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Medical history and risk for lymphoma: results of a population-based case-control study in Germany

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Abstract

Since lymphomas are malignancies of cells of the immune system, associations with disorders characterised by impaired immune functions can be assumed. We investigated the relationship between a history of selected medical conditions and the risk for lymphoma including specified subentities within our population-based case-control study of lymphoma among adults conducted in Germany between 1999 and 2002. Overall, we found decreased risks for a history of repeated diarrhoea, warts, arthrosis, allergies, and appendectomy (at a younger age). Elevated risks for lymphoma correlated with tonsillectomy (at a younger age), whereas null results were found for selected auto-immune disorders in adulthood. Although the numbers are small, most of the results for the subentities corresponded with these findings. These results are compatible with the notion that persistent immunological alterations contribute to the aetiology of lymphoma, but partially inconsistent with the Th1/Th2-shift paradigm.

Keywords: Hodgkin's lymphoma; Non-Hodgkin's lymphoma; Diffuse large B-cell lymphoma; Follicular lymphoma; B-CLL; MALT lymphoma; Multiple myeloma; B-NHL; T-NHL; Urticaria

1. Introduction

In Germany, lymphomas have one of the highest increases in incidence amongst the different cancer sites, with an annual percent change of approximately 2% in males and 3% in females (1970–1998). In contrast to other cancer sites, this increase has continued until recently [1] (for an update see www.dkfz.de, 'cancer atlas'). The latest publication of the German cancer registries indicates this level may now have reached a plateau [2]. However, the aetiology remains largely obscure. The few established risk factors, e.g., immune suppression, human immunodeficiency virus (HIV), and some other viral infections, explain only a few of the cases.

Since lymphomas are malignancies of cells of the immune system, associations with disorders characterised by impaired immune functions can be assumed. For immune deficiency syndromes, a strong elevation in lymphoma risk is well established [3]. For auto-immune disorders, such as, e.g., diabetes type 1, multiple sclerosis, rheumatoid arthritis, or Sjögren's syndrome, indications for a subsequently elevated lymphoma risk have been found. However, with the exception of Sjögren's syndrome, these are not consistent. Associations with a history of allergies were inconsistent. Some tendency towards a decreased Odds Ratio (OR) was seen in more recent years. A history of infectious diseases which may have affected immune regulation has been considered by several authors, but the results have been conflicting [39,42,43].

The aetiology of an increasing incidence of immune-related disorders among children *and adults* has been

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discussed in terms of the so-called ''hygiene hypothesis'', although the hypothesis was originally confined to childhood leukaemia and allergies. Greaves proposed this explanatory model for *acute childhood leukaemia* in 1988 [4,5]. It stated that lack or delayed exposure to common infections, i.e. antigenic challenge, early in infancy might leave the immune system insufficiently prepared for exposure to common viruses some years later leading to inappropriate hypo- or hyper-reactive immune responses.

Independently, Strachan [6] postulated an analogous hypothesis to explain the increasing prevalence of *allergies* in many countries. Having found a strong inverse correlation between the number of siblings and the prevalence of hayfever, he proposed that declining family sizes and higher standards of household hygiene might be associated with an increased risk of atopic diseases. As early as 1966, Leibowitz and colleagues [7] suggested that *multiple sclerosis* might be increased among subjects who spent their childhood in homes with high levels of sanitation. In addition, diabetes type I has been related to factors which are constitutive for the hygiene hypothesis [8–10]. Recent studies indicated that these patterns of early life characteristics might also affect lymphoma risk in *adults* [11,12].

Generally, the hypothesis provides an explanatory model for the observation of an increasing prevalence of allergic diseases (asthma, rhinitis and atopic dermatitis) and auto-immune diseases (multiple sclerosis, diabetes type 1 and Crohn's disease) and a decreasing prevalence of typical infectious diseases (measles, mumps, tuberculosis, rheumatoid fever, hepatitis A) in countries with a so-called ''Western'' lifestyle [13].

An immunological interpretation of the allergy-related hygiene hypothesis was given within the framework of the Th1/Th2 paradigm. Delayed contact to infectious agents during childhood might lead to an impairment of the Th1/Th2 balance that gives rise to a life-long shift of the system in atopic subjects towards a Th2-type response [14,15]. Despite less clear evidence for a shift in the Th2-direction in lymphoma, epidemiological findings are increasingly interpreted in terms of this paradigm [11,16].

