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Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium

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Some autoimmune disorders are increasingly recognized as risk factors for non-Hodgkin lymphoma (NHL) overall, but large-scale systematic assessments of risk of NHL subtypes are lacking. We performed a pooled analysis of self-reported autoimmune conditions and risk of NHL and subtypes, including 29 423 participants in 12 case-control studies. We computed pooled odds ratios (OR) and 95% confidence intervals (CI) in a joint fixed-effects model. Sjögren syndrome was associated with a 6.5-fold increased risk of NHL, a 1000-fold increased risk of parotid gland marginal zone lymphoma (OR = 996; 95% CI, 216-4596), and with diffuse large B-cell and follicular lymphomas. Systemic lupus erythematosus was associated with a 2.7-fold increased risk of NHL and with diffuse large B-cell and marginal zone lymphomas. Hemolytic anemia was associated with diffuse large B-cell NHL. T-cell NHL risk was increased for patients with celiac disease and psoriasis. Results for rheumatoid arthritis were heterogeneous between studies. Inflammatory bowel disorders, type 1 diabetes, sarcoidosis, pernicious anemia, and multiple sclerosis were not associated with risk of NHL or subtypes. Thus, specific autoimmune disorders are associated with NHL risk beyond the development of rare NHL subtypes in affected organs. The pattern of associations with NHL subtypes may harbor clues to lymphomagenesis. (Blood. 2008;111:4029-4038)

Introduction

The etiology of non-Hodgkin lymphoma (NHL) remains largely unexplained, despite its dramatic worldwide rise in incidence in recent decades. The heterogeneity of this group of malignancies with regard to histology, molecular biology, and clinical course is well established,[1] whereas etiologic variation among subtypes has been recognized only recently. Known risk factors for NHL overall include uncommon states of severe immune suppression, such as hereditary and acquired immunodeficiency syndromes.[2] However, growing evidence from studies of the occurrence of specific NHL subtypes in inflammatory and infectious conditions also suggests a role for chronic immune stimulation.[3-7]

Local antigenic drive is central to NHL development in the parotid gland in Sjögren syndrome and in the small intestine in celiac disease.[4,6] Sjögren syndrome[8] and celiac disease[9] are also associated with an increase in risk of malignant lymphomas overall. However, whether these associations are the result of a

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much higher risk of lymphomas originating in the affected organs or whether they also reflect specific associations with other and nonlocalized lymphoma subtypes is less clear.

In rheumatoid arthritis (RA)[10,11] and systemic lupus erythematosus (SLE),[12] an increased risk of malignant lymphomas has been described repeatedly, whereas the evidence is less consistent for other inflammatory disorders that display autoimmune phenomena, such as psoriasis,[13] inflammatory bowel disorders,[14] and sarcoidosis.[15] Discrepant results between studies may be the result of differences in study size and design and of differences in composition of lymphoma subtypes studied and failure to disentangle subtype-specific associations. Indeed, large studies are needed to investigate associations between autoimmune disorders and NHL subtypes, as both disease groups are rare in the population.

Further elucidation of the nature of associations between autoimmune disorders and NHL subtypes may give clues to the underlying biology of autoimmune-related lymphomagenesis, and may also have implications for NHL development in general. The aims of this large pooled study, encompassing almost 30 000 subjects in 12 countries in Europe and North America and Australia, were to investigate associations between a range of autoimmune disorders and risk of NHL, to explore potential variation in associations among NHL subtypes by histology and anatomic site and to identify possible reasons for heterogeneity between studies.

Methods

Study population

We performed a pooled analysis of individual data from 12 case-control studies identified through the InterLymph consortium (www.epi.grants.cancer.gov/InterLymph). Studies that met the following criteria were eligible to contribute to the pooled analysis: case patients diagnosed with incident NHL as adults (17-89 years of age); collection of personal history of one or more autoimmune conditions; population- or hospital-based design; study completion between 1992 and 2005; and electronic datasets available in August 2005. In Table 1, we present selected characteristics of the participating studies.

Eight of the studies have previously reported data on some autoimmune conditions and risk of NHL.[16-24] However, analyses of risk by NHL subtypes according to the World Health Organization (WHO) 2001 classification of lymphoid neoplasms[1] were not performed in 5 of these studies[17-19,21,24] and subtype risk estimation was hampered by low statistical power in the remaining 3 studies.[20,22,23] Case patients were identified through rapid case ascertainment systems in direct collaboration with treating physicians, nurses, and/or pathologists (8 studies) and through regional population-based cancer registries (4 studies), of which one used a rapid clinical reporting system. All but one study included both men and women; the Connecticut study was restricted to women. Individuals with HIV infection were either excluded from the original studies based on reports from the treating physician (5 studies) and/or self-reports (1 study) or excluded from the pooled analysis based on self-reports (4 studies) and/or blood test results (2 studies). Individuals with a history of organ transplantation were also excluded from the pooled analysis.

All studies used a frequency-matched case-control design, except the United Kingdom study and 2 EpiLymph centers (Germany and Czech Republic) where cases and controls were matched individually, and the Aviano-Napoli and Northern Italy studies where no matching criteria were applied. For hospital-based controls (19% of all controls), the disease at admission was examined, and subjects admitted for autoimmune conditions were excluded (27 subjects, 0.9% of all hospital-based controls).

Exposure assessment

The participating studies used either telephone or in-person interviews with trained interviewers and standardized structured questionnaires: one study used a self-completed questionnaire. Included were questions about one or more autoimmune disorders and a range of potential confounding factors. All autoimmune disorders were self-reported, none was confirmed by medical record review, but most studies (70%) asked for personal history of physician-diagnosed autoimmune conditions.

The autoimmune disorders assessed by more than one study, and thus eligible for pooling, included Sjögren syndrome, SLE, RA, systemic sclerosis or scleroderma, poly- or dermatomyositis, immune thrombocytopenic purpura, type 1 diabetes, pernicious anemia, multiple sclerosis, myasthenia gravis, celiac disease, psoriasis, sarcoidosis, and inflammatory bowel disorders (Crohn disease and ulcerative colitis). Autoimmune hemolytic anemia was assessed in 2 studies, and 3 additional studies assessed the broader term hemolytic anemia. These reports were grouped together as hemolytic anemia under the assumption that the majority of subjects reporting hemolytic anemia probably have the autoimmune form of disease. We further classified Sjögren syndrome into primary (report of Sjögren syndrome only) or secondary disease (concomitant report of RA, SLE, or poly- or dermatomyositis) in 8 studies. Participants who reported a diagnosis of diabetes at age 30 or less were classified as having type 1 diabetes.[23] We assessed duration of the autoimmune disorder as years between autoimmune disease onset and NHL diagnosis (cases) or interview (controls). For all conditions, reports of autoimmune disease with a duration of less than 2 years were not counted. If 2 incompatible autoimmune disorders were reported by the same subject (eg, RA and SLE), the most recently diagnosed disorder was retained. Information on treatment with systemic corticosteroids was collected in 7 studies, and on use of immunosuppressants (including methotrexate, cyclophosphamide, cyclosporine, azathioprine, and unspecified immunosuppressive drugs) in 5 studies. Information on treatment with tumor necrosis factor blocking agents was not collected because these agents were introduced after initiation of almost all participating studies.

The pooled analysis was approved by the University of New South Wales Human research Ethics Committee. Each participating study obtained local ethical approval and informed consent from participants and provided a de-identified dataset with individual information on history of assessed autoimmune conditions, matching variables and demographic and potentially confounding variables for their study participants.

Tumor classification

All studies verified NHL diagnoses by histopathology review (report review in 4, slide review in 2, and both in 6 studies). All NHL subtypes according to the WHO classification,[1] except multiple myeloma, were included in this analysis. In most studies, patients with chronic lymphocytic leukemia, which constitutes an NHL subtype according to the WHO classification, were recruited as cases, whereas such patients were excluded in a few studies. Case patients classified by the WHO/ICD-O-3 classification (6 studies) were placed directly into the hierarchical groupings of a proposed nested classification based on the WHO classification,[1] developed by a group of expert hematopathologists for epidemiologic research.[25] Subtype diagnoses using earlier classifications (REAL, 1 study; ICD-O-2 1994, 2 studies; Working Formulation, 3 studies) were converted to hierarchical groups and where possible to WHO subtypes using algorithms from the nested classification.[25] The overall distribution of WHO NHL subtypes in the pooled data and according to the proposed hierarchical groups is given in Table S1 (available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Results are presented in tables for the most frequent NHL subtypes or hierarchical groupings, for which the statistical power was the greatest, whereas results for rare subtypes are presented in the text where relevant. Site of lymphoma, for cases with extranodal NHL, was recorded in 6 studies for a total of 7829 cases. True extranodal sites were defined as extranodal and extralymphatic (excluding spleen, Waldeyer ring, and thymus). Patients with unspecified lymphoma (ie, neither non-Hodgkin nor Hodgkin lymphoma) were not included in most participating studies and thus not in this

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Table 1. Characteristics of case-control studies participating in the pooled analysis of history of autoimmune conditions and risk of non-Hodgkin lymphoma (NHL)

					Cases		Controls		
Study acronym	Location	Years	Age, y	Matching variables	N	Rate,* %	N	Rate,* %	Source
Avi-N	Aviano; Napoli, Italy	1999-2002	18-84	None	225	97	492	91	Patients admitted to hospital for non-neoplastic, nonimmunologic conditions
BC	Vancouver, Victoria, BC	2000-2004	20-80	Age, sex, region	828	79	848	46	Random selection from client registry of Ministry of Health
Connecticut	Connecticut	1995-2001	21-84	Age	598	72	716	47-69	<65 y: RDD; ≥65 y: random selection from CMMS
EpiLymph	Spain	1998-2003	17-96	Age, sex, region	435	82	630	96	Patients admitted to hospital for infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic, or respiratory conditions
	Germany	1999-2002	18-82	Age, sex, region	518	87	710	44	Random selection from population registries
	Ireland	1998-2004	19-85	Age, sex, center	144	90	208	75	Patients admitted to hospital for infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic, or respiratory conditions
	Czech Republic	2001-2003	19-82	Age, sex, region	199	90	304	60	Patients admitted to hospital for infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic, and respiratory conditions
	France	2000-2003	18-82	Age, sex, region	217	91	260	74	Patients admitted to hospital for infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic, and respiratory conditions
	Italy (Sardinia)	1998-2004	25-81	Age, sex, region	219	93	336	66	Random selection from population registries
Italy	Turin, Novara, Forli, Vercelli, Varese, Verona, Florence, Siena, Latina, Ragusa, Imperia	1990-1993	20-74	Age, sex, region	1426	82	1771	74	Random selection from demographic or National Health Service files
NCI-SEER	Detroit, MI; Iowa; Los Angeles, CA; Seattle,WA	1998-2001	20-74	Age, sex, region, race	1316	76	1055	52	<65 y: RDD; ≥65 y: random selection from CMMS
Nebraska	Nebraska	1999-2002	20-75	Age, sex	387	74	535	78	RDD
Northern Italy	Aviano; Milan, Italy	1983-1992	17-85	None	429	>97	1155	>97	Patients admitted for non-neoplastic, nonimmunologic conditions in hospitals where cases diagnosed
NSW	New South Wales, Australian Capital Territory, Australia	2000-2001	20-74	Age, sex, region	694	85	694	61	Random selection from electoral rolls
SCALE	Denmark; Sweden	1999-2002	18-74	Age, sex, country	3055	81	3187	71	Random selection from population registries
UCSF	San Francisco, CA	1988-1993	21-74	Age, sex, region	1305	72	2404	78	<65 y: RDD; ≥65 y: random selection from CMMS
UK	Parts of north and southwest England	1998-2003	16-69	Age, sex, region	828	75	1139	71	Random selection from general practice lists

RDD indicates random digit dialing; CMMS Centers for Medicare and Medicaid Services.
*Participation rate.

pooled analysis. In a few of the participating studies, unspecified lymphomas diagnosed in the same populations were however recorded in parallel, and the numbers were low (maximum 3% of all lymphomas diagnosed during the same time periods).

