Diabetes and the risk of non-Hodgkin's lymphoma and multiple myeloma in the European Prospective Investigation into Cancer and Nutrition

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ABSTRACT

Background

Non-Hodgkin's lymphomas are a heterogeneous group of neoplasms arising from the lymphopoietic system including a wide range of subtypes of either B-cell or T-cell lymphomas. The few established risk factors for the development of these neoplasms include viral infections and immunological abnormalities, but their etiology remains largely unknown. Evidence suggests that certain medical conditions may be linked, through immunosuppression, to the risk of non-Hodgkin's lymphoma. Multiple myeloma is a neoplasm of plasma cells that accounts for approximately 15% of lymphopoietic cancers. Increases in the incidence of non-Hodgkin's lymphoma and multiple myeloma in the past implicate environmental factors as potential causal agents.

Design and Methods

In the European Prospective Investigation into Cancer and Nutrition (EPIC), 1,213 histologically confirmed incident cases of non-Hodgkin's lymphoma and multiple myeloma (594 men; 619 women) were identified during a follow-up of 8.5 years. Cox proportional hazard models were used to explore the association between self-reported diabetes, diagnosed after 30 years of age, and the risk of non-Hodgkin's lymphoma overall and multiple myeloma and various lymphoma subtypes.

Results

We found no association between a personal history of diabetes and the risk of non-Hodgkin's lymphoma overall in men (HR: 1.28, 95% CI: 0.89-1.84), in women (HR: 0.71, 95% CI: 0.41-1.24), or in men and women combined (HR: 1.09, 95% CI: 0.80-1.47). Among the B-non-Hodgkin's lymphoma subtypes, we observed a statistically significant increased risk of B-cell chronic lymphocytic leukemia (HR: 2.0, 95% CI: 1.04-3.86) in men, but not in women (HR: 1.07, 95% CI: 0.33-3.43).

Conclusions

This prospective study did not provide evidence for a role of self-reported diabetes in the etiology of non-Hodgkin's lymphoma overall or multiple myeloma. We found an increased risk of B-cell chronic lymphocytic leukemia among men with diabetes, but not among women. We hypothesize that diabetes may not play a causal role in the etiology of B-cell chronic lymphocytic leukemia, though the underlying pathogenic mechanisms of both disorders may include shared genetic, host and/or environmental susceptibility factors.

Key words: non-Hodgkin's lymphoma, diabetes, cohort study.

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Introduction

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of B-cell or T-cell neoplasms that originate from lymphoid tissues. As a group they are the seventh most commonly diagnosed cancer in Europe, but their etiology still remains largely unknown. In 2004, approximately 121,200 cases of NHL were diagnosed in Europe, causing an estimated 65,200 deaths.[1] The incidence of NHL rose significantly between the 1970s and 1980s, mainly in Western countries, and reached a plateau during the 1990s.[2] A part of this increase is attributed to improved cancer reporting, changes in lymphoma classification, better means of diagnosis and an increase in AIDS-associated lymphoma, while other factors remain elusive. Multiple myeloma (MM) is a neoplasm of plasma cells that accounts for approximately 15% of lymphopoietic cancers.[3] Increases in the incidence of MM in the past implicate environmental factors as potential causal agents.[4]

The strongest risk factors for NHL include rare conditions entailing severe immune suppression, such as hereditary and acquired immunodeficiency syndromes, in which risk is about 10 to 100 times higher than that of the general population.[5] Epstein-Barr virus (EBV), *Helicobacter pylori*, human T-cell lymphotropic virus-1 (HTLV), hepatitis C virus and, more recently, hepatitis B virus are pathogens that have been linked to an increased risk of NHL. Use of various medications such as oral contraceptives, estrogen replacement therapy, anti-convulsant drugs, and various steroids[6,7] have also been suggested to be associated with NHL. Recent evidence suggests that dietary or lifestyle habits, such as smoking and alcohol consumption, might also modify the risk of NHL. Factors that have been associated with MM include high doses of ionizing radiation, and occupational exposure in farming and petrochemical industries.[8] The role of chronic antigenic stimulation in the etiology of MM has also been investigated.[8]

In addition, as possible conditions predisposing to NHL, autoimmune and inflammatory conditions, such as systemic lupus erythematosus, rheumatoid arthritis, celiac disease and Sjögren's syndrome, have been observed to increase the risk of NHL in a number of studies,[9,10] while psoriasis and inflammatory bowel disorders have not been consistently associated. These diseases are characterized by dysregulated lymphocyte reactivity against self-antigens and the production of autoantibodies.[9] Some researchers have hypothesized that the ongoing abnormal lymphocyte activation in immunosuppressed states could predispose to NHL.

