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Pneumonia diagnosis in childhood and incidence of leukemia, lymphoma, and brain cancer: a Danish nationwide cohort study

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Pneumonia diagnosis in childhood and incidence of leukemia, lymphoma, and brain cancer: a Danish nationwide cohort study

Running title: Pneumonia and risk of cancer in children

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Abstract: 236

Abstract

Objectives: There is an ongoing debate on the possible association between infections in early childhood and subsequent cancer risk, but it remains unclear if a hospital admission for infection is associated with risk of childhood cancer diagnosis. We examined if a hospital-based diagnosis of pneumonia was a clinical marker of the three most common childhood cancers.

Design: Population-based cohort study.

Setting: Denmark, hospital diagnoses, 1994-2013.

Methods: Using national health registries, we compared the observed incidence of leukemia, lymphoma, and brain cancer among 83,935 children with a hospital-based pneumonia diagnosis with that expected among children in the general population. We calculated absolute cancer risks and standardized incidence ratios (SIRs) as a measure of relative risk.

Results: The cancer SIRs were substantially increased during the first 6 months of follow-up; lymphoid leukemia: 6.2 [95% confidence interval (CI): 3.5, 10.3]; myeloid leukemia: 14.8 [95% CI: 6.0, 30.6]; Hodgkin lymphoma: 60.8 [95% CI: 26.2, 120], non-Hodgkin lymphoma: 15.9 [95% CI: 5.2, 37.2], and brain cancer: 4.4 [95% CI: 1.9, 8.7]. The 6-month absolute risks of leukemia, lymphoma, and brain cancer were all low, reaching 0.05% when combined. An increased risk persisted beyond 5 years for non-Hodgkin lymphoma and brain cancer. However, the 5-year absolute cancer risk was 0.14%.

Conclusions: The short-term incidence of leukemia, lymphoma, and brain cancer was higher than expected and persisted beyond 5 years for non-Hodgkin lymphoma and brain cancer. However, the absolute cancer risk was low.

Strengths and limitations

- We performed a population-based study
- We used a well-established method to calculate cancer risk, estimating both absolute and relative risks
- We focused on hospital-based pneumonia diagnosis rather than a composite of infections

Keywords: pneumonia, leukemia, lymphoma, brain cancer, risk, epidemiology

Funding

This work was supported by the Danish Childhood Cancer Foundation and by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

Conflict of interest

None of the authors report conflicts of interest, financial interests, activities, relationships, or affiliations relevant to this study.

Data sharing statement

No additional data are available.

Introduction

Presenting signs of cancer in children may be vague and overlap with those of common childhood conditions. While the disease course for leukemia is often short, the symptoms of brain cancer may present already two years before diagnosis.[1] GPs are often essential in the early diagnostic pathways[2], but it is plausible that cancer in some children debut with acute clinical disease necessitating hospitalization. Hospital admission for infection is not clearly associated with risk of childhood cancer. Some studies have shown that overall there is no association with previous admission for infectious diseases and risk of leukemia[3], while others have found that children with common infections requiring hospitalization potentially have a 50% higher risk of a subsequent leukemia diagnosis[4]. Specifically, a hospital diagnosis of pneumonia may be associated with subsequent increased risk of a leukemia diagnosis[5]. Pneumonia is a frequent cause of community-acquired infection leading to hospital contact (annual incidence is up to 40 per 10.000[6]), therefore any association with cancer could be clinically relevant.

We assessed absolute and relative risks of the three most common childhood cancers, leukemia, lymphoma, and brain cancer[7] subsequent to a first hospital-based diagnosis of pneumonia.

Materials and methods

The source population for this registry-based cohort was all Danish children aged 0-17 years who were alive between 1994 and 2013 (n=2,884,552). Access to medical care including hospital admissions is free-of charge (tax-paid). The Danish National Patient Registry (DNPR) captures all contacts with Danish hospitals,[8] and records discharge diagnosis using the International Classification of Diseases (currently the 10th revision). The Danish Cancer Registry (DCR) records incident cancers in Denmark using ICD-10 and ICD-0-3 morphology codes.[9]

We identified all children with a first time hospital-based (inpatient, outpatient clinic, and emergency room) diagnosis of pneumonia recorded in the DNPR during 1994-2013. We linked these cases to the DCR (using a unique personal ID) to identify incident cancers, and then to exclude children with previous cancer diagnoses. Owing to the low cancer incidence in the cohort, we had sufficient sample size to estimate only the risks of the three most common childhood cancers. We used information on registrations of chest imaging during hospitalization (recorded since 2002), to examine the proportion of imaging-confirmed pneumonia diagnoses. We obtained information from the DNPR on prevalent diagnoses of immune deficiencies and congenital diseases, including Down syndrome. We searched for hospitalizations before pneumonia diagnosis to elucidate the extent of previous hospital contacts. All codes used in the study are provided in the Appendix.