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated from unconditional logistic regression models. We first assessed study-specific risk estimates, and where available, the data were checked against previously published results.[17-24] Because of the variation in control ascertainment between the 6 member study centers in EpiLymph (Table 1), this study was treated statistically as 6 separate studies, to allow for assessment of center-specific effects and heterogeneity by center. For studies with individually matched cases and controls, we compared study-specific results using conditional and unconditional regression. Because there were only marginal differences, we used unconditional regression that led to inclusion of a larger number of controls and, thus, increased statistical power. All hypotheses tested were stated a priori in a predefined analysis plan.

Given the rarity of the assessed disorders, with some studies having no exposed cases and/or no exposed controls for one or several autoimmune disorders, we used a joint fixed- effects model for the pooled analysis[26] to allow for inclusion of all studies. For studies with at least one exposed case

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and control, between-study heterogeneity was assessed using a likelihood-ratio test, and where numbers allowed, further explored with the Cochran Q statistic and the I^2 statistic[27] in a 2-stage random-effects model.[26] Because of the potential limitations of the joint fixed-effects model, including underestimation of the standard error and overweighting of larger studies,[26] we compared pooled risk estimates computed using the joint fixed-effects model and the 2-stage random-effects model, and the estimates differed only marginally for all disorders. Statistically significant between-study heterogeneity was found for one disorder, RA, for which pooled estimates using the 2-stage random-effects model are presented. Possible causes of between-study heterogeneity were investigated in relation to differences in study design (such as questionnaire and data collection format, population vs hospital controls, response rates, and control exposure prevalence rates) as an aid in the identification of outlying studies. For all disorders, we also compared risk estimates in logistic regression models stratified by design-related variables, and we did not observe any general differences in effect by these factors.

All models were adjusted for the matching variables age, sex, region/study center and race. We considered additional potential confounders if they were collected across the majority of studies (socioeconomic status, family history of lymphoma) or if the variable was shown to be an important confounder in a participating study. In individual studies, the inclusion of a range of exposures including tobacco smoking, body mass index, sun exposure, and occupational exposure to pesticides and solvents were not found to change study-specific estimates by more than 10%.[17,19-23] Family history of lymphoma and socioeconomic status (assessed as educational level in 10 studies, and from census data in 2 studies) did not change pooled estimates significantly. However, socioeconomic status was considered to be a potentially important study-specific confounder, especially in the United States where socioeconomic status is related to healthcare access, and was thus retained in the pooled model.

We compared risk estimates by sex, autoimmune disease duration, and treatment with systemic corticosteroids and/or immunosuppressants, and age of autoimmune and NHL onset, in stratified logistic regression models. Because there was no statistically significant heterogeneity of results by sex (although few men reported some disorders) and to maximize statistical power, women and men were analyzed together. Median age of autoimmune disease or NHL onset were used as cutoff for computing younger- and older-onset groups. Because of the large predominance of study participants with white origin, stratification by race was not meaningful. All statistical tests were 2-sided, and the level of statistical significance was set to $\alpha = 0.05$. Analyses were performed using the STATA software version 8.2 (Stata, College Station, TX).

Results

Characteristics of the participants are shown in Table 2. Personal history of the assessed autoimmune conditions and pooled risks of NHL overall are shown in Table 3. Results by study are shown in Figure 1 for RA, and in Figures S1 to S13 for the other disorders assessed.

Sjögren syndrome

Sjögren syndrome was associated with a 6.6-fold increased risk of NHL, and secondary Sjögren syndrome yielded a higher risk than the primary form (Table 3). Women with Sjögren (92% of all affected participants) experienced a 6-fold risk increase, whereas a lack of exposed controls precluded risk estimation among men (data not shown). In all Sjögren syndrome and in primary disease, a 5-fold increased risk of NHL persisted with more than 10 years of disease (Table 4). Statistically significant associations were confined to ages 60 years or older at NHL diagnosis. Neither age at Sjögren syndrome onset nor corticosteroid/immunosuppressive drug use modified the results (data not shown).

Sjögren syndrome was linked with an increased risk of B-cell NHL and NHL of unknown lineage (consisting mainly of B-cell NHL in predominantly white populations) (Table 5). There was a 30-fold increase in risk of the marginal zone lymphoma group (Table 6), based on 11 patients with extranodal, 3 with nodal, and one with undetermined (nonsplenic) marginal zone lymphoma. Risk of diffuse large B-cell lymphoma was increased 9-fold (exposed cases, n = 18), and risk of follicular lymphoma 4-fold (n = 7) (Table 6). Neither corticosteroid use nor immunosuppressive treatment affected the relationship between Sjögren syndrome and risk of NHL subtypes (data not shown). Among the 40 Sjögren's patients with NHL of known anatomic site, 10 were extranodal marginal zone (ie, mucosa-associated lymphoid tissue, MALT) lymphomas situated in the parotid gland, corresponding to a 260-fold risk of parotid gland NHL (OR = 258; 95% CI, 78-854), and a 1000-fold risk of parotid gland MALT lymphoma (OR = 996; 95% CI, 216-4596). Risk was also increased for nodal NHL (OR 5.42; 95% CI, 2.20-13.7, n = 21) and for true extranodal nonparotid gland NHL (OR = 5.07; 95% CI, 1.53-16.8, n = 6).

Table 2. Demographic factors of the pooled study participants

Demographic factor	NHL cases, no. (%)	Controls, no. (%)
Pooled total	12 982	16 441
Sex		
Men	7029 (54.1)	8895 (54.1)
Women	5953 (45.9)	7546 (45.9)
Age, y		
<20	25 (0.2)	69 (0.4)
20-29*	357 (2.7)	946 (5.8)
30-39*	898 (6.9)	1699 (10.3)
40-49	1740 (13.4)	2415 (14.7)
50-59	3362 (25.9)	3725 (22.7)
60-69	4144 (31.9)	4670 (28.4)
70-79	2328 (17.9)	2765 (16.8)
80+	126 (1.0)	152 (0.9)
Median (range)	60 (17-89)	58 (16-96)
Education/SES†		
Low	5038 (38.8)	5823 (35.4)
Medium	4483 (34.5)	5974 (36.3)
High	3382 (26.1)	4562 (27.7)
Not recorded	78 (0.6)	82 (0.5)
Race/ethnicity‡		
White	5172 (39.8)	6507 (39.6)
Black	201 (1.5)	324 (2)
Other/unknown	528 (4.1)	556 (3.4)
Missing§	7081 (54.5)	9054 (55.1)

*The inclusion of Hodgkin lymphoma cases in several studies led to an imbalance in the age distribution of controls compared with the NHL cases only.

†Education/socioeconomic status (SES) groups in each study were based on the tertile distribution of years of education (10 studies) or SES levels obtained from census data (2 studies) in controls.

‡Participants with Hispanic origin were mainly categorized as "white" (n = 307), but a few individuals were also categorized as "black" (n = 4) or with "other/unknown" ethnicity (n = 24), based on the original categorization in the participating studies.

§Ethnicity was generally not recorded in the European studies because of the large predominance of individuals with white origin.

Systemic lupus erythematosus

SLE was associated with a 2.7-fold increase in risk of NHL overall (Table 3). The risk was of similar magnitude in both sexes but statistically significant only among women (data not shown). NHL risk was highest among patients with SLE of short duration (2-5 years), but a near 2-fold increase was also observed with more than 10 years of disease (Table 4). The association was confined to patients with older-onset SLE (≥ 39 years), whereas age at NHL

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Table 3. Personal history of selected autoimmune disorders and pooled relative risk of non-Hodgkin lymphoma (NHL)

		Prevalence†		Pooled relative risk	
Disorder*	No. of studies	All NHL: ever/never (%)	Controls: ever/never (%)	OR (95% CI)‡	Study heterogeneity *P*§
Rheumatoid arthritis	12	504/11735 (4.3)	556/15222 (3.7)	1.06 (0.87-1.29)‖	<.01
Psoriasis	7	278/7460 (3.7)	279/10122 (2.8)	1.16 (0.98-1.38)	.82
Ulcerative colitis	9	125/9775 (1.3)	138/12148 (1.1)	1.02 (0.79-1.31)	.84
Type 1 diabetes	9	32/10289 (0.3)	58/13613 (0.4)	0.76 (0.49-1.19)	.79
Sarcoidosis	6	19/7607 (0.2)	27/8856 (0.3)	0.73 (0.40-1.32)	.70
Pernicious anemia	5	13/3410 (0.4)	16/5865 (0.3)	1.08 (0.51-2.30)	.25
Crohn disease	7	23/9230 (0.2)	27/10614 (0.3)	0.89 (0.50-1.56)	.74
Celiac disease	7	33/9343 (0.4)	25/10424 (0.2)	1.50 (0.89-2.54)	.72
Hemolytic anemia	5	21/3242 (0.6)	13/5585 (0.2)	2.57 (1.27-5.21)	.57
Systemic lupus erythematosus	11	57/12034 (0.5)	26/15237 (0.2)	2.69 (1.68-4.30)	.39
Multiple sclerosis	10	15/9666 (0.2)	18/12341 (0.1)	0.96 (0.48-1.92)	.89
Sjögren syndrome	8	52/8178 (0.6)	8/10543 (0.1)	6.56 (3.10-13.9)	.72
Primary Sjögren syndrome	8	23/8176 (0.3)	5/10543 (0.0)	4.75 (1.79-12.6)	.93
Secondary Sjögren syndrome	8	29/8178 (0.4)	3/10542 (0.0)	9.57 (2.90-31.6)	ND
Scleroderma	7	4/7616 (0.1)	7/10093 (0.1)	0.69 (0.20-2.40)	.81
Immune thrombocytopenia	5	4/4095 (0.1)	3/6529 (0.0)	2.13 (0.47-9.73)	.54
Myasthenia gravis	6	4/6385 (0.1)	3/7413 (0.0)	1.45 (0.31-6.82)	.53
Polymyositis/dermatomyositis	5	6/6662 (0.1)	0/7947 (0.0)	ND	ND

ND indicates not determined.

*Restricted to a history of the autoimmune disorder diagnosed at least 2 years before interview/NHL diagnosis.

†Please note that the denominator differs for each AI condition because not all participating studies ascertained history of each AI condition. The exact number of exposed cases and controls contributing from each study are shown in Figures S1 to S13 (including all but the last four disorders listed).

‡Odds ratio (OR) and 95% confidence interval (CI) computed using a joint fixed-effects model adjusted for age (in 5-year categories), sex, race/ethnicity, education/SES, and study center, with no history of the autoimmune disease in question as reference category.

§*P* value for heterogeneity using a likelihood-ratio test, between studies with at least one exposed case and one exposed control (as shown in Figures S1 to S13).

‖Results computed using the two-stage random effects model due to statistically significant between-study heterogeneity ($P < .01$).

diagnosis or corticosteroid/immunosuppressive drug use did not modify the results (data not shown). Risk was increased for B-cell NHL and NHL of unknown lineage (Table 5), and among the B-cell subtypes, for the marginal zone lymphoma group (OR = 7.5; n = 10) and diffuse large B-cell NHL (OR = 2.7; n = 17; Table 6). In the marginal zone lymphoma group, 7 patients had MALT lymphoma (OR = 12.9; 95% CI, 4.91-33.8). The exclusion of patients with secondary Sjögren syndrome did not alter these associations.

Hemolytic anemia

Hemolytic anemia was associated with a 2.6-fold increase in NHL risk (Table 3), which was slightly more pronounced among men than women (data not shown). The association was most evident among participants reporting long disease duration (> 10 years, Table 4). There was a statistically significant positive association with B-cell NHL (Table 5), and a 3-fold increased risk of diffuse large B-cell lymphoma (Table 6).

