Family History of Hemolymphopoietic and Other Cancers and Risk of Non-Hodgkin's Lymphoma

Eva Negri,[1] Renato Talamini,[3] Maurizio Montella,[5] Luigino Dal Maso,[3] Anna Crispo,[5] Michele Spina,[4] Carlo La Vecchia,[1,2] and Silvia Franceschi[6]

[1]Istituto di Ricerche Farmacologiche ''Mario Negri'' and [2]Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy; [3]Servizio di Epidemiologia e Biostatistica and [4]Divisione di Oncologia Medica A, Centro di Riferimento Oncologico, Aviano, Italy; [5]Servizio di Epidemiologia, Istituto Tumori ''Fondazione Pascale,'' Naples, Italy; and [6]IARC, Lyon, France

Abstract

We investigated the risk of lymphomas, hemolymphopoietic (HLP) cancers (including lymphomas), and non-HLP cancers in first-degree relatives of non-Hodgkin's lymphoma (NHL) cases in an Italian case-control study on 225 patients (median age, 59 years) with a new diagnosis of NHL and 504 hospital controls (median age, 63 years), admitted for a wide spectrum of acute, nonneoplastic, nonimmune conditions. We estimated odds ratios (OR) adjusted for sex, age, family size, and other potential confounders. We also built the cohort of all first-degree relatives and computed age and sex adjusted hazard ratios (HR) using proportional hazard models. A history of lymphoma in first-degree relatives was reported by 5 NHL cases and 3 controls [OR, 3.2; 95% confidence interval (95% CI), 0.7-14.4] whereas 14 cases and 11 controls reported a family history of HLP cancers (OR, 3.0; 95% CI, 1.2-7.0). The HR of relatives of NHL cases, compared with relatives of controls, was 4.5 (95% CI, 1.1-18.8) for lymphomas, 3.5 (95% CI, 1.5-7.4) for HLP cancers, 1.6 (95% CI, 1.3-2.0) for all cancers, and 1.0 (95% CI, 0.9-1.1) for all causes of deaths. The HRs were higher for relatives of NHL cases diagnosed before the age of 50 years: 7.1 for HLP cancers, 2.0 for all cancers, and 1.6 for all deaths. A family history of cancer of the liver (OR, 2.1; 95% CI, 1.0-4.2), breast (OR, 2.0; 95% CI, 1.0-3.6), and kidney (OR, 4.6; 95% CI, 1.0-20.9) increased NHL risk. The OR was also elevated for all cancer sites (OR, 1.7 95% CI, 1.2-2.4) and the risk increased with the number of affected relatives also when HLP cancers were excluded. (Cancer Epidemiol Biomarkers Prev 2006;15(2):245–50)

Introduction

For most epithelial cancers, first-degree relatives of affected individuals have a 2- to 5-fold increased risk of developing a cancer at the same site (1, 2). Non-Hodgkin's lymphoma (NHL) or hemolymphopoietic (HLP) cancers have also been found to aggregate in families (3, 4). Most epidemiologic studies found relative risks of NHL/HLP cancers between 1.5 and 4 in relatives of cases of NHL (2, 5-14) and siblings of NHL cases seemed to be at higher risk of developing NHL than other first-degree relatives (7, 9, 10, 13, 14). Two studies found higher risks in male relatives (2, 10) but one study found higher risks in female relatives (13). Similarly, the epidemiologic evidence is not consistent as on the variation of familial risk according to the age at onset of NHL (2, 8, 10) or the histopathologic subtype of NHL (6, 7, 11, 13, 14).

In some (6, 7, 11) but not all (9, 10, 14) studies, the risk of all non-HLP cancers was also increased in relatives of NHL cases by ~30% to 50%. About specific cancer sites, associations were reported with cancer of the stomach (6, 10), breast (2), and prostate (2, 10).

Overall, the epidemiologic evidence on the relation between family history of HLP cancers and risk of NHL is scant, particularly about the variation of the risk according to some characteristics of the proband or of the relative, such as age, sex, and type of relative. Even scantier are the studies investigating the role of a family history of non-HLP cancers, and no study, to our knowledge, has systematically considered the risk of death from all causes in relatives of NHL cases.

