Papers

Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study
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Abstract

Objective To test the hypothesis that reduced exposure to common infections in the first year of life increases the risk of developing acute lymphoblastic leukaemia.

Design and setting The United Kingdom childhood cancer study (UKCCS) is a large population based case-control study of childhood cancer across 10 regions of the UK.

Participants 6305 children (aged 2-14 years) without cancer; 3140 children with cancer (diagnosed 1991-6), of whom 1286 had acute lymphoblastic leukaemia (ALL).

Main outcome measure Day care and social activity during the first year of life were used as proxies for potential exposure to infection in infancy.

Results Increasing levels of social activity were associated with consistent reductions in risk of ALL; a dose-response trend was seen. When children whose mothers reported no regular activity outside the family were used as the reference group, odds ratios for increasing levels of activity were 0.73 (95% confidence interval 0.62 to 0.87) for any social activity, 0.62 (0.51 to 0.75) for regular day care outside the home, and 0.48 (0.37 to 0.62) for formal day care (attendance at facility with at least four children at least twice a week) (P value for trend < 0.001). Although not as striking, results for non-ALL malignancies showed a similar pattern (P value for trend < 0.001). When children with non-ALL malignancies were taken as the reference group, a significant protective effect for ALL was seen only for formal day care (odds ratio = 0.69, 0.51 to 0.93; P = 0.02). Similar results were obtained for B cell precursor common ALL and other subgroups, as well as for cases diagnosed above and below age 5 years.

Conclusion These results support the hypothesis that reduced exposure to infection in the first few months of life increases the risk of developing acute lymphoblastic leukaemia.

Introduction

The idea that infections are involved in the aetiology of childhood leukaemia dates back to the 1940s. Two key papers appeared in 1988. Greaves proposed that a deficit of exposure to infectious agents in infancy and subsequent "delayed" infectious challenge were causal factors in the development of B cell precursor common acute lymphoblastic leukaemia, which is responsible for the childhood peak of acute lymphoblastic leukaemia (ALL) at age 2-5 years. Kinlen proposed that population influx into isolated communities (population mixing) could generate excesses of childhood leukaemia by causing mini-epidemics of one or more infections to which leukaemia may be a rare response. The UK childhood cancer study (UKCCS), a large population based case-control study, was designed to test several hypotheses, one of which was that leukaemias and lymphomas may be caused by abnormal responses to common infectious agents. Here, we focus on Greaves's hypothesis that immunological isolation in infancy increases the risk of B cell precursor common ALL (cALL). No single protective agent or transmission pathway has been identified, so proxy variables for exposure to infection must be used. The literature on infectious illnesses occurring in day care settings suggests that social interactions with other children outside the home may be important. Several studies of childhood leukaemia have used such proxies.

Precise molecular subclassification of cALL is potentially important for these analyses. The two largest subgroups are those with hyperdiploidy (hyperdiploid ALL) and with fusion of the TEL and AML1 genes (TEL-AML1 ALL). Most (possibly all) children with these lesions have affected clones present at the time of birth, so initiation usually occurs in utero. However, the modest level of concordance in identical twins with one affected by cALL (approximately 10%), together with the much greater frequency of these lesions in cord blood than the lifetime risk of the cALL subtype, indicates that at least one postnatal event also occurs in the development of CALL. Greaves's original hypothesis relates to the promotional factors that affect the frequency of this second event.

The UKCCS included all childhood cancers. In this paper we compare social activity of cases and controls during the first year of life for ALL and subgroups of ALL. We also compare ALL with non-ALL malignancies. We excluded children aged under 2 years at the time of diagnosis (cases) or pseudodiagnosis (controls) in order to avoid both dilution of results through overlap for younger children of the two time windows in which associations in opposite directions are predicted and the potential for early symptoms of leukaemia to influence attendance at day care.

