Chapter 8

Infection During the First Year of Life and Acute Leukemia: Epidemiological Evidence

Janet Flores-Lujano, Juan Carlos Núñez-Enríquez, Angélica Rangel-López, David Aldebarán-Duarte, Arturo Fajardo-Gutiérrez and Juan Manuel Mejía-Aranguré

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52717

1. Introduction

The role of infection in the etiology of leukemia was revealed for the first time more than ninety years ago through a series of cases reported by Gordon Ward in the year 1917. These cases included 1457 children with acute leukemia, but the results were inconclusive. Later, in another study by Poynton, Thursfield and Paterson, the authors reported that it was not possible to attribute the etiology of leukemia to a single infectious agent and emphasized the importance of host susceptibility in the acquirement of an infection and the development of acute leukemia.[1,2]

In 1937, in a study conducted in England by Kellet, it was mentioned that an infection could be the causative agent for acute leukemia when the infection is widely distributed but has low infectivity. This conclusion was supported by Cooke in 1942 in a study involving 33 pediatric care units in the United States, who found that the peak age of 2 to 5 years in children with acute leukemia correlated with the peak of increased incidence of diseases, such as measles and diphtheria. [3,4]

One of the most important scientific contributions in this regard was made by Kinlen et al., who found a relationship between high incidence rates of acute leukemia and Non-Hodgkin's lymphoma and infections in children living near rural areas. Kinlen's findings resulted in the emergence of a hypothesis proposing that leukemia could be caused by exposure to an infectious agent in a susceptible population and, in this case, a mixed population (rural-urban), causing an abnormal immune response that increases the risk of developing the disease. [5,7]

Moreover, Greaves et al. provided a new approach to the hypothesis that had been raised by Kellet, now basing it on biological and epidemiological data on acute leukemia. These authors suggested the hypothesis of late infection, which is explained by two stages: the first stage occurs with a mutation in utero at the same time that precursor B cells are developing and a second stage, during the postnatal period, in which the cell that undergoes a mutation is exposed to a common infection late in the first year of the child's life. [8-13]

2. Measuring exposure to infection with proxy variables

Over time, in epidemiological studies that have attempted to determine whether an association between early infections and the development of leukemia exists, some indicators have been used to quantify the exposure to infection. These indicators are designated as "proxies" and include socioeconomic status, surgical history, allergic diseases, immunizations, attendance at daycare, breastfeeding, neonatal infections, and prenatal history, among others. [14-25]

2.1. Socioeconomic status

In several epidemiological studies that have assessed infections during the first year of life in children, it was considered to be important to adjust for socioeconomic status because a high socioeconomic status is consistently associated with the development of leukemia and protection against infection. On the contrary, those who have a low socioeconomic status are at a higher risk for the presence of common infections. [26-30] It is important to note, however, that the methods used to measure this variable are not consistent. For example, Steensel-Moll et al. measured socioeconomic status in The Netherlands (1973-1980) according to the parents' education, while other authors have used, for example, the number of people per room, home ownership, and family income as indicators of socioeconomic status. [15-17,21,22,31-33]

2.2. Prenatal history

The study of prenatal history is interesting as a proxy because it assesses the association between infections and the development of leukemia before birth in an indirect manner, taking into account the fact that, being part of a binomial mother-fetus, the child may have been exposed to infection during the intrauterine period if the mother had an infection during pregnancy. For example, in a study by Fedrick and Alberman in 1972, a positive association was reported between influenza during pregnancy and the development of leukemia and lymphoma, where a RR of 9 ($p < 0.001$) was obtained. Other studies have used other variables associated with pregnancy for the same purpose. For example, whether antimicrobials and/or antiviral drugs were used if the mother had infections was considered. [34] Moreover, the authors of several studies considered a history of antibiotic and/or antiviral use by mothers during pregnancy to reflect the fact that they had been exposed to an infectious process. In this regard, Infante-Rivard et al. noted during 1989 to 1995 that the use of antimicrobials during pregnancy increased the risk of leukemia, with an OR of 1.5 (95% CI:1.02-2.21). When the data were fur-

ther adjusted for the child's age being <4 years at diagnosis, the OR was 1.78 (95% CI: 1.04-3.04). Furthermore, in 2010, these results were supported by the German study of Kaatsch et al., who reported an OR of 1.47 (95% CI: 1.06-2.04). [33,35] These findings, however, are inconsistent with those reported by other authors. [36-45]

2.3. Neonatal infections

While there are maternal protective barriers during pregnancy that help to prevent infections that may occur in the child at some point after birth, when these barriers cease to exist and the immune system is not well developed, the child is at greater risk for developing infections. Therefore, many epidemiological studies have considered the neonatal period to be a crucial step in the assessment of the relationship between infections and the development of acute leukemia. In 1999, McKinney et al. reported that the presence of neonatal infection was associated with a decreased risk of acute lymphoblastic leukemia (ALL) in Scottish children, with an OR of 0.49 (95% CI: 0.26 to 0.95) being more evident in cases of skin infections, such as omphalitis and/or infection in the skin around the umbilical cord, with an OR of 0.20 (95% CI: 0.05 to 0.87) for all leukemias and for acute lymphoblastic leukemia, regardless of birth type (vaginal or by cesarean section). [46]

2.4. Breastfeeding

Breast milk is considered to be the first vaccine that a child receives during the first months of life, and it protects against infections by stimulating the immune system. There are many mechanisms by which breast milk exerts its antimicrobial and immunological properties. Among the most important mechanisms are the immunoglobulins, interleukins, lactoferrin, mucin, various types of enzymes (e.g., lysozyme and lipases), opsonins, cytokines, prostaglandins and other small peptides. Also involved in these functions are T and B lymphocytes, which are present in breast milk. Thus, the study of breastfeeding as a protective factor against infections during the first year of life has generated scientific interest. [47-50] In most epidemiological studies, it has been documented that breastfeeding favorably influences both the response to infection and the modulation of the child's immune system. [21,33,51-64]

These factors require further investigation, as there is inconsistency among the epidemiological studies conducted thus far regarding whether a child's immune system will respond appropriately to an infectious agent after the child has been breastfed for the first six months of life. However, if the child has had recurrent common infections, his/her immune system will have an adequate response to a delayed infection.

