

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Allergy-associated symptoms in relation to childhood non-Hodgkin's as contrasted to Hodgkin's lymphomas: A case-control study in Greece and meta-analysis

Stavroula K. Dikalioti^a, Ellen T. Chang^{b,c}, Nick Dessypris^a,
Charalampia Papadopoulou^a, Nick Skenderis^d, Apostolos Pourtsidis^e,
Maria Moschovi^f, Sophia Polychronopoulou^g, Fani Athanasiadou-Piperopoulou^h,
Vassiliki Sidiⁱ, Maria Kalmanti^j, Eleni Th. Petridou^{a,*}

^a Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 11527 Athens, Greece

^b Cancer Prevention Institute of California, Fremont, CA, USA

^c Division of Epidemiology, Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA

^d Department of Pediatrics, University of Thessaly School of Medicine and Larissa University Hospital Larissa, P.O. Box 1425, Larissa 41110, Greece

^e Department of Pediatric Haematology–Oncology, “P. & Al. Kyriakou Children’s Hospital, Athens, Greece

^f Haematology–Oncology Unit, First Department of Pediatrics, Athens University Medical School, “Aghia Sophia” Children’s Hospital, Athens, Greece

^g Department of Pediatric Haematology–Oncology, “Aghia Sophia” Children’s Hospital, Athens, Greece

^h 2nd Department of Pediatrics, Aristotelion University of Thessaloniki, AHEPA General Hospital, Greece

ⁱ Pediatric Oncology Department, Hippokration Hospital, Thessaloniki 54622, Greece

^j Department of Pediatric Haematology–Oncology, University Hospital of Heraklion, Heraklion, Greece

KEYWORDS

Asthma
Allergy
Childhood
Lymphoma

Abstract An increase of the prevalence of childhood allergic diseases and the incidence of childhood Hodgkin’s (HL) and non-Hodgkin’s lymphoma (NHL) were reported in the late 20th century. Among adults, several studies point to an inverse association with lymphoma; it remains to be confirmed whether allergy is also related to childhood lymphomas and whether the association, if any, is of an aetiological nature. Between 1996 and 2008, 277 children (aged 0–14 years) with HL ($N = 111$) or NHL ($N = 166$) were enrolled in Nationwide Registry for Childhood Hematological Malignancies (NARECHEM), a Greek hospital-based-registry of childhood hematological malignancies. Hospital controls were individually matched to cases on age and sex. Multivariate conditional logistic regression was used to estimate odds

* Corresponding author. Address: Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 75 Mikras Asias Str., Goudi, Athens 11527, Greece. Tel.: +30 210 7462187; fax: +30 210 7462105.

E-mail address: epetrid@med.uoa.gr (E.Th. Petridou).

0959-8049/\$ - see front matter © 2011 Elsevier Ltd All rights reserved.

doi:[10.1016/j.ejca.2011.12.010](https://doi.org/10.1016/j.ejca.2011.12.010)

ratios (ORs) with 95% confidence intervals (CIs) for associations of allergic diseases and other covariates with childhood HL or NHL risk. Subsequently, we combined our results with those of a French case–control study in a meta-analysis amounting to a total of 330 NHL cases/1478 controls and 239 HL cases/959 controls. After controlling for sociodemographic, perinatal and environmental factors, childhood NHL was less prevalent among children with allergy-associated symptoms overall (OR:0.50, 95% CI:0.27–0.92) or a history of asthma (OR:0.43, 95% CI:0.21–0.88). By contrast, allergy did not seem to be associated with childhood HL risk, although statistical power was limited. Fewer seaside holidays and higher birth weight were also associated with increased childhood NHL risk. The combined OR of the two studies for the association of asthma with NHL risk was: 0.52, 95% CI:0.32–0.84, whereas for HL: 0.86, 95% CI:0.51–1.45. Allergy seems to be strongly and inversely associated with childhood NHL. It remains to be elucidated in future investigations comprising larger populations, focusing on specific disease subtypes and employing more pertinent study-designs, whether this association is genuinely protective.

© 2011 Elsevier Ltd All rights reserved.