Diabetes is a common, increasing frequent health condition associated with a wide range of metabolic, immunological, and hormonal aberrations.[11] Recent observations indicate that autoimmunity plays a role in type 2 diabetes.[12] This condition has been described as an acute-phase disease of the innate immune system, in which oversecretion of cytokines may contribute to the development of insulin resistance and impairment of insulin secretion in pancreatic β-cells.[12] Approximately 135 million people worldwide are affected by type 2 diabetes and the number of adults with diabetes in the world is expected to rise to at least 300 million by 2025, making it a serious public health concern.[13] An increased risk of cancer, in particular pancreatic cancer, liver cancer, breast cancer, MM, and cancer of the endometrium among patients with diabetes has been observed in several studies.[11,14-16] The proposed biological mechanism relates to insulin resistance, a prediagnostic stage of type 2 diabetes, and insulin-like growth factors, both of which have been shown to stimulate tumor cell proliferation in experiments.[17-20]

Epidemiological studies exploring the role of type 2 diabetes in the etiology of NHL have yielded inconsistent results. Two of the four cohort studies found an elevated risk of NHL[5,11,21] among diabetic individuals. Four population and hospital-based case-control studies also demonstrated positive associations,[22-25] while five others reported no or inverse associations.[26-29] The inconsistency of the findings to date may partly be attributed to differences in study design, lack of information on potential confounders, use of inappropriate comparison populations and ascertainment of cases from cancer or mortality registries.

The aim of this study was to take advantage of a large prospective study to evaluate the association between a personal history of diabetes and the risk of NHL and MM and various lymphoma subtypes in Europe.

Design and Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing multicenter prospective cohort study designed to investigate the relation between nutritional status, lifestyle, and environmental factors and the risk of cancer and other chronic diseases. The cohort comprises 521,457 eligible participants from the general population, enrolled between 1992 and 2000, aged 20 years or above. Participants were recruited from 23 study centers in ten European countries: Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), Greece, Italy (Florence, Varese, Naples, Ragusa and Turin), the Netherlands (Bilthoven and Urecht), Norway, Spain (Granada, Murcia, Asturias, Pamplona, and San Sebastian with the co-ordination center in Barcelona), Sweden (Malmo and Umea), and the United Kingdom (Oxford and Cambridge). There were some exceptions made in the French cohort, where recruitment was based on female participants of a health insurance agency for school and university employees; the Utrecht cohort and Florence cohort, where female participants were recruited from breast cancer screening programs; the Ragusa cohort, based on blood donors and their spouses; and most of the Oxford cohort, where mainly vegetarian volunteers and healthy eaters were recruited. Only women were enrolled in France, Norway, Utrecht, and Naples.

The study design and methods for collecting baseline data have been described in detail elsewhere by Riboli *et al.*[30] All eligible participants provided written informed consent. Approval for the EPIC study was obtained from the ethical review boards of the

International Agency for Research on Cancer (IARC) and local participating centers.

Study population

Of the 521,457 eligible participants, we excluded participants if they were prevalent cases of cancer at any site at the time of enrolment, participants with missing data on lifestyle and dietary questionnaire, or those who were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement, which was calculated from body weight, height and age (n=41,604). Participants were also excluded if they were members of the French cohort because case ascertainment was incomplete in France (n=69,426). We further excluded 65 cases with Hodgkin's disease and 29 uncertain lymphoma cases, as well as all participants with missing data on diabetes (n=16,856). The current analyses are related to a total of 393,477 EPIC participants and 1,213 incident cases of NHL (594 men, 619 women).