Statistical analysis

The children were followed for the occurrence of cancer from the date of the pneumonia diagnosis until death, emigration or end of follow-up November 30, 2013. We computed the absolute cancer risk at 6 months and 5 years following the pneumonia diagnosis.

We compared the observed cancer incidence among children with pneumonia with that expected among children in the general population (based on national cancer incidence rates by age, sex, and calendar year). Standardized incidence ratios (SIRs) were calculated as a measure of relative risk. We computed SIRs for acute myeloid leukemia, acute lymphoid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and brain cancer diagnosed during 0-6 months, between 6 months and 5 years, and 5+ years after a pneumonia diagnosis. We stratified by gender, age, and prevalent disease to examine its potential impact on cancer risk.

All statistical analyses were conducted using the SAS statistical software package, v. 9.2 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency, record number 1-16-02-1-08.

Results

Patient characteristics

We followed 83,935 children with pneumonia and no previous cancer diagnosis for a median of 10 years. In the cohort as a whole, 47,650 (57%) were boys, and median age was 1.5 years. Pneumonia diagnosis was made during an inpatient stay among 89%, during an outpatient clinic visit in 6%, and in the emergency room in 5% of the children. Pneumonia was registered as the main condition leading to hospitalization for 69,479 (83%) children. Of the 49,510 children diagnosed with pneumonia after 2002, 36,230 (73%) had chest imaging performed during their hospital contact. Pneumonia was registered as caused by bacteria in 14% and by viruses in 22% of children in the study cohort (see the Appendix for specification of etiology), while the agent was unspecified for 64% of the children. Among the children, 8733 (10%) had a congenital malformation (Table 2), including 489 children with Down syndrome. The prevalence of immune deficiencies recorded in the DNPR at the time of pneumonia diagnosis was low (n=137). The majority had one or no previous hospitalizations, while 25% had 2 or more previous hospitalizations with a minimum duration of 3 days.

Risk of leukemia, lymphoma, and brain cancer

A total of 168 cancers were diagnosed during follow-up (826,281 person-years), including 37 diagnosed with cancer within 1 month, adding up to 43 cancers within the first 6 months following the pneumonia episode. The most frequent cancer morphology codes are provided in Table 1.

The absolute risks of leukemia, lymphoma, and brain cancer were all low, combined it reached 0.05% at 6 month and 0.14% at 5 years.

During complete follow-up, the combined SIR of leukemia, lymphoma, and brain cancer was almost 2-fold increased. The SIRs were substantially increased during the first 6 months of follow-up: 6.2 [95% CI: 3.5, 10.3] for lymphoid leukemia, 14.8 [95% CI: 6.0, 30.6] for myeloid leukemia, 60.8 [95% CI: 26.2, 120] for Hodgkin lymphoma, 15.9 [95% CI: 5.2, 37.2] for non-Hodgkin lymphoma, and 4.4 [95% CI: 1.9, 8.7] for brain cancer. The increased risk of lymphoid leukemia, myeloid leukemia, and non-Hodgkin lymphoma persisted up to 5 years after a hospital pneumonia diagnosis. Beyond 5 years of follow-up, more children than expected were diagnosed with non-Hodgkin lymphomas and brain cancers (Table 1).

The stratified analyses for the overall cancer occurrence showed slightly higher SIRs among girls than among boys. Children up to 14 years of age had an approximately two-fold increased SIR, whereas teenagers aged 15-17 years had a four-fold increased SIR (Table 2). Children with imaging-confirmed diagnoses had a SIR of almost three, whereas children without confirmed diagnosis had a SIR around the unity (Table 2). Though numbers were low, children diagnosed with immune deficiencies or congenital malformations had higher SIRs for cancer than children without these conditions. However, importantly the increased risk was not confined to children with such known conditions. While the overall SIR for children without previous hospitalizations was around unity, the SIR for children with one of two visits was almost 2-fold increased, and the SIR for those with 3 or more visits was three-fold increased (Table 2).