2.5. Attendance at daycare

The child's attendance at daycare also represents a quantifiable index of infection during the first year of life in relation to the development of leukemia. For its implementation in epidemiological studies, investigators have used the age of entry to kindergarten, the hours spent in child care, the number of partners in the nursery, the presence of infection during their stay in

the nursery, the social activities being undertaken by the child during the first year, the type of staff who attended to the child during their stay and the hours they remained at home, among others. There is evidence reported by some studies that there is a dose-response effect with respect to the number of hours that a child remains in a nursery and a lower risk of developing leukemia, and the more a child is in contact with other children, the risk is increased for common and recurring infections, thus favoring a better stimulation and maturation of the immune system. [17,65] In the UK, Gilham et al. also found child attendance at day care during the first year of life to have a protective effect, reporting an OR = 0.69 (95% CI: 0.51 to 0.93, p = 0.02), but this effect was more significant when the child attended during the first 3 months of age, with an OR = 0.52 (95% CI: 0.32 to 0.83, p = 0.007). [66]

2.6. Immunizations

Knowing the vaccination history of children is another important approach to understanding the role of infections in the modern-day development of childhood acute leukemia. This is based on the assumption that vaccines are infectious antigenic stimuli that enable the formation of antibodies and, therefore, a better performance of the immune system. Vaccines could also be the mechanism by which the development of acute leukemia is prevented. [67] Meanwhile, Schüz et al. conducted a study in Germany (1999) and reported that, in children older than 4 years of age, there was an increased risk of developing leukemia in those with a history of fewer than three vaccines, with an OR of 1.8 (95% CI: 1.2-2.7), and a low risk in children with a history of 4-6 shots, with an OR of 1.3 (95% CI:1.0-1.7), which supports the following dose-response relationship: as the number of vaccines given to children increases, the risk of developing acute leukemia decreases. [68] The role of immunization is still controversial, however, because, as mentioned above, while some authors conclude that immunizations provide protection, others have reported the opposite result. [67,69-74]

2.7. Allergic diseases

The role of allergic diseases (e.g., rhinitis, atopic dermatitis, asthma, and urticaria) as a protective factor for the development of leukemia has been controversial in epidemiological reports. Two hypotheses have been proposed to explain the causal relationship between allergic diseases and cancer, including acute leukemia.

The first hypothesis that we will mention is that of "immune surveillance", which postulates that the immune system can recognize the antigens of malignant cells as foreign and respond to remove them from the body, preventing the potential development of cancer in most cases. Therefore, it is believed that the presence of an allergic disease would increase the surveillance, providing better control and identifying and eliminating any malignant cells, resulting in an increased incidence of malignancy in people who are immunocompromised compared with those with an intact immune system. [75,76]

The second hypothesis refers to a "chronic stimulation of the immune system" that would be conferred by allergens that trigger the carcinogenic potential through both the proliferation

http://dx.doi.org/10.5772/52717

of large numbers of immune cells and the increased likelihood of genetic errors caused by pro-oncogenic mutations, which could not be repaired in subsequent divisions. [77-78]

Linabery et al. conducted a meta-analysis to investigate the relationship between allergic diseases and the development of acute leukemia. Three studies reported a positive association in this regard, with an OR of 1.42 (95% CI: 0.60-3.35). Six studies examined whether there was an association between acute lymphoblastic leukemia (ALL) (OR = 0.69; 95% CI: 0.54 to 0.89) and acute myeloid leukemia (AML) (OR = 0.87; 95% CI: 0.62-1.22), but there was heterogeneity among the results. We also performed such a study in asthmatics, and inverse associations were observed between asthma (OR = 0.79; 95% CI: 0.61-1.02), eczema (OR = 0.74; 95% CI: 0.58-0.96) and hay fever (OR = 0.55, 95% CI: 0.46-0.66) and the development of ALL. [79]

2.8. Surgical history

The individual susceptibility of children who suffer from common diseases and recurrences has been considered to be the main factor leading to surgical interventions that are performed as part of the treatment of these infections. Some examples of these treatments are adenoidectomy, tonsillectomy, interventions for ear surgery, and appendectomy. It is worth noting that these anatomical structures are important parts of the lymphatic tissue and immune system, especially during the first two years of life. Thus, their removal would result in immune dysfunction and an increased risk of infections that occur especially during the first year of life, and this mechanism could be involved in the development of acute leukemia during that time. It is for this reason that epidemiological studies that examine infections as an exposure factor in the development of leukemia are controlled by this variable, but there is no epidemiological evidence that surgical interventions studied as a proxy are associated with the development of childhood acute leukemia. [68]

3. Epidemiological studies

Some types of infections that have been evaluated in most epidemiological studies are respiratory tract infections, gastroenteritis, and those caused by specific infectious agents, such as streptococcus and influenza virus. Other diseases that have been considered are exanthematous diseases, allergic diseases (e.g., asthma, acute rhinitis, and atopic dermatitis) and gastrointestinal diseases because these diseases are recurrent during the first year of life. This recurrence would result in the child's immune system performing better when mature, decreasing the risk of aberrant responses to infections that could result in the development of acute leukemia. [80,81] This finding was consistent with that of Perillat et al., who conducted a study in France in a sample of 280 children with acute leukemia (cases) and 288 healthy children (controls). The authors reported that if the child suffered from recurrent infections before 2 years of age, he/she would be protected from the development of acute leukemia, with an OR = 0.6 (95% CI: 0.4-1.0). These results were statistically significant and consistent with those reported by Neglia et al. [21,22,32,68]

However, Schüz et al. (1999) conducted a case-control study in Germany during 1992-1997. They studied 1184 families of children with acute leukemia (cases) and 2588 families of healthy children (controls) and found no association between common infections and an increased incidence of leukemia. It is notable, however, that they reported that when the children had a history of surgical procedures, such as appendectomy/tonsillectomy, at least once in their life, their risk of developing acute leukemia increased, with an OR of 1.4 (95% CI: 1.0-1.9). These authors also observed a significant association with pneumonia, with an OR of 1.7 (95% CI: 1.2-2.3), whereas bronchitis was not associated with the development of acute leukemia, with an OR of 1.1 (95% CI: 0.9-1.4). Moreover, they observed a moderate risk (OR = 1.3; 95% CI: 1.0-1.7) when the children were breastfed for no more than 1 month, specifically in children diagnosed with common ALL. [68]

Neglia et al. performed a case-control study in children under 15 years of age in the U.S. The cases of newly diagnosed ALL were ascertained from the Children's Cancer Group (CCG), and the controls were randomly selected using a random digit-dialing methodology and individually matched to the cases by age, race and telephone area code and exchange between January 1, 1989, and June 15, 1993. They observed a slight decrease in the risk of developing acute leukemia when the child had repeated ear infections during their first year of life, with ORs of 0.86 (95% CI: 0.61-1.22), 0.83 (95% CI: 0.63-1.09) and 0.71 (95% CI: 0.50-1.01) for 1 episode, 2-4 episodes and 5 or more episodes, respectively, and continuous infections were associated with an OR of 0.69 (95% CI: 0.35-1.37; p = 0.026), but these results were not statistically significant. Moreover, it should be noted that these results are similar to a dose-response gradient, as the risk of developing acute leukemia was decreased with an increasing number of infections in the child during the first year of life. This association was more evident in children aged 2 to 5 years with pre-B ALL who presented with ear infections (between 2 and 4 episodes), with an OR of 0.65 (95% CI: 0.43-1.00). No other factor studied was associated with the development of acute leukemia. Furthermore, no association was observed between day care and the development of common acute lymphoblastic leukemia (ALL), with an OR of 1.05 (95% CI: 0.80-1.37). [32]