Celiac disease

Celiac disease was not associated with risk of NHL overall (Table 3). However, those diagnosed with celiac disease at an older age (≥ 33 years) had an increased risk (OR = 2.34; 95% CI, 1.06-5.21, n = 19). There were no clear differences in risk by sex, or celiac disease duration (Table 4). Risk of T-cell NHL was increased 6-fold (n = 9, Table 5) because of a substantially increased risk of enteropathy-type T-cell NHL (ETTL; OR = 255; 95% CI, 30-2199, n = 3), and of anaplastic large cell lymphoma (OR = 24; 95% CI, 8.8-65; 2 nodal, 4 true extranodal, including 1 small intestine). The risk of small intestinal NHL was increased 30-fold (OR = 31; 95% CI, 10-96, n = 5).

Psoriasis

Psoriasis was not associated with risk of NHL overall (Table 3), and there was no large variation in risk by sex or psoriasis duration (Table 4). However, a weak positive association was observed among psoriatic patients with a late NHL diagnosis (> 60 years, OR = 1.28; 95% CI, 1.01-1.63, n = 159). There was a statistically significant 1.6-fold increase in risk of T-cell NHL (Table 5) and a doubled risk of anaplastic large cell lymphoma (OR = 2.25; 95% CI, 1.00-5.06; 3 nodal, 1 parotid gland, 1 bone, 2 unknown site). There were no statistically significant associations with the cutaneous T-cell NHL subtypes mycosis fungoides and Sezary syndrome (OR = 1.38; 95% CI, 0.50-3.83, n = 4) or cutaneous NHL of any type (OR = 1.61; 95% CI, 0.86-3.03, n = 11).

Rheumatoid arthritis

RA was not associated with risk of NHL overall, but there was statistically significant heterogeneity of the results among studies (Table 3; Figure 1). This heterogeneity could not be fully explained by any single study center but was reduced among studies that used physician-diagnosed RA as the definition of the exposure (7 studies: OR = 1.15; 95% CI, 0.94-1.41, *P* for heterogeneity = .15; I^2 = 30.2%). The heterogeneity also appeared to be related to the prevalence of reported RA among controls in different studies. For the 6 studies within the lowest tertile of age- and sex-adjusted RA control prevalence, the pooled NHL risk was borderline significantly increased, whereas it was decreased for the 5 studies in the highest tertile (Figure 1). RA and concomitant use of corticosteroids or immunosuppressants was positively associated with risk of NHL (OR = 1.57; 95% CI, 1.12-2.21), whereas RA without such use was not (OR = 1.04; 95% CI, 0.77-1.41). We did not assess risk by RA duration or NHL subtype

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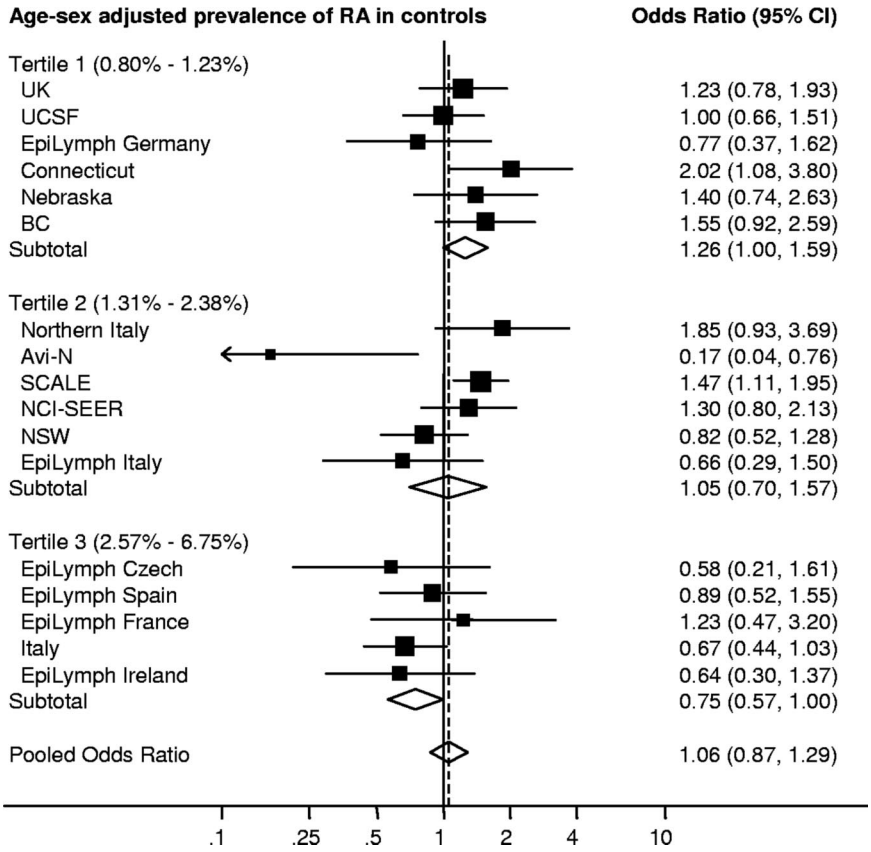

Figure 1. Personal history of rheumatoid arthritis (RA) and risk of non-Hodgkin lymphoma (NHL) by study. Individual study results are sorted and stratified by the age- and sex-adjusted prevalence of RA in controls.

because of the between-study heterogeneity and the lower statistical power in multiple stratified models.

Other disorders

Overall risk of NHL was not linked to a history of inflammatory bowel disorders (ulcerative colitis or Crohn disease), type 1 diabetes, sarcoidosis, pernicious anemia, or multiple sclerosis (Table 3). Examination by autoimmune disease duration (Table 4), sex or age at autoimmune disease, or NHL diagnosis (data not shown) did not affect these results. Type 1 diabetes was borderline significantly associated with the nested group of chronic lymphocytic leukemia/small lymphocytic lymphoma/prolymphocytic leukemia/mantle cell lymphoma (Table 6), but there was no statistically significant association with any of these 4 subtypes in separate analyses (data not

Table 4. Personal history of selected autoimmune disorders and pooled relative risk of non-Hodgkin lymphoma (NHL) by autoimmune disease duration

	Never			2-5 years			6-10 years			More than 10 years		
Disorder*	Cases	Controls	OR (95% CI)†	Cases	Controls	OR (95% CI)†	Cases	Controls	OR (95% CI)†	Cases	Controls	OR (95% CI)†
Psoriasis	7460	10 122	1.00 (referent)	41	40	1.35 (0.86-2.10)	31	47	0.81 (0.51-1.28)	200	188	1.19 (0.97-1.47)
Ulcerative colitis	9775	12 148	1.00 (referent)	12	19	0.83 (0.39-1.75)	9	13	0.73 (0.30-0.75)	86	90	1.08 (0.80-1.47)
Type 1 diabetes	10 289	13 613	1.00 (referent)	1	3	1.08 (0.11-10.4)	1	3	0.66 (0.07-6.55)	30	52	0.76 (0.48-1.20)
Sarcoidosis	7607	8856	1.00 (referent)	1	3	0.43 (0.04-4.19)	1	3	0.34 (0.03-3.28)	11	15	0.78 (0.35-1.71)
Pernicious anemia	3410	5865	1.00 (referent)	2	2	2.10 (0.28-15.6)	2	0	ND	4	6	1.13 (0.31-4.08)
Crohn disease	9230	10 614	1.00 (referent)	3	4	0.92 (0.20-4.25)	4	3	1.91 (0.41-8.85)	12	16	0.73 (0.34-1.57)
Celiac disease	9343	10 424	1.00 (referent)	6	5	1.30 (0.39-4.28)	3	5	0.69 (0.16-2.93)	20	13	1.82 (0.89-3.69)
Hemolytic anemia	3242	5585	1.00 (referent)	3	2	2.37 (0.39-14.4)	2	2	2.13 (0.29-15.8)	15	9	2.50 (1.08-5.83)
Systemic lupus erythematosus	12 034	15 237	1.00 (referent)	10	1	14.6 (1.85-115)	11	6	2.46 (0.90-6.75)	26	16	1.89 (1.00-3.55)
Multiple sclerosis	9666	12 341	1.00 (referent)	1	3	0.55 (0.06-5.37)	3	0	ND	6	11	0.61 (0.22-1.68)
Sjögren syndrome	8178	10 543	1.00 (referent)	15	3	4.54 (1.31-15.8)	13	1	15.7 (2.04-121)	20	4	5.07 (1.72-14.9)
Primary Sjögren syndrome	8176	10 543	1.00 (referent)	6	2	2.84 (0.57-14.2)	2	1	2.64 (0.23-30.3)	12	2	6.37 (1.42-28.6)
Secondary Sjögren syndrome	8178	10 542	1.00 (referent)	9	1	7.92 (1.00-62.8)	11	0	ND	8	2	3.78 (0.79-18.1)

ND indicates not determined.

*Restricted to a history of the autoimmune disorder with onset at least 2 years before interview/NHL diagnosis. Numbers of participants reporting a particular disease may not add up to the number reporting that disease according to Table 3 because of missing data on disease duration in a few individuals.

†Odds ratios (OR) and 95% confidence intervals (CI) computed in a joint-fixed effects model adjusted for age (in 5-year categories), sex, race/ethnicity, education/SES, and study center.

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Table 5. Personal history of selected autoimmune disorders and pooled relative risk of non-Hodgkin lymphoma (NHL) by cell lineage (B-cell, T-cell, unknown cell lineage)

		Cases					
	Controls:	B cell† (n = 10,723)		T cell‡ (n = 745)		Unknown cell lineage (n = 1514)	
Disorder*	Ever/never	Ever/never	OR (95% CI)§	Ever/never	OR (95% CI)§	Ever/never	OR (95% CI)†
Psoriasis	279/10 122	231/5971	1.11 (0.92-1.33)	22/351	1.63 (1.03-2.57)	25/1138	1.30 (0.83-2.03)
Ulcerative colitis	138/12 148	96/7996	1.04 (0.79-1.37)	8/504	1.53 (0.73-3.21)	21/1275	0.96 (0.59-1.56)
Type 1 diabetes	58/13 613	29/8430	0.85 (0.53-1.35)	0/564	ND	3/1295	0.56 (0.17-1.86)
Sarcoidosis	27/8856	14/6627	0.61 (0.32-1.18)	4/465	2.49 (0.85-0.27)	1/515	0.66 (0.08-0.17)
Pernicious anemia	16/5865	13/2719	1.32 (0.61-2.84)	0/153	ND	0/538	ND
Crohn disease	27/10 614	17/7726	0.79 (0.421-.47)	2/494	1.47 (0.34-6.35)	4/1010	1.58 (0.52-0.78)
Celiac disease	25/10 424	22/7916	1.16 (0.652-.08)	9/554	6.21 (2.82-13.6)	2/873	1.66 (0.36-7.62)
Hemolytic anemia	13/5585	17/2466	2.62 (1.25-5.52)	1/176	2.08 (0.24-17.7)	3/600	2.32 (0.63-8.53)
Systemic lupus erythematosus	26/15 237	45/9886	2.44 (1.49-3.99)	3/669	2.43 (0.72-8.24)	9/1479	4.53 (2.00-10.3)
Multiple sclerosis	18/12 341	14/8172	1.06 (0.52-2.16)	0/594	ND	1/900	0.80 (0.10-6.33)
Sjögren syndrome	8/10 543	45/6800	6.52 (3.061-3.93)	1/505	2.03 (0.25-16.6)	6/873	16.3 (4.70-56.4)
Primary Sjögren syndrome	5/10 543	21/6798	4.97 (1.86-13.29)	0/505	ND	2/873	5.54 (0.87-35.5)
Secondary Sjögren syndrome	3/10 542	24/6800	9.11 (2.72-30.46)	1/505	5.13 (0.51-51.8)	4/873	37.7 (7.38-192)

ND indicates not determined.

*Restricted to a history of the autoimmune disorder diagnosed at least 2 years before interview/NHL diagnosis.