Assessment of end-points

Incident lymphoma cases were identified through population cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom, and through active follow-up in Germany and Greece. Active follow-up methods included health insurance records, cancer and pathology hospital registries, and directly contacting participants or next of kin. Mortality data were obtained from cancer or mortality registries at the regional or national level. Follow-up began at the date of recruitment and ended at either the date of diagnosis of lymphoma, death or last complete follow-up. Date of complete follow-up varied for the different study centers. Participants were censored as follows: December 2002 (Granada); December 2003 (Florence, Varese, Naples; Murcia; Bilthoven; Aarhus, Copenhagen), December 2004 (Ragusa, Turin; Asturias, Navarra; Cambridge, Oxford; Utrecht; Malmö; Norway); June 2005 (Umeå); December 2005 (San Sebastian). For Germany and Greece, the end of the follow-up was considered to be the last known contact, date of diagnosis, or date of death, whichever came first.

Lymphoma cases were initially identified according to the second revision of the International Classification of Disease for Oncology (ICD-O-2). All cases were subsequently recoded using the WHO classification system of tumors of hematopoietic and lymphoid tissue, which is based on ICD-O-3.[31] The conversion was made with the help of a web-based program available from the SEER webpage and involved expertise of a pathologist (TR) as well as experts from the EPIC centers (see Appendix, and also a publication by Morton *et al.*[32]). Cases in which ICD-O-2 codes could not be translated unequivocally into a lymphoma diagnosis according to the WHO classification system were categorized as lymphomas unclassified ("nos").

In the current analyses, we considered the following subtypes of NHL: overall NHL including MM; within NHL the B-cell lymphomas (B-NHL) and T-cell lymphomas (T-NHL), and among B-NHL the subtypes diffuse large B-cell lymphomas, follicular lymphomas, B-cell chronic lymphocytic leukemia (B-CLL) and MM. Other rare subtypes were not considered because of the small number of cases.

Assessment of exposure

Information on socio-demographics, lifestyle characteristics and medical history, were collected via questionnaire at the time of entry into the study. Diabetes status was self-reported and was obtained through a questionnaire in which participants were asked if they had ever been diagnosed with 'diabetes' and if so, at what age. No distinction was made between the types of diabetes. However, it is likely that the vast majority of them were type 2 diabetics, as most diagnoses were made after the age of 30. Information on the use of insulin treatment was also obtained at baseline through a questionnaire.

Detailed information was obtained on smoking status (life-long non-smoker; current smoker <15 per day, 15-24 per day, >25 per day; past smoker <10 years; past smoker >10 years; other smoker including pipes and cigars), alcohol intake in grams per day (no ethanol, <5 grams per day, 5-14 grams per day, 15-29 grams per day, >30 grams per day), level of education (no degree or primary school, technical or professional school, secondary school, university degree), occupation, age at puberty and reproductive history, use of contraception and hormonal drugs, current illnesses and history of previous illnesses including surgical operations. Assessment of physical activity included household, recreational and occupational activities. Average metabolic equivalent-hours (MET-hr) were derived for recreational and household activities, based on the types and durations of activities reported separately for summer and winter. Physical activity was coded by cross-classifying participants on the basis of sex-specific quartiles of recreational and household activities and categories of occupational activity, and was coded as inactive, moderately inactive, moderately active and active.

Participants' height and weight were measured at baseline, except in Norway and Oxford, where self-reported height and weight were obtained via questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters. BMI was split into categories using WHO cut-off points[33] as follows: underweight < 18.50, normal 18.50 – 24.99, overweight 25 – 29.99 and obese ≥30. There were few underweight participants in the cohort and therefore, 'underweight' and 'normal' categories were collapsed and used as the reference group in both men and women. Waist circumference was split into two categories, according to the International Diabetes Federation's (IDF)[34,35] definition of central obesity, using ethnic-specific cut-points for European men and women. The waist to hip ratio was calculated as waist circumference divided by hip circumference, measured to the nearest 0.5 cm.