1. Introduction

Lymphomas, notably Hodgkin's (HL) and non-Hodgkin's lymphomas (NHL), are the third most frequent malignancy in children under age 15 years, following leukaemia and central nervous system tumours.¹ The overall incidence rate of NHL among children in Europe is around 10 per million; an increasing trend in the occurrence of the disease was noted in the last decades of the 20th century, with annual increases of 0.8–0.9% from the 1970s to the early 1990s.^{2,3} HL is less common, with a mean incidence rate estimated at 5.8 per million in European children and a 1% annual increase among 10- to 14-year-olds from 1978 to 1997.⁴ During a later period (1996–2010), however, no statistically significant secular trends in the incidence of either childhood NHL or HL were identified in Greece.^{5,6} Part of the reported rise in NHL and HL incidence might be attributed to improved diagnosis and cancer registration methods,⁴ but changing environmental exposures might also play a role.⁷

Little is known about the aetiology of childhood lymphomas. Even the established association of high birth weight with leukaemia⁸ is debated with regard to lymphomas.⁹ Severe congenital^{10,11} or acquired^{12–14} immune impairment has been implicated in the pathogenesis of NHL and, to a lesser extent, HL,^{15,16} but the role of less profound immune dysfunction in lymphoma development is unclear. Allergic diseases such as eczema, hay fever and asthma are considered chronic inflammatory disorders originating from an aberrant immune response to innocuous environmental antigens. These conditions, especially asthma, have also been reported to have increased in prevalence and severity in most developed countries, including Greece, in the 1980s and early 1990s, showing a less clear pattern in more recent years.^{17–20} The rising prevalence of asthma during the late 20th century may also point to environmental risk factors or lifestyles⁷ that may be shared by asthma and childhood lymphomas. Indeed, intense

early-life exposure to a range of infectious agents has been reported as being protective for asthma²¹ leukaemia^{22,23} and lymphomas²⁴ among children.

Several studies among adults suggest that allergic diseases (as indicators of a germ-deficient childhood environment) are inversely associated with lymphoma onset, especially NHL,²⁵ whereas other studies indicate a positive association, especially for HL^{26–28} or no effect.^{29,30} To our knowledge, only two previous studies have found an association of asthma with childhood NHL.^{31,32} Given the paucity of data, we sought to explore the relation of a range of allergic conditions with risk of both HL and NHL among children using consecutive data registration of lymphomas by the Nationwide Registry for Childhood Hematological Malignancies (NARECHEM) in Greece⁵ and to combine our results with those of the already published case control study in France.³²

2. Materials and methods

During the 11-year period between 1996–2008, 374 patients aged 0–14 years with incident childhood lymphoma were newly diagnosed in all six paediatric haematology-oncology departments across Greece and contributed to NARECHEM. For administrative reasons, during specific time periods detailed datasets were not available in two of the participating departments, resulting in the exclusion of 67 patients (18%) from this study. An additional 30 patients (8%) were excluded due to refusals, incapacitation or abandonment of the child. Eventually a total of 277 incident lymphoma cases (166 NHL and 111 HL) were included in the analyses.

For every child with lymphoma, a suitable control was individually matched on age (± 6 months) and sex among those hospitalised for minor paediatric ailments, in the same hospital and at the same time as the corresponding cases. Out of 277 control children, 135 were admitted for viral or other infections, such as pneumonia and axillary lymphadenitis, 59 for gastrointestinal

or genitourinary conditions, such as gastroenteritis, abdominal pain and haematuria, 51 for cardiovascular or nervous system conditions namely, such as arrhythmia, transient loss of consciousness, febrile convulsions and headache, 14 for muscle-osteoarticular conditions, such as joint pain and myalgias and 18 for other conditions including accidental poisoning, obesity and diabetes mellitus.