In the present paper, we address the role of factors of medical history in the aetiology of lymphoma among adults based on a recently conducted population-based case-control study in Germany and discuss the results in the context of these mechanistic models.

2. Patients and methods

2.1. Study population

The study was carried out from 1999 to 2002 in six regions of Germany as a population-based case-control study among 18–80 year old adults, matched 1:1 for gender, age (+/− year of birth), and study region. Details of the study design have been published elsewhere in Ref. [12]. Briefly, the cases were recruited from hospitals and office-based physicians involved in the diagnosis and treatment of lymphoma in the study regions. They were interviewed by trained interviewers and asked for a 20 ml blood sample. The participation rate was 87.4%. Diagnoses were collected in form of copies of the official pathology reports of the respective pathologies which were verified by reference pathologists for approximately 46% of the cases. In late 2003, for quality assurance of the diagnoses, a 10% random sample of all of the cases included was re-evaluated within a reassessment system in the context of the European collaboration, Epilymph. The German lymphoma study is imbedded in this multicentre study that is coordinated by the International Agency for Research on Cancer (IARC) (Lyon), (for details on Epilymph and further international cooperation see Becker and colleagues report in Ref. [12]). All cases are classified according to the World Health Organisation (WHO) classification system [17]. Subsequent to the quality assurance step within Epilymph, the codification of all German cases was checked by the German member of the pathology expert panel and this led, when considered with newly received reference pathology reports, to some changes in the number of cases. We included in the analysis 12 acute lymphoblastic leukaemia (ALL) cases (7 B-ALL, 2 T-ALL and 3 ALL not otherwise specified), (together with the respective controls) which had previously been left out, and removed 2 cases whose final diagnoses were not confirmed lymphomas. The study therefore comprised 710 case-control pairs (390 males, 320 females) from which 115 cases (16.2%) were Hodgkin's lymphoma (HL), 554 (78.0%) B-cell non-Hodgkin's lymphoma (B-NHL) and 35 (4.9%) T-cell NHL. Four cases were diagnosed as having ALL not otherwise specified, one case was diagnosed as having HL *and* NHL, and one case was a lymphoma not otherwise specified. The number of cases in the main subentities differs slightly from the initial publication [12] and they are therefore presented within Table 3. The controls were drawn randomly from population registers of the study regions which have an almost 100% coverage due to compulsory registration by law. The controls were individually matched for gender, age and study region. The participation rate was 44.3%.

Medical history was obtained from study participants by self-report. With the exception of three conditions (warts, aphtae, and herpes), the questionnaire asked throughout whether the patient was informed *by a physician* as having been diagnosed of the respective disease. For each positive response, the approximate age of the first physician-diagnosed disease was also collected.

Data analysis was carried out for all lymphomas combined, the major subgroups HL, B-NHL and T-NHL,

and the more frequent subentities (diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukaemia of B-cell type (B-CLL), mucosa-associated lympoid tissue (MALT) lymphoma and multiple myeloma). We present the 'exposures' under consideration and the respective results for all lymphomas combined, and selective results for some subentities. More detailed analyses are left for subsequent pooled analyses of all centres within Epilymph.

2.2. Statistical analysis

All lymphomas combined were analysed using matched conditional logistic regression taking the matching variables gender, age and study region into account. Due to sparse data, subentities were analysed by unconditional logistic regression using the matching variables for adjustment. Relative risks were estimated by OR and associated 95% confidence limits (95% CL) using the SAS® (Statistical Analysis System) procedure PHREG for conditional and LOGISTIC for unconditional logistic regression (SAS version 8, SAS Institute, Inc., Cary, North Carolina). If relevant, OR was adjusted in both approaches for smoking in five categories (non-current smokers as the reference category, 1–9 cigarettes/day, 10–19 cigarettes/day, 20–29 cigarettes/day, $\geqslant$30 cigarettes/day) or educational level in three categories (low: <10 years of schooling and none or regular vocational training, medium: 10–$\leqslant$13 years of schooling and no advanced college or university degree, high: $\geqslant$13 years of schooling and/or advanced university degree the medium educational level is taken as the reference).

