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Abstract
Introduction Lymphomas belong to the few cancer sites with increasing incidence over past decades, and only a few risk factors have been established. We explored the association between education and the incidence of lymphoma in the prospective EPIC study.

Materials and methods Within 3,567,410 person-years of follow-up, 1,319 lymphoma cases [1,253 non-Hodgkin lymphomas (NHL) and 66 Hodgkin lymphomas (HL)] were identified. Cox proportional hazard regression was used to examine the association between highest educational level (primary school or less, technical/

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professional school, secondary school, university) and lymphoma risk.
Results Overall, no consistent associations between educational level and lymphoma risk were observed; however, associations were found for sub-groups of the cohort. We observed a higher risk of B-NHL (HR = 1.31, 95% CI = 1.02–1.68; $n = 583$) in women with the highest education level (university) but not in men. Concerning sub-classes of B-NHL, a positive association between education and risk of B cell chronic lymphatic leukaemia (BCLL) was observed only in women. In both genders, the risk of diffuse large B cell lymphoma (DLBCL) was significantly lower for subjects with university degree (HR = 0.46, 95% CI = 0.27–0.79) versus lowest educational level. No association was found for HL.
Conclusion We could not confirm an overall consistent association of education and risk of HL or NHL in this large prospective study; although, education was positively related to the incidence of BCLL and B-NHL (in women) but inversely to incidence of DLBCL. Due to limited number of cases in sub-classes and the large number of comparisons, the possibility of chance findings can not be excluded.

Keywords Lymphomas · SES · Education · Cohort study

Introduction

Lymphomas are a heterogeneous group of malignant diseases of immune system cells. They are among the 10 most frequent malignancies in Europe (3.2% of incident cancer cases in 2006) (Ferlay et al. 2007). While the incidence of Hodgkin lymphoma (HL) is stable, the number of non-Hodgkin lymphoma (NHL) have increased for unknown reasons in past decades (Bray et al. 2001), though, recently, a plateau has been reported in several countries (Adamson et al. 2007).

The best known risk factors of NHL are related to down-regulation of immune function; either genetically determined or acquired (Fisher and Fisher 2004). Evidence suggests that other factors including lifestyle habits (e.g., smoking and alcohol consumption) might affect lymphoma risk (Alexander et al. 2007a, b). However, these variables alone do not explain the rising incidence of NHL. Socio-economic status (SES) represents an indirect measure of known and unknown environmental risk factors; thus, it is of interest to investigate the effect of an individual's SES—and variables contributing to SES, such as education—on lymphoma risk. In the present evaluation the association between the highest level of obtained education and the risk of lymphoma is analyzed.

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Materials and methods

The multi-centre prospective cohort study [European prospective investigation into cancer and nutrition (EPIC)] was designed to investigate the association between diet, lifestyle factors, and risk of cancer and other chronic diseases. During the recruitment phase (1992–2000) subjects between 35 and 70 years of age were enrolled in 10 European countries. In total, 521,448 participants joined the cohort. In most study centers, the participants were recruited from the general population residing in a given geographical area. Specific cohorts were made of mainly by blood donors (Spain, Ragusa), teaching women (France) and people participating in screening programs (Naples, Utrecht), or health-conscious subjects (Oxford) (Riboli et al. 2002).

Participants completed a lifestyle questionnaire (level of education, occupation, lifetime smoking and alcohol consumption, reproductive history, medical history, and physical activity) as well as a country-specific validated dietary questionnaire to assess the habitual diet over the past year. The majority of subjects also provided a blood specimen and had anthropometric measurements taken.

In seven countries (Denmark, Italy, Norway, The Netherlands, Spain, Sweden, and the United Kingdom) incident cancer cases were identified via the population-based cancer registries and in the remaining three countries by active follow-up (Germany, France, and Greece).

Of the 521,448 participants, prevalent cancer cases ($n = 24{,}335$) and subjects with incomplete follow-up information ($n = 2{,}745$) were excluded. The French cohort ($n = 69{,}427$) was excluded because lymphoma incidence has not been assessed in sufficient detail. Furthermore, 16,494 persons with missing information on educational level and 14 cases of uncertain lymphoma diagnosis were excluded. The current analysis was based on 408,433 EPIC participants (3,567,410 person-years of follow-up) including 1,319 incident lymphoma cases (66 HL, 1,253 NHL).