Using a design similar to that of Perillat et al. (2002) and Neglia et al. (2000), Jourdan-Da et al. evaluated the role of childhood infections in the risk of developing acute leukemia in France. This study included 473 cases of acute leukemia and 567 population-based controls. They found a strong inverse association between gastrointestinal infections and the need to assist the child in day care, with an OR of 0.6 (95% CI: 0.4-0.8). Additionally, a history of asthma decreases the risk of developing leukemia (OR = 0.5; 95% CI: 0.3-0.9). Breastfeeding was not associated with the development of leukemia, but an increasing order of the child's birth increases the risk of developing acute lymphoblastic leukemia, with an OR of 2.0 (95% CI: 1.1-3.7). [15,16,32]

Meanwhile, Rudant et al., also in France, used a case-control design of a National Register (ESCALE) and included 765 incident cases of acute leukemia and 1,681 controls. They observed positive associations when the child presented with recurrent common infections, a history of asthma or a history of eczema, with ORs of 0.7 (95% CI: 0.6-0.9), 0.7 (95% CI: 0.4-1.0) and 0.7 (95% CI: 0.6 -0.9), respectively. Having regular contact with farm animals

(OR = 0.6; 95% CI: 0.5-0.8) and breastfeeding (OR = 0.7; 95% CI: 0.5-1.0) were found to be protective factors for this disease, as was also found in children who had visited farms often in their first year of life, with an OR of 0.4 (95% CI: 0.3-0.6). No significant association was found for assistance of the child in daycare before one year of age (OR = 0.8; 95% CI: 0.6-1.1). One can conclude that repeated infections, such as asthma, play an important role in the etiology of leukemia. [82]

Moreover, Urayama et al., in the USA, conducted two epidemiological studies, namely a case-control study and a meta-analysis. The first study showed that in non-Hispanic white children who attended day care before 6 months of age, the risk of developing leukemia was decreased (OR = 0.90; 95% CI: 0.82-1.00), but this association was not observed in the population of Hispanic children. However, Hispanic children who had ear infections were found to have a decreased risk of developing acute leukemia, with an OR of 0.45 (95% CI: 0.25 to 0.79). Did not report any associations for the other variables studied. In the second study (meta-analysis), these authors evaluated the association between daycare attendance during infancy and the risk of developing acute leukemia; specifically, they wanted to assess whether early exposure to infection protected children from the disease. They concluded that the risk of developing acute leukemia was decreased in children who were exposed to common infections in the first year of life (OR = 0.76; 95% CI: 0.67 to 0.87). [24,25] These findings are consistent with the findings of Perillat et al., Jourdan-Da et al., Dockerty et al., and Ma X et al. [15-19,21,22]

In New Zealand, Dockerty et al. conducted a case-control study that included 121 children diagnosed with acute leukemia and 303 controls (with ages less than 14 years in both groups). They found that exposure to the influenza virus is a risk factor for developing leukemia; that is, a child infected with the influenza virus during the first year of life has a 7-fold risk of developing acute leukemia compared with children who had influenza, with an OR of 6.8 (95% CI: 1.8-25.7). [15,32]

Cardwell et al., using a different epidemiological case-control nested design in a cohort, reported positive evidence of upper respiratory tract infections as a risk factor for the development of acute leukemia (OR = 1.56; 95% CI: 1.08-2.27) and acute lymphoblastic leukemia (OR = 1.59; 95% CI: 1.02-2.49). Similarly, in children presenting with an exanthematous disease, namely chicken pox, we obtained ORs of 2.41 (95% CI: 1.14-5.09) and 2.62 (95% CI: 1.12-6.13) for acute leukemia and acute lymphoblastic leukemia, respectively. [83]

MacArthur et al. conducted a study that included 399 cases and 399 controls who were matched for age and gender and lived in the same area. They evaluated the relationship between vaccination, infectious diseases and common infection and use of medications in children, but their results were not statistically significant, as they found no relationship between childhood diseases and acute leukemia.[84]

Chan et al. performed a population-based, case-control study in China and found that the incidence of roseola and/or fever rash in the first year of life is a protective factor for the development of acute leukemia, with an OR of 0.33 (95% CI: 0.16 to 0.68); however, the risk of developing acute leukemia was increased if the child had a history of tonsillitis in

the period 3-12 months before the reference date (OR = 2.56; 95% CI: 1.22-5.38). No association was found between acute leukemia incidence and daycare attendance. In a study similar to that of Chan et al., Roman et al. found that exposure to fungal infections during the first year of life increases the risk of developing acute leukemia, with an OR of 1.4 (95% CI: 1.0-1.9).[14,85]

4. Infections during the first year of life and development of acute leukemia in children with Down syndrome

In the literature, there are few epidemiological studies that have evaluated the effect of early infections and breastfeeding on the development of acute leukemia in children with Down syndrome; however, the results obtained are very interesting. One such study was conducted by Canfield et al. in a population of children diagnosed with acute leukemia between January 1997 and October 2002 (data were obtained from the records of the Children's Oncology Group). The sample group consisted of 158 children with Down syndrome and leukemia, and the control group consisted of 173 children with Down syndrome, all of whom were randomly selected. The results of this study were that children with Down syndrome who had infections during the first 2 years of life had a lower risk of developing acute leukemia, with an OR of 0.55 (95% CI: 0.33 to 0.92), compared with children with Down syndrome who had not been infected. [86,87]

In another study that was conducted in children with Down syndrome in Mexico City, however, this association could not be verified. That study sought to assess whether breastfeeding and infections during the first year of life were associated with the development of acute leukemia. In that study, both breastfeeding and the development of infections during the first year of life in children with Down syndrome were protective factors for the development of leukemia, with ORs of 0.84 (95% CI: 0.43-1.61) and 1.70 (95% CI: 0.82-3.52), respectively, but the results were not statistically significant. Infections requiring hospitalization were also evaluated, and it was found that children >6 years of age had a higher risk of developing acute leukemia, with an OR of 3.57 (95% CI: 1.59-8.05). Thus, these results do not support those of the previously mentioned study or the hypothesis proposed by Greaves that infections are a protective factor for developing acute leukemia. [88]

