

THE EPIDEMIOLOGY OF NON-HODGKIN'S LYMPHOMA IN THE NORTH-EAST OF ITALY: A HOSPITAL-BASED CASE-CONTROL STUDY

S. FRANCESCHI,* D. SERRAINO,* E. BIDOLI,* R. TALAMINI,* U. TIRELLI,† A. CARBONE‡ and C. LA VECCHIA§||

* Epidemiology Unit, † Department of Medical Oncology, ‡ Department of Pathology, Aviano Cancer Center, Via Pedemontana Occ. 33081 Aviano (PN), Italy, § "Mario Negri" Institute for Pharmacological Research, Milan, Italy and || Institute of Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland

(Received 14 November 1988. Revision accepted 28 January 1989)

Abstract—We conducted a study on 208 cases of non-Hodgkin's lymphoma and 401 controls in the North-East of Italy in order to investigate the role of indicators of socio-economic status, personal habits, past history of various disorders and medical treatments potentially affecting the immune system, and occupational exposures in the aetiology of such neoplasia. None of the several investigated characteristics appeared to be a strong determinant, i.e. relative risk, $RR > 2.0$, of non-Hodgkin's lymphoma. Cases and controls appeared to be very similar as regards education, main life-time occupation and alcohol consumption. Positive associations, however, emerged with chronic infectious diseases, mainly tuberculosis and malaria ($RR = 1.8$, 95% confidence interval, **CI**: 1.1–2.9). Non significantly increased risks were also found for smoking habit (RR ever vs never smokers = 1.5, 95% **CI**: 1.0–2.3), episodes of herpes zoster infection ($RR = 1.4$; 95% **CI**: 0.7–2.6) and occupation in chemical and petrochemical industries ($RR = 1.6$; 95% **CI**: 0.9–3.1, and 1.8; 95% **CI**: 0.9–3.8, respectively). Conversely, farming as well as specific exposure to herbicides and pesticides did not seem to affect the risk of non-Hodgkin's lymphoma in the present investigation.

Key words: Non-Hodgkin's lymphoma, immune disorders, chronic diseases, occupation.

INTRODUCTION

NON-HODGKIN'S lymphoma certainly constitutes a difficult diagnosis and problems of misclassification, particularly with Hodgkin's disease, cast doubts on the interpretation of geographical variations and temporal trends. In Italy, mortality rates for **NHL**, apart from a small excess in the most industrialized Northern area [1], do not show any urban/rural pattern [2] and by far the strongest positive correlations on a regional scale emerge with the number of hospital beds and per capita gross internal product [3]. In Britain, an analysis contrasting broadly urban and rural districts showed an excess of NHL in rural areas [4]. Many high incidence **NHL** areas occurred close together, well beyond random expectation [5]. Furthermore, districts with high lymphoid malignancies did not overlap, with few exceptions, with those with high leukemia [6].

Abbreviations: **CI**, confidence interval; **ICD**, International Classification of Disease; **NHL**, non-Hodgkin's lymphoma; **RR**, relative risk.

Correspondence to: Dr Silvia Franceschi, Epidemiology Unit, Aviano Cancer Center, Via Pedemontana Occidentale, 33081 Aviano (PN), Italy.

The present report deals with a hospital-based case-control study, conducted in the North-East of Italy, in order to clarify the influence on NHL risk of (1) a wide spectrum of life-style habits, including various indicators of socio-economic status; (2) past history of various disorders and medical treatments potentially affecting the immune system; and (3) occupational exposures.

MATERIALS AND METHODS

Between June 1985 and March 1988 we have been conducting a case-control study of NHL in an area of the North-East of Italy—the province of Pordenone. Trained interviewers identified and questioned patients admitted for non-Hodgkin's lymphoma and for a wide spectrum of other conditions to Aviano Cancer Center and all general hospitals in the area under surveillance.