Thus, in this article, we investigate the risk of NHL, HLP, and non-HLP cancers and of death from all causes in first-degree relatives of NHL cases, using data from a case-control study conducted in Italy, an area with medium/high prevalence of hepatitis C virus infection (15) and where the correlates of NHL may differ from the United States and northern Europe, where most other studies have been conducted.

Materials and Methods

Between January 1999 and July 2002, we conducted a case-control study on NHL in the province of Pordenone, North-Eastern Italy, and in Naples, Southern Italy (15, 16). Cases were patients between 18 and 84 years of age with incident, histologically confirmed NHL. They were admitted to the National Cancer Institute of Aviano, the ''Santa Maria degli Angeli'' General Hospital of Pordenone, the ''Pascale'' National Cancer Institute, and four General Hospitals of Naples. Cases were classified according to the International Classification of Disease for Oncology (17) and NHL subtypes were classified using the Revised European-American Lymphoma/World Heath Organization classification (18, 19). A total of 240 NHL cases were identified, of whom seven were excluded because of previous or concomitant cancer. Among the remaining 233 patients, two refused participation and six patients did not provide blood samples, thus leaving 225 cases (participation rate, 97%) recruited in the study. HIV test was negative for all cases (15) and the median age was 59 years. Histologic type was follicular for 36 cases (16%), diffuse for 112 (50%), other B-cell for 54 (24%; including 16 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma), T-cell for 16 (7%), and unknown for 7 (3%). Among B-cell lymphomas, 78 (39%) were low grade and 124 (61%)

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Requests for reprints: Eva Negri, Istituto di Ricerche Farmacologiche ''Mario Negri,'' Via Eritrea 62, 20157 Milano, Italy. Phone: 39-02-3901-4525; Fax: 39-02-3320-0231. E-mail: evanegri@marionegri.it

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intermediate/high grade; for 155 (69%) NHL, the primary site was nodal and for 70 (31%), extranodal.

Controls were patients between 18 and 84 years of age, admitted for a wide spectrum of acute conditions to the same hospitals where NHL cases had been interviewed. Specifically excluded from the control group were patients admitted for malignant diseases, conditions related to alcohol and tobacco consumption, hepatitis, any chronic diseases that might have changed lifestyle habits, hematologic, allergic, and autoimmune diseases. A total of 554 controls were contacted, of whom 550 accepted to participate. Blood samples were available for 504 controls (median age, 63 years) with a participation rate of 92%. Of these, 27% were admitted to the hospital for trauma, 23% for nontraumatic orthopedic diseases, 22% for acute surgical conditions, 14% for eye diseases, and 14% for a variety of other illnesses (including skin, ear, nose, and throat, and dental conditions, etc.).

All study participants signed an informed consent according to the recommendations of the Ethical Committee of the Aviano National Cancer Institute. Trained interviewers administered a structured questionnaire to cases and controls during their hospital stay. The questionnaire included information on sociodemographic indicators, tobacco smoking, alcohol drinking, dietary habits, behaviors, and exposures that entailed risk of hepatitis C virus transmission. Information on family history included number of brothers, sisters, sons, and daughters. For each first-degree relative (parents, siblings, and children), we recorded the vital status, current age/age at death, whether the relative had a history of cancer, site of cancer, and age at diagnosis.

Each case and control provided a 15-mL sample of blood the day the interview took place. Sera were screened for antibodies against hepatitis C virus using a third-generation MEIA (AxSYM HCV, version 3.0, Abbott, Wiesbaden, Germany). Positive samples were tested for hepatitis C virus antibodies using a third-generation line immunoassay (Innogenetics, Ghent, Belgium) and for serum hepatitis C virus RNA using Amplicor version 2.0 (Roche, Pleasanton, CA). Finally, hepatitis C virus genotyping of hepatitis C virus RNA–positive samples was done using a second-generation LiPA (Innogenetics). Samples were considered hepatitis C virus positive when hepatitis C virus antibodies or hepatitis C virus RNA was detected.

