90 (0.65-1.23)	9	1.45	**0.57**	0.58 (0.30-1.13)	13	1.87	**0.56**	0.58 (0.33-1.00)
AML	6	2.79	**1.25**	1.27 (0.55-2.92)	12	4.88	**1.32**	1.33 (0.73-2.43)	<5	2.65		**-**	5	3.97	**1.36**	1.38 (0.55-3.49)
CNS tumors	42	2.95	**1.28**	1.27 (0.92-1.74)	83	5.11	**1.31**	1.30 (1.04-1.63)	25	3.38	**1.32**	1.29 (0.86-1.95)	41	5.02	**1.30**	1.27 (0.92-1.76)
Astrocytoma	7	1.57	**0.66**	0.66 (0.31-1.40)	17	3.27	**0.82**	0.81 (0.49-1.32)	<5	1.33		**-**	8	3.15	**0.77**	0.76 (0.37-1.55)
Medulloblastoma	6	3.35	**1.46**	1.44 (0.62-3.36)	10	5.03	**1.31**	1.28 (0.66-2.48)	<5	4.71		**-**	6	6.52	**1.67**	1.56 (0.65-3.74)
Bone tumors	7	2.98	**1.37**	1.39 (0.64-2.04)	11	4.04	**0.85**	0.88 (0.47-1.62)	6	5.22	**2.87**	3.05 (1.25-7.39)	7	5.26	**1.30**	1.37 (0.62-3.03)
Germ cell tumor	<5	2.17		-	14	6.86	**1.82**	1.85 (1.05-3.27)	<5	3.33		-	7	7.29	**2.13**	2.09 (0.93-4.69)
Neuroblastoma	8	2.62	**1.16**	1.16 (0.56-2.40)	9	2.76	**0.93**	0.93 (0.47-1.83)	6	4.11	**1.83**	1.77 (0.75-4.20)	6	3.73	**1.25**	1.20 (0.52-2.80)
Retinoblastoma	6	4.26	**2.11**	2.14 (0.89-5.10)	7	4.55	**1.78**	1.78 (0.80-3.94)	<5	5.33		**-**	<5	3.66		**-**
Rhabdomyosarcoma	5	3.40	**1.32**	1.30 (0.52-3.27)	10	6.33	**1.70**	1.67 (0.86-3.24)	5	5.88	**2.38**	2.30 (0.88-5.98)	7	7.69	**2.28**	2.19 (0.97-4.95)
Wilms tumors	6	2.44	**1.37**	1.41 (0.61-3.26)	7	2.60	**1.00**	1.02 (0.48-2.21)	<5	2.68		**-**	<5	2.48		**-**

[a]Crude odds ratios.

[b]Odds ratios adjusted for maternal age (continuous).

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for maternal occupational exposure to livestock or animal dust and offspring cancer risk, stratified by birth years of interest and exposure window.

Cancer type	Births 1968-2016								Births 1989-2016							
	Pregnancy				Offspring birth to cancer diagnosis				Pregnancy				Offspring birth to cancer diagnosis			
	N	**%**	**OR[a]**	**OR[b] (95% CI)**	**N**	**%**	**OR[a]**	**OR[b] (95% CI)**	**N**	**%**	**OR[a]**	**OR[b] (95% CI)**	**N**	**%**	**OR[a]**	**OR[b] (95% CI)**
Controls	1115	1.26			2344	2.25			567	1.20			1096	2.03		
Leukemias	14	0.97	**0.70**	0.71 (0.42-1.22)	36	2.17	**1.00**	1.03 (0.73-1.44)	7	0.88	**0.69**	0.70 (0.33-1.49)	17	1.90	**1.02**	1.03 (0.63-1.69)
ALL	10	0.87	**0.63**	0.65 (0.34-1.22)	20	1.52	**0.71**	0.73 (0.46-1.14)	5	0.80	**0.61**	0.61 (0.25-1.50)	10	1.43	**0.78**	0.79 (0.42-1.49)
AML	<5	1.41		**-**	10	4.12	**1.80**	1.90 (0.98-3.67)	<5	1.63		**-**	5	3.73	**1.81**	1.87 (0.74-4.76)
CNS tumors	16	1.19	**1.01**	1.00 (0.60-1.65)	31	1.97	**0.82**	0.81 (0.57-1.17)	9	1.24	**1.01**	0.97 (0.49-1.90)	7	0.85	**0.38**	0.36 (0.17-0.78)
Astrocytoma	10	2.39	**1.87**	1.83 (0.95-3.54)	11	2.18	**0.83**	0.82 (0.45-1.51)	7	3.17	**2.65**	2.58 (1.14-5.81)	<5	1.58		**-**
Medulloblastoma	<5	1.81		**-**	<5	1.06		**-**	<5	1.27		**-**	<5	1.11		**-**
Bone tumors	5	2.19	**1.53**	1.81 (0.72-4.57)	6	2.19	**0.81**	0.83 (0.36-1.90)	<5	1.72		**-**	<5	2.19		**-**
Germ cell tumor	<5	1.21		-	5	2.51	**1.07**	1.15 (0.46-2.87)	<5	1.19		-	<5	4.12		**-**
Neuroblastoma	<5	1.45		**-**	8	2.73	**1.73**	1.72 (0.83-3.59)	<5	1.32		**-**	6	3.80	**2.33**	2.29 (0.97-5.44)
Retinoblastoma	5	4.03	**2.8**	2.67 (1.01-7.03)	<5	3.20		**-**	<5	3.95		**-**	<5	3.85		**-**

			7									
Rhabdomyosarcoma	<5	0.00	-	<5	0.65	-	<5	0.00	-	<5	0.00	-
Wilms tumors	<5	1.46	-	<5	0.43	-	<5	0.93	-	<5	0.00	-

[a]Crude odds ratios.

[b]Odds ratios adjusted for maternal age (continuous).