3. Results

Table 1 presents the ORs for lymphomas in relation to self-reported physician-diagnosed diseases up to three years prior to the lymphoma diagnosis or date of admission to the study (=date of interview), respectively. Allergies are considered in a separate table (Tables 4 and 5). Among the diseases with an infectious aetiology, decreased ORs were seen for a history of repeated diarrhoea and warts, the former reaching statistical significance. Among the non-infectious diseases, arthrosis was associated with a 21% decreased OR for lymphoma, almost reaching statistical significance. In the combined analysis of all lymphomas, null results were observed for several auto-immune disorders which were in other studies repeatedly associated with lymphoma: diabetes and, on the basis of very few cases, Crohn's disease, ulcerative colitis, and rheumatoid arthritis. For some diseases, different trends were seen for men and women (data not shown): For non-B-type hepatitis, the OR was non-significantly increased (OR = 1.6, CL = 0.9–2.6) in males, while it was non-significantly decreased (OR = 0.7, CL = 0.4–1.1) in females. Opposite effects were also present for herpes labialis (males: OR = 0.8, CL = 0.6–1.0; females: OR = 1.3, CL = 0.9–1.8). When age at diagnosis of diabetes was taken into account, only 1 control was diagnosed before age 40 years, in contrast to 6 lymphoma patients. Early diagnosis of diabetes which is indicative of type 1 diabetes led to a non-significantly increased OR (OR = 6.0, CL = 0.7–49.8, data not shown).

Lymphomas comprise a multitude of pathogenetically different subentities with little information as to what extent they are aetiologically different or share common environmental factors. Thus, we conducted a detailed analysis in two directions: firstly, we considered whether the decreased ORs described above can be seen for the more frequent subentities (Table 2). Secondly, we examined whether an analysis of all lymphomas combined masked associations between specific factors and individual subentities (Table 3).

Table 2 shows that almost all findings seen overall appear to be reproduced when the individual subentities are considered with a few exceptions: no inverse association was seen between diarrhoea and multiple myeloma, between warts and follicular lymphoma, CLL and HL. For the latter, the association with warts was in fact statistically significant in the other direction. Notice that many of these observations were based on small numbers so that most of them cannot be confirmed statistically.

Table 3 summarises the associations between specific diseases in the subject's medical history up to three years prior to the lymphoma diagnosis and distinct lymphoma subentities which presented ORs of (borderline) statistical significance. Particularly strong associations were found for MALT lymphoma with ulcus ventriculi, and T-NHL with malaria and rheumatoid arthritis.

When all reported diseases prior to lymphoma diagnosis/date of interview were considered, MALT lymphoma were strongly associated with a reported diagnosis of *H. pylori* (OR = 7.33, 95%CL = 2.84-18.9) and Hepatitis B virus infection (OR = 5.2, 95%CL = 0.99–26.8).

Urticaria was found to be related to follicular lymphomas and HL. The association persisted when we included in an additional analysis only urticaria diagnoses 5 years prior to the lymphoma diagnosis. The ORs were: OR = 1.83 (95%CI = 0.96–3.46) for follicular lymphoma and OR = 2.56 (95%CI = 1.27–5.13) for HL. Even with a time-span of 7 years, the result for HL remained statistically significant (data not shown).

Table 4 reports associations between medical history of atopic disorders and lymphoma risk. Overall, consistently decreased ORs for the immediate type I allergies (statistically significant for allergic asthma, allergy to pollen, and mite-dust allergy, marginally significant for food allergies) and some delayed type IV allergies (contact eczema by chromium or nickel, non-significant)

Table 1
Odds ratio[a] (OR) and 95%-confidence limits (CL) for subjects with a medical history of selected disorders and risk for all lymphomas combined