Statistical Analysis. We computed odds ratios (OR) of NHL and the corresponding 95% confidence intervals (95% CI) using unconditional multiple logistic regression models (20), and adjusting for age, sex, and study center (model 1) and further for years of education, place of birth, seropositivity for hepatitis C virus, which were associated with NHL risk in this study (15), and number of brothers, sisters, sons, and daughters because a larger family size implies more relatives at risk of developing a cancer and, consequently, a higher probability for the proband of having a positive family history (model 2). In this analysis, the study units were the cases and the controls.

We also built the cohort of all first-degree relatives of cases and controls. In this analysis, each relative of a case or of a control was a study unit, in a similar way as done by Chatterjee et al. (10). We considered four end points: (*a*) all lymphomas [i.e., Hodgkin's lymphomas (HL), NHLs, or unspecified lymphomas]; (*b*) all HLP cancers; (*c*) all cancers (HLP and non-HLP); and (*d*) all deaths. The group HLP cancers included HL, NHL, multiple myeloma, and all leukemias. A relative that did not present the end point was censored either at the current age (if alive) or at the age at death (for end points other than any death). We used Cox proportional hazard regression models to compute age-adjusted hazard ratios (HR) to develop the end point (21). Dummy variables allowed to estimate the HR of developing the end point for relatives of cases, as compared with relatives of controls, also according to various characteristics of the index case (histologic subtype, grade, and localization). We also fitted models in strata of characteristics of the relative (type of relative and sex) or of the index case/control (age and sex). All models were adjusted for sex of the relative, except sex-specific analyses. Interaction tests were done by comparing the difference in -2 log likelihood of the models with and without interaction terms to the χ^2 distribution with degrees of freedom given by the number of interaction terms.

From the number of siblings and children reported by the study subjects, the total number of first-degree relatives (including parents) was 1,791 for NHL cases and 4,079 for controls. Information was missing or incomplete for 120 (6.7%) relatives of NHL cases and 159 (3.9%) relatives of controls, thus leaving 1,671 and 3,920 relatives, respectively, available for the analysis.

Results

Table 1 shows the distribution of NHL cases and controls according to sex, age, study center, education, place of birth, and hepatitis C virus test and the corresponding ORs. No clear difference emerged between cases and controls according to education whereas being born in Southern Italy (OR, 2.1) and being hepatitis C virus positive (OR, 2.6) were risk factors for NHL. The family size was similar in the two groups: the mean numbers of relatives of cases and controls were 1.9 and 1.8 for sisters, 2.0 and 1.9 for brothers, 1.1 and 1.1 for daughters, and 1.2 and 1.2 for sons (data not shown). None of these differences was statistically significant.

The ORs of NHL according to family history of various HLP cancers are shown in Table 2. For all types of HLP cancers, a family history was more frequent in cases than in controls. History of lymphoma (HL or NHL) in first-degree relatives was reported by 5 NHL cases and 3 controls and the OR was 3.2 (95% CI, 0.7-14.4), whereas 14 cases and 11 controls reported a family history of any HLP cancer, corresponding to an OR of 3.0 (95% CI, 1.2-7.0).

Table 3 presents the HR of developing a lymphoma, a HLP cancer or any cancer, and of death in first-degree relatives of the NHL cases compared with first-degree relatives of the

Table 1. Distribution of cases of NHL and controls according to selected characteristics (Italy, 1999-2002)

	NHL	Controls	OR* (95% CI)
	N (%)	*N* (%)	
Sex			
Males	120 (53.3)	341 (67.7)	
Females	105 (46.7)	163 (32.3)	
Age (y)			
<45	47 (20.8)	104 (20.6)	
45-64	107 (47.6)	177 (35.1)	
≥65	71 (31.6)	223 (44.3)	
Study center			
Aviano/Pordenone	127 (56.4)	280 (55.6)	
Naples	98 (43.6)	224 (44.4)	
Education (y)			
<7	97 (43.1)	251 (49.8)	1†
7-11	69 (30.7)	127 (25.2)	1.4 (0.9-2.1)
≥12	59 (26.2)	126 (25.0)	1.2 (0.8-1.8)
Place of birth			
Northern Italy	98 (43.6)	248 (49.2)	1†
Southern Italy	127 (56.4)	256 (50.8)	2.1 (1.2-3.6)
Hepatitis C virus seropositivity			
No	181 (80.4)	459 (91.1)	1†
Yes	44 (19.6)	45 (8.9)	2.6 (1.6-4.3)

*OR adjusted for age, sex, and the above listed variables.
†Reference category.