Statistical analyses

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals

(CI). Age was the primary time variable in all models. Age at entry was defined as the participants' age at recruitment and exit time was age at diagnosis of lymphoma, death, loss to follow-up or censoring at the end of the follow-up period, whichever came first. A likelihood ratio test was carried out to check for interactions by including a cross-product term for gender and diabetes. Models were stratified by study Center and age at EPIC study recruitment in 1-year categories, in order to control for differences in questionnaire design, follow-up procedures, and other center effects. We obtained crude risk estimates of NHL for the following potential confounders: physical activity, smoking status, alcohol intake, level of education, medical history of hyperlipidemia, hypertension, as well as anthropometric measurements including height, weight, BMI, waist to hip ratio, and waist circumference. To calculate p values for trends across quintiles of anthropometric variables and categories of socio-demographic variables, participants were assigned a score according to their quintile or category which was entered as a continuous term in the Cox regression models. Participants with missing responses for a specific variable were excluded from a given analysis. A covariate was considered a confounder if there was at least a 10% change in the risk estimate for NHL and its subtypes when models were compared with and without the covariate term. In addition, likelihood ratio tests were carried out to check for confounders. Inclusion of any of the adjustment variables did not alter risk estimates appreciably and were not included in the final Cox model. However, we also present risk estimates corrected for BMI and smoking status.

We confirmed the proportional hazards assumption for diabetes status in relation to NHL using the likelihood ratio test, comparing models with and without product terms for diabetes and follow-up time (years). All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Analyses were performed using Stata version 9.2.

Results

We analyzed the association between self-reported diabetes and the risk of NHL and MM and individual lymphoma subtypes, separately for men and women. Overall, 139,431 men and 254,046 women were followed-up for an average of 8.5 years (Table 1). Of the 1,213 NHL cases, there were 1,079 cases of B-NHL and 43 of T-NHL. The most frequent subtypes of B-NHL were B-CLL (n=224), diffuse large B-cell lymphoma (n=152) and follicular lymphoma (n=138); 91 NHL cases and 166 cases of B-NHL could not be further specified.

The characteristics of the EPIC participants were compared at baseline for men and women separately (Table 2). Among cases with NHL and MM, the prevalence of diabetes was 5.39% and 2.10% for men and women, respectively. The average age at diagnosis of

Table 1. Frequency of non-Hodgkin's lymphoma (including multiple myeloma) subtypes and diabetes status by country among 139,431 men and 254,046 women in the EPIC study.

	Cohort size		*Person-years*		*NHL cases*		*Diabetes cases*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
Italy	13,999	30,458	120,532	262,606	51	74	313	633
Spain	15,116	24,809	156,203	244,699	49	51	875	1,114
UK	22,337	48,463	190,444	411,510	103	127	555	636
Netherlands	9,766	26,411	81,710	233,466	14	75	122	563
Greece	10,586	14,981	72,944	109,229	22	11	751	991
Germany	21,567	27,896	178,231	231,920	74	42	1183	792
Sweden	21,171	24,889	222,314	261,261	144	113	595	445
Denmark	24,889	27,557	188,589	212,652	137	94	717	432
Norway	–	28,582	–	172,920	–	32	–	422
Total	139,431	254,046	1,212,292	2,140,266	594	619	5,111	6,028

	NHL subgroups			*B-NHL subgroups*					
	B-NHL	*T-NHL*	*NHL nos*	*DLBCL*	*FL*	*BCLL*	*MM*	*Other*	*B nos*
Italy	112	9	4	14	23	17	27	28	12
Spain	92	5	3	18	15	22	21	16	5
UK	202	6	22	25	25	35	53	34	36
Netherlands	83	4	2	17	16	15	20	10	9
Greece	31	1	1	4	3	9	7	3	6
Germany	104	5	7	9	13	23	33	16	15
Sweden	212	4	41	15	14	39	74	20	54
Denmark	213	7	11	46	24	61	43	27	19
Norway	30	2	0	4	5	3	3	7	10
Total	1,079	43	91	152	138	224	281	161	166

NHL nos: non-Hodgkin's lymphoma not specified; DLBCL: diffuse large B-cell lymphoma (incl. Burkitt); FL: follicular lymphoma (all grades); BCLL: B-cell chronic lymphatic leukemia (incl. SLL, PLL); MM = Multiple myeloma/plasmacytoma; B nos: B-cell lymphomas not specified; Other: other subtypes incl. BALL (B-cell acute lymphatic leukemia incl. ALL), LPL (lymphoplasmocytic lymphoma/Waldenström's disease), ML (marginal zone B-cell lymphoma), and BO (B-cell lymphoma, other).

diabetes was 48.8 years and 47.3 years for men and women, respectively. Use of insulin treatment for diabetes, among cases, was reported by 28.6% of the men and 22.2% of the women.