Author, Year (Country)	Van Steensel et al., 1986 (The Netherlands)	Schüz et al., 1999 (Germany)	Dockerty et al., 1999 (New Zealand)
Design of study	Case-control study (1973-1980)	Two-part case-control study (1980-1994)	Case-control study (1991-1995)
Size of sample	492 cases, 480 controls; Age: 0-14 years	1184 cases, 2588 controls; Age: 0-14 years	121 cases, 303 controls; Age: 0-14 years
Data collection	Mailed questionnaire; addressed to the diagnosed	Telephone interviews with the parents	Mothers interviewed at the home; standardized

			questionnaires and serological tests were conducted
Variables	Breastfeeding; birth order; family size; social class; number of rooms in the household; infections; hospitalization or consultation for infections; primary infections (measles, chicken pox, mumps, or rubella); periods of fever	First-born child; duration of breastfeeding; deficit in social contacts; routine immunizations; infections; tonsillectomy or appendectomy; allergies of the child; allergies of the mother	Social class; marital status; ethnic group; educational level of the parent; home ownership; length of gestation; age of the mother at the child's birth; weight of the child at birth; exposure of the mother to X-rays during the first trimester; exposure of the child to X-rays or radiotherapy before onset of the illness; tobacco smoking by the mother in the first trimester or before the pregnancy
Odds ratios and relevant results	Common colds (RR: 0.8, 95% CI: 0.6-1.0); periods of fever (RR: 0.9; 95% CI: 0.7-1.2); and primary infections (RR: 0.8; 95% CI: 0.4-2.0). These variables were adjusted for birth order, family size, social class, and residential space. Infectious diseases requiring hospitalization (RR: 0.6; 95% IC: 0.4-1.0).	Routine immunizations between 0-3 years of age and having had a tonsillectomy or appendectomy increased the child's risk of developing leukemia (OR: 3.2; 95% CI: 2.3-4.6 and OR: 1.4; 95% CI: 1.1-1.9, respectively), whereas allergies showed a protective effect (OR: 0.6; 95% IC: 0.5-0.8).	A positive association was found between infection caused by influenza during the first year of life and the risk of developing leukemia (OR: 6.8; 95% CI: 1.8-25.7). No other variable was related to acute leukemia.
Author, Year (Country)	Neglia et al., 2000 (USA)	Infante et al., 2000 (Canada)	Rosenbaum et al., 2000 (USA)
Design of study	Case-control study (January 1, 1989-June 15,1993)	Case-control study (1989-1995)	Case-control study (1980-1991)
Size of sample	1842 cases, 1986 controls; Age: <15 years	491 cases, 491 controls; Age: 0-9 years	255 cases, 760 controls; Age: 0-14 years; 31 county regions (cases)
Data collection	Structured interview	Structured questionnaire administered to the mothers by telephone	Standardized questionnaires mailed to the parents
Variables	Interview of the mother; gender; age; race; educational level of the mother; educational level of the father; family income; immunophenotype class.	Educational level of the mother; family income at the time of the child's diagnosis; mother's age; father's age; tobacco use by the mother; infections during the pregnancy; child's birth order; attendance at day care or a nursery; principal feeding method (breast or bottle); length of breastfeeding; history of recurrent infections of the mother; use of antibiotics during pregnancy	Gender; race; educational level of the mother; birth order; feeding status at birth (breast, bottle); age at the diagnosis; day care or preschool program; family outcome; maternal employment during the pregnancy
Odds ratios and relevant results	Neither attendance at nor time remaining in daycare was associated with the risk of developing leukemia. For children with 1-4 episodes of ear infections or sustained infections, the association between infections and	Early attendance at daycare or at a nursery and breastfeeding were protective factors against the development of acute leukemia (OR: 0.49; 95% CI: 0.31-0.77 and OR: 0.68; 95% CI: 0.49-0.95, respectively).	Children who attended day care for >36 months had a lower risk of developing leukemia (OR: 1.32, 95% CI: 0.70-2.52) than those who attended day care for 1-18 months (OR: 1.74; 95% CI:

	the development of acute leukemia was not statistically significant.		0.89-3.42) or for 19-36 months (OR: 1.32; 95% CI: 0.64-2.71).
Author, Year (Country)	Perillat et al., 2002 (France)	Chan et al., 2002 (China)	Jourdan-Da et al., 2004 (France)
Design of study	Case-control study	Population-based, case-control study (November 1994-December 1997)	Case-control study (1995-1998)
Size of sample	280 incident cases, 288 hospital controls	116 cases, 788 controls; Age: 2-14 years; the Hong Kong Pediatric Hematology and Oncology Study Group	473 cases, 567 population-based controls
Data collection	Standardized, face-to-face interviews of the mothers	Standardized, face-to-face interviews	Questionnaire
Variables	Diagnosed categories (acute leukemia classification and immunophenotype); gender; age; ethnic origin; hospital where the case was identified; educational level of the mother; occupation of the mother at the time of the interview; socio-professional categories; place of residence; birth order; number of siblings; daycare attendance; age at the start of daycare; repeated infections before the age of 2 years; incidence of surgical operation for early ear-nose-throat infections before the age of 2 years; breastfeeding	Medical history (infectious illnesses) in the first year of life; breastfeeding; daycare/social contacts of the index patient and siblings; household environment; community environment	Gender; age at the time of diagnosis; region of the residence at the time of diagnosis; socio-professional categories; educational level of the mother; educational level of the father; birth weight; term of pregnancy; birth order; mother's age at birth; Down syndrome; breastfeeding; infections in the first year of life
Odds ratios and relevant results	An inverse association was found between the development of acute leukemia and attendance at daycare (OR: 0.6; 95% CI: 0.4-1.0), repeated (≥4 per year) early common infections before the age of 2 years (OR: 0.6; 95% CI: 0.4-1.0), and surgery for infection of the nose, ear, or throat before the age of 2 years (OR: 0.5; 95% CI: 0.2-1.0). A statistically significant interaction was found between attendance at daycare and repeated common infections.	If the child had rubella and/or fever during the first year of life, the risk was lowered (OR: 0.33; 95% CI: 0.16-0.68). A change of residence during the first year of life presented a lower risk of the child developing leukemia (OR: 0.47; 95% CI: 0.23-0.98), whereas with such a change during the second year, the risk increased (OR: 3.92; 95% CI: 1.47-10.46).	A strong association was found between childhood gastrointestinal illnesses and attendance at daycare and a lowered risk of developing leukemia (OR: 0.6; 95% CI: 0.4-0.8); however, no association was found for breastfeeding. Birth order (4th or later) showed a significant association with an increased risk of acute lymphoblastic leukemia (OR: 2.0; 95% CI: 1.1-3.7), while prior episodes of asthma were associated with a lower risk of developing acute lymphoblastic leukemia (OR: 0.5; 95% CI: 0.3-0.9).
Author, Year (Country)	Rosenbaum et al., 2005 (USA)	Ma et al., 2005 (USA)	Roman et al., 2007 (United Kingdom)
Design of study	Population-based, case-control study (1980-1991)		Population-based, case-control study (1991-1996)