The guardians of all eligible children were informed of the study objectives and interviewed in person using a structured questionnaire covering socio-demographic, anthropometric, perinatal and selected medical history characteristics. Guardians were also asked to report the child's history of allergy-associated symptoms/conditions (hereafter called "allergy") including asthma, hay fever, eczema, allergies to food or medications or an allergic reaction severe enough to require urgent medical attention. To minimise the inclusion of "non-atopic wheezers" among those with a reported history of bronchiolitis or bronchitis, two paediatricians (SD, NS) blinded to case-control status reviewed the questionnaires as well as the medical records of each child. Thus, all eight children (3 NHL, 1HL and 4 controls) with reported wheezing symptoms below the age of 2 years but no other history of allergic conditions were classified as non-allergic. The study protocol was approved by the Ethics Committee of the Athens University Medical School.

Given that HL and NHL are distinct pathophysiologic entities, we performed separate analyses by lymphoma type. Frequency distributions of study variables were initially compared between childhood HL or NHL cases and their matched controls using chi-square tests for trend or contrasts. Subsequently, the data were modelled using multiple conditional logistic regression analyses, treating HL or NHL as the outcome variable and allergic conditions as well as a series of potential confounders as predictor variables. Covariates were coded as follows: days spent annually at seaside resorts (0, 1–14, 15–29 or 30+ days), birth weight (in 500 g increments), birth order (continuous), maternal age at birth (in 5-year increments), maternal education (mandatory, lyceum, tertiary), maternal smoking during pregnancy (yes versus no), breastfeeding duration (in 2-month increments), residential crowding index (<0.50, 0.50 [reference] or >0.50 rooms/person) and allergy presence (yes versus no). The SAS statistical package was used in all the analyses.³³

To maximise statistical power of the main end-point of our study, we estimated the combined odds ratios (OR) and 95% confidence intervals (CI) of the individual results regarding the association of asthma and lymphoma risk derived from our study and a national registry-based case control study (ESCALE) that was carried out in France comprising 128 cases of HL and 848 population controls (5–14 years old), as well as

164 cases of NHL (2–14 years old) and 1312 population controls.³² The process was planned a priori and was statistically feasible, as two studies suffice for such an approach.³⁴ To avoid bias deriving from the different population groups or study designs, we combined the results using the fixed-effects (Mantel–Haenszel) model³⁵ after assessing the between-studies heterogeneity using Cochran Q statistic (at the 0.05 level of significance). Data were analysed with the SAS statistical software (SAS v9, SAS Institute, Carry, NC).

3. Results

Tables 1 shows the distribution of the 166 cases of NHL and 111 cases of HL, respectively, along with those of the individual age- and sex-matched controls by socio-demographic, perinatal, environmental and allergy-related variables. The prevalence of allergy or asthma was statistically significantly lower among NHL cases, but not HL cases, compared with controls. NHL cases as opposed to their age and sex matched controls spent fewer days at seaside resorts and were heavier at birth, whereas no substantial differences were observed between HL cases and their matched controls. These data are not directly interpretable, however, due to mutual confounding.

As shown in Table 2, a positive history of allergy was associated with a 50% lower risk of childhood NHL after adjusting for days spent annually at seaside resorts, birth weight, maternal age at birth, maternal education, maternal smoking during pregnancy, breastfeeding duration, birth order and residential crowding index. Given that asthma comprises a sizeable proportion of all allergy-related conditions, we analysed a positive history of asthma separately and found that it was also associated with a statistically significant 57% lower risk of childhood NHL after multivariate adjustment. The positive association of fewer days spent annually at seaside resorts and higher birth weight with childhood NHL risk remained robust in the multivariate models. With respect to childhood HL, no apparent effect of allergy or asthma was identified after multivariate adjustment, although power to detect an association was limited.

Subsequently, we estimated the combined OR between the Greek and the French study that was equal to 0.52, 95% CI 0.32–0.84 regarding the association of asthma with NHL (Fig. 1) and 0.86, 95% CI 0.51–1.45 with HL (Fig. 2). No heterogeneity was observed between the two studies either in NHL (Q value = 0.46 p -value = 0.50) or in HL data (Q -value = 0.56, p -value = 0.46).

4. Discussion

In Greece, we found that children with NHL were less likely (OR: 0.50) to report a history of allergy or

Table 1

Distribution of 166 children with non-Hodgkin's lymphoma (NHL), 111 children with Hodgkin's lymphoma (HL) and their age- and sex- matched controls by socio-demographic, perinatal, environmental and allergy-related variables.