Discussion

We found that a hospital-based diagnosis of pneumonia was a rare presentation of occult childhood cancer. The children hospitalized with pneumonia had a higher short-term incidence of leukemia, lymphoma, and brain cancer than expected, and had a persistently increased risk of non-Hodgkin lymphoma and brain cancer more than five years after the pneumonia. However, the absolute risk of cancer was low, which accords with the low incidence of childhood malignancies.

The association between hospital-based diagnoses of common infections and subsequent cancer occurrence are conflicting. A Danish population-based study found no overall association with previous admission for infectious diseases and risk of leukemia. However, the study did not explore risks according to type of infection[3]. By contrast, a French case-control study indicated that common infections occurring in children during the first year of life potentially were associated with decreased risk of leukemia, whereas children with infections requiring hospitalization could be at increased risk of a leukemia diagnosis[4] . Supporting the latter finding, a Taiwan case-control study found that a hospital diagnosis of pneumonia was associated with subsequent increased risk of myeloid leukemia diagnosis[5].We confirmed that children presenting with pneumonia had a subsequent higher occurrence of leukemia, lymphoma, and brain cancer than other Danish children.

The strengths of our study include its population-based design in the setting of a uniformly organized health care system. In agreement with the overall completeness of chest x-ray records in the DNPR[10], we found that the majority of diagnoses were based on imaging procedures. As well, cancer diagnoses in the DCR have high completeness and validity.[9] We included children with immune deficiency and congenital malformations, which are known to have higher incidence of both pneumonia and cancer. However, in the analyses excluding these children the results

remained unchanged. Our study also had potential limitations. We could not separate the order of the diagnoses among those diagnosed with pneumonia and cancer during same admission, nor identify children in whom lymphoma was initially falsely interpreted as pneumonia.

There are several possible explanations for our findings. Chest x-rays and blood tests performed as part of work-up for pneumonia may have yielded findings suspicious of cancer leading on to further examinations. In addition, some children lymphoma with a mediastinal mass or with lung involvement may have initially have been misdiagnosed as pneumonia. Children with cancer have higher GP consultation rates in than controls the year preceding the cancer diagnosis[11]. In agreement, we found higher SIRs for children with previous hospital contacts, thus pneumonia may not have been the first clinical disease in all children. Whereas increased diagnostic effort may partially explain the higher short-term occurrence of cancer, it is unlikely to explain the increased risk of lymphoma and brain cancer observed more than five years after pneumonia. There is an ongoing debate on whether or not infectious diseases in children may modulate the child's immune response potentially leading to decreased or increased risk of cancer[12-14]. We did not attempt to address or clarify this hypothesis as our data would not allow us to do so. However, we speculate if the associations demonstrated may be due to cancer-related impairment of the immune system, making a child more vulnerable to severe infections such as pneumonia. In children with an aggressive type of cancer, the infection may lead on to cancer diagnosis, whereas in children with a more indolent cancer, the infection occurs in the preclinical phase[1].

Based on the low absolute cancer risks observed, our findings do not warrant a change in the work-up of children diagnosed with pneumonia during a hospital admission.

Contributors HTS and KKS conceived the study idea. KKS reviewed the literature. KKS and HTS designed the study and directed the analyses, which were carried out by DKF. All authors participated in the interpretation of the results. KKS organized the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version

Table 1: Risk of leukemia, lymphoma, and brain cancer by follow-up interval

	Observed/expected numbers of cancer and SIRs [95% CI]					
	0-<6 months of follow-up		6 months-<5 years		5+ years	
Lymphoid leukemia[a]	15/2	6.2 [3.5, 10.3]	27/16	1.7 [1.1, 2.4]	8/10	0.8 [0.3, 1.5]
Myeloid leukemia[b]	7/<1	14.8 [6.0, 30.6]	8/3	2.6 [1.1, 5.2]	2/3	0.8 [0.1, 2.7]
Hodgkin lymphoma[c]	8/<1	60.8 [26.2, 120]	2/1	1.4 [0.2, 5.0]	6/8	0.7 [0.3, 1.5]
Non-Hodgkin lymphoma[d]	5/<1	15.9 [5.2, 37.2]	8/3	2.7 [1.2 ,5.3]	11/6	1.7 [0.9, 3.0]
Brain[e]	8/2	4.4 [1.9, 8.7]	23/14	1.7 [1.1, 2.5]	30/20	1.5 [1.0, 2.2]

Abbreviations: SIR, standardized incidence ratio; CI, confidence interval

Some of the most frequent morphology codes were as follows:

[a] 42 of 50 children had precursor cell lymphoblastic leukemia, not otherwise specified.