†Apart from subgroups of patients displayed in Table 6, patients with B-cell NHL also included 289 patients with lymphoplasmacytic lymphoma, 116 with hairy-cell leukemia, 106 with Burkitt lymphoma, 24 with precursor B-cell lymphoma, and 927 with unspecified B-cell NHL (see also Table S1).

‡The T-cell NHL group consisted of 389 patients with peripheral T-cell NHL (127 with anaplastic large cell lymphoma, 20 with cutaneous T-cell lymphoma not otherwise specified, 14 with primary cutaneous anaplastic large cell lymphoma, 53 with angioimmunoblastic, 19 with enteropathy-type, 4 with subcutaneous panniculitis-like, 2 with hepatosplenic T-cell lymphoma, and 150 with other peripheral T-cell NHLs), 29 with precursor T-cell NHL, 19 with NK/T-cell lymphoma nasal type or aggressive NK-cell leukemia, 7 with T-cell large granular lymphocytic leukemia, 7 with T-cell prolymphocytic leukemia and 44 with unspecified T-cell NHL (see also Table S1).

§Odds ratios (OR) and 95% confidence intervals (CI) computed using a joint-fixed effects model adjusted for age (in 5-year categories), sex, race/ethnicity, education/SES, and study center, with no history of the autoimmune disease in question as reference category.

shown). Scleroderma, immune thrombocytopenia, myasthenia gravis, or poly- or dermatomyositis were all rarely reported (Table 3) and subanalyses were therefore not pursued.

Discussion

In these large pooled analyses, we found evidence that an increased risk of NHL is associated with only a few autoimmune disorders and that these associations are stronger for some NHL subtypes than others. Besides confirming the known link between all NHL combined and Sjögren syndrome and SLE, we demonstrated an increased risk of marginal zone and diffuse large B-cell lymphomas in both of these disorders, and an increased risk of specific T-cell NHL subtypes in celiac disease and psoriasis. Our results further indicate an association between hemolytic anemia and risk of NHL, and diffuse large B-cell lymphoma.

Table 6. Personal history of selected autoimmune disorders and pooled relative risk of major B-cell non-Hodgkin lymphoma (NHL) subtypes or subtype groups*

	Diffuse large B-cell lymphoma (n = 3709)		Follicular lymphoma (n = 2712)		CLL/SLL/PLL/MCL‡ (n = 2096)		Marginal-zone lymphoma group§ (n = 744)	
Disorder†	Ever/ never	OR (95% CI)‖	Ever/never	OR (95% CI)‖	Ever/never	OR (95% CI)‖	Ever/never	OR (95% CI)‖
Psoriasis	70/1974	1.11 (0.85-1.46)	43/1381	0.95 (0.68-1.32)	69/1260	1.18 (0.89-1.57)	10/200	1.08 (0.56-2.08)
Ulcerative colitis	38/2664	1.23 (0.85-1.78)	20/2040	0.89 (0.55-1.45)	16/1579	1.02 (0.59-1.79)	6/417	1.28 (0.54-3.04)
Type 1 diabetes	7/2875	0.59 (0.27-1.31)	4/1963	0.53 (0.19-1.49)	13/1800	1.97 (1.00-3.88)	2/506	1.17 (0.27-5.00)
Sarcoidosis	5/2217	0.69 (0.26-1.80)	4/1810	0.63 (0.22-1.82)	2/1363	0.39 (0.09-1.66)	1/410	0.64 (0.08-4.80)
Pernicious anemia	8/1138	2.12 (0.87-5.16)	0/917	ND	0/110	ND	3/204	2.29 (0.58-8.94)
Crohn disease	10/2523	1.49 (0.71-3.13)	1/1970	0.16 (0.02-1.23)	2/1574	0.49 (0.11-2.16)	3/406	2.41 (0.69-8.46)
Celiac disease	11/2574	1.83 (0.89-3.74)	6/1795	1.13 (0.45-2.85)	3/1937	0.73 (0.21-2.52)	0/518	ND
Hemolytic anemia	8/951	3.22 (1.31-7.89)	3/756	1.46 (0.40-5.37)	1/245	2.90 (0.31-27.2)	1/143	2.23 (0.24-21.0)
Systemic lupus erythematosus	17/3347	2.74 (1.47-5.11)	9/2455	1.70 (0.77-3.74)	6/2045	2.10 (0.825-.42)	10/583	7.52 (3.39-16.7)
Multiple sclerosis	5/2897	1.03 (0.38-2.80)	5/2267	1.08 (0.39-2.98)	2/1483	1.07 (0.23-4.96)	2/603	1.37 (0.30-6.20)
Sjögren syndrome	18/2350	8.92 (3.83-20.7)	7/1794	3.91 (1.39-11.0)	1/1397	0.62 (0.07-5.07)	15/396	30.6 (12.3-76.1)
Primary Sjögren syndrome	8/2348	6.57 (2.12-20.3)	2/1794	1.78 (0.34-9.37)	1/1397	1.01 (0.11-9.15)	8/396	23.1 (7.16-74.6)
Secondary Sjögren syndrome	10/2350	12.8 (3.49-47.3)	5/1794	7.55 (1.75-32.7)	0/1397	ND	7/396	44.6 (10.6-187)

ND indicates not determined.

*In analyses of B-cell NHL subtypes, all controls (see Table 5) were used for modeling of risk of diffuse large B-cell lymphoma, follicular lymphoma, and CLL/SLL/PLL/MCL. However, in modeling of risk of the marginal-zone lymphoma group, studies using the older working classification of lymphomas were excluded (Italy, Northern Italy, University of California–San Francisco, representing about 30% of all participants).

†Restricted to a history of the autoimmune disorder diagnosed at least 2 years before interview/NHL diagnosis.

‡Includes patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), prolymphocytic leukemia (PLL), and mantle cell lymphoma (MCL) (25).

§Includes patients with extranodal (MALT), nodal, splenic, and undetermined marginal-zone lymphoma (25).

‖Odds ratios (OR) and 95% confidence intervals (CI) computed using a joint-fixed effects model adjusted for age (in 5-year categories), sex, race/ethnicity, education/SES, and study center, with no history of the autoimmune disease in question as reference category.

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The risk of NHL was increased almost 7-fold in patients with Sjögren syndrome, which is in the lower range compared with other reports,[8,10] but not unexpected in comparison with cohorts of hospitalized Sjögren patients with presumably more severe disease.[10] Relative risks of NHL subtypes in Sjögren syndrome have seldom been quantified.[21] We observed a 250-fold increase in risk of parotid gland NHL and a dramatic 1000-fold increase in risk of parotid gland MALT lymphoma. This finding is consistent with prior Sjögren lymphoma case series,[28] and with biologic evidence of antigen-driven clonal expansions in affected salivary glands.[6] However, we also noted positive associations with other subtypes, most notably diffuse large B-cell lymphoma, and with nodal lymphomas regardless of WHO subtype in Sjögren syndrome, associations that were much less dramatic in relative terms but more important in terms of patient numbers. Interestingly, in a recent registry-based study of incident Sjögren patients who developed NHL, the majority of the lymphomas were of the diffuse large B-cell type.[8]

In SLE, we observed a close to 3-fold increased risk of NHL, consistent with the hitherto largest cohort studies showing a 3- to 4-fold increase.[12] The patients with SLE were at an increased risk of marginal zone lymphoma, predominantly of the MALT type, and of diffuse large B-cell lymphoma, which is in accordance with recent descriptive data.[29] We also observed a positive association with risk of NHL in hemolytic anemia, in line with a previous study based on patients hospitalized with autoimmune hemolytic anemia,[30] and we provide the first report of a possible association between hemolytic anemia and diffuse large B-cell lymphoma. However, these results should be interpreted with caution because hemolytic anemia could represent secondary phenomena[31] and was not characterized in detail in all participating studies. Of note, the increased risks of NHL in Sjögren syndrome, SLE, and hemolytic anemia persisted with more than 10 years of autoimmune disease duration, making misclassification of incipient lymphomas an improbable explanation for our findings.

In celiac disease, we did not observe an association with risk of NHL overall, but the risk was doubled among patients diagnosed at age more than or equal to 33 years. Previous population-based studies showed a 2- to 6-fold increase in risk of NHL in celiac disease.[9,32] However, in the largest cohort study,[32] the increase was confined to celiac disease patients diagnosed as adults, and there was a trend of decreasing NHL risk over successive calendar periods. If true, such a trend may partly explain our results for NHL overall. We confirmed previous reports of a strong association with ETTL and of NHL located in the small intestine.[33,34] In addition, we observed a marked association with anaplastic large cell lymphoma, which has not been described previously but is consistent with prior observations of nonintestinal T-cell NHL in celiac disease.[35] Because only 1 of 6 cases of anaplastic large cell lymphoma was situated in the small intestine, misdiagnosis of ETTL with numerous CD30 positive cells is an improbable explanation for the association. The indication that only those diagnosed with celiac disease later in life may be at risk of NHL could imply that early diagnosis and early start of diet therapy reduce the risk of lymphoma. This hypothesis is not new but has not been adequately tested.[23]

In psoriasis, previously reported results of risk of NHL overall are mixed.[36,37] Whereas some have noted an increase in risk of T-cell NHL,[20,36,37] little is known about T-cell subtype-specific risks. A possible misclassification of early cutaneous T-cell NHL (ie, mycosis fungoides) as psoriasis could have resulted in false positive associations. Therefore, our finding of an increased risk of T-cell NHL of the anaplastic large cell type and not the cutaneous T-cell NHL forms is especially informative and supports a true risk increase of T-cell lymphoma in psoriasis. However, in 2 of 7 cases of anaplastic large cell lymphoma with no site information, misdiagnosis of transformed mycosis fungoides with numerous $CD30^+$ cells cannot be excluded.

In RA, we did not find an increased risk of NHL overall, unlike most previous reports.[10,11,38] However, a moderately increased NHL risk was observed among RA patients treated with corticosteroids or immunosuppressants, supporting a gradient in risk by treatment or disease severity.[38] In most participating studies, the prevalence of RA reported by the controls was higher than expected,[39] which could reflect a degree of misclassification with other joint or connective tissue disorders. The indication of a positive association between RA and NHL in studies with a low RA control prevalence as opposed to an inverse association among studies with a high RA control prevalence lends some support for this interpretation. An alternative explanation for the overall null result is a possible underrepresentation of RA patients with severe disease and presumably higher risk of lymphoma[38] through self-selection in case-control studies as opposed to in registry-based cohort studies.[10]

Inflammatory bowel disorders, type 1 diabetes, sarcoidosis, pernicious anemia, and multiple sclerosis were not associated with risk of NHL overall, consistent with the majority of previous reports,[14,30,40-42] and there was no strong evidence for subtype-specific associations. In Crohn's disease, a recent large meta-analysis[43] reported a moderately increased risk of lymphoma overall, but latency was not evaluated; therefore a possible risk inflation by initial misdiagnoses of lymphomas cannot be excluded.

It is thus noteworthy that Sjögren syndrome, SLE, and perhaps hemolytic anemia were all associated with risk of diffuse large B-cell NHL, and Sjögren syndrome and SLE also with marginal zone lymphoma. Celiac disease and psoriasis were both associated with T-cell NHL of the anaplastic large cell type in addition to the well-known close link between celiac disease and ETTL. Biologically, the importance of antigen-driven immune stimulation for the development of MALT lymphoma in the parotid gland in Sjögren syndrome,[44] and ETTL in celiac disease[4] is well documented. In Sjögren patients, there is also evidence that oligoclonal expansions of B cells, arising in the parotid gland, may give rise to MALT lymphomas at distant sites.[45] Whether local antigen-driven immune responses or inflammatory processes are relevant for the development of distant NHL, specifically diffuse large B-cell lymphoma, is not known. However, in Sjögren syndrome and RA, recent evidence favors aspects of disease severity and inflammatory load as the strongest determinants of NHL risk.[8,38] These same studies also noted an increased occurrence of diffuse large B-cell lymphoma in particular.[8,38] Thus, it could be hypothesized that disease severity, chronic B-cell activation, and/or inflammation harbor determinants of risk of diffuse large B-cell lymphoma common to a group of autoimmune disorders, including Sjögren syndrome, RA, SLE, and autoimmune hemolytic anemia. Such determinants may include, apart from B-cell stimulation, factors related to cytokine profiles, T-cell subset balance, and apoptotic resistance,[8,46] any of which could be relevant also for lymphomagenesis in general.[47] In celiac disease and psoriasis, disorders characterized by an increase in T-cell activity,[37,48] determinants of T-cell NHL risk may be similar, but acting to enhance oncogenic events in proliferating T cells rather than B cells.