Overall NHL risk

There was no statistically significant association between self-reported diabetes and overall NHL and MM risk in men (HR: 1.28, 95% CI: 0.89– 1.84), in women (HR: 0.71, 95% CI: 0.41–1.24), or in men and women combined (HR: 1.09, 95% CI: 0.80– 1.47) (Table 3). The interaction term for diabetes and gender was of borderline statistical significance (p=0.06). In order to reduce misclassification between type 1 and type 2 diabetes, we excluded participants diagnosed with diabetes before 30 years of age (n=886), as they were assumed to be type 1 diabetics, but the risk estimates did not change materially in men or in women (HR: 1.29, 95% CI: 0.90–1.87; HR: 0.64, 95% CI: 0.35 – 1.17, respectively). The results did not change after exclusion of cases of NHL and MM occuring within 1 or 2 years of the diagnosis of diabetes (*data not shown*).

We investigated the association between NHL and MM and insulin treatment. Among men, compared to non-diabetics (used as the reference group), diabetics not treated with insulin were at higher risk (HR: 1.48, 95% CI: 0.94 – 2.36) than those who were treated with insulin (HR: 1.05, 95% CI: 0.52–2.14). Among women, the risk of NHL and MM fell from 0.73 (0.34–1.56) among diabetics not receiving insulin treatment to 0.36 (0.1–1.44) among those who used insulin, compared to non-diabetics. However, information for the duration of treatment was not available and therefore analyses could not be carried out to evaluate the long-term and independent effect of insulin treatment.

Risk of lymphoma subtypes

Among the subtypes, we did not observe an association between diabetes and overall B-NHL, although hazard ratios were slightly elevated for men (Table 4). We observed a statistically positive association between diabetes and the risk of B-CLL in men (HR: 2.0, 95% CI: 1.04–3.86), but not in women (HR: 1.07, 95% CI: 0.33–3.43). Among other B-NHL subtypes, increased risks were generally observed for diffuse large B-cell lymphoma, follicular lymphoma and MM among men, although these increases did not reach statistical significance. In women, non-significant reduced risks were observed for diffuse large B-cell lymphoma and follicular lymphoma. There was no statistically significant relationship between diabetes and risk of T-NHL in men or women (Table 4).

Discussion

This large prospective study did not provide evidence for a role of self-reported diabetes in the etiology of overall NHL and MM. An increased risk for a major B-cell lymphoma subtype, B-CLL, was observed among men, but not women.

Our study exploring the relationship between a personal history of diabetes and risk of NHL and MM in Europe has some important merits. A major strength includes the prospective nature of the study, which included a large number of participants from the general population. NHL cases were histologically confirmed primary incident cancers, systematically classified according to the WHO classification of tumors of hematopoietic and lymphoid tissue, an internationally recognized classification scheme. Histological confirmation also allowed us to investigate various subtypes of NHL, which is important because of possible etiological heterogeneity among them. Other strengths of the study include a comprehensive follow-up of the cohort, an extensive evaluation of confounding factors, such as anthropometric and socio-demographic variables, and use of a validated protocol to assess body fat distribution. A large range of lifestyle risk factors were assessed, which enabled us to evaluate confounding by known and potential risk factors.

In our study, diabetes was self-reported, raising the question of misclassification of diabetes status. However, we do not think this was a major concern because type 2 diabetes is a condition that patients are generally aware of and evaluations of the validity of self-reported diabetes status have suggested good to very good agreement between self-reports and medical records.[17] No distinction was made between the type of diabetes diagnosed, whether type 1 or type 2, or according to the severity of the disease. Type 1 diabetes does not involve hyperinsulinemia and has not been considered in the etiology of NHL. As mentioned before, we carried out separate analyses excluding participants aged <30 years at the time of their diagnosis of diabetes (n=886) and the risk estimates did not change appreciably. We, therefore, think that it is unlikely that biases occurred in this regard. Associations may change with a longer follow-up period. A case-control study by Vineis *et al.*, which took into consideration different latency periods between the diagnoses of diabetes and NHL, did, however, show that NHL risk was not associated with a longer duration of diabetes.[26] Finally, inferences from risk estimates for specific NHL subtypes may have been hampered by small numbers.