Outcome assessment

Originally, the diagnosis of lymphoma cases in the EPIC database was based on the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). Since a new WHO classification of tumors of the hematopoietic and lymphoid tissues was published (Jaffe and Vardiman 2001) and is internationally widely used, all lymphoma cases were reclassified by a trained physician. Where it was not possible to convert from ICD-O-2 code into the lymphoma diagnosis according to the WHO classification, the respective lymphomas remained unclassified.

The current analysis considered the following seven (sub-) groups of lymphoma: HL, B cell non-Hodgkin lymphoma (B-NHL, $n = 1{,}118$), and T cell non-Hodgkin lymphoma (T-NHL, $n = 66$). Among B-NHL, the entities diffuse large B cell lymphoma (DLBCL, $n = 155$), follicular lymphoma (FL, $n = 140$), B cell chronic lymphatic leukaemia (BCLL, $n = 229$), and multiple myeloma/plasmacytoma (MM, $n = 296$) were analyzed. 20.8% of cases were unclassified.

Statistical analysis

In this analysis, the highest level of education attained was categorized into four groups: (I) primary school or less, (II) technical/professional school, (III) secondary school, (IV) university. For the analysis of (the low numbers of) HL and T-NHL, we collapsed categories II and III into one. Cox proportional hazards regression was used to examine the association between education (using primary school or less as the reference category) and lymphoma risk entering education as a categorical variable. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. Education may have a different impact on SES in females and males, the analyses were stratified by gender. The analyses were further stratified by center, and age at recruitment in 1-year categories. In the regression models, we adjusted for cigarette smoking [never smokers, smokers of <15 cigarette/day, 15–24 cigarette/day, ≥ 24 cigarette/day at recruitment, ex-smokers (<10 years), ex-smokers (≥ 10 years), missing information], alcohol consumption and energy intake (continuous). Heterogeneity between level of education and lymphoma risk between countries was assessed using likelihood chi-square tests.

Results

Subjects in the highest education category were younger at recruitment, had a lower BMI, and higher average intake of alcohol than those in the lowest education category; these differences were slightly stronger in women than in men (Table 1). In both genders, there were less current smokers in the highest education level than in all three lower classifications. However, never smokers were more frequently men with the highest education level while in females the highest proportion of never smokers was found in the lowest and the highest education categories.

Table 1 Gender-specific baseline characteristics of the analytical EPIC cohort, stratified by educational level

	Primary school or less	Technical/professional school	Secondary school	University degree
Men, *N* (%)	50,042 (33.7)	35,837 (24.2)	19,057 (12.8)	38,530 (26.0)
Lymphoma (*N*)	266	172	66	139
HL (*N*)	14	12	1	10
NHL (*N*)	252	160	65	129
Age at recruitment (years)[a]	56.1 (50.1/61.4)	52.1 (45.6/58.5)	48.4 (40.1/55.6	51.2 (43.3/57.5)
BMI (kg/m^2)[a]	27.1 (24.9/29.6)	26.1 (24.0/28.4)	25.5 (23.4/27.8)	25.4 (23.4/27.6)
Alcohol (g/d)[a]	12.9 (3.1/33.7)	12.8 (4.3/29.4)	11.3 (3.5/26.3)	14.8 (5.9/30.8)
Energy intake (kcal/day)[a]	2,404 (1,962/2,923)	2,342 (1,929/2,821)	2,404 (1,974/2,895)	2,304 (1,922/2,737)
Smoking status (%)				
Never	27	30.3	37.8	40.7
Former	37.2	37.8	32.8	35.4
Current	34.8	31.1	28.4	23
Physical activity (%)				
Inactive	22.1	16.7	19.2	17.6
Moderately inactive	26.1	28.3	36.1	37.9
Moderately active	24.4	24.6	22.9	24.8
Active	27.5	30.4	21.8	19.8
Women, *N* (%)	91,064 (32.9)	74,308 (26.9)	46,708 (16.9)	52,887 (19.1)
Lymphoma (*N*)	259	200	94	122
HL (*N*)	12	7	2	8
NHL (*N*)	247	193	92	114
Age at recruitment (years)[a]	54.3 (48.0/60.6)	51.0 (44.3/56.5)	47.7 (40.5/53.8)	46.4 (38.8/52.9)
BMI (kg/m^2)[a]	26.9 (23.8/30.1)	24.3 (22.1/27.1)	23.7 (21.7/26.4)	23.1 (21.3/25.6)
Alcohol (g/day)[a]	1.3 (0/7.0)	3.7 (1.0/10.5)	3.1 (0.7/10.1)	5.7 (1.5/12.5)
Energy intake (kcal/day)[a]	1,821 (1,489/2,221)	1,806 (1,499/2,164)	1,834 (1,522/2,205)	1,855 (1,543/2,211)
Smoking status (%)				
Never	59.6	23	47.3	54.8
Former	16.5	26.7	26.5	26.7
Current	22.9	25.3	24.5	17.4
Physical activity (%)				
Inactive	39.9	17.8	21	16.6
Moderately inactive	31.5	35.4	35.9	37.7
Moderately active	16.2	23.6	22.7	26.7
Active	12.5	23.1	20.4	19.1