[b] 10 of 17 children had acute myeloid leukemia, not otherwise specified.

[c] 10 of 16 children had nodular sclerosis classical Hodgkin lymphoma.

[d] 5 of 24 children had diffuse large B-cell, not otherwise specified; 5 had mature T-cell lymphoma, not otherwise specified; 4 had Burkitt lymphoma, not otherwise specified, and 4 had anaplastic large cell lymphoma.

[e] 15 of 61 children had glioblastoma; 8 had medulloblastoma, not otherwise specified, and 28 had other or unspecified brain cancer.

Table 2: **Risk of leukemia, lymphoma, and brain cancer, stratified analysis**

	N	Observed/expected numbers of cancer	SIR [95% CI]
All	83,935	168/90	1.9 [1.6, 2.2]
Boys	47,650	89/53	1.7 [1.3, 2.1]
Girls	36,285	79/37	2.2 [1.7, 2.7]
Age			
0-4	70,476	135/76	1.8 [1.5, 2.1]
5-9	8145	14/8	1.7 [0.9, 2.8]
10-14	3114	8/3	2.3 [1.0, 4.5]
15-17	2200	11/3	4.2 [2.1, 7.5]
Previous hospitalizations			
0	18,114	20/17	1.2 [0.7, 1.9]
1	45,161	94/50	1.9 [1.5, 2.3]
2	11,953	24/14	1.8 [1.1, 2.6]
3+	8707	30/10	3.1 [2.1, 4.4]
Congenital malformations			
Yes	8733	31*/9	3.7 [2.5, 5.2]
a) Downs Syndrome	489	9/1	16.2 [7.4, 30.8]
No	75,202	137/81	1.7 [1.4, 2.0]
Immune deficiency			
Yes	137	2/0.1	17.5 [2.1, 63.2]
No	83,798	166/90	1.9 [1.6, 2.2]
Imaging examination (after 2002)			
Yes	36,230	66/25	2.7 [2.1, 3.4]
No	13,280	9/8	1.1 [0.5, 2.1]

* Congenital malformations included conditions related to the nervous system (Q00-Q07); eye, ear, face and neck (Q10-Q18); the circulatory system (Q20-Q28); the respiratory system (Q30-Q34); cleft lip and cleft palate (Q35-Q37); the digestive system (Q38-Q45); genital organs (Q50-Q56); the urinary system (Q60-Q64); malformations and deformations of the musculoskeletal system (Q65-Q79); and other (Q80-Q99).

Appendix: ICD codes used in the study

Pneumonia: ICD-10: J12–J18 (excl. previous pneumonia episodes ICD-8: 480–486, 073 and 471)

The cohort included 14% with bacterial pneumonia (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae, Chlamydophilia pneumoniae*, and Enterobacteriaceae), 22% with viral pneumonia (including adenovirus, respiratory syncytial virus, parainfluenza virus, metapneumonvirus, and unspecified viruses), while the agent was unspecified for 64% of the children.

Covariates

Immune deficiencies: ICD-10: D80.0-D82.9

Congenital malformations: ICD-8: 74099-75999; ICD-10: Q00-99

Down syndrome: ICD-8: 75939, ICD-10: Q90

Chest imaging: x-ray or CT scan: UXRC00, UXCC75, UXCC77

Cancer: Lymphoid leukemia (C91), myeloid leukemia (C92), non-Hodgkin lymphoma (C82-85, and C90), Hodgkin lymphoma (C81), brain cancer (C71, C751-753, D330-332, D352-354, D430-432, and D443-445)

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 1, 2, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 2,4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 2,4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Page 4,5 Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 4,5
Bias	9	Describe any efforts to address potential sources of bias page 4
Study size	10	Explain how the study size was arrived at page 4,5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page 4 (standardization, stratification)
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses page 5
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 4,6
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 5, 12
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) page 6
Outcome data	15*	Report numbers of outcome events or summary measures over time page 6,7, 11, 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 6,7, 11, 12

		(*b*) Report category boundaries when continuous variables were categorized page 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period page 6,7, 11, 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses page 6,12
Discussion		
Key results	18	Summarise key results with reference to study objectives page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 8,9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Running title: Pneumonia and risk of cancer in children

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Abstract: 236

Abstract

Objectives: There is an ongoing debate on the possible association between infections in early childhood and subsequent cancer risk, but it remains unclear if a hospital admission for infection is associated with risk of childhood cancer diagnosis. We examined if a hospital-based diagnosis of pneumonia was a clinical marker of the three most common childhood cancers.