The strengths of this pooled analysis include the large sample size, the ability to adjust for confounding factors, and the exclusion

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of subjects with recent onset autoimmune disorders, which could represent autoimmune phenomena triggered by yet undiagnosed lymphomas. Because of the large size of the pooled dataset, we were able to explore differences in risk by sex and autoimmune disease duration. Unique aspects of our analysis were the ability to assess risk estimates for NHL subtypes according to an epidemiologically oriented classification system[25] and by location, and to compare patterns of subtype associations between different autoimmune disorders. However, despite the large study size, low numbers of exposed subjects was still a limitation in some analyses.

A limitation inherent to the design of the participating case-control studies is the use of self-reported autoimmune disease history, which has the potential for exposure misclassification, already discussed in relation to RA and hemolytic anemia. A comparison of our control prevalences with population prevalence data from different countries showed good concordance,[49-52] except for ulcerative colitis, where the study control prevalences were higher than published prevalence estimates,[53] and in hemolytic anemia and sarcoidosis, where no published rates could be identified. Based on these comparisons, we think that misclassification of self-reports may have been less frequent for most of the autoimmune disorders studied than for RA. In future studies of autoimmune disorders based on self-reports, we recommend a careful assessment of disease aspects reflecting established diagnostic criteria. A detailed assessment of disease severity and treatment may not only help to sort out possible diagnostic misclassification but could also shed more light on the specific determinants of lymphoma risk.

In conclusion, we observed that associations with NHL risk in Sjögren syndrome and celiac disease are less subtype-specific than previously described, and are not confined to associations with rare NHL subtypes developing in the affected organs. Our results further suggest new patterns of associations with some NHL subtypes in specified autoimmune disorders. These patterns may be based on common mechanisms of lymphomagenesis, which could be relevant for the development of the indicated NHL subtypes in a group of autoimmune disorders as well as beyond the setting of overt autoimmune disease.

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Authorship

Contribution: K.E.S., C.M.V., E.A.E., J.T., H.H., P.V., A.S.C., P.M.B., E.A.H., E.W., J.J.S., C.L.V., T.Z., N.B., S.D.S., B.C.-H.C., L.D.M., P.C., M.M., L.F., A.S., P.B., S.D., R.S., J.R.C., A.E.G., and W.C. designed and performed individual studies and collected data; K.E.S., C.M.V., M.F., E.A.E., O.M.-M., J.T., H.H., P.V., A.S.C., P.M.B., E.A.H., E.W., J.J.S., C.L.V., T.Z., N.B., S.D.S., B.C.-H.C., L.D.M., P.C., M.M., L.F., A.S., P.B., S.D., R.S., J.R.C., E.C.B., B.B., A.E.G., and W.C. interpreted data; M.F. performed statistical analysis; K.E.S., C.M.V., and M.F. drafted the manuscript; K.E.S., C.M.V., M.F., E.A.E., O.M.-M., J.T., H.H., P.V., A.S.C., P.M.B., E.A.H., E.W., J.J.S., C.L.V., T.Z., N.B., S.D.S., B.C.-H.C., L.D.M., P.C., M.M., L.F., A.S., P.B., S.D., R.S., J.R.C., E.C.B., B.B., A.E.G., and W.C. contributed with manuscript revisions leading to a final manuscript version.

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References

1. Jaffe ES HN, Stein H, Vardiman JW, eds. Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.
2. Smith MT, Skibola CF, Allan JM, Morgan GJ. Causal models of leukaemia and lymphoma. IARC Sci Publ. 2004:373-392.
3. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet. 1991;338:1175-1176.
4. Cellier C, Delabesse E, Helmer C, et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma: French Coeliac Disease Study Group. Lancet. 2000;356:203-208.
5. Derringer GA, Thompson LD, Frommelt RA, Bijwaard KE, Heffess CS, Abbondanzo SL. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. Am J Surg Pathol. 2000;24:623-639.
6. Yamamoto K. Pathogenesis of Sjogren's syndrome. Autoimmun Rev. 2003;2:13-18.
7. Lecuit M, Abachin E, Martin A, et al. Immunoproliferative small intestinal disease associated with Campylobacter jejuni. N Engl J Med. 2004;350:239-248.
8. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT. Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis. 2006;65:796-803.
9. Mearin ML, Catassi C, Brousse N, et al. European multi-centre study on coeliac disease and non-Hodgkin lymphoma. Eur J Gastroenterol Hepatol. 2006;18:187-194.
10. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med. 2005;165:2337-2344.
11. Franklin J, Lunt M, Bunn D, Symmons DP, Silman AJ. Incidence of lymphoma in a large primary-care derived cohort of inflammatory polyarthritis. Ann Rheum Dis. 2006;65:617-622.
12. Bernatsky S, Boivin JF, Joseph L, et al. An international cohort study of cancer in systemic lupus

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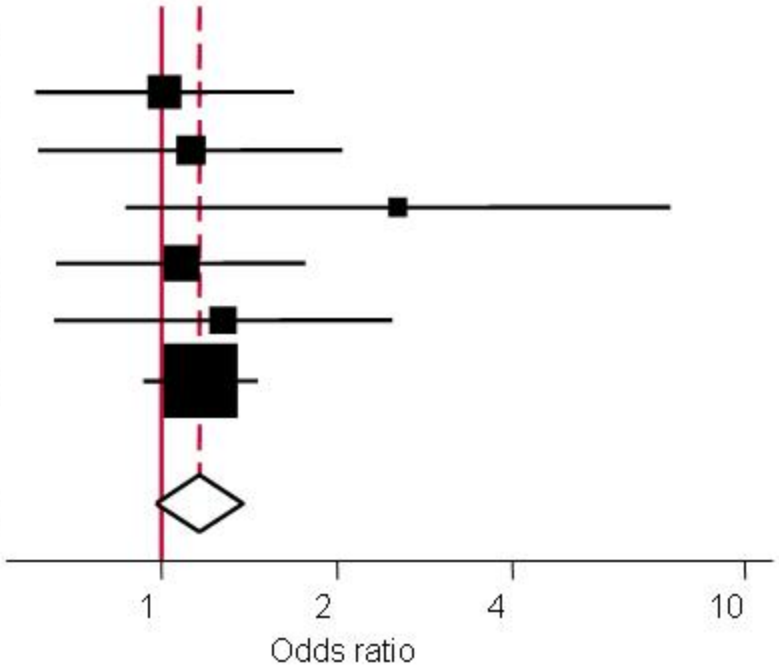
erythematosus. Arthritis Rheum. 2005;52:1481-1490.

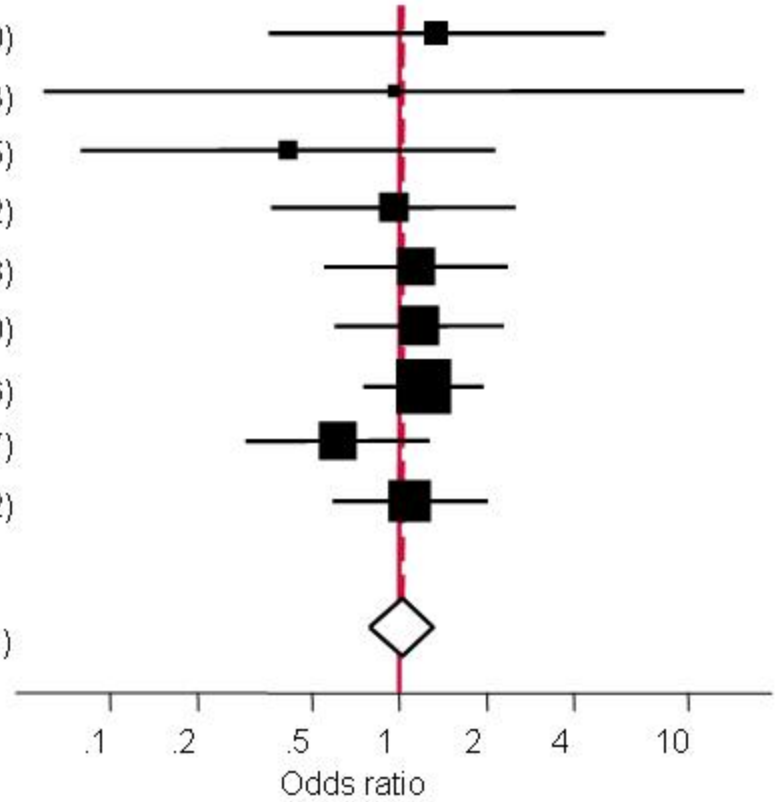
13. Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol. 2001; 137:778-783.
14. Askling J, Brandt L, Lapidus A, et al. Risk of haematopoietic cancer in patients with inflammatory bowel disease. Gut. 2005;54:617-622.
15. Askling J, Grunewald J, Eklund A, Hillerdal G, Ekbom A. Increased risk for cancer following sarcoidosis. Am J Respir Crit Care Med. 1999;160: 1668-1672.
16. Kamel OW, Holly EA, van de Rijn M, Lele C, Sah A. A population based, case control study of non-Hodgkin's lymphoma in patients with rheumatoid arthritis. J Rheumatol. 1999;26:1676-1680.
17. Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur J Cancer Prev. 2000;9:59-64.
18. Vineis P, Crosignani P, Sacerdote C, et al. Haematopoietic cancer and medical history: a multicentre case control study. J Epidemiol Community Health. 2000;54:431-436.
19. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol. 2003;158:316-327.
20. Zhang Y, Holford TR, Leaderer B, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control. 2004;15: 419-428.
21. Engels EA, Cerhan JR, Linet MS, et al. Immune-related conditions and immune-modulating medications as risk factors for non-Hodgkin's lymphoma: a case-control study. Am J Epidemiol. 2005;162:1153-1161.
22. Becker N, Deeg E, Rudiger T, Nieters A. Medical history and risk for lymphoma: results of a population-based case-control study in Germany. Eur J Cancer. 2005;41:133-142.
23. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst. 2006;98:51-60.
24. Scotti L, Tavani A, Bosetti C, et al. Diabetes and risk of non-Hodgkin lymphoma: a case-control study. Tumori. 2007;93:1-3.
25. Morton LM, Turner JJ, Cerhan JR, et al. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007; 110:695-708.
26. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. Stat Med. 2001;20:2115-2130.
27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-1558.
28. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome. Arthritis Rheum. 1999; 42:1765-1772.
29. Bernatsky S, Ramsey-Goldman R, Rajan R, et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. Ann Rheum Dis. 2005;64:1507-1509.
30. Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. Eur J Cancer. 2006;42:3028-3033.
31. Kern WF. Acquired Hemolytic Anemias: PDQ Hematology. Hamilton, ON: Decker; 2002:115-135.
32. Askling J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology. 2002;123:1428-1435.
33. Holmes GK, Stokes PL, Sorahan TM, Prior P, Waterhouse JA, Cooke WT. Coeliac disease, gluten-free diet, and malignancy. Gut. 1976;17: 612-619.
34. Egan LJ, Walsh SV, Stevens FM, Connolly CE, Egan EL, McCarthy CF. Celiac-associated lymphoma: a single institution experience of 30 cases in the combination chemotherapy era. J Clin Gastroenterol. 1995;21:123-129.
35. Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut. 2005;54:54-59.
36. Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. J Invest Dermatol. 2001; 117:1531-1537.
37. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol. 2006;126: 2194-2201.
38. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54:692-701.
39. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature. 2003;423:356-361.
40. Romer FK, Hommelgaard P, Schou G. Sarcoidosis and cancer revisited: a long-term follow-up study of 555 Danish sarcoidosis patients. Eur Respir J. 1998;12:906-912.
41. Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst. 2003; 95:1797-1800.
42. Sumelahti ML, Pukkala E, Hakama M. Cancer incidence in multiple sclerosis: a 35-year follow-up. Neuroepidemiology. 2004;23:224-227.
43. von Roon AC, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP. The risk of cancer in patients with Crohn's disease. Dis Colon Rectum. 2007;50:839-855.
44. Bombardieri M, Barone F, Humby F, et al. Activation-induced cytidine deaminase expression in follicular dendritic cell networks and interfollicular large B cells supports functionality of ectopic lymphoid neogenesis in autoimmune sialoadenitis and MALT lymphoma in Sjogren's syndrome. J Immunol. 2007;179:4929-4938.
45. Gasparotto D, De Vita S, De Re V, et al. Extrasalivary lymphoma development in Sjogren's syndrome: clonal evolution from parotid gland lymphoproliferation and role of local triggering. Arthritis Rheum. 2003;48:3181-3186.
46. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet. 2007;369: 587-596.
47. Rothman N, Skibola CF, Wang SS, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006;7:27-38.
48. Jabri B, Sollid LM. Mechanisms of disease: immunopathogenesis of celiac disease. Nat Clin Pract Gastroenterol Hepatol. 2006;3:516-525.
49. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England: relationship to ethnicity and country of birth. Arthritis Rheum. 1995;38:551-558.
50. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol. 1997;84: 223-243.
51. Staples JA, Ponsonby AL, Lim LL, McMichael AJ. Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect. 2003;111: 518-523.
52. Dube C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. Gastroenterology. 2005;128(Suppl):57-67.
53. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol. 2006;101:1559-1568.