Size of sample	255 cases, 760 controls; Age: 0-14 years	294 incident cases, 376 controls; Age: 0-14 years	455 cases, 1031 controls; Age: 0-14 years
Data collection	Questionnaire	Personal interview of the parents	Interview of the parents
Variables	Gender; race; birth year; mother's educational level; family income; maternal smoking status; infant feeding at birth; birth order; attendance at daycare before 25 months of age; year of diagnosis of leukemia; age at diagnosis of leukemia; allergies; history of allergies; common infections (e.g., colds, otitis media, influenza, croup, bronchiolitis, pneumonia, vomiting, diarrhea)	Age; gender; household income; mother's educational level; mother's age at birth; birth weight; birth order; duration of breastfeeding; day care attendance; infections during infancy	Gender; age; diagnosis of an infectious disease
Odds ratios and relevant results	The results showed that infection late in the first year of the child's life was associated with an increase in the risk of developing leukemia.	Attendance at daycare and infections during infancy were associated with a decrease in the risk of developing acute lymphoblastic leukemia within the white, Hispanic population (OR: 0.42; 95% CI: 0.18-0.99 and OR: 0.32; 95% CI: 0.14-0.74, respectively); corresponding data for the Hispanic population, even for those living in the same area, did not agree.	The cases had more episodes of infection than did the controls, which was more notable in the neonatal period (≤1 month): 18% of the controls and 24% of the cases with leukemia were diagnosed with an average of <1 infection (OR: 1.4; 95% CI: 1.1-1.9; $p < 0.05$). The cases with ≥1 episodes of infection in the neonatal period tended to be diagnosed with acute lymphoblastic leukemia at a relatively young age.
Author, Year (Country)	MacArthur et al., 2007 (Canada)	Cardwell et al., 2008 (United Kingdom)	Urayama et al., 2010 (USA)
Design of study	Population-based, case-control study (January 1,1990 - December 31,1994)	Nested case-control (cohort) study	Case-control study (1995-1999)
Size of sample	399 cases, 399 controls; Age: 0-14 years	62 cases, 2215 matched controls	669 cases, 977 controls; Age: 1-14 years
Data collection	Standardized personal interviews in the child's home	Data-based	
Variables	Gender; age; mother's age; father's age; numbers of live births; annual household income; mother's education; father's education; ethnicity; vaccinations; illness and infections; breastfeeding; allergies; immunosuppressant medication for the child; vitamins; antibiotics for the child	Gender; age; consultations; number of consultations; antibiotic prescriptions; common infections	Gender; mother's age at the child's birth; mother's educational level; annual household income; birth weight; breastfeeding; mother's tobacco use; daycare attendance; history of common infections in the child; ethnicity
Odds ratio and relevant results	No association was found between early infections and acute leukemia; however, vitamin use was associated with a risk of developing acute leukemia (OR; 1.66; (95% CI: 1.18-2.33); the use of	One or more infections in the first year of life reduced the risk of leukemia (OR: 10.5; 95% CI: 0.69-1.59;	When variables were evaluated separately, both attendance at daycare at 6 months of age and birth order reduced the risk of leukemia (OR: 0.90; 95% CI:

	immunosuppressants by the child decreased the risk of leukemia (OR: 0.37; 95% CI: 0.16-0.84); breastfeeding for >6 months had a protective effect against the development of leukemia ($p < 0.05$).	$p = 0.83$) and of acute lymphoblastic leukemia (OR: 1.05; 95% CI: 0.64-1.74; $p = 0.84$).	0.82-1.00 and OR: 0.68; 95% CI: 0.50-0.92, respectively) in a white, non-Hispanic population, but not in a Hispanic population; however, if these children had ear infections, the risk of developing acute leukemia was reduced (OR: 0.45, 95% CI: 0.25-0.79).
Author, Year (Country)	Rudant J et al., 2010 (France)	Urayama et al., 2011 (USA)	
Design of study	National registry-based, case-control study ESCALE (2003-2004)	Observational studies (1993-2008)	
Size of sample	765 incident cases, 1,681 controls.	14 case-control study	
Data collection	Questionnaire, interviews by telephone	Searches of the PubMed database and bibliographies of the publications	
Variables	Mother's educational level; parental professional category; place of residence at the time of diagnosis; mother's age at the child's birth; number of children age <15 years in the household; birth order; breastfeeding; duration of breastfeeding; early common infections; surgical operation for ear, nose, or throat infections; history of allergies; contact with animals; farm visits before the age of 2 years	N/A	
Odds ratios and relevant results	Negative associations were found for children with repeated common infections (OR: 0.7; 95% CI: 0.6-0.9); with a history of asthma or eczema (OR: 0.7; 95% CI: 0.4-1.0 and OR: 0.7; 95% CI: 0.6-0.9, respectively); with attendance at daycare before 1 year of age (OR: 0.8; 95% CI: 0.6-1.1); and with prolonged breastfeeding (OR: 0.7; 95% CI: 0.5-1.0).	Attendance at daycare is associated with a reduced risk of acute lymphoblastic leukemia (OR: 0.76; 95% CI: 0.67-0.87).	

Table 1. Summary of reviewed articles concerning the epidemiology of early infection and acute childhood leukemia.

5. Conclusions

The vast majority of the epidemiological studies conducted thus far on the association between infection during the first year of life and the development of acute leukemia in children have corresponding case-control designs. Additionally, the results of these studies appear to suggest a lower risk of developing acute leukemia among children who were ex-

posed to early infections compared with those who were not exposed. No such association, however, has been reported by other authors; therefore, infections that occur during the first year of life are still considered to be a controversial exposure factor. To achieve better epidemiological evidence, the consistent study of proxy variables in different studies should be performed to enable a better quantification of exposure.

Acknowledgements

This work was funded by the Consejo Nacional de la Ciencia y la Tecnología (CONACYT) through its program, Fondo Sectorial de Investigación en Salud y Seguridad Social (SALUD 2007-1-71223/FIS/IMSS/PROT/592); the Fondo Sectorial de Investigación para la Educación (CB-2007-1-83949/FIS/IMSS/PROT/616) and by Instituto Mexicano del Seguro Social (FIS/IMSS/PROT/G10/846).