Table 2. OR of NHL according to family history of HLP cancers in first-degree relatives (Italy, 1999-2002)

Cancer type	NHL	Controls	OR* (95% CI)	OR† (95% CI)
Hodgkin's lymphoma	2	0	∞ (P = 0.48)‡	—
NHL or unspecified	3	3	2.1 (0.4-11.0)	1.8 (0.3-9.7)
All lymphomas	5	3	3.2 (0.7-14.4)	3.2 (0.7-14.4)
Leukemias	7	8	2.1 (0.7-6.1)	2.0 (0.6-5.9)
Myeloma	2	0	∞ (P = 0.48)§	—
All HLP cancers§	14	11	3.0 (1.3-7.0)	3.0 (1.2-7.0)

*OR adjusted for age, sex, and study center. Reference category: no family history.
†OR adjusted for age, sex, study center, years of education, place of birth, seropositivity for hepatitis C virus, and number of brothers, sisters, sons, and daughters. Reference category: no family history.
‡P value for one-sided Fisher's exact test.
§Includes all the types listed above.

controls, also in strata of sex and type of relative. For the four end points considered, the HRs were 4.5 (95% CI, 1.1-18.8), 3.5 (95% CI, 1.5-7.4), 1.6 (95% CI, 1.3-2.0), and 1.0 (95% CI, 0.9-1.1). For lymphomas and all HLP cancers, the risks were higher in female relatives. The risk of lymphomas was higher in parents/children (HR, 9.3) than in siblings (HR, 1.9) of NHL cases whereas the opposite was true for all HLP cancers (HR, 2.3 and 5.3, respectively). Interaction tests, however, were not significant ($P > 0.10$). The admission diagnosis of controls did not have a major impact on the HR estimates. When, in turn, controls with one of four major categories of admission diagnoses were excluded from the analyses, the HR ranged between 2.8 and 3.7 for all HLP cancers, between 1.5 and 1.6 for all cancers, and between 1.0 and 1.1 for all causes of death.

Table 4 shows the HR for the same four end points according to various characteristics of the index case. Relatives of male cases, compared with relatives of male controls, had higher HRs than relatives of female cases, compared with relatives of female controls, for all lymphomas (7.0 versus 2.4), all HLP cancers (3.4 versus 2.9), and all cancers (1.7 versus 1.3), but interaction tests with sex were not significant. The risk of death for all causes was similar (HR, 1.0) for relatives of cases and controls of either sex. The HRs were higher for relatives of younger NHL cases for all lymphomas, HLP cancers, and all cancers, although not significantly so. Relatives of young NHL cases also had a higher risk of death than relatives of young controls (HR, 1.6; 95% CI, 1.1-2.2) and the X_1^2 for interaction with age was 6.49 (P = 0.01). The point estimates of the HR varied but were above unity for lymphoma, HLP cancers, and all cancers across categories of histologic subtypes, grade, and primary site of the lymphoma. The only significant interaction was for the end point all cancers, between nodal and extranodal lymphomas (X_1^2 = 8.21, P = 0.004).

The ORs of NHL according to family history of various non-HLP cancers are shown in Table 5. The OR was significantly increased for cancers of the liver (OR, 2.1; 95% CI, 1.0-4.2), breast (OR, 2.0; 95% CI, 1.0-3.6), and kidney (OR, 4.6; 95% CI, 1.0-20.9). The OR was also elevated for all sites (OR, 1.7 95% CI, 1.2-2.4) and the risk increased with the number of relatives with a history of cancer. The pattern was similar also when HLP cancers were excluded although the estimates were closer to unity.

Discussion

In this study, a family history of HLP cancers in first-degree relatives was directly associated with risk of NHL and the risk was higher when the index case was younger. Relatives of NHL cases diagnosed below the age of 50 also had a higher age-adjusted risk of death. The risk of NHL was also increased in subjects with a family history of cancers of the liver, breast, and kidney or any cancer.