Variable	NHL cases <i>N</i> (%)	NHL controls <i>N</i> (%)	<i>p</i> -value	HL cases <i>N</i> (%)	HL controls <i>N</i> (%)	<i>p</i> -value
Sex			Matched			Matched
Male	129 (77.7)	129 (77.7)		70 (63.1)	70 (63.1)	
Female	37 (22.3)	37 (22.3)		41 (36.9)	41 (36.9)	
Age, years			Matched			Matched
<5	35 (21.1)	35 (21.1)		7 (6.3)	8 (7.2)	
5–9	69 (41.6)	70 (42.2)		24 (21.6)	21 (18.9)	
10+	62 (37.3)	61 (36.7)		80 (72.1)	82 (73.9)	
Allergy-associated symptoms or conditions			0.02			0.29
Yes	31 (18.7)	49 (29.5)		26 (23.4)	33 (29.7)	
No	135 (81.3)	117 (70.5)		85 (76.6)	78 (70.3)	
Asthma			0.01			0.36
Yes	16 (9.6)	32 (19.3)		15 (13.5)	20 (18.0)	
No	150 (90.4)	134 (80.7)		96 (86.5)	91 (82.0)	
Days spent annually at seaside resorts			0.04			0.42
0	61 (36.7)	34 (20.5)		37 (33.4)	29 (26.1)	
1–14	30 (18.1)	43 (25.9)		19 (17.1)	24 (21.7)	
15–29	42 (25.3)	56 (33.7)		29 (26.1)	29 (26.1)	
30+	33 (19.9)	33 (19.8)		26 (23.4)	29 (26.1)	
Birth weight, g			0.01			0.43
<3000	31 (18.7)	43 (25.9)		23 (20.7)	24 (21.6)	
3000–3499	58 (34.9)	66 (39.8)		34 (30.6)	42 (37.9)	
3500–3999	57 (34.3)	47 (28.3)		41 (37.0)	33 (29.7)	
4000+	20 (12.1)	10 (6.0)		13 (11.7)	12 (10.8)	
Maternal age at birth, years			0.33			0.71
<20	11 (6.6)	11 (6.6)		8 (7.2)	11 (9.9)	
21–24	36 (21.7)	36 (21.7)		33 (29.7)	35 (31.6)	
25–29	60 (36.1)	71 (42.8)		48 (43.3)	34 (30.6)	
30–34	37 (22.3)	34 (20.5)		14 (12.6)	18 (16.2)	
35+	22 (13.3)	14 (8.4)		8 (7.2)	13 (11.7)	
Maternal education			0.44			0.20
Mandatory education	54 (32.5)	52 (31.3)		33 (29.7)	45 (40.5)	
Lyceum	72 (43.4)	86 (51.8)		57 (51.4)	51 (46.0)	
Tertiary education	40 (24.1)	28 (16.9)		21 (18.9)	15 (13.5)	
Maternal smoking during pregnancy			0.66			0.86
No	136 (81.9)	139 (83.7)		92 (82.9)	93 (83.8)	
Yes	30 (18.1)	27 (16.3)		19 (17.1)	18 (16.2)	
Breastfeeding duration, months			0.97			0.68
0	40 (24.1)	47 (28.3)		20 (18.0)	27 (24.4)	
<2	46 (27.7)	37 (22.3)		30 (27.0)	23 (20.7)	
2–3	29 (17.5)	27 (16.3)		24 (21.6)	22 (19.8)	
4–5	15 (9.0)	17 (10.2)		7 (6.3)	13 (11.7)	
6+	36 (21.7)	38 (22.9)		30 (27.1)	26 (23.4)	
Birth order			0.05			0.43
1	59 (35.5)	66 (39.8)		35 (31.5)	42 (37.8)	
2	69 (41.6)	77 (46.4)		49 (44.2)	47 (42.4)	
3	26 (15.7)	19 (11.4)		22 (19.8)	15 (13.5)	
4+	12 (7.2)	4 (2.4)		5 (4.5)	7 (6.3)	
Residential crowding index, rooms/person			0.20			0.15
<0.50	37 (22.3)	28 (16.9)		22 (19.8)	22 (19.8)	
0.50	59 (35.5)	74 (44.6)		41 (36.9)	54 (48.7)	
>0.50	70 (42.2)	64 (38.5)		48 (43.3)	35 (31.5)	