Disease or condition	ICD-10	All lymphomas combined		
		Cases/controls	OR	(95% CL)
Infectious diseases				
Typhus	A01	10/11	0.90	(0.37–2.22)
Infection with *Helicobacter pylori*	A04.5	18/28	0.74	(0.40–1.38)
Diarrhoea	A09	21/36	0.57	(0.33–0.99)
Tuberculosis	A16.9	21/16	1.31	(0.69–2.52)
Brucellosis	A23	0/1	–	–
Diphtheria	A36	54/49	1.21	(0.79–1.84)
Herpes labialis	B00.1	335/341	0.96	(0.78–1.19)
Herpes at other sites	B00.9	64/75	0.86	(0.60–1.23)
Warts	B07	316/341	0.85	(0.68–1.06)
Hepatitis B	B16.9	11/7	1.57	(0.61–4.05)
Hepatitis of other type	B19.9	73/71	1.03	(0.73–1.47)
Malaria	B54	10/9	1.11	(0.45–2.73)
Leishmaniasis of the skin	B55.1	0/1	–	–
Non-infectious diseases				
Cancer	C00-C97	56/72	0.75	(0.51–1.09)
Colorectal polyps	D12	39/35	1.13	(0.70–1.83)
Diabetes	E14.9	46/40	1.15	(0.75–1.77)
Cataract	H26.9	45/42	1.09	(0.68–1.75)
Rheumatic fever	I00	11/7	1.57	(0.61–4.05)
Hypertension	I10	185/200	0.90	(0.69–1.17)
Sinusitis	J32.9	197/212	0.89	(0.71–1.13)
Aphthae	K12.0	82/94	0.86	(0.62–1.18)
Ulcus ventriculi	K25.7	36/35	1.00	(0.62–1.62)
Ulcus duodeni	K26.9	31/36	0.88	(0.53–1.45)
Gastritis	K29.5	101/111	0.89	(0.66–1.20)
Crohn's disease	K50.9	1/2	0.50	(0.05–5.51)
Ulcerative colitis	K51.9	1/1	1.00	(0.06–16.0)
Diverticulitis	K57.9	15/14	1.08	(0.51–2.29)
Coeliac disease	K90.0	2/0	–	–
Psoriasis	L40.9	29/33	0.93	(0.56–1.56)
Urticaria	L50	72/62	1.18	(0.83–1.69)
Lupus erythematosus	L93	2/0	–	–
Gout	M10.9	45/39	1.17	(0.75–1.82)
Rheumatoid arthritis	M13.0	11/18	0.65	(0.30–1.38)
Arthrosis	M19.9	110/136	0.79	(0.59–1.05)
Bechterew disease	M45	3/1	2.99	(0.31–28.7)

ICD, International classification of diseases.
[a] Method of evaluation: conditional logistic regression.

were found. The inverse association between allergies and lymphoma risk was not seen for 'other' allergies and allergies to medications which can be drug-specific either type I or type IV reactions. The described associations were uniform for both genders. However, the inverse associations were more pronounced in females than in males (data not shown). Adjustment for educational level altered the results only marginally (data not shown).

Table 5 presents the association of allergic asthma, allergy to pollen, mite-dust allergy and food allergies with the major subentities. Allergies showed none or only a weak inverse association with follicular lymphoma, CLL and, partially, T-NHL. For the other subentities, the ORs decreased, although the small numbers allow statistical confirmation in only a few instances.

Finally, Table 6 shows results regarding the medical history of surgical treatment of tonsillitis and appendicitis and dependence on age at surgery. Overall, surgical interventions were not associated with the lymphoma risk (data not shown), nor were tonsillectomies and appendectomies. However, when age at intervention was taken into account, elevated risks with decreasing age at tonsillectomy were found. Having had a appendectomy between age 7 and 12 was associated with a decrease risk of lymphoma.

A markedly increased cancer risk with young age at tonsillectomy was evident for all of the subentities investigated, with the exception of multiple myeloma (Table 7). An equivalent presentation for appendectomy did not provide meaningful results due to the much weaker associations and sparse data (data not shown).

Table 2
Odds ratio[a] (OR) and 95%-confidence limits (CL) for relevant disorders in relation to lymphoma subentities

Disease and subentity	Cases/controls	OR[a]	(95% CL)
Diarrhoea	21/36	0.57	(0.33–0.95)
Follicular lymphoma	4/36	0.80	(0.27–2.32)
Diffuse large B-cell lymphoma	2/36	0.23	(0.06–0.99)
CLL	4/36	0.72	(0.25–2.10)
Multiple myeloma	4/36	1.08	(0.37–3.18)
MALT	1/36	0.60	(0.08–4.61)
B-NHL total	17/36	0.58	(0.32–1.04)
T-NHL	1/36	0.56	(0.07–4.27)
HL	3/36	0.64	(0.18–2.23)
Warts	316/341	0.87	(0.71–1.08)
Follicular lymphoma	51/341	1.32	(0.85–2.07)
Diffuse large B-cell lymphoma	63/341	0.71	(0.49–1.01)
CLL	51/341	1.07	(0.70–1.64)
Multiple myeloma	26/341	0.58	(0.35–0.96)
MALT	13/341	0.87	(0.41–1.85)
B-NHL total	236/341	0.82	(0.65–1.03)
T-NHL	11/341	0.51	(0.24–1.07)
HL	66/341	1.55	(1.00–2.39)
Arthrosis	110/136	0.76	(0.57–1.01)
Follicular lymphoma	17/136	0.87	(0.49–1.58)
Diffuse large B-cell lymphoma	24/136	0.63	(0.38–1.03)
CLL	18/136	0.73	(0.41–1.28)
Multiple myeloma	13/136	0.71	(0.37–1.36)
MALT	6/136	0.80	(0.31–2.09)
B-NHL total	99/136	0.76	(0.56–1.03)
T-NHL	4/136	0.64	(0.21–1.93)
HL	7/136	0.67	(0.29–1.56)
Cancer	56/72	0.76	(0.52–1.10)
Follicular lymphoma	7/72	0.67	(0.29–1.53)
Diffuse large B-cell lymphoma	16/72	0.80	(0.44–1.44)
CLL	10/72	0.71	(0.35–1.46)
Multiple myeloma	5/72	0.47	(0.18–1.23)
MALT	1/72	0.21	(0.03–1.62)
B-NHL total	48/72	0.67	(0.45–0.99)
T-NHL	3/72	1.22	(0.35–4.31)
HL	5/72	1.31	(0.48–3.55)