Risk of lymphoma overall

Diabetes has not been consistently associated with a risk of NHL in previous studies. This study concurs with the results of seven cohort and case-control studies that have investigated this association. Ragozzino *et al.*[21] initially reported increased risk for lymphoma among diabetics in a prospective cohort of residents in Minnesota, USA, but subsequent reanalyses[36] found no association. Adami *et al.*,[16] in another cohort study with a long follow-up of 26 years, found no association between diabetes and hematopoietic cancer among men or women, calculated after a 1-year latency. On the other hand, a cohort study[11] of just over 2,000 Danish men and women found an increased risk of developing tumors of the lymphatic and hematopoietic tissues in diabetic patients. Five population and hospital-based case-control studies reported no or inverse

Table 2. Baseline characteristics of 139,431 male and 254,046 female participants in EPIC by diabetes status.

	Men				*Women*			
	Diabetes N=5,111		*No Diabetes N=134,320*		*Diabetes N=6,028*		*No Diabetes N=248,018*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Age (years)	58.0		51.9		56.8		50.1	
Body mass index (kg/m^2)	28.2		26.4		29.3		25.3	
Waist-to-hip ratio	0.972		0.937		0.855		0.792	
Hypertension	1,968	44.07	24,340	20.95	2500	50.85	37,456	17.83
Hyperlipidemia	1,783	42.45	22,903	22.10	1917	39.15	25,091	13.70
Total physical activity								
Inactive	1632	33.39	21,800	18.24	2619	48.02	51,994	25.46
Moderately inactive	1437	29.40	37208	31.13	1065	29.43	70,708	34.62
Moderately active	992	20.30	29696	24.84	709	13.00	44,374	21.73
Active	826	16.90	30827	25.79	521	9.55	37,153	18.19
Smoking status								
Life-long non-smoker	1236	24.26	41,247	30.98	3764	62.74	123,820	50.48
Current cigarettes <15/day	430	8.44	12,588	9.45	447	7.45	30,387	12.39
Current cigarettes 15-24/day	462	9.07	12,649	9.50	329	5.48	18,007	7.34
Current cigarettes 25+/day	294	5.77	6,967	5.23	98	1.63	4,161	1.70
Ex-smoker <10 years	846	16.60	17,430	13.09	456	7.60	22,602	9.21
Ex-smoker 10+ years	1418	27.83	28,834	21.66	673	11.22	33,088	13.49
Other smoking	409	8.03	13,431	10.09	232	3.87	13,214	5.39
Alcohol intake, g/day								
No ethanol intake	652	12.76	8,401	6.25	2162	35.87	41,409	16.70
<5 g/day	1249	24.44	28783	21.43	2381	39.50	101,689	41.00
5-14 g/day	1138	22.27	35194	26.20	963	15.98	67,562	27.24
15-29 g/day	897	17.55	27920	20.79	333	5.52	24,018	9.68
30+ g/day	1175	22.99	34022	25.33	189	3.14	13,340	5.38
Education								
No degree/primary school	2394	48.38	40,004	30.68	3233	57.24	72,330	30.31
Technical/professional school	1068	21.58	32,966	25.28	1144	20.25	67121	28.13
Secondary school	514	10.39	21,833	16.74	743	13.16	50471	21.15
University degree	972	19.64	35,609	27.31	528	9.35	48690	20.41
Body mass index								
Underweight/ normal	1108	21.68	49,094	36.55	1372	22.76	134577	54.26
Overweight	2460	48.13	65,470	48.74	2129	35.32	78,367	31.60
Obese	1543	30.19	19,756	14.71	2527	41.92	35,074	14.14

Table 3. Relative risk (HR) with 95% confidence intervals (CI) for the development of non-Hodgkin's lymphoma (including MM) among 139,431 men and 253,427 women in the EPIC study.