Table 2

Multivariate adjusted odds ratios (OR) and 95% confidence intervals (CIs) for associations of socio-demographic, perinatal, environmental and allergy-related variables with risk of childhood Hodgkin's and non-Hodgkin's lymphoma^a.

Variable	Category/increment	OR	95% CIs	p-value
Non-Hodgkin's lymphoma				
Allergy-associated symptoms/conditions	Yes versus No	0.50	0.27–0.92	0.03
Days spent annually at seaside resorts	15 days more	0.79	0.61–1.00	0.05
Birth weight	500 g more	1.37	1.04–1.81	0.03
Alternative to allergy introduced variable				
Asthma	Yes versus No	0.43	0.21–0.88	0.02
Hodgkin's lymphoma				
Allergy-associated symptoms/conditions	Yes versus No	0.72	0.38–1.37	0.32
Days spent annually at seaside resorts	15 days more	0.84	0.64–1.10	0.21
Birth weight	500 g more	1.13	0.80–1.60	0.49
Alternative to allergy introduced variable				
Asthma	Yes versus No	0.66	0.28–1.57	0.35

^a Also controlling for maternal age at birth, maternal education, maternal smoking during pregnancy, breastfeeding, birth order and residential crowding index.

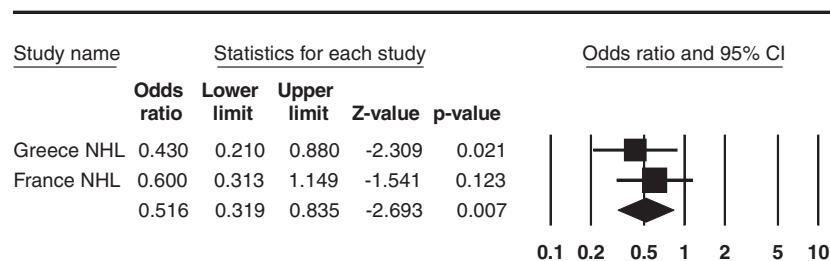


Fig. 1. Forest plot presenting the meta-analysis based on odds ratios (ORs) for the association of non-Hodgkin's lymphoma (NHL) and asthma between the Greek and the French study. ORs in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled OR with its 95% CI is depicted as a diamond.

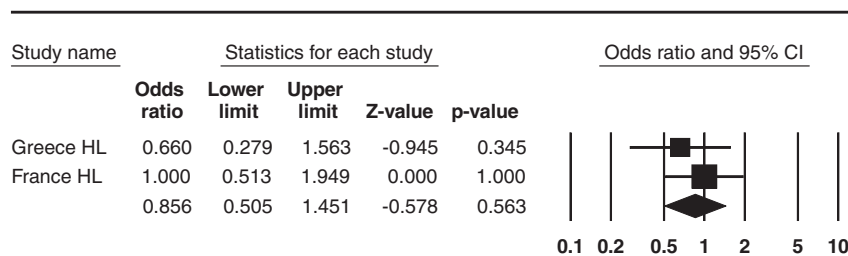


Fig. 2. Forest plot presenting the meta-analysis based on odds ratios (ORs) for the association of HL and asthma between the Greek and the French study. ORs in the individual studies are presented as squares with 95% confidence interval (CIs) presented as extending lines. The pooled OR with its 95% CI is depicted as a diamond.

asthma in particular. These results are in line and of the same magnitude of the effect estimate (OR: 0.60) with those reported from a same size study conducted in France³² and a smaller one conducted in Italy.³¹ By contrast, a history of allergy was not associated with the risk of the other distinct types of childhood lymphoma, notably HL either in our study or the one from France. Likewise, the combined results springing from the meta-analysis of the Greek and the French dataset remained

robust both with regard to the inverse association with NHL and the lack of association with HL. The differing results observed for allergy with respect to NHL and HL risk are of note, given that history of allergy and asthma was captured in an identical manner across the two groups, making it unlikely that our results were due to systematic reporting bias.