CLL, chronic lymphocytic leukaemia; MALT, mucosa-associated lympoid tissue; B-NHL, B-cell non-Hodgkin's lymphoma; T-NHL, T-cell non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.
[a] Method of evaluation: conditional logistic regression.

4. Discussion

4.1. Findings for all lymphomas combined

In the present analysis of the subject's medical history and lymphoma risk, we found decreased risks for a history of repeated diarrhoea, warts, arthrosis, allergies, and appendectomy (at younger age). Elevated risks for lymphoma correlated with tonsillectomy (at younger age), whereas null results were found for certain autoimmune disorders in adulthood.

To our knowledge, this is the first time that diarrhoea has been correlated with lymphoma risk. Taken as an indicator for repeated abdominal infections, it may be consistent with inverse associations which we found in a previous study on abdominal infections and different cancer sites combined (stomach, colorectal, breast), and particularly strong with colorectal cancer [18]. An

Table 3
Odds ratio[a] (OR) and 95%-confidence limits (CL) for other selected disorders in relation to lymphoma subentities (in parentheses: number of male/female cases)

Subentity and disease	Cases/controls	OR[a]	(95% CL)
Follicular lymphoma (55/37)			
Urticaria	16/62	2.06	(1.12–3.80)
Herpes (other than labialis)	3/75	0.25	(0.08–0.82)
CLL (30/74)			
Hepatitis (other than B)	17/71	1.71	(0.93–3.14)
MALT (14/15)			
Infection with *Helicobacter pylori*	2/28	1.88	(0.41–8.69)
Hepatitis B	1/7	2.94	(0.34–25.6)
Hypertension	4/200	0.28	(0.09–0.84)
Ulcus ventriculi	5/35	3.86	(1.36–10.9)
Multiple myeloma (33/43)			
Herpes labialis	44/341	1.55	(0.95–2.52)
B-NHL total (252/302)			
Hypertension	164/200	0.88	(0.68–1.14)
Rheumatoid arthritis	8/18	0.51	(0.22–1.18)
T-NHL (16/19)			
Malaria	2/9	6.18	(1.16–32.9)
Ulcus ventriculi	4/35	2.91	(0.95–8.95)
Rheumatoid arthritis	3/18	4.51	(1.21–16.8)
HL (49/66)			
Sinusitis	26/212	0.61	(0.37–1.02)
Urticaria	16/62	2.68	(1.37–5.23)

[a] Method of evaluation: unconditional logistic regression.

Table 4
Odds ratios[a] (OR) and 95% confidence limits (CL) for subjects with a medical history of selected allergies and risk for all lymphomas combined

Allergic disorder	All lymphomas combined		
	Cases/controls	OR[a]	(95% CL)
Any allergy	290/314	0.85	(0.68–1.07)
Antibody-mediated (type I) hypersensitivity			
Allergic asthma	18/35	0.43	(0.23–0.81)
Allergy to pollen (hay fever)	69/100	0.63	(0.44–0.88)
Mite-dust allergy	39/60	0.62	(0.40–0.96)
Food allergies	57/75	0.77	(0.53–1.11)
Cell-mediated (type IV) hypersensitivity			
Allergic contact eczema	83/101	0.73	(0.52–1.03)
by chromium or nickel (only)	20/28	0.62	(0.32–1.21)
by chemical products (only)	12/10	1.05	(0.45–2.46)
Type I or type IV hypersensitivity			
Allergy to any medication	92/96	1.01	(0.73–1.38)
to antibiotics (only)	40/49	0.82	(0.53–1.29)
to analgesics (only)	10/11	1.15	(0.44–2.97)
Other allergies			
others	68/75	0.88	(0.60–1.29)

OR adjusted for smoking.
[a] Method of evaluation: unconditional logistic regression.