	With *NHL N=1,213*		*Without NHL N=392,264*		*HR[a] (95% CI)*	*HR[b] (95% CI)*
Type 2 diabetes	N	%	N	%		
Men	32	5.39	5,079	3.66	1.28 (0.89–1.84)	1.26(0.88–1.81)
Women	13	2.10	6,015	2.37	0.71 (0.41–1.24)	0.72 (0.41–1.26)
Men and women combined	45	3.71	11,094	2.83	1.09 (0.8–1.47)	1.07 (0.80–1.45)

[a]Results stratified by age at recruitment and study center. [b]Results stratified by age at recruitment and study center and adjusted for tobacco smoking and BMI at baseline.

Table 4. Relative risk (HR) and 95% confidence intervals (CI) for non-Hodgkin's lymphoma subtypes among 139,431 men and 253,427 women in the EPIC study.

	T-NHL		*B-NHL*		*DLBCL*		*FL*		*BCLL*		*MM*	
Type 2 diabetes	N_{cases}	HR[a] (95% CI)	N_{cases}	HR[a] (95% CI)	N_{cases}	HR[a] (95% CI)	N_{cases}	HRa (95% CI)	N_{cases}	HR[a] (95% CI)	N_{cases}	HR[a] (95% CI)
Men	27	0.77 (0.1–5.76)	521	1.37 (0.94 - 1.99)	72	1.70 (0.67 – 4.3)	53	1.52 (0.46 – 5.0)	125	2.0 (1.04 – 3.86)	145	1.27 (0.61 – 2.63)
Women	16	–	558	0.72 (0.41–1.29)	80	0.46 (0.6–3.36)	85	0.74 (0.18–3.0)	99	1.07 (0.33–3.43)	136	0.64 (0.20–2.06)

[a]Results stratified by age at recruitment and study center. DLBCL, diffuse large B-cell lymphoma. FL, follicular lymphoma.

associations.[26-29] Although results are contradictory, the bulk of evidence published to date suggests no association of diabetes with overall NHL risk.

Insulin treatment

Use of insulin treatment has been rising along with the prevalence of diabetes. In our study, we found a weak inverse relation between insulin treatment and risk of developing NHL, which is consistent with the findings of studies by Fortuny *et al*.[23] and Zhang *et al*.[37] It has been suggested that this effect may be related to continuous stimulation of the immune system by insulin,[23] which is chronically inoculated several times a day. In such a case, longer duration of insulin use should be related to greater protection from NHL, because of stronger immune system stimulation by older insulins of animal origin. However, we could not reach any conclusions about use of insulin and lymphoma risk from the data in our study. Treatment effects could be confounded by the duration of the disease and our findings may be due to chance or sparse data.

Lymphoma subtypes

In our analyses, diabetes was associated with the subsequent risk of B-CLL in men. We also found suggestive positive associations between diabetes and the risk of overall B-cell lymphomas, diffuse large B-cell and follicular lymphomas and MM among men, but these results were not statistically significant. It is not clear why such associations were stronger for men than for women. Among previous studies, type 2 diabetes was observed to increase the risk of MM,[23] but not B-CLL.

B-CLL is a neoplastic disease characterized by the accumulation of small, mature-appearing lymphocytes in blood, bone marrow, and lymphoid tissues.[38] A family history of CLL or other hematolymphoproliferative cancers, and exposure to some environmental and occupational factors, such as pesticides and ionizing radiation, have been suggested as risk factors for CLL. To our knowledge, the potential role of type 2 diabetes has not been investigated specifically in the etiology of B-CLL, but the phenomenon of autoimmunity has been inconsistently linked to B-CLL in previous epidemiologiced studies,[10,38,39] implying that there is some evidence of familial aggregation patterns for CLL. In support of a role of autoimmunity in type 2 diabetes, Pietropaolo *et al*. reported the presence of islet cell autoimmunity associated with an impairment of the acute-phase insulin secretion in type 2 diabetic patients.[12] It has been suggested that cytokines such as tumor necrosis factor-α might contribute to the development of insulin resistance in type 2 diabetes by inhibiting the tyrosine kinase activity of insulin receptors, and that interleukins may promote an impairment of insulin secretion in pancreatic β-cells.[12]