Although the use of hospital controls has long been debated (20), we included in the comparison group only subjects admitted for a wide spectrum of acute, nonneoplastic, non-immunologic diseases, unrelated to tobacco smoking and hepatitis (22) Moreover, hospital admission for controls is unlikely to be related to the same genetic aspects as familial NHL. Exclusion in turn of controls with major categories of admission diagnoses did not change the results. The practically complete participation (much greater than that of most population-based studies) and the availability of serum samples from overall cases and controls, in addition to the comparable catchment area of cases and controls, contribute to the strength of our study.

Information on family history was self-reported and may thus be inaccurate. It is possible that NHL cases tend to recall cancers in the family better than controls. A review of studies evaluating the accuracy and completeness of reporting of family history in first-degree relatives found satisfactory results for breast, colon, and prostate cancer and less so for

Table 3. HR of developing selected cancers and of dying in relatives of cases of NHL compared with relatives of controls according to selected characteristics of the relative (Italy, 1999-2002)

Characteristic of the relative (no. relatives)	Event in relatives							
	All lymphomas		HLP cancers*		All cancers		All deaths	
	N	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)
All relatives of								
Controls (3,920)	3	1†	11	1†	273	1†	1,186	1†
NHL (1,671)	5	4.5 (1.1-18.8)	14	3.4 (1.5-7.4)	162	1.6 (1.3-2.0)	484	1.0 (0.9-1.1)
Female relatives of								
Controls (1,960)	1	1†	4	1†	112	1†	499	1†
NHL (820)	3	8.1 (0.8-78.1)	9	6.1 (1.8-19.7)	71	1.7 (1.3-2.3)	197	1.0 (0.9-1.2)
Male relatives of								
Controls (1,960)	2	1†	7	1†	151	1†	687	1†
NHL (851)	2	2.6 (0.4-18.8)	5	1.8 (0.6-5.7)	91	1.5 (1.2-2.0)	287	1.0 (0.9-1.2)
Parents/children of								
Controls (2,063)	1	1†	7	1†	136	1†	766	1†
NHL (907)	4	9.3 (1.0-83.4)	7	2.3 (0.8-6.5)	88	1.5 (1.1-2.0)	335	1.0 (0.9-1.1)
Siblings of								
Controls (1,857)	2	1†	4	1†	127	1†	420	1†
NHL (764)	1	1.9 (0.12-22.1)	7	5.3 (1.4-16.8)	74	1.8 (1.3-2.4)	149	1.0 (0.9-1.2)

NOTE: Estimates from proportional hazard models adjusted for sex of the relative (when appropriate).
*HLP cancers including lymphomas.
†Reference category.

Table 4. HR of developing selected cancers and of dying in relatives of cases of NHL compared with relatives of controls according to selected characteristics of the index case/control (Italy, 1999-2002)