Table 5
Odds ratios[a] (OR) and 95% confidence limits (CL) for subjects with a medical history of selected allergies and risk for lymphoma subentities

Disease and subentity	Cases/controls	OR[a]	(95% CL)
Allergic asthma	18/35	0.51	(0.29–0.92)
Follicular lymphoma	2/35	0.42	(0.10–1.78)
Diffuse large B-cell lymphoma	5/35	0.63	(0.24–1.65)
CLL	1/35	0.21	(0.03–1.56)
Multiple myeloma	3/35	0.82	(0.24–2.78)
MALT	1/35	0.64	(0.08–4.98)
B-NHL total	13/35	0.48	(0.25–0.92)
T-NHL	1/35	0.54	(0.07–4.18)
HL	3/35	0.60	(0.17–2.12)
Allergy to pollen (hayfever)	69/100	0.66	(0.47–0.92)
Follicular lymphoma	14/100	1.08	(0.58–2.03)
Diffuse large B-cell lymphoma	16/100	0.78	(0.44–1.39)
CLL	12/100	1.15	(0.59–2.25)
Multiple myeloma	5/100	0.52	(0.20–1.35)
MALT	2/100	0.56	(0.13–2.50)
B-NHL total	58/100	0.83	(0.58–1.18)
T-NHL	2/100	0.31	(0.07–1.33)
HL	9/100	0.35	(0.17–0.75)
Mite-dust allergy	39/60	0.63	(0.41–0.97)
Follicular lymphoma	7/60	0.77	(0.33–1.75)
Diffuse large B-cell lymphoma	8/60	0.57	(0.26–1.23)
CLL	5/60	0.73	(0.28–1.91)
Multiple myeloma	1/60	0.17	(0.02–1.22)
MALT	1/60	0.37	(0.05–2.86)
B-NHL total	29/60	0.65	(0.41–1.04)
T-NHL	3/60	0.96	(0.28–3.32)
HL	7/60	0.72	(0.30–1.72)
Food allergy	57/75	0.77	(0.53–1.12)
Follicular lymphoma	15/75	1.55	(0.83–2.90)
Diffuse large B-cell lymphoma	14/75	0.88	(0.47–1.63)
CLL	10/75	1.27	(0.61–2.61)
Multiple myeloma	1/75	0.11	(0.02–0.84)
MALT	2/75	0.65	(0.15–2.86)
B-NHL total	49/75	0.88	(0.60–1.30)
T-NHL	1/75	0.21	(0.03–1.66)
HL	7/75	0.52	(0.22–1.24)

OR adjusted for smoking.
[a] Method of evaluation: unconditional logistic regression.

Table 6
Odds ratios[a] (OR) and 95% confidence limits (CL) for subjects who had undergone tonsillectomy and appendectomy with regard to the risk of all lymphomas combined

	All lymphomas combined		
	Cases/controls	OR[a]	(95% CL)
Tonsillectomy	192/174	1.17	(0.92–1.50)
Tonsillectomy above the age of 18 years or none	596/619	1.0	–
Age at tonsillectomy (years)			
18–13	33/35	0.99	(0.59–1.65)
12–7	39/39	1.12	(0.70–1.79)
⩽6	37/17	2.27	(1.25–4.13)
Appendectomy	181/178	1.02	(0.80–1.31)
Appendectomy above the age of 18 years or none	625/603	1.0	–
Age at appendectomy (years):			
18–13	41/45	0.86	(0.56–1.33)
12–7	31/52	0.60	(0.38–0.95)
⩽6	8/10	0.88	(0.34–2.31)

OR adjusted for educational level.
[a] Method of evaluation: conditional logistic regression.

inverse association was also reported for early gastrointestinal infections and the risk for childhood acute leukaemia [19]. Specific strains of *E. coli* appear to be important causes of diarrhoea in developing and industrialised countries [20]. Enterotoxin secreted by enterotoxigenic *E. coli* was recently shown to suppress colon cancer cell proliferation [21]. Furthermore, *E. coli* lipopolysaccharides induce a Th1-like immune response in mice [22], which may apply to humans as well and contribute to the inverse association between abdominal infections and cancer risk.