Methods

Participants

This case-control study was conducted in 10 regions across the United Kingdom between 1991 and 1996. The UKCCS study design, data collection and consenting procedures, ethical approvals, and participation rates are described in detail elsewhere. Briefly, children diagnosed as having a confirmed malignancy were ascertained through paediatric oncology units, and two controls matched to each case for sex, month and year of birth, and region of residence at diagnosis were randomly selected from population registers. Age at diagnosis of the case was designated as the age at "pseudodiagnosis" of the matched control. A structured questionnaire was used to interview...
Results

Most (89%) mothers of controls reported some social activity with children outside the family in the first year of life (table 2). Any such activity was associated with a reduced risk of ALL (odds ratio = 0.66; P < 0.001). The risk ratios for cALL alone and for the cytogenetic subgroups TEL-AML1 and hyperdiploid were similarly reduced. Analyses of non-ALL malignancies combined gave a similar result; the only individually statistically significantly reduced risk was for the largest group—central nervous system tumours. With respect to the case-case comparison (ALL vs non-ALL malignancies), the dichotomous variable “any social activity” was not significantly reduced. Analyses restricted to 2-5 year olds produced similar results (table 2), but we found no evidence that the association was stronger in the childhood peak (2-5 years) than at older ages.

Each category of malignancy showed a significant inverse trend as level of social activity increased (table 2). The statistically significant trend (P = 0.04) for the comparison of ALL with non-ALL malignancies (right hand column) is due largely to the reduced odds ratio for formal day care (odds ratio = 0.69, 95% confidence interval 0.51 to 0.93). Analyses restricted to cases aged 2-5 years gave similar results, although statistical significance was reduced.

The proportion of children who had an older sibling living in the home at the time of birth was similar for ALL (56%), cALL (54%), non-ALL malignancies (57%), and controls (57%), and we observed no significant trends with numbers of older siblings in any diagnostic group (table 3). As any relation between social activity and ALL might be expected to be more marked among children born into households without other children, we repeated the analyses in table 2 for children with and without older siblings. The odds ratio for formal day care was 0.61 (0.42 to 0.87) for ALL in children without older siblings and 0.38 (0.26 to 0.54) for those with older siblings, a non-significant difference in the opposite direction to that anticipated.

Estimated risks for children starting day care in the first year of life showed no marked trends with age at first attendance (table 4). The greatest reduction in risk of ALL, however, was seen in children who attended formal day care during the first three months of life, for whom the odds ratio remained 0.52 (0.32 to 0.83; P = 0.007).

Discussion

The UKCCS was a large, nationwide, population based investigation into the causes of childhood cancer. One of the principal hypotheses tested was that immunological isolation in infancy increases the risk of cALL. In this report we assess immunological isolation indirectly, mainly by lack of social activity, as indicated by day care attendance in the first year of life. The overall results for ALL show a consistent and statistically significant reduction in risk for each level of social activity in the first year of life and a dose-response trend across increasing levels of activity. Results were similar for cALL and other ALL subgroups, although the numbers for TEL-AML1 ALL were small. The findings were similar when we restricted the analysis to children aged 2-5 years at diagnosis. However, because we also saw similar trends for non-ALL malignancies, we repeated the analyses for ALL with non-ALL malignancies as the comparison group. The estimated risk for formal day care attendance in the first year of life remained significant (odds ratio = 0.69, 95% confidence interval 0.51 to 0.93; P = 0.02); the effect was most marked for formal day care within the first three months of life (odds ratio = 0.52, 0.32 to 0.83; P = 0.007).