The magnitude of the association is sizeable but the study design does not allow exploring whether it is

genuine in nature. Several hypotheses have been entertained with regard to the pathophysiology of the reported inverse association of allergy with NHL. According to the “cancer immunosurveillance hypothesis,” the immune system has the ability to recognise and eliminate nascent transformed cells in the body, thus preventing a majority of potential cancers from developing.³⁶ The presence of an allergic condition could be a surrogate marker of increased vigilance of the immune system in scrutinising, identifying and destroying cancer cells.³⁷ Another less plausible explanation could point to the antitumor activity of histamine,³⁸ a chemical mediator of allergic reactions, that protects natural killer cells and T cells against oxygen radical-induced damage and death by suppressing oxygen radical formation, and also optimises lymphocyte activation by cytokines.³⁹ Clinical trials in malignancies such as metastatic malignant melanoma⁴⁰ and acute myeloid leukaemia^{40,41} have demonstrated the potential to improve treatment outcome when histamine dihydrochloride is combined with immunotherapy, further supporting a possible antitumour effect of histamine.

Against these explanations is the hypothesis that in allergic individuals, antigenic stimulation subjects the immune system to a chronically hyperreactive state, leading to an inflammatory cascade of cellular and cytokine reactions that tax the host immune response, provoke tissue injury and eventually result in lymphoid neoplasia.⁴² In addition, a prospective cohort study of pregnant women found no association between specific IgE reactivity and subsequent NHL risk except just before diagnosis; these results may suggest that individuals with pre-clinical NHL experience immune suppression that leads to the reduction of allergic symptoms.²⁹ However, this example of reverse causality in a maternity cohort may not be pertinent to children.

Inverse associations of allergy have been also reported for acute lymphoblastic leukaemia, a haematological malignancy in close affinity with NHL,³⁷ as well as among adults suffering from NHL. A powerful pooled analysis of adulthood NHL also showed an apparent protective effect of asthma, hay fever and allergy against B-cell NHL.²⁵

The findings of the Greek study should be interpreted in light of several limitations. Most notably, the data were based on parent-reported diagnoses. However, for relatively mild conditions such as hay fever, asthma and eczema, self-reported data may be more accurate than medical records because participants may not have required medical attention for minor ailments. The effect seems to be specific to NHL but NARECHEM relies on data provided by clinicians and no information on specific subtypes was available at least before 2007 when ICD-O-3 classification was introduced in their records. Although we cannot exclude the possibility of information bias, it is noteworthy that we observed an increased

occurrence of allergy among controls, whereas it is generally assumed that cases are more likely to recall mild medical conditions, resulting in recall bias in the opposite direction.⁴³ Thus, provided that such an error occurred, it is possible that we underestimated the strength of the association between allergy and childhood NHL or HL risk. Furthermore, compared to studies among adults, misclassification or recall bias may be expected to have been less present in the current study, as the period of recollection referred to a shorter (0- to 14-year) time span than for adults.

Given the changing lifestyle patterns in contemporary Greece and the inter-relatedness of several covariates it was not easy to develop a composite score in order to assess the role of the SES or proxies of early childhood infection on lymphomagenesis among cases and controls. Moreover, some may argue that lower socioeconomic status might be a component of control children admitted for accidental injuries. This is a rather common adversity for young Greek children that may occur in and around the house. It is worth noting, however, that socioeconomic factors were not found in Greece to be important indicators of accidental poisoning.⁴⁴ Provided the limited numbers of control children that were admitted due to this adversity, we believe no major bias was introduced in the analysis. On the positive side, NARECHEM has nationwide coverage of lymphoma cases across Greece and the catchment areas of the participating paediatric hospitals generating the control series reaches more than half of the childhood population in the country. Furthermore, the hospital environment also maximised the quality of information derived from guardians and minimised the refusal rate.