NHL subtypes	Number of cases
B-cell	**10,723**
Diffuse large B-cell lymphoma	3,709
Follicular lymphoma	2,712
CLL / SLL / PLL / MCL	2,096
Chronic lymphocytic leukemia / small lymphocytic leukemia(CLL/SLL)	*1,674*
Prolymphocytic leukemia (PLL)	*9*
Mantle cell lymphoma (MCL)	*413*
Marginal zone lymphoma	744
Splenic marginal zone lymphoma	*109*
Extranodal marginal zone lymphoma, MALT type	*307*
Nodal marginal zone lymphoma	*93*
Undetermined marginal zone lymphoma	*235*
Burkitt lymphoma	106
Lymphoplasmacytic lymphoma	289
Hairy cell leukemia	116
Precursor B-cell lymphoma	24
B-cell lymphoma, not otherwise specified	927
T-cell	**745**
Mycosis fungoides / Sézary syndrome	248
Peripheral T-cell lymphoma (PTCL)	389
Anaplastic large cell lymphoma	*127*
Enteropathy-type T-cell lymphoma	*19*
Cutaneous T-cell lymphoma, not otherwise specified	*20*
Angioimmunoblastic T-cell lymphoma	*53*
Subcutaneous panniculitis-like T-cell lymphoma	*4*
Hepatosplenic T-cell lymphoma	*2*
Primary cutaneous anaplastic large cell lymphoma	*14*
PTCL, not otherwise specified	*150*
Adult T-cell leukemia / lymphoma	2
Extranodal NK/T-cell lymphoma nasal type/aggressive NK-cell leukemia	19
T-cell large granular lymphocytic leukemia	7
T-cell prolymphocytic leukemia	7
Precursor T-cell leukemia/lymphoma	29
T-cell lymphoma, not otherwise specified	44
NHL, not otherwise specified	**1,514**
Precursor leukemia/ lymphoma, not otherwise specified	57
Mature NHL, not otherwise specified	1,457
Pooled total	**12,982**

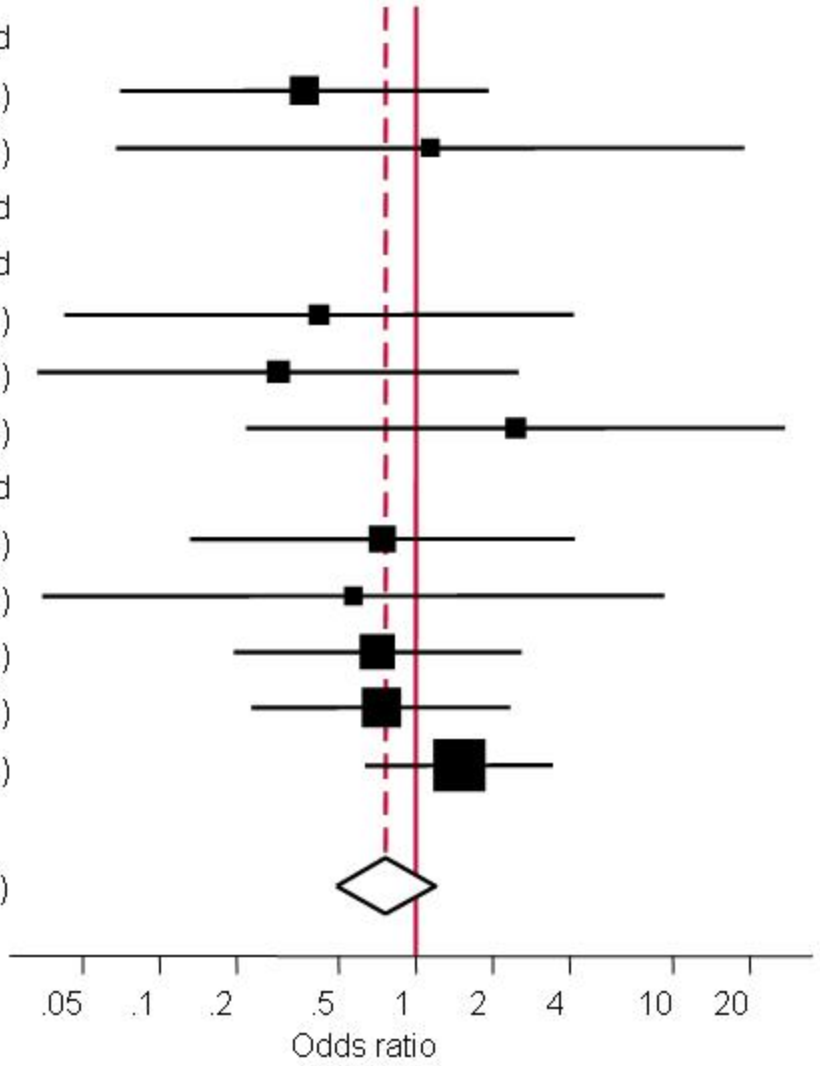
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	3 / 489	Not defined
EpiLymph Germany	28 / 485	37 / 668	1.01 (0.61 - 1.69)
Connecticut	22 / 575	23 / 693	1.12 (0.61 - 2.05)
Northern Italy	7 / 422	7 / 1149	2.54 (0.87 - 7.46)
Italy	34 / 1603	33 / 1737	1.08 (0.66 - 1.77)
UCSF	15 / 1290	23 / 2381	1.28 (0.65 - 2.49)
SCALE	172 / 2860	153 / 3005	1.17 (0.93 - 1.46)
Pooled Odds Ratio	278 / 7460	279 / 10122	1.16 (0.98 - 1.38)



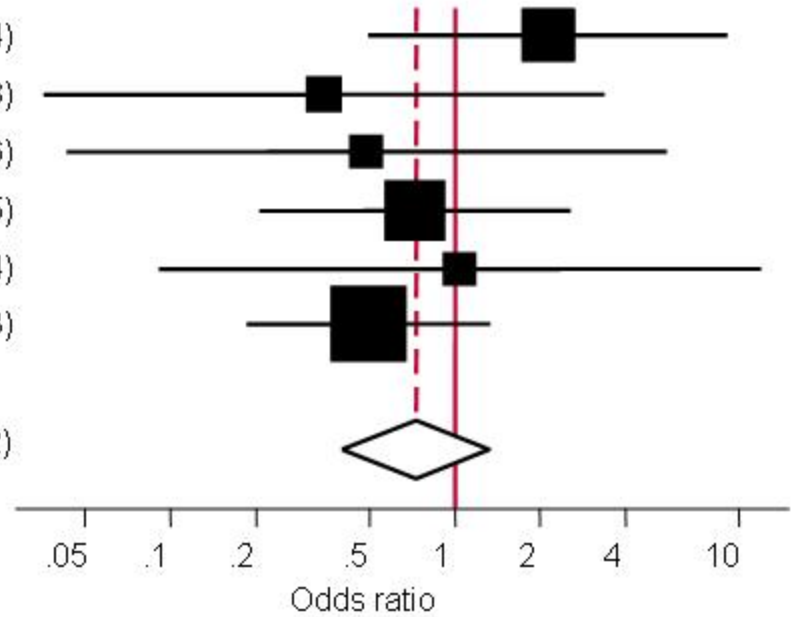
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	4 / 221	6 / 486	1.34 (0.35 - 5.10)
EpiLymph Germany	1 / 514	1 / 705	0.96 (0.06 - 15.53)
NSW	2 / 639	5 / 689	0.41 (0.08 - 2.15)
Northern Italy	6 / 423	15 / 1141	0.95 (0.36 - 2.52)
BC	16 / 775	14 / 822	1.14 (0.55 - 2.38)
NCI-SEER	22 / 1294	15 / 1040	1.17 (0.60 - 2.30)
Italy	42 / 1590	34 / 1735	1.21 (0.75 - 1.96)
UCSF	10 / 1295	29 / 2375	0.61 (0.29 - 1.27)
SCALE	22 / 3024	19 / 3155	1.09 (0.58 - 2.02)
Pooled Odds Ratio	125 / 9775	138 / 12148	1.02 (0.79 – 1.31)



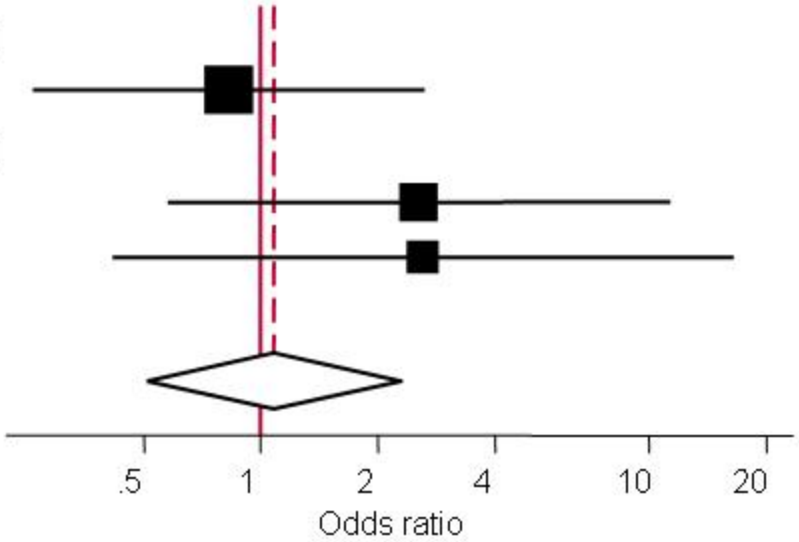
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
EpiLymph Ireland	0 / 140	2 / 205	Not defined
EpiLymph France	2 / 215	6 / 253	0.37 (0.07 - 1.92)
EpiLymph Czech	1 / 191	1 / 287	1.13 (0.07 - 19.14)
EpiLymph Italy	0 / 218	2 / 334	Not defined
Aviano-Naples	0 / 225	0 / 492	Not defined
Nebraska	1 / 385	3 / 532	0.42 (0.04 - 4.14)
EpiLymph Spain	1 / 432	5 / 623	0.29 (0.03 - 2.52)
EpiLymph Germany	2 / 514	1 / 708	2.44 (0.22 - 27.48)
Northern Italy	0 / 429	7 / 1149	Not defined
UK	2 / 825	4 / 1130	0.74 (0.13 - 4.18)
NCI-SEER	1 / 756	1 / 586	0.57 (0.03 - 9.37)
Italy	4 / 1634	6 / 1763	0.71 (0.19 - 2.59)
UCSF	4 / 1298	11 / 2391	0.73 (0.23 - 2.35)
SCALE	14 / 3033	9 / 3167	1.47 (0.63 - 3.43)
Pooled Odds Ratio	32 / 10289	58 / 13613	0.76 (0.49 – 1.19)