[a] Median (25th/75th percentile)

No overall significant association was found between level of education and B-NHL, although women with a university degree had a significantly increased risk of B-NHL compared with women in the lowest category (Table 2). Among the sub-group of B-NHL, women with a university degree had a 2.28-times (95% CI 1.33–3.91) higher risk of BCLL than females of the lowest educational level, but no such association was seen for men. In addition, there was a significant inverse association between acquired university degree and DLBCL (HR: 0.46, 95% CI 0.27–0.79). We observed no relationship between educational level and the risk of FL and MM. There was no indication of heterogeneity of the observed results by country (all p-interactions $\geq$0.05). Body mass index as well as height and weight separately, and physical activity did not alter the associations (data not shown).

Our data do not show a statistically significant association between education and the risk of HL (Table 3). However, in the multivariate model, subjects with a university degree had 2.18-times (95% CI 0.99–4.82) higher risk of T-NHL compared with subjects with the lowest educational level.

Table 2 Associations between level of education and the risk of B-NHL and sub-classes in the EPIC cohort

	Primary school or less		Technical/professional school				Secondary school				University degree			
	N_{cases}	HR	N_{cases}	HR[a]	HR[b]	95% CI	N_{cases}	HR[a]	HR[b]	95% CI	N_{cases}	HR[a]	HR[b]	95% CI
Whole cohort														
B-NHL	448	1 (reference)	314	1.07	1.07	(0.92, 1.24)	145	1.11	1.09	(0.89, 1.33)	211	1.03	1.03	(0.86, 1.22)
DLBCL	71	1 (reference)	44	0.8	0.82	(0.55, 1.22)	22	0.85	0.88	(0.53, 1.46)	18	0.46‡	0.46	(0.27, 0.79)
FL	52	1 (reference)	35	1.1	1.12	(0.71, 1.78)	25	1.47	1.49	(0.90, 2.49)	28	1.31	1.36	(0.83, 2.24)
BCLL	86	1 (reference)	62	1.14	1.12	(0.80, 1.58)	28	1.26	1.24	(0.80, 1.93)	53	1.39	1.35	(0.94, 1.94)
MM	124	1 (reference)	84	1.09	1.07	(0.79, 1.43)	36	1.06	1	(0.67, 1.48)	52	0.93	0.93	(0.66, 1.30)
Men														
B-NHL	227	1 (reference)	138	0.98	0.98	(0.79, 1.22)	60	1.03	1.02	(0.76, 1.37)	110	0.84	0.85	(0.67, 1.08)
DLBCL	38	1 (reference)	19	0.76	0.8	(0.45, 1.44)	10	1.07	1.17	(0.56, 2.44)	8	0.34‡	0.36	(0.16, 0.79)
FL	21	1 (reference)	12	1.03	1.1	(0.52, 2.34)	7	1.17	1.21	(0.49, 2.95)	14	1.21	1.3	(0.62, 2.75)
BCLL	51	1 (reference)	35	1.15	1.15	(0.74, 1.79)	14	1.14	1.14	(0.62, 2.09)	28	0.98	0.98	(0.61, 1.59)
MM	64	1 (reference)	42	1.01	0.97	(0.64, 1.46)	15	0.91	0.86	(0.48, 1.55)	29	0.77	0.78	(0.50, 1.24)
Women														
B-NHL	221	1 (reference)	176	1.18	1.17	(0.95, 1.45)	85	1.21	1.19	(0.91, 1.55)	101	1.31‡	1.31	(1.02, 1.68)
DLBCL	33	1 (reference)	25	0.83	0.84	(0.49, 1.46)	12	0.73	0.74	(0.37, 1.48)	10	0.61	0.61	(0.29, 1.27)
FL	31	1 (reference)	23	1.15	1.17	(0.65, 2.08)	18	1.65	1.7	(0.90, 3.18)	14	1.39	1.43	(0.73, 2.80)
BCLL	35	1 (reference)	27	1.15	1.15	(0.67, 1.96)	14	1.45	1.45	(0.76, 2.77)	25	2.28‡	2.28	(1.33, 3.91)
MM	60	1 (reference)	42	1.2	1.19	(0.78, 1.82)	21	1.26	1.16	(0.67, 2.00)	23	1.22	1.17	(0.70, 1.96)