Potential limitations

Studies of this type, in which participants are recruited after their disease status is known and information on exposure is obtained retrospectively by questionnaire, are susceptible to several well documented biases. Participants who respond may differ from those who do not; some responses may systematically differ between cases and controls; and behavioural variables, such as...
Table 2 Levels of social activity in the first year of life for acute lymphoblastic leukaemia (ALL), ALL subgroups, and non-ALL malignancies

<table>
<thead>
<tr>
<th>Activity level</th>
<th>ALL</th>
<th>cALL</th>
<th>TEL-AML1</th>
<th>Hyperdiploid ALL</th>
<th>Non-ALL malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
</tr>
<tr>
<td>Aged over 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any social activity</td>
<td>5343 (85.7)</td>
<td>1020 (80.2)</td>
<td>0.66 (0.56 to 0.77)</td>
<td>640 (80.9)</td>
<td>0.67 (0.55 to 0.82)</td>
</tr>
<tr>
<td>No social activity</td>
<td>895 (14.4)</td>
<td>252 (19.8)</td>
<td>1.00 (19.1)</td>
<td>151 (20.3)</td>
<td>1.00 (18.7)</td>
</tr>
<tr>
<td>Social activity, but no day care</td>
<td>2940 (45.5)</td>
<td>587 (46.1)</td>
<td>0.73 (0.62 to 0.87)</td>
<td>358 (45.3)</td>
<td>0.74 (0.60 to 0.91)</td>
</tr>
<tr>
<td>Informal day care only</td>
<td>1768 (28.3)</td>
<td>325 (25.6)</td>
<td>0.62 (0.51 to 0.75)</td>
<td>218 (27.3)</td>
<td>0.67 (0.53 to 0.84)</td>
</tr>
<tr>
<td>Formal day care</td>
<td>735 (11.8)</td>
<td>108 (8.5)</td>
<td>0.48 (0.37 to 0.62)</td>
<td>64 (8.1)</td>
<td>0.44 (0.32 to 0.60)</td>
</tr>
</tbody>
</table>

P for trend: <0.001 0.004 0.4 <0.001 0.01 0.2

Table 3 Number of older children in household ("siblings") at time of index birth for acute lymphoblastic leukaemia (ALL), ALL subgroups, and non-ALL malignancies

<table>
<thead>
<tr>
<th>No of siblings</th>
<th>ALL</th>
<th>cALL</th>
<th>TEL-AML1</th>
<th>Hyperdiploid ALL</th>
<th>Non-ALL malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
<td>Odds ratio* (95% CI)</td>
</tr>
<tr>
<td>Cases aged over 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6159</td>
<td>1270</td>
<td>789</td>
<td>118</td>
<td>416</td>
</tr>
<tr>
<td>None</td>
<td>2690</td>
<td>565</td>
<td>1.00</td>
<td>365</td>
<td>(46.3)</td>
</tr>
<tr>
<td>1</td>
<td>2216</td>
<td>443</td>
<td>0.96</td>
<td>266</td>
<td>(33.7)</td>
</tr>
<tr>
<td>2</td>
<td>892</td>
<td>182</td>
<td>0.99</td>
<td>115</td>
<td>(14.6)</td>
</tr>
<tr>
<td>≥3</td>
<td>382</td>
<td>60</td>
<td>0.99</td>
<td>43</td>
<td>(5.4)</td>
</tr>
</tbody>
</table>

P for trend: <0.001 0.004 0.4 <0.001 0.001 0.2

Cases aged 2-5 years

Total | 2463 | 673 | 473 | 82 | 248 | 548 |
| None | 1071 | 308 | 1.00 | 221 | (46.7) | 1.00 |
| 1 | 366 | 96 | 0.95 | 65 | (13.7) | 0.89 (0.65 to 1.25) |
| 2 | 153 | 36 | 0.99 | 23 | (4.9) | 0.72 (0.44 to 1.19) |

P for trend: <0.001 0.004 0.4 <0.001 0.001 0.2

Notes:
*Odds ratio for cases compared with all controls, adjusted for age at diagnosis/pseudo diagnosis, sex, region, maternal age, mother working at time of birth, and deprivation.
†Excluding missing values.
‡Trend across categories none through to formal day care.
social activity outside the home, may be affected by the pre-clinical effects of incipient disease.

Some systematic differences between cases and controls existed in this study. Analysis of census data revealed that controls who agreed to take part were living in more affluent areas, and some control parents were interviewed when their children were older than their matched cases. The average interval from diagnosis or pseudodiagnosis to interview was six months for cases and 14 months for controls. W e investigated the possibility of under-reporting by combining the two lowest categories in the combined exposure variable, and this did not affect the results.