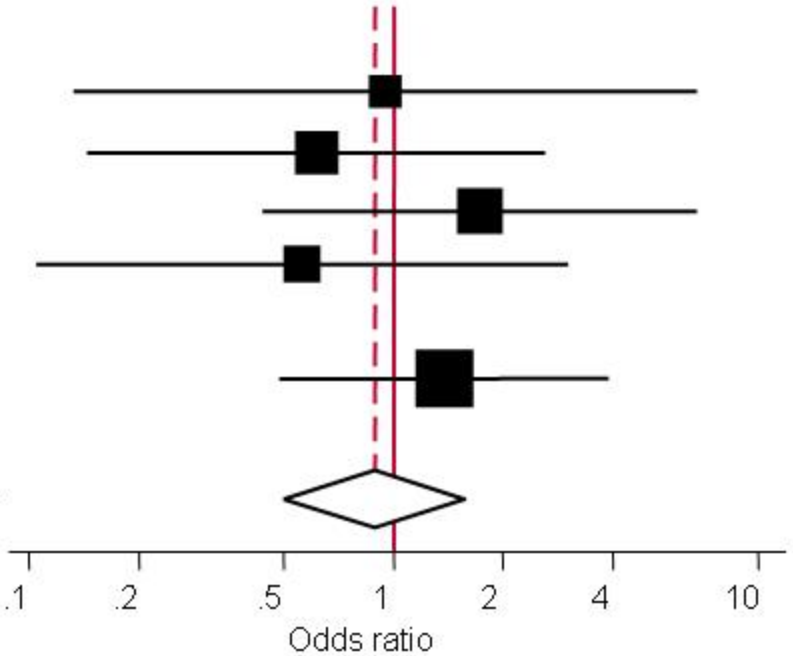
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
EpiLymph Germany	5 / 513	3 / 707	2.14 (0.50 - 9.14)
NSW	1 / 640	3 / 691	0.35 (0.04 - 3.38)
BC	1 / 793	2 / 837	0.49 (0.04 - 5.56)
NCI-SEER	5 / 1311	5 / 1050	0.72 (0.20 - 2.55)
UCSF	1 / 1304	2 / 2402	1.04 (0.09 - 11.94)
SCALE	6 / 3046	12 / 3169	0.50 (0.19 - 1.33)
Pooled Odds Ratio	19 / 7607	27 / 8856	0.73 (0.40 – 1.32)



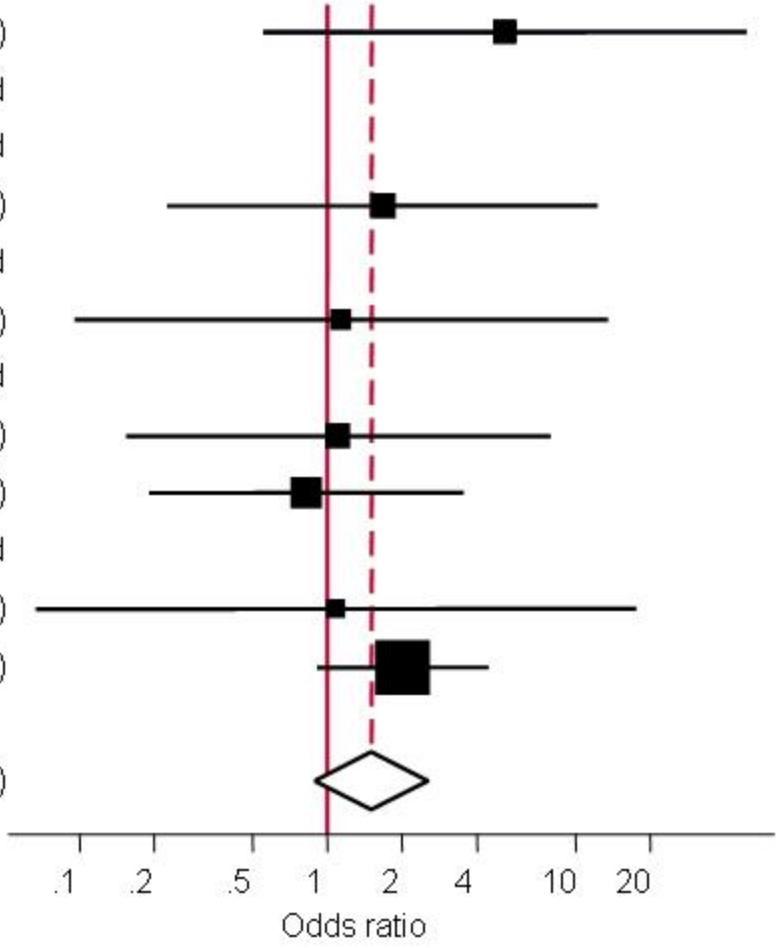
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	0 / 492	Not defined
NSW	5 / 636	7 / 687	0.83 (0.26 - 2.65)
Northern Italy	0 / 429	4 / 1152	Not defined
UK	5 / 818	3 / 1132	2.55 (0.57 - 11.33)
UCSF	3 / 1302	2 / 2402	2.61 (0.41 - 16.48)
Pooled Odds Ratio	13 / 3410	16 / 5865	1.08 (0.51 – 2.30)



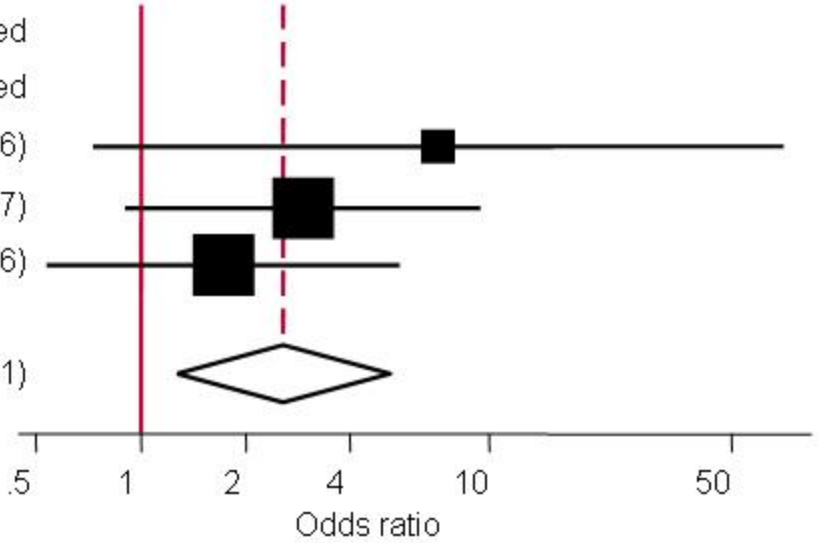
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
EpiLymph Germany	0 / 515	2 / 705	Not defined
NSW	2 / 639	2 / 692	0.95 (0.13 - 6.81)
BC	3 / 791	5 / 833	0.61 (0.14 - 2.61)
NCI-SEER	7 / 1309	3 / 1052	1.72 (0.44 - 6.79)
Italy	2 / 1634	5 / 1764	0.56 (0.10 - 3.02)
UCSF	0 / 1305	4 / 2400	Not defined
SCALE	9 / 3037	6 / 3168	1.38 (0.49 - 3.90)
Pooled Odds Ratio	23 / 9230	23 / 9230	0.89 (0.50 – 1.56)



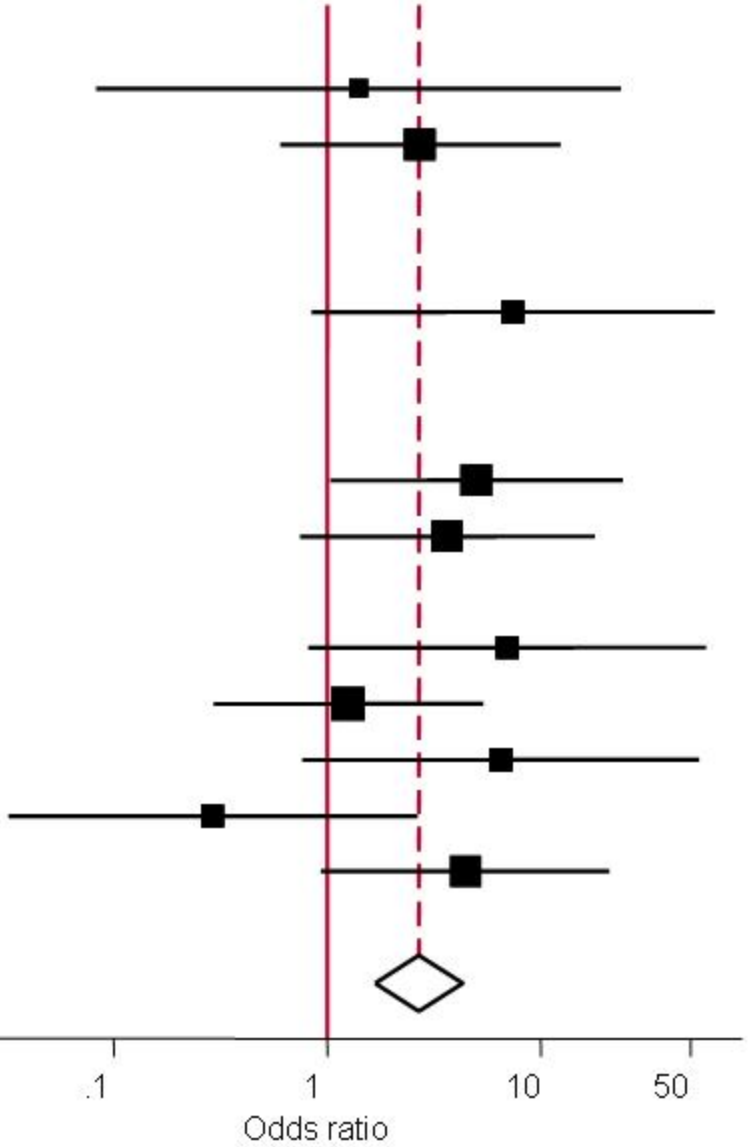
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
EpiLymph Ireland	4 / 136	1 / 206	5.20 (0.55 - 49.05)
EpiLymph France	0 / 217	1 / 258	Not defined
EpiLymph Czech	0 / 193	2 / 285	Not defined
EpiLymph Italy	2 / 216	2 / 334	1.66 (0.23 - 12.28)
Aviano-Naples	0 / 225	0 / 492	Not defined
EpiLymph Spain	1 / 432	2 / 626	1.14 (0.10 - 13.59)
EpiLymph Germany	1 / 515	0 / 708	Not defined
NSW	2 / 639	2 / 692	1.10 (0.15 - 7.92)
BC	3 / 791	5 / 833	0.82 (0.19 - 3.53)
NCI-SEER	0 / 1316	0 / 1055	Not defined
Italy	1 / 1635	1 / 1769	1.08 (0.07 - 17.65)
SCALE	19 / 3028	9 / 3166	2.02 (0.91 - 4.49)
Pooled Odds Ratio	33 / 9343	25 / 10424	1.50 (0.89 – 2.54)