Characteristic of the index case/control	Event in relatives							
	All lymphomas		HLP cancers*		All cancers		All deaths	
	N	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)	*N*	HR (95% CI)
Males								
Controls (2,704)	1	1†	7	1†	159	1†	813	1†
NHL (879)	2	7.0 (0.6-77.0)	7	3.4 (1.2-9.7)	79	1.7 (1.3-2.3)	242	1.0 (0.9-1.1)
Females								
Controls (1,216)	2	1†	4	1†	104	1†	373	1†
NHL (792)	3	2.4 (0.4-14.6)	7	2.9 (0.8-9.9)	83	1.3 (1.0-1.8)	242	1.0 (0.9-1.2)
Age <50 y								
Controls (757)	0	1†	1	1†	32	1†	1	1†
Case (433)	3	∞	4	7.1 (0.8-63.3)	35	2.0 (1.2-3.2)	65	1.6 (1.1-2.2)
Age ≥50 y								
Controls (3,163)	3	1†	10	1†	231	1†	1	1†
Case (1,238)	2	1.8 (0.3-11.1)	10	2.7 (1.1-6.4)	127	1.5 (1.2-1.9)	419	1.0 (0.9-1.1)
All controls (3,920)	3	1†	11	1†	273	1†	1,186	1†
NHL by								
Histologic subtype								
Follicular (283)	2	8.6 (1.4-51.4)	2	2.3 (0.5-10.2)	32	1.7 (1.1-2.4)	71	0.8 (0.7-1.1)
Diffuse (837)	2	4.3 (0.7-25.9)	10	5.5 (2.3-13.1)	81	1.7 (1.4-2.2)	254	1.1 (0.9-1.3)
T-cell (131)	1	10.5 (1.1-101)	1	2.9 (0.4-22.8)	12	1.6 (0.9-2.8)	30	0.9 (0.7-1.4)
Other (420)	0	—	1	0.9 (0.1-6.9)	37	1.4 (1.0-2.0)	129	1.0 (0.8-1.2)
Grade (B-cell NHL only)								
Low (574)	2	4.6 (0.8-27.8)	3	1.8 (0.5-6.5)	59	1.6 (1.2-2.1)	161	1.0 (0.8-1.1)
Intermediate/high (914)	2	3.8 (0.6-22.6)	10	4.9 (2.1-11.6)	87	1.7 (1.3-2.1)	275	1.1 (0.9-1.2)
Unknown (52)	0	—	0	—	4	1.2 (0.5-3.3)	18	0.9 (0.5-1.4)
Primary site								
Nodal (1,131)	5	—	11	4.4 (1.9-10.1)	122	1.9 (1.6-2.4)	321	1.1 (0.9-1.2)
Extranodal (540)	0	—	3	1.9 (0.5-6.6)	40	1.1 (0.8-1.5)	163	0.9 (0.8-1.1)

NOTE: Estimates from proportional hazard models adjusted for sex of the relative. Reference category: relatives of controls.
*HLP cancers including lymphomas.
†Reference category.

endometrial and ovarian cancer. The positive predictive value of self-reported family history (i.e., the proportion of subjects who actually have a positive family history among those who report it) was generally higher for cancer cases than controls (23). It is difficult to evaluate the role of underreporting and differential misclassification on the results. In a study of NHL lymphoma where self-reported family history was cross checked with hospital records and general practitioner notes, the risk of NHL was 4.4 (95% CI, 2.0-10.0) for a self-reported family history of leukemia or lymphoma and 4.0 (95% 1.1-14.1)

Table 5. OR of NHL according to family history of nonhemolymphopoietic cancers in first-degree relatives (Italy, 1999-2002)

Cancer site	NHL	Controls	OR* (95% CI)	OR† (95% CI)
Oral cavity/pharynx	7	17	1.0 (0.4-2.4)	1.0 (0.4-2.6)
Esophagus	4	3	2.6 (0.6-12.1)	2.7 (0.6-12.8)
Stomach	10	24	0.8 (0.4-1.6)	1.1 (0.5-2.3)
Colorectum	10	30	0.7 (0.3-1.6)	0.8 (0.4-1.7)
Liver	18	20	2.3 (1.2-4.6)	2.1 (1.0-4.2)
Pancreas	4	6	1.1 (0.3-4.3)	1.3 (0.4-5.2)
Larynx	0	5	—	—
Lung	24	43	1.3 (0.8-2.3)	1.4 (0.8-2.4)
Skin	3	4	1.7 (0.4-7.9)	2.1 (0.4-10.2)
Breast	22	28	1.9 (1.0-3.5)	2.0 (1.0-3.6)
Uterus	7	17	0.8 (0.3-2.1)	0.8 (0.3-2.0)
Prostate	4	8	1.1 (0.3-3.7)	1.3 (0.4-4.5)
Bladder	2	4	0.9 (0.2-5.3)	0.8 (0.1-4.9)
Kidney	5	3	4.5 (1.0-20.2)	4.6 (1.0-20.9)
Brain and central nervous system	2	6	1.0 (0.2-5.1)	1.3 (0.2-6.8)
All sites				
Any	108	185	1.6 (1.2-2.3)	1.7 (1.2-2.4)
1 relative	72	130	1.5 (1.1-2.2)	1.5 (1.0-2.2)
2 relatives	24	37	1.9 (1.1-3.4)	2.0 (1.1-3.7)
3 or more	12	18	2.0 (0.9-4.4)	2.4 (1.0-5.6)
All sites excluding hemopoietic cancers				
Any	101	180	1.5 (1.1-2.1)	1.5 (1.1-2.2)
1 relative	70	129	1.4 (1.0-2.1)	1.4 (1.0-2.1)
2 relatives	20	33	1.7 (0.9-3.3)	1.8 (1.0-3.4)
3 or more	11	18	1.7 (0.7-3.8)	2.0 (0.9-4.8)