B-NHL B cell non-Hodgkin lymphoma, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *BCLL* B-cell chronic lymphatic leukaemia, *MM* multiple myeloma/plasmacytoma

[a] Stratified for gender, age and centre

[b] Stratified for gender, age and centre; adjusted for smoking (never smokers, <15 cigarette/day, 15–24 cigarette/day,≥15 cigarette/day, ex-smokers (<10 years), ex-smokers (10+ years), missing information), energy intake (without energy from alcohol consumption; continuous), alcohol consumption (continuous)

‡ Statistically significant association

Table 3 Associations between level of education and the risk of HL and T-NHL in the EPIC cohort

	Primary school or less (reference category)		Secondary/technical/professional school			University degree		
	N_{cases}	HR	N_{cases}	HR[a]	HR[b] (95% CI)	N_{cases}	HR[a]	HR[b] (95% CI)
Whole cohort								
HL	26	1.00 (reference)	22	0.77	0.82 (0.45–1.51)	18	1.24	1.41 (0.73–2.71)
T-NHL	16	1.00 (reference)	15	1.01	1.19 (0.56–2.53)	14	1.77	2.18 (0.99–4.82)
Males								
HL	14	1.00 (reference)	13	0.94	1.03 (0.46–2.31)	10	1.29	1.52 (0.64–3.62)
Females								
HL	12	1.00 (reference)	9	0.6	0.59 (0.23–1.51)	8	1.17	1.22 (0.45–3.31)

HL Hodgkin lymphoma, *T-NHL* T cell non-Hodgkin lymphoma

[a] Stratified for gender, age and centre

[b] Stratified for gender, age and centre; adjusted for smoking (never smokers, <15 cigarette/day, 15–24 cigarette/day, ≥15 cigarette/day, ex-smokers (<10 years), ex-smokers (10+ years), missing information), energy intake (without energy from alcohol consumption; continuous), alcohol consumption (continuous)

Discussion

In this large European cohort study, a possible increased risk for T-NHL among subjects with a university degree was found, while no consistent association between highest obtained education level and overall risk of HL was detected. Among B-NHL sub-entities, there was a significantly inverse association between educational level and DLBCL in the whole cohort, while a significant positive association between BCLL as well as total

B-NHL incidence and education level was observed in females.

Up to date, limited and contradictory literature is published about educational level or other SES indicators and NHL risk. Earlier studies found an increased risk of MM with higher socioeconomic status (Blattner et al. 1981; Velez et al. 1982) but this may be due to underreporting or under-recognition of lymphoma among those with lower SES. However, more recent studies have indicated a reduced risk for MM among individuals with higher education or SES (Boffetta et al. 1989; Baris et al. 2000).