Author details

Janet Flores-Lujano, Juan Carlos Núñez-Enríquez, Angélica Rangel-López,
David Aldebarán-Duarte, Arturo Fajardo-Gutiérrez and Juan Manuel Mejía-Aranguré*

*Address all correspondence to: arangurejm@hotmail.com

Research Unit in Clinical Epidemiology, Hospital of Pediatrics, National Medical Center 21st Century, Mexican Institute of Social Insurance (IMSS), Mexico City, Mexico

References

[1] Ward, G. The infective theory of acute leukemia. British Journal of Children's Diseases 1917; 14 10-20

[2] Poynton, F.; Thursfield, H. & Paterson, D. The Severe Blood Diseases of Childhood, London XIX. British Journal of Children's Diseases. 1922,128

[3] Kellet, C. Acute myeloid leukemia in one of identical twins. Archives of disease in childhood 1937;12(70) 239-252

[4] Cooke, J. V. The incidence of acute leukemia in children. The Journal of the American Medical Association 1942; 119 547-550

[5] Kinlen, L. Epidemiological evidence for an infective basis in childhood leukaemia. British Journal of Cancer 1995;71(1) 1-5

[6] Kinlen, L.; Dickson, M. & Stiller, C. Childhood leukemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. British Journal of Cancer 1995;310 763-768

[7] Kinlen, L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet 1998;2(8624) 1323-1327

[8] Greaves, M. Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia 1988;2(2) 120-125

[9] Greaves, MF & Alexander, FE. An infectious etiology for common acute lymphoblastic leukemia in childhood? Leukemia 1993;7(3) 349-360

[10] Greaves, M.; Colman, S.; Beard, M.; Bradstock, K.; Cabrera, M.; Chen, PM.; Jacobs, P.; Lam-Po-Tan, P.; MacDougall, L. & Williams, C. Geographical distribution of acute lymphoblastic leukemia subtypes: second report of the collaborative group study. Leukemia 1993;7(1) 27-34

[11] Greaves, M. & Alexander, F. Epidemiological characteristics of childhood acute lymphocytic leukemia. Leukemia 1994;8(10) 1793-1794, ISSN 0887-6924

[12] Greaves, M. Science, Medical and the future: Childhood leukaemia. British Medical Journal 2002;2(324) 283-287

[13] Greaves, M. Infection, immune responses and the aetiology of childhood leukemia. Nature Reviews Cancer 2006;6(3) 93-203

[14] Chan, L.; Lam, T.; Li, C.; Lau, Y.; Li, C.; Yuen, H.; Lee, C.; Ha, S.; Yuen, P.; Leung, N.; Patheal, S.; Greaves, M. & Alexander, F. Is the timing of exposure to infection a major determinant of acute lymphoblastic leukaemia in Hong Kong?.Paediatric and Perinatal Epidemiology 2002;16(2) 154-165

[15] Dockerty, J.; Skegg, D.; Elwood, J.; Herbison, G.; Becroft, D. & Lewis, M. Infections, vaccinations, and the risk of childhood leukaemia. British Journal of Cancer, 1999; 80(9) 1483-1489

[16] Jourdan-Da, S.; Perel, Y.; Méchinaud, F.; Plouvier, E.; Gandemer, V.; Lutz, P.; Vannier, J.; Lamagnére, J.; Margueritte, G.; Boutard, P.; Robert, A.; Armari, C.; Munzer, M.; Millot, F.; De Lumley, L.; Berthou, C.; Rialland, X.; Pautard, B.; Hémon, D. &Clavel, J. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. British Journal of Cancer 2004; 90(1) 139-145

[17] Ma, X.; Buffler, P.; Wiemels, J.; Selvin, S.; Metayer, C.; Loh, M.; Does, M. &Wiencke, J. Ethnic difference in daycare attendance, early infections, and risk of childhood acute lymphoblastic leukemia. Cancer Epidemiology, Biomarkers & Prevention 2005;14(8) 1928-1934

[18] Ma, X.; Metayer, C.; Does, M. &Buffler, P. Maternal pregnancy loss, birth characteristics, and childhood leukemia (United States). Cancer Causes & Control 2005;16(9) 1075-1083

[19] Ma, X.; Urayama, K.; Chang, J.; Wiemels, J. &Buffler, P. Infection and pediatric acute lymphoblastic leukemia. Blood Cells, Molecules & Diseases 2009;42(2) 117-120

[20] Roman, E.; Simpson, J.; Ansell, P.; Lightfoot, T. & Smith, A. Infectious proxies and childhood leukemia: Findings from the United Kingdom Childhood Cancer Study (UKCCS). Blood Cells, Molecules and Diseases 2009;42(2) 126–128

[21] Perillat, F.; Clavel, J.; Jaussent, I.; Baruchel, A.; Leverger, G.; Nelken, B.; Philippe, N.; Schaison, G.; Sommelet, D.; Vilmer, E. &Hemon, D. Breast-feeding, fetal loss and childhood acute leukemia. European Journal of Pediatrics 2002;161(4) 235-237

[22] Perrillat, F.; Clavel, J.; Auclerc, M.; Baruchel, A.; Leverger, G.; Nelken, B.; Philippe, N.; Schaison, G.; Sommelet, D.; Vilmer, E. &Hémon, D. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. British Journal of Cancer 2002;8(86) 1064-1069

[23] Rosenbaum, P.; Buck, G. &Brecher, M. Early child-care and preschool experiences and the risk of childhood acute lymphoblastic leukemia. American Journal of Epidemiology 2000;152(12) 1136-1144

[24] Urayama, K.; Buffler, P.; Gallagher, E.; Ayoob, J. & Ma, X. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. International Journal of Epidemiology 2010;39(3) 718–732

[25] Urayama, K.; Ma, X.; Selvin, S.; Metayer, C.; Chokkalingam, A.; Wiemels, J.; Does, M.; Chang, J.; Wong, A.; Trachtenberg, E. &Buffler, P. Early life exposure to infections and risk of childhood acute lymphoblastic leukemia. International Journal of Cancer 2011;128(7) 632-643

[26] Githens, J.; Elliot, F. & Saunders, L. The relation of socioeconomic factors to incidence of childhood leukemia. Public Health Reports 1965;80 573–578

[27] Alexander, F.; Cartwright, R.; McKinney, P. & Ricketts, T. Leukaemia incidence, social class and estuaries: an ecological analysis. Journal of Public Health Medicine, 1990;12(2) 109–117

[28] Draper, GJ. The Geographical Epidemiology of Childhood Leukaemia and Non-Hodgkin Lymphomas in Great Britain, 1966–83, OPCS Studies on Medical and Population Subjects No. 53 1991. London: OPCS; (ed).

[29] Stiller, C. & Boyle, P. Effect of population mixing and socioeconomic status in England and Wales, 1979–85, on lymphoblastic leukaemia in children. British Medical Journal 1996;313 1297–1300

[30] Borugian, M.; Spinelli, J.; Mezei, G.; Wilkins, R.; Abanto, Z. & McBride, M. Childhood leukemia and socioeconomic status in Canada. Epidemiology 2005;16(4) 526–531

[31] Van Steensel, H.; Valkenburg; H. & van Zanen G. Childhood leukemia and infectious diseases in the first year of life: a register-based case-control study. American Journal of Epidemiology 1986;124(4) 590-594

[32] Neglia, J.; Linet, M.; Shu, X.; Severson, R.; Potter, J.; Mertens, A.; Wen, W.; Kersey, J. & Robison, L. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. British Journal of Cancer 2000;82(1) 234-240

[33] Infante, C.; Fortier, I. & Olson E. Markers of infection, breast-feeding and childhood acute leukemia. British Journal of Cancer 2000;83,(11) 1559-1564

[34] Fedrick, J &Alberman, ED. Reported influenza in pregnancy and subsequent cancer in the child. British Medical Journal, 1972;27(2) 485-488

[35] Kaatsch P, Scheidemann-Wesp U, Schüz J. Maternal use of antibiotics and cancer in the offspring: results of a case-control study in Germany. Cancer Causes Control 2010 21(8) 1335-1345.