*OR adjusted for age, sex, and study center. Reference category: no family history.
†OR adjusted for age, sex, study center, years of education, place of birth, seropositivity for hepatitis C virus, and number of brothers, sisters, sons, and daughters. Reference category: no family history.

for confirmed cases (6). For non-HLP cancers, the OR was 1.5 (95% 1.1-2.2) for self-reported family history and 1.9 (95% 1.0-3.4) for confirmed family history. This suggests that overreporting or misreporting is not a major problem.

Another limitation of this study is its sample size, which does not allow to adequately address subgroups. Thus, differences between subgroups should be considered with caution and evaluated in the light of the existing epidemiologic literature. Similarly, lack of significant heterogeneity across subgroups can be due to the low power of the study. Although we presented data on family history of lymphomas, these results were based on five and three events only in relatives of cases and controls, respectively, and thus the estimates are very unstable. For this reason, and also considering that (*a*) possible errors in reporting the type of cancer from the interviewees may have occurred, (*b*) the cancers in relatives have been diagnosed in different calendar periods and classification of HLP cancers has changed over time, and (*c*) the OR was increased for all types of HLP cancers, we will chiefly discuss results on all HLP cancers together.

The classification of lymphatic neoplasms is controversial. Although we collected data also on Hodgkin's lymphoma cases (15, 16), we did not analyze them together because (*a*) there is evidence suggesting that risk factors for Hodgkin's lymphoma and NHL differ; (*b*) Hodgkin's lymphoma cases were much younger than NHL cases and controls and thus first-degree relatives of Hodgkin's lymphoma cases belonged to different generations than those of NHL cases or controls; and (*c*) this improves comparability with previous articles. Chronic lymphocytic leukemia is similar to small lymphocytic lymphoma and was included among NHL in our study, as done by most authors.

In this study, the estimated HR of HLP cancers in relatives of NHL cases was 3.4, in line with estimates from other studies, which ranged from 1.5 to 4.0 (2, 5-14). Thus, for NHL, the risk associated to family history seems to be of the same order of magnitude as for solid cancers (1).

In our study, we found higher risks of HLP cancers in female relatives, in siblings, and in relatives of younger cases although interaction tests were not significant. Given the overall results from epidemiologic studies (risks higher in male relatives in two studies and the opposite in other two), it does not seem that there are striking differences between first-degree relatives of NHL cases according to sex. Conversely, epidemiologic studies consistently report higher risks in siblings than in parents/children, although the differences in risk between different types of relatives are generally small (7-10, 13, 14). This suggests that a recessive model of inheritance may play a role in familial NHL (24). However, this may also reflect changes in diagnostic ascertainment across different generations or censoring at younger ages in siblings, as compared with parents, in the presence of age-dependent risks. For several epithelial cancers, familial risks seem to be higher at younger ages (1). Epidemiologic studies on NHL yielded contrasting results (2, 8, 10), and thus no clear conclusion can be drawn on the change in risk according to age.

In our study, first-degree relatives of NHL cases were at higher risk for all cancers (OR, 1.7; 95% CI, 1.2-2.4), also when HLP cancers were not considered (OR, 1.5; 95% CI, 1.1-2.2), and there was a direct trend in risk with increasing number of relatives with cancer. Differential reporting cannot be excluded but is unlikely to explain such a pattern of trend in risk. Several other studies found an increased risk of NHL in those with a family history of non-HLP cancers (6, 7, 11), with risk estimates of ~1.3 to 1.5, although other studies did not confirm this finding (9, 10, 14).