In conclusion, this study provides empirical evidence that allergic disorders, including asthma, are inversely associated with the risk of developing childhood NHL. Given the specificity of the association with NHL, our results indicate that the reported parallel rising trends in both conditions in the latter part of the 20th century are more likely to be due to shared aetiological factor(s) rather than a direct link between allergy and NHL. Additional studies, preferably of prospective design, undertaken by large consortia are needed in order to examine the combined effect of allergic history and laboratory confirmation by NHL subtype.

Funding

This study was supported in part by the National and Kapodistrian University of Athens and a stipend to Dr. S. K. Dikalioti by Onassis Public Benefit Foundation in the context of her Ph. D. Thesis.

Conflict of interest statement

None declared.

References

- Curado MP, Edwards B, Shin HR, et al. *Cancer incidence in five continents*, vol. IX. Lyon: IARC Scientific Publications No. 160;2007.
- Weidmann C, Black RJ, Masuyer E, Parkin DM. Incidence of non-Hodgkin's lymphoma in children between 1970 and 1990 in nine European countries. *Eur J Cancer* 1999;**35**:1235–7.
- Izazugaza MI, Steliarova-Foucher E, Martos MC, Zivkovic S. Non-Hodgkin's lymphoma incidence and survival in European children and adolescents (1978–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;**42**:2050–63.
- Clavel J, Steliarova-Foucher E, Berger C, Danon S, Valerianova Z. Hodgkin's disease incidence and survival in European children and adolescents (1978–1997): report from the Automated Cancer Information System project. *Eur J Cancer* 2006;**42**:2037–49.
- Petridou ET, Pourtsidis A, Dessypris N, et al. Childhood leukaemias and lymphomas in Greece (1996–2006): a nationwide registration study. *Arch Dis Child* 2008;**93**:1027–32.
- NARECHEM – Nationwide Registry of Childhood Hematological Malignancies. Available from: <http://narechem.gr/>.
- Antonopoulos CN, Sergentanis TN, Papadopoulou C, et al. Maternal smoking during pregnancy and childhood lymphoma: A meta-analysis. *Int J Cancer* 2011;**129**:2694–703.
- Caughey RW, Michels KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. *Int J Cancer* 2009;**124**:2658–70.
- Papadopoulou C, Antonopoulos CN, Sergentanis TN, et al. Is birth weight associated with childhood lymphoma? A meta-analysis. *Int J Cancer* 2012;**130**:179–89.
- Aghamohammadi A, Parvaneh N, Tirgari F, et al. Lymphoma of mucosa-associated lymphoid tissue in common variable immunodeficiency. *Leuk Lymphoma* 2006;**47**:343–6.
- Seidemann K, Henze G, Beck JD, et al. Non-Hodgkin's lymphoma in pediatric patients with chromosomal breakage syndromes (AT and NBS): experience from the BFM trials. *Ann Oncol* 2000;**11**(Suppl. 1):141–5.
- Biggar RJ, Frisch M, Goedert JJ. Risk of cancer in children with AIDS. AIDS–Cancer Match Registry Study Group. *JAMA* 2000;**284**:205–9.
- Franceschi S, Dal Maso L, La Vecchia C. Advances in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer* 1999;**83**:481–5.
- Cucchiara S, Escher JC, Hildebrand H, et al. Pediatric inflammatory bowel diseases and the risk of lymphoma: should we revise our treatment strategies? *J Pediatr Gastroenterol Nutr* 2009;**48**:257–67.
- Beral V, Newton R. Overview of the epidemiology of immunodeficiency-associated cancers. *J Natl Cancer Inst Monogr* 1998:1–6.
- Bierman PJ, Vose JM, Langnas AN, et al. Hodgkin's disease following solid organ transplantation. *Ann Oncol* 1996;**7**:265–70.
- Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996–2005: a population study. *Am J Epidemiol* 2010;**172**:728–36.
- Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–43.