While previous findings on allergies and lymphoma risk have provided an inconsistent picture (for a Review, see Briggs and colleagues Ref. [23]), more recent articles have reported consistently an inverse association between lymphoma and allergies, that is concordant with our results. The risk was clearly decreased for antibody-mediated hypersensitivities and possibly decreased for cell-mediated hypersensitivities which is not easy to understand within a simple mechanistic model of immune regulation (see below). The overall result of a decreased lymphoma risk fits into a broader body of evidence about an inverse relationship between allergies and different cancer sites (see, for e.g., Vena and colleagues in Ref. [24] for an overview, Schlehofer and colleagues [25,26], Negri and colleagues [27], Holly and Bracci [16], Schwartzbaum and colleagues [28]).

Tonsillectomy may be an indicator of recurrent severe tonsillitis. Infectious agents causing tonsillitis are type A streptococci (involved in approximately 20% of cases) and viruses (involved in approximately 80% of cases), among them the adenoviruses and Epstein-Barr virus (EBV) [29]. Age appears to be the most important factor in distinguishing between viral and bacterial tonsillitis. In a group of 59 children with acute tonsillitis, Sun and colleagues [30] found 71% of those which were caused by streptococcus to be older than 6 years, while 70% of those caused by EBV were younger than 6 years of age. Similar proportions were also published by Putto and colleagues [31]. The epithelial cells of the oropharynx are the first targets of infection with EBV. EBV infection is discussed as potential mechanism involved in recurrent bouts of acute tonsillitis [32]. It can be speculated that in young children recurrent tonsillitis is indicative of a disturbed host-virus balance which may as well apply to viral defence mechanisms of relevance for lymphomagenesis in adulthood.

Table 7
Odds ratios [a](OR) and 95% confidence limits (CL) for subjects who had undergone tonsillectomy with regard to the risk of lymphoma subentities

Disease and subentity	Cases/controls	OR[a]	(95% CL)
Follicular lymphoma			
Tonsillectomy	34/174	1.84	(1.15–2.93)
Tonsillectomy above the age of 18 years or none	70/619	1.0	
Age at tonsillectomy (years)			
18–13	7/35	1.77	(0.75–4.20)
12–7	7/39	1.69	(0.71–4.00)
⩽6	8/17	4.93	(1.97–12.3)
Diffuse large B cell lymphoma			
Tonsillectomy	39/174	1.02	(0.67–1.54)
Tonsillectomy above the age of 18 years or none	137/619	1.0	
Age at tonsillectomy (years)			
18–13	6/35	0.80	(0.33–1.96)
12–7	5/39	0.65	(0.25–1.69)
⩽6	7/17	2.16	(0.84–5.54)
CLL			
Tonsillectomy	30/174	1.42	(0.88–2.29)
Tonsillectomy above the age of 18 years or none	86/619	1.0	
Age at tonsillectomy (years)			
18–13	6/35	1.43	(0.57–3.57)
12–7	6/39	1.62	(0.64–4.10)
⩽6	6/17	4.01	(1.43–11.3)
Multiple myeloma			
Tonsillectomy	15/174	0.78	(0.42–1.43)
Tonsillectomy above the age of 18 years or none	68/619	1.0	
Age at tonsillectomy (years)			
18–13	5/35	1.49	(0.55–4.00)
12–7	2/39	0.65	(0.15–2.80)
⩽6	1/17	1.00	(0.13–8.12)
MALT			
Tonsillectomy	7/174	1.12	(0.46–2.72)
Tonsillectomy above the age of 18 years or none	24/619	1.0	
Age at tonsillectomy (years)			
18–13	2/35	1.56	(0.34–7.11)
12–7	2/39	1.86	(0.40–8.56)
⩽6	1/17	2.82	(0.32–24.7)
B-NHL total			
Tonsillectomy	154/174	1.24	(0.96–1.61)
Tonsillectomy above the age of 18 years or none	467/619	1.0	
Age at tonsillectomy (years)			
18–13	29/35	1.14	(0.68–1.91)
12–7	27/39	1.08	(0.65–1.81)
⩽6	28/17	2.97	(1.57–5.62)
T-NHL			
Tonsillectomy	7/174	0.86	(0.36–2.06)
Tonsillectomy above the age of 18 years or none	29/619	1.0	
Age at tonsillectomy (years)			
18–13	1/35	0.61	(0.08–4.69)
12–7	2/39	1.09	(0.24–4.86)
⩽6	2/17	3.46	(0.69–17.3)
HL			
Tonsillectomy	30/174	1.32	(0.80–2.19)
Tonsillectomy above the age of 18 years or none	95/619	1.0	
Age at tonsillectomy (years)			
18–13	3/35	0.77	(0.22–2.64)
12–7	10/39	1.47	(0.66–3.26)
⩽6	7/17	2.05	(0.72–5.84)