About specific cancers sites, we found significantly elevated risks for liver, breast, and kidney cancers. Given the many sites considered, and hence the multiple tests done, the possibility of false-positive findings must be borne in mind.

In previous studies (2, 7, 8, 10), the risk of NHL associated with family history of breast cancer ranged between 1.04 and 1.7 and the risk was 1.92 for breast cancer diagnosed before age 50 in the Utah population database (2). Thus, overall, the epidemiologic literature is consistent with a weak association.

One of the main risk factors for liver cancer is hepatitis C virus infection, which has been found to increase the risk of NHL, too, particularly in areas with medium/high hepatitis C virus prevalence, although the estimated risks are much smaller than for liver cancer (25). It is possible that shared environmental risk factors, including hepatitis C virus infection—or other factors associated with exposure to hepatitis C virus, including other still unidentified viruses that share with hepatitis C virus major transmission routes—may explain the association we found between liver cancer and NHL in this study. However, adjustment for hepatitis C virus infection did not substantially modify the OR and the risk of NHL associated with family history of liver cancer was similar in hepatitis C virus–positive and hepatitis C virus–negative subjects. Other two studies that investigated this association reported ORs of 0.9 (8) and 1.3 (10).

The suggestion of an association between kidney cancer and NHL is consistent with data from other two studies, one finding a nonsignificant OR of 1.3 (10) and the other an OR of 1.2 (7) in parents and a statistically significant OR of 3.4 in siblings of NHL cases. Furthermore, a study on second cancers found an increased risk of kidney cancer after NHL and vice versa (26). Although the (scant) epidemiologic evidence suggests an association between these two cancer sites, the reasons for it remain largely unexplained.

An association between NHL and melanoma and/or other skin cancers has been repeatedly reported in second cancer studies (26-28) and has been attributed to shared etiologic factors (29), mainly sunlight and other sources of UV radiation, the major risk factor for skin cancer. However, the hypothesis that UV exposure increases the risk of NHL is not supported by studies measuring UV exposure directly (30, 31). Consequently, shared genetic predisposition cannot be ruled out. The OR of NHL for a family history of melanoma/skin cancer was 2.0 in this study, although the small number of subjects does not allow any meaningful inference and ranged between 1.0 and 1.7 in three other studies (7, 8, 10).

We did not find statistically significant associations with either stomach (OR, 1.1) or prostate (OR, 1.3) cancer as reported in other studies (2, 6, 10). Our data, however, were too scanty to rule out a moderate association.

Finally, we also considered total mortality in the cohort of first-degree relatives. It is conceivable that most of the interviewees were aware of the vital status of their first-degree relatives and that underreporting or differential reporting should be a minor problem with this end point. This is also confirmed by the fact that the risk of dying was the same in relatives of cases and controls overall (HR, 1.0). The similar death rate also provides reassurance that cases and controls came from families with a comparable general health status.

However, we found a significant 60% increase in the risk of death in relatives of NHL cases diagnosed below age 50. Because we did not record the cause of death, we could not investigate which causes were responsible for this difference. A history of cancer was reported for 24 (37%) of the 65 deceased relatives of young NHL cases and for 26 (36%) of the 72 deceased relatives of young controls. This suggests that either a history of cancer was underreported or cancer alone did not explain the difference in mortality between the relatives of young cases and of young controls. We compared the relatives of young NHL cases to the relatives of young controls, and not to those of all controls as done by Chatterjee et al. (10), because first-degree relatives of young subjects belonged, in general, to different (later) generations than relatives of older subjects, and the cancer incidence, as well as

total mortality, varies substantially across generations. When we compared relatives of young NHL cases to the relatives of all controls, the risk of death became 1.2 and was no longer significant.

In conclusion, this study supports and further quantifies previous assertions of an increased risk of lymphomas/HLP cancers in first-degree relatives of NHL cases in a Southern European population and suggests that they may be at increased risk of non-HLP cancers, too. The observation that first-degree relatives of young NHL cases are at an overall increased risk of death is interesting but needs further confirmation.

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Eva Negri, Renato Talamini, Maurizio Montella, et al.

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