It is difficult to tease out a possible causal sequence between type 2 diabetes and B-CLL. On the one hand, a possible biological link may be mediated through cytokine activity. There is substantial evidence suggesting that excess fat activates the production of cytokines, which may induce insulin resistance. Interleukin-6, a pleiotropic cytokine expressed by a variety of different cell types, including lymphoid and endothelial cells, fibroblasts, skeletal muscle, and adipose tissue, is involved in the regulation of energy balance.[40] Circulating levels of interleukin-6 are raised in insulin-resistant states, such as obesity, which has also been linked with an increased risk of NHL.[41] A common polymorphism in the interleukin-6 gene has been associated with insulin resistance[42] and may predict the development of type 2 diabetes. Interleukin-6 has been implicated in the neoplastic process of a variety of malignancies, including prostate[43] and pancreatic cancer.[44] Because cytokines control lymphoid cell development and differentiation, cytokine activity might influence the pathogenesis of NHL. Interleukin-6 promotes normal plasma cell development and proliferation of myeloma cells in culture, and has been associated with an increased risk of plasma cell neoplasms.[45] Cozen *et al.* found that the variant allele of the interleukin promoter single nucleotide polymorphism -572 was associated with a 2-fold increased risk of plasma cell neoplasms, compared to the risk in family and population controls.[45] Increased concentrations of interleukin-6 and interleukin-12 were also found in blood plasma, culture supernatant and isolated and broken lymphocytes from patients with B-CLL.[46]

On the other hand, B-CLL patients have been observed to develop autoimmune diseases, frequently, implying immune dysregulation.[47] It has been postulated that the association of certain autoimmune diseases with B-CLL reflects reverse causality due to undetected cases of CLL manifesting in patients who express autoimmune disorders as their first symptom. This hypothesis is based on the rationale that during the course of B-CLL, some degree of activation of B cells may lead to an autoimmune disorder in CLL. The source of the autoantibodies is either uncontrolled production of malignant B cells or disturbances of residual normal B cells involved in the immune system.[48]

We, however, hypothesize that diabetes may not play a causal role in the etiology of B-CLL, but that the two diseases may share a common pathway in the early stages of development, or may have common genetic or environmental etiological factors. Common factors, such as obesity, diet, physical activity and other lifestyle habits, may play a role in the development of both B-CLL and type 2 diabetes. Obesity is closely related to diabetes in terms of etiology, which is best demonstrated by the increase in plasma concentrations of inflammatory mediators, such as C-reactive protein and interleukin-6, in both conditions. In such a case, inflammatory conditions may be markers of impaired immunological states and an indicator of the risk, rather than a cause. Studies on markers of inflammation and adipose tissue biology will help us to understand the pathogenesis and the consequences of these conditions better.

In conclusion, we found no evidence that type 2 diabetes plays a causal role in the development of NHL overall. The positive association of self-reported diabetes with B-CLL in men should be interpreted with caution, because of the small numbers involved. Given

the large size of the cohort and the prospective nature of the study design, it is unlikely that the study had major biases. In future, focusing on lifestyle factors, such as diet and physical activity, may be of help to elucidate the etiology of lymphomas. In addition, research on biomarkers focusing on insulin, the family of insulin-like growth factors, and blood glucose levels should also help to clarify whether a biological mechanism links the metabolic abnormalities, characterized by type 2 diabetes, to carcinogenesis.

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Authorship and Disclosures

AK takes taking primary responsibility for the paper. She conducted the statistical analyses and wrote the manuscript; VG contributed to the study design and statistical analyses; PV supervised the project and monitored all statistical analyses, RK, RCHV, PB, NB and KTK provided data for analyses and contributed to the text; JL, SR, ORN, AT, KO, MMB, VB, TP, AT, GM, AM, SG, RT, PHMP, HBBdM, ELEA, M-DC, AN, CM-G, AA, GH, GB, JM, TJK, NEA, SB, NS, TN, MMB, HB, VB and TP provided data for analyses, ER provided data for analyses and supervised the project. The authors reported no potential conflicts of interest.

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