Design: Population-based cohort study.

Setting: Denmark, hospital diagnoses, 1994-2013.

Methods: Using national health registries, we compared the observed incidence of leukaemia, lymphoma, and brain cancer among 83,935 children with a hospital-based pneumonia diagnosis with that expected among children in the general population. We calculated absolute cancer risks and standardized incidence ratios (SIRs) as a measure of relative risk.

Results: The cancer SIRs were substantially increased during the first 6 months of follow-up; lymphoid leukaemia: 6.2 [95% confidence interval (CI): 3.5, 10.3]; myeloid leukaemia: 14.8 [95% CI: 6.0, 30.6]; Hodgkin lymphoma: 60.8 [95% CI: 26.2, 120], non-Hodgkin lymphoma: 15.9 [95% CI: 5.2, 37.2], and brain cancer: 4.4 [95% CI: 1.9, 8.7]. The 6-month absolute risks of leukaemia, lymphoma, and brain cancer were all low, reaching 0.05% when combined. An increased risk persisted beyond 5 years for non-Hodgkin lymphoma and brain cancer. However, the 5-year absolute cancer risk was 0.14%.

Conclusions: The short-term incidence of leukaemia, lymphoma, and brain cancer was higher than expected and persisted beyond 5 years for non-Hodgkin lymphoma and brain cancer. However, the absolute cancer risk was low.

Strengths and limitations

- We performed a population-based study using a well-established method to calculate cancer risk, estimating both absolute and relative risks
- We focused on hospital-based pneumonia diagnosis rather than a composite of infections
- We could not separate the order of diagnoses among those diagnosed with pneumonia and cancer during same admission
- We did not have information from the medical files, and therefore could not depict if some children were initially misdiagnosed as pneumonia, and later diagnosed with mediastinal lymphoma

Keywords: pneumonia, leukaemia, lymphoma, brain cancer, risk, epidemiology

Funding: This work was supported by the Danish Childhood Cancer Foundation and by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

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Data sharing statement: No additional data are available.

Introduction

Presenting signs of cancer in children may be vague and overlap with those of common childhood conditions. While the disease course for leukaemia is often short, the symptoms of brain cancer may present already two years before diagnosis.[1] GPs are often essential in the early diagnostic pathways[2], but it is plausible that cancer in some children debut with acute clinical disease necessitating hospitalization. Hospital admission for infection is not clearly associated with risk of childhood cancer. Some studies have shown that overall there is no association with previous admission for infectious diseases and risk of leukemia[3], while others have found that children with common infections requiring hospitalization potentially have a 50% higher risk of a subsequent leukaemia diagnosis[4]. Specifically, a hospital diagnosis of pneumonia may be associated with subsequent increased risk of a leukaemia diagnosis[5]. Pneumonia is a frequent cause of community-acquired infection leading to hospital contact (annual incidence is up to 40 per 10.000[6]), therefore any association with cancer could be clinically relevant. If absolute cancer risks in children with a hospital-based diagnosis of pneumonia are high, then this could have implications for the diagnostic approach in these children.

We assessed absolute and relative risks of the three most common childhood cancers, leukaemia, lymphoma, and brain cancer[7] subsequent to a first hospital-based diagnosis of pneumonia.

Materials and methods

The source population for this registry-based cohort was all Danish children aged 0-17 years who were alive between 1994 and 2013 (n=2,884,552). Access to medical care including hospital admissions is free-of charge (tax-paid). The Danish National Patient Registry (DNPR) captures all contacts with Danish hospitals,[8] and records discharge diagnosis using the International

Classification of Diseases (currently the 10th revision). The Danish Cancer Registry (DCR) records incident cancers in Denmark using ICD-10 and ICD-0-3 morphology codes.[9]

We identified all children with a first time hospital-based (inpatient, outpatient clinic, and emergency room) diagnosis of pneumonia recorded in the DNPR during 1994-2013. We linked these cases to the DCR (using a unique personal ID) to identify incident cancers, and then to exclude children with previous cancer diagnoses. Owing to the low cancer incidence in the cohort, we had sufficient sample size to estimate only the risks of the three most common childhood cancers. We used information on registrations of chest imaging during hospitalization (recorded since 2002), to examine the proportion of imaging-confirmed pneumonia diagnoses. We obtained information from the DNPR on prevalent diagnoses of immune deficiencies and congenital diseases, including Down syndrome. We searched for hospitalizations before pneumonia diagnosis to elucidate the extent of previous hospital contacts. All codes used in the study are provided in the Appendix.