OR adjusted for educational level.
[a] Method of evaluation: unconditional logistic regression.

4.2. Findings among the subentities

Many of the observations in the analyses on subentities, although partially significant, were based on very small numbers and argue for further consideration in the context of larger studies. However, our preliminary results indicate that most of the associations with medical risk factors that were seen for all lymphomas combined were also risk factors for *several* subentities. In other words, our results do not indicate that associations found overall are due to strong associations with only one or a few specific subentities and null effects for the residual subgroups.

However, the opposite was found as well: null results overall masked moderate associations of specific factors with individual subentities (e.g., for follicular lymphoma, MALT lymphoma, HL). One example is the strongly increased OR for MALT lymphoma among subjects with a history of ulcus ventriculi or *Helicobacter pylori*. *Helicobacter pylori* was proposed to be causal for MALT lymphoma in the early 1990's (Wotherspoon and colleagues [33]), and is a strong risk factor for Ulcus ventriculi.

A further example is the association of urticaria with HL and follicular lymphoma. It is known that HL patients have an increased risk for urticaria. However, the present evaluation suggests that urticaria may precede the lymphoma diagnosis by years.

4.3. Limitations of our study

One limitation of our study is the possibility of exposure misclassification, as this data was based on self-reports of physician-diagnosed diseases rather than on medical records. However, we do not consider a *differential* misclassification a major problem of the study. We attempted to minimise selection bias by using a population-based design. However, participation among the controls was below 50%. Thus, selection bias cannot be excluded and may have led to a differential participation depending upon type or severity of the respective disease. For example, the protective effect of a cancer diagnosis suggests that controls with a previous cancer diagnosis might have been more willing to participate in the study. By contrast, neither the severity of the disorder nor an apparent relationship with the scope of the study should have affected the participation of subjects suffering from, e.g., allergies, juvenile diabetes, or having had tonsillectomy in childhood. Finally, we explored many exposures and cannot exclude that some of the associations might be chance findings.

4.4. Mechanistic issues

The parallelism between allergies and adult lymphoma regarding the association with common childhood factors (Vineis and colleagues, [11] and Becker and colleagues, [12]) may give rise to the speculation that the underlying biological processes that mediated the effects of early life events on disease risk, are comparable for both diseases. Accordingly, allergies which usually precede lymphoma should be an indicator of an *increased* risk of lymphoma later in life. However, the present results and an increasing number of other reports, show an apparently decreased risk of lymphoma among atopic individuals. This may imply that the assumption of a simple parallelism is wrong, or, alternatively, factors which are relevant for lymphoma, but not for allergies, may counterbalance common patterns.

Following the Th1/Th2 balance hypothesis, Th1-related disorders, such as many auto-immune diseases, should be less prevalent among atopic individuals and, possibly, among lymphoma patients. However, in a number of studies Th1-related disorders even among atopic subjects are increased [34] (see also Ref. [35]), and Th1-driven and Th2-driven disorders may co-exist [36–38]. Correspondingly, auto-immune diseases are either not decreased (e.g. Ref. [39]) or even increased (e.g. Refs. [11,40]) in lymphoma patients compared with their respective controls. In addition, the present results do not indicate a decreased prevalence of rheumatoid arthritis or diabetes among lymphoma patients. The non-significant association observed for juvenile diabetes was actually based on an increased OR.

These inconsistencies indicate the limits of the Th1/Th2 concept and suggest a different view, that includes the upstream events which control the regulation of the Th1/Th2 balance as part of the answer, as has been proposed by several authors [35,41]. This has to be taken into account when genetic investigations and tests on the disease-relevance of polymorphisms are carried out as has been planned for the German lymphoma study, as well as for the large European (Epilymph) and international (Interlymph) projects.

Conflict of Interest Statement

None declared.

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