[36] Van Steensel-Moll, H.; Valkenburg, H.; Vandenbroucke, J. & van Zanen, G. Are maternal fertility problems related to childhood leukaemia? International Journal of Epidemiology 1985;14(4) 555-559

[37] Thapa, P.; Whitlock, J.; Brockman-Worrell, K.; Gideon, P.; Mitchel, E Jr.; Roberson, P.; Pais, R. & Ray, W. Prenatal Exposure to Metronidazole and Risk of Childhood Cancer A Retrospective Cohort Study of Children Younger than 5 Years. Cancer 1998;83(7), 1461-1468

[38] Gilman, E.; Wilson, L.; Kneale, G. & Waterhouse, J. Childhood cancers and their association with pregnancy drugs and illnesses. Paediatric and Perinatal Epidemiology 1989;3(1) 66-94

[39] Rodvall, Y.; Pershagen, G.; Hrubec, Z.; Ahlbom, A.; Pedersen, N. &Boice, J. Prenatal X-ray exposure and childhood cancer in Swedish twins. International Journal of Cancer 1990;46(3) 362-365

[40] vanDuijn, C.; van Steensel-Moll, H.; Coebergh, J. & van Zanen, G. Risk factors for childhood acute non-lymphocytic leukemia: An association with maternal alcohol consumption during pregnancy? Cancer Epidemiology, Biomarkers & Prevention 1994;3(6) 457-460

[41] Roman, E.; Ansell, P. & Bull, D. Leukaemia and non-Hodgkin's lymphoma in children and young adults: are prenatal and neonatal factors important determinants of disease? British Journal of Cancer 1997;76(3) 406–415

[42] Naumburg, E.; Bellocco, R.; Cnattingius. S.; Jonzon, A. &Ekbom, A. Perinatal exposure to infection and risk of childhood leukemia. Medical and Pediatric Oncology 2002;38(6) 391-397

[43] Wen, W.; Shu, X.; Potter, J.; Severson, R.; Buckley, J.; Reaman, G. & Robison, L. Parental medication use and risk of childhood acute lymphoblastic leukemia. Cancer 2002;95(8) 1786-1794

[44] Alexander, F.; Patheal, S.; Biondi A.; Brandalise, S.; Cabrera, M.; Chan, L.; Chen, Z.; Cimino, G.; Cordoba, J.; Gu, L.; Hussein, H.; Ishii, E.; Kamel, AM.; Labra, S.; Magalhães, I.; Mizutani, S.; Petridou, E.; de Oliveira, M.; Yuen, P.; Wiemels, J. & Greaves, M. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. The Journal of Cancer Research 2001;61(6) 2542-6

[45] Shaw, A.; Infante-Rivard, C. & Morrison, H. Use of medication during pregnancy and risk of childhood leukemia (Canada). Cancer Causes Control 2004;15(9) 931-937

[46] McKinney, P.; Juszczak E.; Findlay E.; Smith K. & Thomson, C. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. British Journal of Cancer 1999;80(11) 1844-51

[47] Field, C. The immunological components of human milk and their effect on immune development in infants. The Journal of Nutrition 2005;13(1) 1-4

[48] Macías, S.; Rodríguez, S.; &Ronayne, P. Leche materna: composición y factores condicionantes de la lactancia. ArchivosArgentinos de Pediatría 2006;104(5) 423-430

[49] Parker, L. Breast-feeding and cancer prevention. European Journal of Cancer 2001;37(2) 55-8

[50] Riveron, R. Valor inmunológico de la leche materna. Revista Cubana de Pediatría1995;67(2) 1-16

[51] Altinkaynak, S.; Selimoglu, M.; Turgut, A.; Kilicaslan, B. &Ertekin, V. Breast-feeding duration and childhood acute leukemia and lymphomas in a sample of Turkish children. Journal of Pediatric Gastroenterology and Nutrition 2006;42(5) 568-572

[52] Bener, A.; Denic, S. &Galadari, S. Longer Breast-feeding and protection against childhood leukaemia and lymphomas. European Journal of Cancer 2001;37(2) 234-238

[53] Beral, V.; Fear, N.; Alexander, F. & Appleby, P. Breastfeeding and childhood cancer. UK Childhood Cancer Study Investigators. British Journal of Cancer 2001;85(11) 1685-1694

[54] [54] Davis, K. Review of the evidence for an association between infant feeding and childhood cancer. International Journal of Cancer supplement 1998;11 29-33

[55] Guise, J.; Austin, D. & Morris C. Review of case-control studies related to breastfeeding and reduced risk of childhood leukemia. Pediatrics 2005;116(5) 724-731

[56] Ip, S.; Chung, M.; Raman, G.; Chew, P.; Magula, N.; DeVine, D.; Trikalinos, T. & Lau, J. Breastfeeding and maternal and infant health outcomes in developed countries. Evidence Report/Technology Assessment 2007;153 1-186

[57] Kwan, L.; Buffler, P.; Abrams, B. &Kiley, V. Breastfeeding and the risk of childhood leukemia: a meta-analysis. Public Health Reports 2004;119(6) 521-535

[58] Kwan, M.; Buffler, P.; Wiemels, J.; Metayer, C.; Selvin, S.; Ducore, J. & Block, G. Breastfeeding patterns and risk of childhood acute lymphoblastic leukaemia. British Journal of Cancer 2005;93(3) 379-384

[59] Shu, X.; Clemens, J.; Zheng, W.; Ying, D.; Ji, B. & Jin, F. Infant breastfeeding and the risk of childhood lymphoma and leukaemia. International Journal of Epidemiology 1995;24(1) 27-32

[60] Shu, X.; Linet, M.; Steinbuch, M.; Wen, W.; Buckley, J.; Neglia, J.; Potter, J.; Reaman, G. & Robison, L. Breast-feeding and risk of childhood acute leukemia. Journal National Cancer Institute 1999;91(20) 1765-1772

[61] Stuebe, A. The risks of not breastfeeding for mothers and infants. Reviews in Obstetrics and Gynecology 2009;2(4) 222-231

[62] Cushing, A.; Samet, J.; Lambert, W.; Skipper, B.; Hunt, W.; Young, S. & McLaren, L. Breastfeeding reduces risk of respiratory illness in infants. American Journal of Epidemiology 1998;147(9) 863-870

[63] Lancashire, R.; Sorahan, T. & OSCC. Breastfeeding and childhood cancer risks: OSCC data. British Journal of Cancer 2003;88(7) 1035-1037