- McNeill G, Tagiyeva N, Aucott L, Russell G, Helms PJ. Changes in the prevalence of asthma, eczema and hay fever in pre-pubertal children: a 40-year perspective. *Paediatr Perinat Epidemiol* 2009;**23**:506–12.
- Priftis K, Panagiotopoulou-Gartagani P, Tapratzi-Potamianou P, et al. Hospitalizations for childhood asthma in Athens, Greece, from 1978 to 2000. *Pediatr Allergy Immunol* 2005;**16**:82–5.
- Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011;**364**:701–9.
- van Steensel-Moll HA, Valkenburg HA, van Zanen GE. Childhood leukemia and infectious diseases in the first year of life: a register-based case–control study. *Am J Epidemiol* 1986;**124**:590–4.
- Petridou E, Kassimos D, Kalmanti M, et al. Age of exposure to infections and risk of childhood leukaemia. *BMJ* 1993;**307**:774.
- Michos A, Dessypris N, Pourtsidis A, et al. Delayed exposure to infections and childhood lymphomas: a case–control study. *Cancer Causes Control* 2009;**20**:795–802.
- Vajdic CM, Falster MO, de Sanjose S, et al. Atopic disease and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis. *Cancer Res* 2009;**69**:6482–9.
- Gutensohn N, Cole P. Childhood social environment and Hodgkin's disease. *N Engl J Med* 1981;**304**:135–40.
- Gutensohn NM. Social class and age at diagnosis of Hodgkin's disease: new epidemiologic evidence for the “two-disease hypothesis”. *Cancer Treat Rep* 1982;**66**:689–95.
- Hjalgrim H, Smedby KE, Rostgaard K, et al. Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma. *Cancer Res* 2007;**67**:2382–8.
- Melbye M, Smedby KE, Lehtinen T, et al. Atopy and risk of non-Hodgkin lymphoma. *J Natl Cancer Inst* 2007;**99**:158–66.
- Fabbro-Peray P, Daurès JP, Rossi JF. Environmental risk factors for non-Hodgkin's lymphoma: a population-based case–control study in Languedoc-Roussillon, France. *Cancer Causes Control* 2001;**12**:201–12.
- Magnani C, Pastore G, Luzzatto L, Terracini B. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case–control study. *Tumori* 1990;**76**:413–9.
- Rudant J, Orsi L, Monnereau A, et al. Childhood Hodgkin's lymphoma, non-Hodgkin's lymphoma and factors related to the immune system: The ESCAL study (SFCE). *Int J Cancer* 2011;**129**:2236–47.
- SAS/STAT user's guide. 4th ed. Cary, NC: SAS Institute Inc.;1989.
- Valentine JC, Pigott TD, Rothstein HR. How many studies do you need?: a primer on statistical power for meta-analysis. *J Educ Behav Stat* 2010;**35**:215–47.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Nat Cancer Inst* 1959;**22**:719–48.
- Burnet M. Cancer – a biological approach. *Br Med J* 1957;**1**:841–7.
- Linabery AM, Jurek AM, Duval S, Ross JA. The association between atopy and childhood/adolescent leukemia: a meta-analysis. *Am J Epidemiol* 2010;**171**:749–64.
- Holly EA, Lele C, Bracci PM, McGrath MS. Case–control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *Am J Epidemiol* 1999;**150**:375–89.
- Hellstrand K. Histamine in cancer immunotherapy: a preclinical background. *Semin Oncol* 2002;**29**:35–40.
- Perz JB, Ho AD. Histamine dihydrochloride for the treatment of acute myeloid leukemia, malignant melanoma and renal cell carcinoma. *Future Oncol* 2008;**4**:169–77.
- Yang LP, Perry CM. Histamine dihydrochloride: in the management of acute myeloid leukaemia. *Drugs* 2011;**71**:109–22.
- Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* 2005;**60**:1098–111.
- Grulich AE, Vajdic CM, Kaldor JM, et al. Birth order, atopy, and risk of non-Hodgkin lymphoma. *J Natl Cancer Inst* 2005;**97**:587–94.
- Petridou E, Kouri N, Polychronopoulou A, et al. Risk factors for childhood poisoning: a case–control study in Greece. *Inj Prev* 1996;**2**:208–11.