Statistical analysis

The children were followed for the occurrence of cancer from the date of the pneumonia diagnosis until death, emigration or end of follow-up November 30, 2013. We computed the absolute cancer risk at 6 months and 5 years following the pneumonia diagnosis.

We compared the observed cancer incidence among children with pneumonia with that expected among children in the general population (based on national cancer incidence rates by age, sex, and calendar year). Standardized incidence ratios (SIRs) were calculated as a measure of relative risk. We computed SIRs for acute myeloid leukaemia, acute lymphoid leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and brain cancer. Follow-up was divided into first 6 months, 6 months to

5 years, and 5+ years. We stratified the patients by gender, age, calendar period, and prevalent disease to examine its potential impact on cancer risk.

All statistical analyses were conducted using the SAS statistical software package, v. 9.2 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency, record number 1-16-02-1-08.

Results

Patient characteristics

We followed 83,935 children with pneumonia and no previous cancer diagnosis for a median of 10 years. The incidence of pneumonia diagnosis was stable over the 20-year period. In the cohort as a whole, 47,650 (57%) were boys, and median age was 1.5 years. Pneumonia diagnosis was made during an inpatient stay among 89%, during an outpatient clinic visit in 6%, and in the emergency room in 5% of the children. Pneumonia was registered as the main condition leading to hospitalization for 69,479 (83%) children. Of the 49,510 children diagnosed with pneumonia after 2002, 36,230 (73%) had chest imaging performed during their hospital contact. Pneumonia was registered as caused by bacteria in 14% and by viruses in 22% of children in the study cohort (see the Appendix for specification of aetiology), while the agent was unspecified for 64% of the children. Among the children, 8733 (10%) had a congenital malformation (Table 1), including 489 children with Down syndrome. The prevalence of immune deficiencies recorded in the DNPR at the time of pneumonia diagnosis was low (n=137). The majority had one or no previous hospitalizations, while 25% had 2 or more previous hospitalizations with a minimum duration of 3 days.

Risk of leukaemia, lymphoma, and brain cancer

A total of 168 cancers were diagnosed during follow-up (826,281 person-years), including 37 diagnosed with cancer within 1 month, adding up to 43 cancers within the first 6 months following the pneumonia episode. The most frequent cancer morphology codes are provided in Table 2.

The absolute risks of leukaemia, lymphoma, and brain cancer were all low, combined it reached 0.05% at 6 month and 0.14% at 5 years.

During complete follow-up, the combined SIR of leukaemia, lymphoma, and brain cancer was almost 2-fold increased (Table 1). The SIRs were substantially increased during the first 6 months of follow-up: 6.2 [95% CI: 3.5, 10.3] for lymphoid leukaemia, 14.8 [95% CI: 6.0, 30.6] for myeloid leukaemia, 60.8 [95% CI: 26.2, 120] for Hodgkin lymphoma, 15.9 [95% CI: 5.2, 37.2] for non-Hodgkin lymphoma, and 4.4 [95% CI: 1.9, 8.7] for brain cancer (Table 2). The increased risk of lymphoid leukaemia, myeloid leukaemia, and non-Hodgkin lymphoma persisted up to 5 years after a hospital pneumonia diagnosis. Beyond 5 years of follow-up, more children than expected were diagnosed with non-Hodgkin lymphomas and brain cancers (Table 2).

The stratified analyses for the overall cancer occurrence showed slightly higher SIRs among girls than among boys. Children up to 14 years of age had an approximately two-fold increased SIR, whereas teenagers aged 15-17 years had a four-fold increased SIR (Table 1). The SIR increased over time from 1.2-fold increased during 1994-1998 to 2.5-fold increased during 2009-2013.

Children with imaging-confirmed diagnoses had a SIR of almost three, whereas children without confirmed diagnosis had a SIR around the unity (Table 1). Though numbers were low, children diagnosed with immune deficiencies or congenital malformations had higher SIRs for cancer than children without these conditions. However, importantly the increased risk was not confined to children with such known conditions. While the overall SIR for children without previous

hospitalizations was around unity, the SIR for children with one of two visits was almost 2-fold increased, and the SIR for those with 3 or more visits was three-fold increased (Table 1).