[64] Paricio, J.; Lizán, M.; Otero, A.; Benlloch, M.; Beseler, B.; Sánchez, M.; Santos, L. & Rivera, L. Full breastfeeding and hospitalization as a result of infections in the first year of life. Pediatrics 2006;118(1) e92-e99

[65] Menegaux, F.; Olshan, A.; Neglia, J.; Pollock, B. &Bondy, M. Day care, childhood infections and risk of neuroblastoma. American Journal of Epidemiology 2004;159(9) 843-851

[66] Gilham, C.; Peto, J,; Simpson J, Roman E, Eden TO, Greaves MF, Alexander FE; UKCCS Investigators. Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. British Medical Journal 2005;330(7503) 1294

[67] Kneale, G.; Stewart, A. & Wilson, L. Immunizations against infectious diseases and childhood cancers. Cancer immunology, immunotherapy 1986;21(2) 129–132

[68] Schüz, J.; Kaletsch, U.; Meinert, R.; Kaatsch, P. &Michaelis, J. Association of childhood leukaemia with factors related to the immune system. British Journal of Cancer 1999;80(3-4) 585-90

[69] Haro, AS. The effect of BCG-vaccination and tuberculosis on the risk of leukemia. Developments in biological standardization, (Part A), 1986;58 433-449

[70] Hartley, A.; Birch, J.; McKinney, P.; Blair, V.; Teare, M.; Carrette, J.; Mann, J.; Stiller, C.; Draper, G. & Johnston, H. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC): past medical history in children with cancer. Journal of Epidemiology and Community Health 1988;42(3) 235–242

[71] Nishi, M. & Miyake, H. A case-control study of non-T cell acute lymphoblastic leukaemia of children in Hokkaido, Japan. Journal of Epidemiology & Community Health 1989;43(4) 352–355

[72] Buckley, J.; Buckley, C.; Ruccione, K.; Sather, H.; Waskerwitz, M.; Woods, W. & Robison, L. Epidemiological characteristics of childhood acute lymphocytic leukemia. Analysis by immunophenotype. The Children's Cancer Group. Leukemia 1994;8 856–864

[73] Petridou, E; Trichopoulos, D; Kalapothaki, V; Pourtsidis, A; Kogevinas, M; Kalmanti, M; Koliouskas, D; Kosmidis, H; Panagiotou, J; Piperopoulou, F. &Tzortzatou, F. The risk profile of childhood leukemia in Greece: a nationwide case-control study. British Journal of Cancer 1997;76(9) 1241–1247

[74] Petridou, E.; Dalamaga, M.; Mentis, A.; Skalkidou, A.; Moustaki, M.; Karpathios, T; Trichopoulos, D. & Childhood Haematologists-Oncologists Group. Evidence on the infectious etiology of childhood leukemia: the role of low herd immunity (Greece). Cancer Causes & Control 2001;12(7) 645-52

[75] Markiewicz MA, Gajewski TF. The immune system as anti-tumor sentinel: molecular requirements for an anti-tumor immune response. Critical Reviews in Oncogenesis. 1999;10(3):247-260

[76] Rosenbaum, P.; Buck, G. &Brecher, M. Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia. Paediatric and Perinatal Epidemiology 2005;19(2) 152-164

[77] Eriksson, N.; Mikoczy, Z, &Hagmar, L. Cancer incidence in 13811 patients skin tested for allergy. Journal of Investigational Allergology& Clinical Immunology 2005;15(3) 161-166

[78] Turner, M.; Chen, Y.; Krewski, D. &Ghadirian, P. International journal of cancer. Journal international du cancer. International Journal of Cancer 2006;118(12) 3124-32

[79] Linabery, A.; Jurek, A.; Duval, S. & Ross, J. The association between atopy and childhood/adolescent leukemia: a meta-analysis. American Journal of Epidemiology 2010;171(7) 749-64

[80] McNally, R. & Eden, T. An infectious aetiology for childhood acute leukaemia: a review of the evidence. British Journal of Haematology 2004;127(3) pp.243-263,

[81] McNally, R.; Cairns, D.; Eden, O.; Alexander, F.; Taylor, G.; Kelsey, A. & Birch, J. (2002). An infectious aetiology for childhood brain tumours?. Evidence from space-time clustering and seasonality analyses. British Journal of Cancer 2002;86(7) 1070-1077

[82] Rudant, J.; Orsi, L.; Menegaux, F.; Petit, A.; Baruchel, A.; Bertrand, Y.; Lambilliotte, A.; Robert, A.; Michel, G.; Margueritte, G.; Tandonnet, J.; Mechinaud, F.; Bordigoni, P.; Hémon, D. &Clavel, J. (2010). Childhood acute leukemia, early common infections, and allergy: The ESCALE Study. American Journal of Epidemiology 2010;172(9) 1015-1027

[83] Cardwell, C.; McKinney, P.; Patterson, C. & Murray, L. Infections in early life and childhood leukaemia risk: a UK case-control study of general practitioner records. British Journal of Cancer 2008;99(9) 1529-33

[84] MacArthur, A.; McBride, M.; Spinelli, J.; Tamaro, S.; Gallagher, R. &Theriault, G. (2008). Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood Leukemia Study. American Journal of Epidemiology 2008;167(5) 598-606

[85] Roman, E.; Simpson, J.; Ansell, P.; Kinsey, S.; Mitchell, C.; McKinney, P.; Birch, J.; Greaves, M.; Eden, T. & United Kingdom Childhood Cancer Study Investigators. Childhood acute lymphoblastic leukaemia and infections in the first year of life: A report from the United Kingdom Childhood Cancer Study. American Journal of Epidemiology 2007;165(5) 496–504

[86] Canfield, K.; Spector, L.; Robison, L.; Lazovich, D.; Roesler, M.; Olshan, A.; Smith, F.; Heerema, N.; Barnard, D.; Blair, C. & Ross, J. Childhood and maternal infections and risk of acute leukaemia in children with Down syndrome: a report from the Children's Oncology Group. British Journal of Cancer 2004;91(11) 1866-18872

[87] Ross, J.; Spector, L.; Robison, L. &Olshon, A. Epidemiology of leukemia in children with Down syndrome. Pediatric Blood & Cancer 2005;44(1) 8-12

[88] Flores, J.; Pérez, M.; Fuentes, E.; Gorodezky, C.; Bernaldez, R.; Del Campo, M.; Martínez, A.; Medina, A.; Paredes, R.; De Diego, J.; Bolea, V.; Rodríguez, M.; Rivera, R.; Palomo, M.; Romero, L.; Pérez, P.; Alvarado, M.; Salamanca, F.; Fajardo, A. &Mejía, J. Breastfeeding and early infection in the aetiology of childhood leukaemia in Down syndrome. British Journal of Cancer 2009;101(5) 860-864