Comparison with other studies

Other case-control studies of childhood leukaemia have looked at social activity and day care. Diversity exists for both ages at diagnosis and ages of day care attendance, as well as the definition of day care used. The only study that quantified exposure to other children reported a significant protective effect. Other studies suggest a reduction in risk of around 30-40% for day care attendance or social activity, though lack of statistical power often leads to imprecise risk estimates.

The difficulty of establishing small effects reliably is illustrated by the lack of consensus among studies investigating an association between childhood ALL and birth order or mother’s parity. Although reduced risks in children with several older siblings have been seen in some studies, most studies, like ours, have found no such effects. As well as sibling position, other studies have considered different proxies for exposure to the spectrum of infectious agents. The only European study with comparable numbers of ALL cases to our series inferred social contact from parents’ employment status and found no association. Several investigators have reported reduced risks of ALL or cALL in children with many infections, or with specific infections in infancy, such as frequent otitis media or roseola, but others have not found such associations.

In support of an infectious aetiology for childhood ALL, several ecological studies have reported that marked influxes of population into isolated areas are followed by transiently increased rates of childhood leukaemia. Furthermore, evidence of inherited susceptibility to ALL associated with HLA and alleles of other immune system genes is consistent with the suggestion that infection may be associated with ALL. The UKCCS has recently reported statistically significant associations between cALL and specific HLA-DPB1 variants. This is further supported by evidence that immunisation of infants may protect against ALL.

Possible mechanisms

The hypotheses proposed by Greaves and Kinlen differ with respect to their speculation as to the underlying mechanisms and the roles of specific infections, viral or otherwise, as well as the postulated timing of key events. Kinlen has proposed that the mini-epidemics that generate excesses of childhood leukaemia are due to one or a small number of specific though unknown leukaemia causing agents, probably viruses. For Greaves, however, the consequences of immunological isolation in the first year of life were predicted to be, firstly, inadequate priming of the naive immune system and, secondly, continuing susceptibility to infections responsible for a later challenge, which, in the absence of adequate priming may precipitate a highly dysregulated immune response. This, in turn, was predicted to promote the development of cALL indirectly by proliferative stress to the bone marrow, which facilitated further mutations.

The effect of the later infectious challenge is thus immunological
What already known on this topic

Childhood leukaemia is a biologically diverse disease and is likely to arise by several aetiological pathways

The common, B cell precursor, form of acute lymphoblastic leukaemia accounts for the incidence peak between 2 and 5 years of age, and immunological isolation may be a causal factor

Children attending day care have an increased risk of contracting a variety of common infections

What this study adds

Children attending day care centres on a regular basis in the first few months of life are less likely to develop acute lymphoblastic leukaemia than are children who do not

rather than leukemogenic. Our study has examined the question of exposures in infancy by using social activity outside the home as proxy but does not contribute to the debate on underlying biological mechanisms.

Conclusion

Our results provide further support that social activity with other infants and children during the first few months of life protects against subsequent risk of ALL. The effect is less pronounced among cases diagnosed at age 2-5 years than at older ages and is not confined to cALL. The most plausible interpretation is that this protection comes from exposure to common infections. Similar associations have been reported for type 1 diabetes and allergies in children.1-4 Whether early exposure to one or more specific infections, or to a spectrum of non-specific agents, protects against each of these disparate diseases remains to be clarified. Nevertheless, we conclude that some degree of early exposure to infection seems to be important for child health.

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Contributors: FEA, TOBE, MFG, JP, ER, and JS were involved in the design and conduct of the study throughout. FE A, CG, JP, and JS were responsible for management and analysis of the data. All authors contributed to writing the manuscript. ER is the guarantor.

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Children attending day care centres on a regular basis in the first few months of life are less likely to develop acute lymphoblastic leukaemia than are children who do not.
Papers

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