Discussion

We found that a hospital-based diagnosis of pneumonia was a rare presentation of occult childhood cancer. The children hospitalized with pneumonia had a higher short-term incidence of leukaemia, lymphoma, and brain cancer than expected, and had a persistently increased risk of non-Hodgkin lymphoma and brain cancer more than five years after the pneumonia. However, the absolute risk of cancer was low, which accords with the low incidence of childhood malignancies.

The association between hospital-based diagnoses of common infections and subsequent cancer occurrence are conflicting. A Danish population-based study found no overall association with previous admission for infectious diseases and risk of leukaemia. However, the study did not explore risks according to type of infection[3]. By contrast, a French case-control study indicated that common infections occurring in children during the first year of life potentially were associated with decreased risk of leukaemia, whereas children with infections requiring hospitalization could be at increased risk of a leukaemia diagnosis[4]. Supporting the latter finding, a Taiwan case-control study found that a hospital diagnosis of pneumonia was associated with subsequent increased risk of myeloid leukaemia diagnosis[5].We confirmed that children presenting with pneumonia had a subsequent higher occurrence of leukaemia, lymphoma, and brain cancer than other Danish children.

The strengths of our study include its population-based design in the setting of a uniformly organized health care system. In agreement with the overall completeness of chest x-ray records in the DNPR[10], we found that the majority of diagnoses were based on imaging procedures. As well,

cancer diagnoses in the DCR have high completeness and validity.[9] We included children with immune deficiency and congenital malformations, which are known to have higher incidence of both pneumonia and cancer. However, in the analyses excluding these children the results remained unchanged. Our study also had potential limitations. We could not separate the order of the diagnoses among those diagnosed with pneumonia and cancer during same admission, nor identify children in whom lymphoma was initially falsely interpreted as pneumonia. We used hospital-based diagnosis of pneumonia within the setting of a developed country. Accordingly, generalisability may be transferrable to other industrial Western societies, but not necessarily to undeveloped countries, neither to pneumonia diagnosis in the general practice setting.

There are several possible explanations for our findings. Chest x-rays and blood tests performed as part of work-up for pneumonia may have yielded findings suspicious of cancer leading on to further examinations. In addition, lymphoma with a mediastinal mass or with lung involvement may have initially been misdiagnosed as pneumonia in some cases. Children with cancer have higher GP consultation rates in than controls the year preceding the cancer diagnosis[11]. In agreement, we found higher SIRs for children with previous hospital contacts, thus pneumonia may not have been the first clinical disease in all children. Whereas increased diagnostic effort may partially explain the higher short-term occurrence of cancer, it is unlikely to explain the increased risk of lymphoma and brain cancer observed more than five years after pneumonia. There is an ongoing debate on whether or not infectious diseases in children may modulate the child's immune response potentially leading to decreased or increased risk of cancer[12-14]. We did not attempt to address or clarify this hypothesis as our data would not allow us to do so. However, we speculate if the associations demonstrated may be due to cancer-related impairment of the immune system, making a child more vulnerable to severe infections such as pneumonia. In children with an

aggressive type of cancer, the infection may lead on to cancer diagnosis, whereas in children with a more indolent cancer, the infection occurs in the preclinical phase[1].

Based on the low absolute cancer risks observed, our findings do not warrant a change in the work-up of children diagnosed with pneumonia during a hospital admission.

Contributors HTS and KKS conceived the study idea. KKS reviewed the literature. KKS and HTS designed the study and directed the analyses, which were carried out by DKF. All authors participated in the interpretation of the results. KKS organized the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version