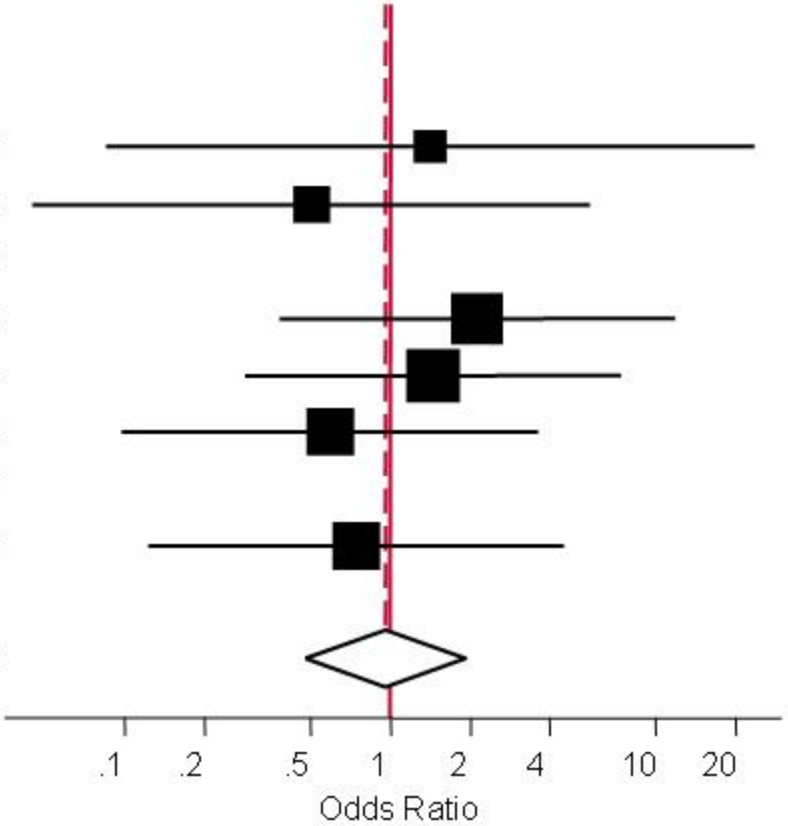
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	2 / 490	Not defined
EpiLymph Germany	2 / 516	0 / 710	Not defined
Northern Italy	3 / 426	1 / 1155	7.16 (0.73 - 70.46)
BC	10 / 776	4 / 832	2.92 (0.90 - 9.47)
UCSF	6 / 1299	6 / 2398	1.73 (0.54 - 5.56)
Pooled Odds Ratio	21 / 3242	13 / 5585	2.57 (1.27 – 5.21)



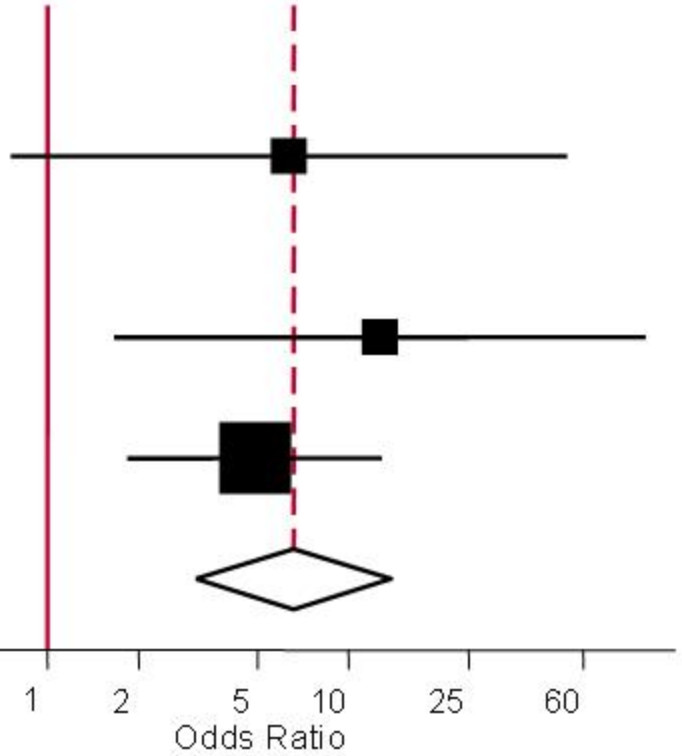
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
EpiLymph Ireland	1 / 139	0 / 207	Not defined
EpiLymph France	1 / 216	1 / 258	1.40 (0.08 - 23.66)
EpiLymph Czech	5 / 188	3 / 285	2.72 (0.60 - 12.26)
EpiLymph Italy	2 / 216	0 / 336	Not defined
Aviano-Naples	0 / 225	0 / 492	Not defined
Nebraska	5 / 381	1 / 534	7.36 (0.84 - 64.37)
EpiLymph Spain	0 / 433	5 / 623	Not defined
EpiLymph Germany	2 / 514	0 / 709	Not defined
Connecticut	8 / 589	2 / 714	5.00 (1.04 - 24.04)
NSW	7 / 634	2 / 692	3.65 (0.75 - 17.79)
Northern Italy	0 / 429	0 / 1156	Not defined
BC	6 / 787	1 / 838	6.93 (0.82 - 58.81)
NCI-SEER	5 / 1311	3 / 1052	1.26 (0.29 - 5.37)
Italy	6 / 1627	1 / 1768	6.48 (0.77 - 54.71)
UCSF	1 / 1304	5 / 2399	0.29 (0.03 - 2.64)
SCALE	8 / 3041	2 / 3174	4.42 (0.93 - 20.96)
Pooled Odds Ratios	57 / 12034	26 / 15237	2.69 (1.68 – 4.30)



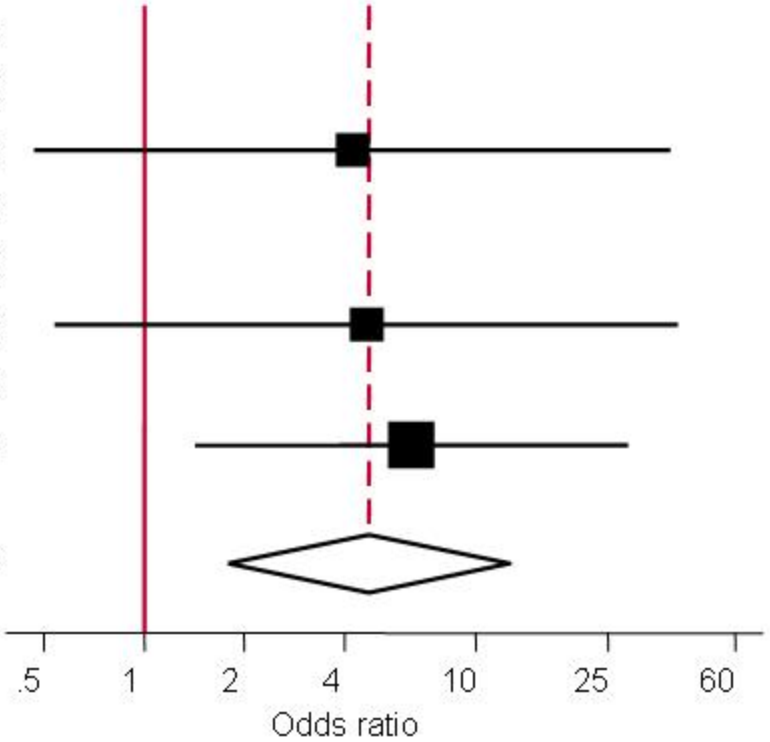
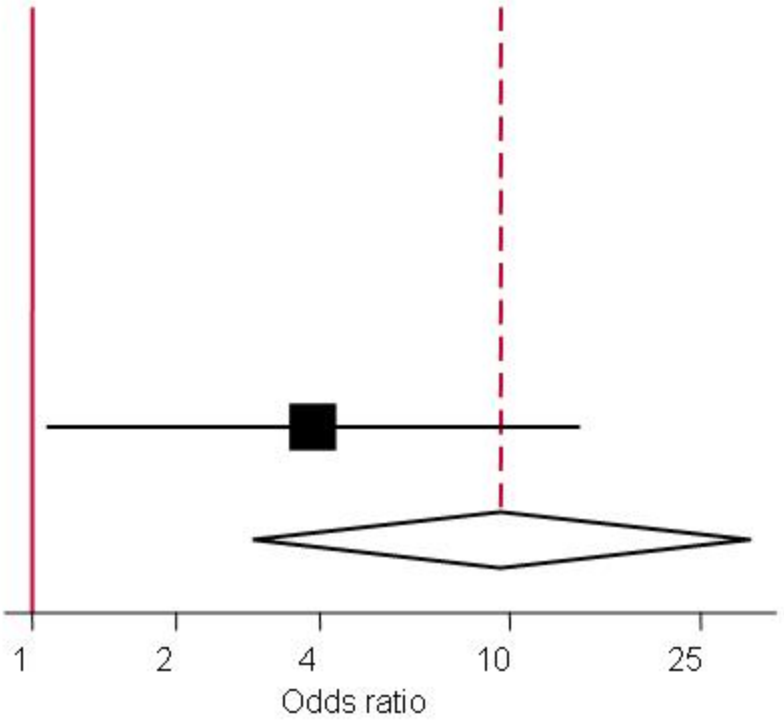
Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	0 / 492	Not defined
EpiLymph Germany	2 / 516	0 / 710	Not defined
Connecticut	1 / 596	1 / 715	1.41 (0.08 - 23.42)
NSW	1 / 640	2 / 692	0.50 (0.05 - 5.66)
Northern Italy	0 / 429	1 / 1155	Not defined
BC	4 / 790	2 / 837	2.13 (0.38 - 11.83)
UK	3 / 825	3 / 1134	1.45 (0.28 - 7.40)
NCI-SEER	2 / 1314	3 / 1052	0.59 (0.10 - 3.61)
UCSF	0 / 1304	3 / 2399	Not defined
SCALE	2 / 3027	3 / 3155	0.75 (0.12 - 4.53)
Pooled Odds Ratio	15 / 9666	18 / 12341	0.96 (0.48 – 1.92)



Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	0 / 492	Not defined
EpiLymph Germany	0 / 518	1 / 709	Not defined
Connecticut	6 / 591	1 / 715	6.35 (0.76 - 53.27)
Northern Italy	0 / 429	0 / 1156	Not defined
BC	6 / 786	0 / 838	Not defined
NCI-SEER	15 / 1301	1 / 1054	12.65 (1.65 - 96.74)
UCSF	2 / 1303	0 / 2404	Not defined
SCALE	23 / 3025	5 / 3175	4.88 (1.84 - 12.92)
Pooled Odds Ratio	52 / 8178	8 / 10543	6.56 (3.10 – 13.88)



Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	0 / 492	Not defined
EpiLymph Germany	0 / 518	1 / 709	Not defined
Connecticut	4 / 591	1 / 715	4.24 (0.47 - 38.36)
Northern Italy	0 / 429	0 / 1156	Not defined
BC	1 / 786	0 / 838	Not defined
NCI-SEER	5 / 1301	1 / 1054	4.67 (0.54 - 40.63)
UCSF	1 / 1303	0 / 2404	Not defined
SCALE	12 / 3023	2 / 3175	6.39 (1.42 - 28.69)
Pooled Odds Ratio	23 / 8176	5 / 10543	4.75 (1.79 – 12.57)



Study	Cases Ever/Never	Controls Ever/Never	OR (95% CIs)
Aviano-Naples	0 / 225	0 / 492	Not defined
EpiLymph Germany	0 / 518	0 / 709	Not defined
Connecticut	2 / 591	0 / 715	Not defined
Northern Italy	0 / 429	0 / 1156	Not defined
BC	5 / 786	0 / 838	Not defined
NCI-SEER	10 / 1301	0 / 1054	Not defined
UCSF	1 / 1303	0 / 2404	Not defined
SCALE	11 / 3025	3 / 3174	3.88 (1.07 - 14.00)
Pooled Odds Ratio	29 / 8178	3 / 10542	9.57 (2.90 - 31.63)