Based on the result from our large prospective study, we did not observe consistent significant association between education and risk of B-NHL, including MM. The significant positive association between B-NHL and education in women is driven largely by the result for BCLL. We, however, do not have a clear explanation for the difference between men and women so that we suggest that chance might be the cause of these divergent gender results.

In the present analysis, subjects, especially males, with a university degree had a decreased risk of DLBCL. It was postulated that this inverse association may be partly due to a higher average BMI in lower education classes. Two studies (Skibola et al. 2004; Willett et al. 2005) have shown positive association between obesity ($BMI > 30$) and NHL, which was most pronounced for DLBCL. However, sub-analyses in our cohort did not show an influence of a higher BMI (neither adjustment for BMI nor in stratified analysis with BMI 25–30 and >30) on DLBCL risk (data not shown).

Concerning T-NHL, study participants with a university degree had a 2.18-times higher risk than subjects in the reference group. To the best of our knowledge, this has not been evaluated in previous studies. However, the findings are based on a total of only 45 incident cases. Furthermore, there was no strong prior on the association between education and the risk of T-NHL and the observed association might have been a chance finding. Additionally, T-NHL is a group of different sub-entities, which may in itself have different etiologies.

Earlier case-control studies reported a positive association between educational level and HL (Bonelli et al. 1990; Serraino et al. 1991); however, we could not confirm these results in our cohort. Based on the presented results, an effect of education on the risk of HL in older adults (mainly 35–65 years) does not exist. The “two disease hypothesis” suggests that the pathogenesis of HL among older subjects is different from that among younger persons. This hypothesis includes a modified role of SES in both age groups: research results reported a higher risk of HL for higher socioeconomic status amongst young cases (Alexander et al. 1991), but for lower socioeconomic status in the oldest group (Alexander et al. 1991).

The strengths of the present study are its prospective study design and the fact that the sub-classification and verification were performed by an experienced physician. Additionally, the wide range of variables assessed at baseline allowed for adjusting for a number of potential confounders. Subjects with higher education differed from less educated participants by BMI, smoking habits, alcohol consumption, and physical activity, which themselves have been shown to be associated with lymphoma risk of risk of lymphoma subentities. However, taking these factors into account in our analyses did not appreciably alter the observed associations. Some limitations of this study must be mentioned as well: Although education of the index subject is frequently used as an indicator for socio-economic position, it does not take possible social advancements and status later in life into account (Regidor 2004) and, thus, is not completely comparable with other studies reporting results on association between SES and lymphoma risk. Moreover, the SES of an index person is in part determined by the SES of the partner. We also realize that when only using education as a SES indicator the measurement error is more pronounced in women than in men. This is especially relevant for older women, who adapt the SES of their partners after marriage. It is, thus, warranted that not only a subject’s education is assessed as an indicator of her/his socioeconomic position, but also the education and possibly the job position of the participant’s partner. Additionally, educational attainment as an indicator of socioeconomic position is most likely not fully comparable among different European countries. However, we addressed this problem at least in part by running our statistical analysis stratified by country. Also, we did not observe statistically significant heterogeneity of the association between education and lymphoma risk by country. Furthermore, the hypothesis that the social-economic status in childhood is most relevant for the risk of developing lymphoma cannot be analysed with the available data as information on SES during childhood is lacking. Finally, due to the still limited number of incident cases in some lymphoma sub-classes we cannot exclude the possibility of chance findings.

In summary, we could not detect consistent associations between education level and risk of HL or NHL in this cohort of European men and women. A suggestive positive association between highest education level and risk of T-NHL as well as B-NHL and BCLL in women only was found. The risk of DLBCL was significantly lower in subjects with a university degree. Based on available literature (see above), and also with respect to the results of this prospective study, it has to be concluded that the current scientific evidence for an impact of SES on lymphoma risk is diffuse and no clear picture emerges so far. On one hand this is due to the heterogeneity of this cancer entity (leading to sub-groups with low numbers of cases), but also on the lack of a most precise definition of the socio-economic status as discussed above.

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