Table 1: **Risk of leukaemia, lymphoma, and brain cancer, stratified analysis**

	N	Observed/expected numbers of cancer	SIR [95% CI]
All	83,935	168/90	1.9 [1.6, 2.2]
Boys	47,650	89/53	1.7 [1.3, 2.1]
Girls	36,285	79/37	2.2 [1.7, 2.7]
Age			
0-4	70,476	135/76	1.8 [1.5, 2.1]
5-9	8145	14/8	1.7 [0.9, 2.8]
10-14	3114	8/3	2.3 [1.0, 4.5]
15-17	2200	11/3	4.2 [2.1, 7.5]
Previous hospitalizations			
0	18,114	20/17	1.2 [0.7, 1.9]
1	45,161	94/50	1.9 [1.5, 2.3]
2	11,953	24/14	1.8 [1.1, 2.6]
3+	8707	30/10	3.1 [2.1, 4.4]
Calendar period			
1994-1998	21,618	96/81	1.2 [1.0-1.4]
1999-2003	21,067	61/49	1.3 [1.0-1.6]
2004-2008	20,644	54/29	1.9 [1.4-2.5]
2009-2013	20,607	30/12	2.5 [1.7-3.5]
Congenital malformations			
Yes	8733	31*/9	3.7 [2.5, 5.2]
a) Downs Syndrome	489	9/1	16.2 [7.4, 30.8]
No	75,202	137/81	1.7 [1.4, 2.0]
Immune deficiency			
Yes	137	2/0.1	17.5 [2.1, 63.2]
No	83,798	166/90	1.9 [1.6, 2.2]
Imaging examination (after 2002)			

Yes	36,230	66/25	2.7 [2.1, 3.4]
No	13,280	9/8	1.1 [0.5, 2.1]

* Congenital malformations included conditions related to the nervous system (Q00-Q07); eye, ear, face and neck (Q10-Q18); the circulatory system (Q20-Q28); the respiratory system (Q30-Q34); cleft lip and cleft palate (Q35-Q37); the digestive system (Q38-Q45); genital organs (Q50-Q56); the urinary system (Q60-Q64); malformations and deformations of the musculoskeletal system (Q65-Q79); and other (Q80-Q99).

Table 2: Risk of leukaemia, lymphoma, and brain cancer by follow-up interval

	Observed/expected numbers of cancer and SIRs [95% CI]					
	0-<6 months of follow-up		6 months-<5 years		5+ years	
Lymphoid leukaemia[a]	15/2	6.2 [3.5, 10.3]	27/16	1.7 [1.1, 2.4]	8/10	0.8 [0.3, 1.5]
Myeloid leukaemia[a]	7/<1	14.8 [6.0, 30.6]	8/3	2.6 [1.1, 5.2]	2/3	0.8 [0.1, 2.7]
Hodgkin lymphoma[c]	8/<1	60.8 [26.2, 120]	2/1	1.4 [0.2, 5.0]	6/8	0.7 [0.3, 1.5]
Non-Hodgkin lymphoma[d]	5/<1	15.9 [5.2, 37.2]	8/3	2.7 [1.2 ,5.3]	11/6	1.7 [0.9, 3.0]
Brain[e]	8/2	4.4 [1.9, 8.7]	23/14	1.7 [1.1, 2.5]	30/20	1.5 [1.0, 2.2]

Abbreviations: SIR, standardized incidence ratio; CI, confidence interval

Some of the most frequent morphology codes were as follows:

[a] 42 of 50 children had precursor cell lymphoblastic leukaemia, not otherwise specified.

[b] 10 of 17 children had acute myeloid leukaemia, not otherwise specified.

[c] 10 of 16 children had nodular sclerosis classical Hodgkin lymphoma.

[d] 5 of 24 children had diffuse large B-cell, not otherwise specified; 5 had mature T-cell lymphoma, not otherwise specified; 4 had Burkitt lymphoma, not otherwise specified, and 4 had anaplastic large cell lymphoma.

[e] 15 of 61 children had glioblastoma; 8 had medulloblastoma, not otherwise specified, and 28 had other or unspecified brain cancer.

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Appendix: ICD codes used in the study

Pneumonia: ICD-10: J12–J18 (excl. previous pneumonia episodes ICD-8: 480–486, 073 and 471)

The cohort included 14% with bacterial pneumonia (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae, Chlamydophilia pneumoniae*, and Enterobacteriaceae), 22% with viral pneumonia (including adenovirus, respiratory syncytial virus, parainfluenza virus, metapneumonvirus, and unspecified viruses), while the agent was unspecified for 64% of the children.

Covariates

Immune deficiencies: ICD-10: D80.0-D82.9

Congenital malformations: ICD-8: 74099-75999; ICD-10: Q00-99

Down syndrome: ICD-8: 75939, ICD-10: Q90

Chest imaging: x-ray or CT scan: UXRC00, UXCC75, UXCC77

Cancer: Lymphoid leukaemia (C91), myeloid leukaemia (C92), non-Hodgkin lymphoma (C82-85, and C90), Hodgkin lymphoma (C81), brain cancer (C71, C751-753, D330-332, D352-354, D430-432, and D443-445)