Cases

The cases studied were men and women below the age of 80 with histologically confirmed NHL, diagnosed within two years before the interview, i.e. after June 1983, who had been admitted as in-patients or referred for follow-up to the out-patient clinics of the forementioned hospitals. All histological specimens were reviewed by one pathologist (A.C.) and cases registered under International



THIS MATERIAL MAY BE PROTECTED BY COPYRIGHT LAW TITLE 17 U.S. CODE

Classification of Disease (ICD) code 200, i.e. lymphosarcoma and reticulosarcoma, and 202, i.e. other NHL, were included. Among 232 cases who were thus identified, 18 died before interview and six lacked histopathological confirmation. No one refused to collaborate. The present analysis is therefore based on a total of 208 (110 males and

98 females) cases aged 18–80 (median age = 58). No effort was made in order to trace individuals with NHL below age 15. They tend to be referred to other centres and, anyway, would have required a different type of interview. The distribution of cases according to histologic classification [7] is shown in Table 1.

TABLE 1. DISTRIBUTION OF 208 CASES OF NON-HODGKIN'S LYMPHOMA ACCORDING TO HISTOLOGIC CLASSIFICATION, ITALY, 1984–88

Working formulation	Rappaport terminology	No.	(%)
Low grade			
A. Malignant lymphoma, small lymphocytic consistent with chronic lymphocytic leukemia plasmacytoid	Diffuse well-differentiated lymphocytic	28	(13)
B. Malignant lymphoma, follicular, predominantly small cleaved cell diffuse areas sclerosis	Nodular poorly differentiated lymphocytic	9	(4)
C. Malignant lymphoma, follicular mixed, small cleaved and large cell diffuse areas sclerosis	Nodular mixed lymphocytic histiocytic	12	(6)
Intermediate grade			
D. Malignant lymphoma, follicular, Predominantly large cell diffuse areas sclerosis	Nodular histiocytic	10	(5)
E. Malignant lymphoma, diffuse small cleaved cell	Diffuse poorly differentiated lymphocytic	12	(6)
F. Malignant lymphoma, diffuse mixed, small and large cell sclerosis epithelioid cell component	Diffuse mixed lymphocytic-histiocytic	39	(19)
G. Malignant lymphoma, diffuse large cell cleaved cell non-cleaved cell sclerosis	Diffuse histiocytic	28	(14)
High grade			
H. Malignant lymphoma large cell, immunoblastic plasmacytoid clear cell polymorphous epithelioid cell component	Diffuse histiocytic	30	(14)
I. Malignant lymphoma lymphoblastic convoluted cell, non-convoluted cell	Diffuse lymphoblastic	4	(2)
J. Malignant lymphoma small non-cleaved cell. Burkitt's follicular areas	Diffuse undifferentiated	4	(2)
Miscellaneous		32	(15)

Contro

The 80 adn conditi matchi and co would hospita from th causing conditi well as modifi tracts, allergi A total 55) we were fe (mostl orthop disorde (includ such a

Questi

The cators, and ot tion ar food it Furti was eli acquire chronic pyelon or any inflam ulcerat disease i.e. sys disease dermat Hashin conditi eczema compre egories A posit least or Vaccin medica were a history tially c asbesto dust, p zene, s and pe (farmir employ present

Data a.

Rela with th

Controls

The comparison group was made of patients below age 80 admitted as inpatients for a wide spectrum of acute conditions to the above mentioned hospitals. No individual matching was performed, but the catchment areas of cases and controls were strictly comparable, i.e. control subjects would have been referred, if affected by NHL, to the hospital where cases were contacted. Specifically excluded from the comparison group were patients whose diagnosis causing the current admission was of malignant disorders, conditions related to alcohol and tobacco consumption as well as any disease which might have resulted in diet modifications, e.g. disorders of respiratory and digestive tracts, cardiovascular disease, diabetes, etc. Haematologic, allergic and auto-immune conditions were also excluded. A total of 401 control subjects, 17–79 yr old (median age = 55) were interviewed. Of these, 215 were males and 186 were females; 34% were admitted for traumatic conditions (mostly fractures and sprains), 30% had non-traumatic orthopaedic conditions (mostly low back pain and disc disorders), 22% were admitted for surgical conditions (including plastic surgery), and 14% had other illnesses such as ear, nose, throat, skin or teeth disorders.

Questionnaire

The questionnaire concerned socio-demographic indicators, personal habits, including smoking, alcohol, coffee and other methylxanthine-containing beverage consumption and frequency of intake per week of a few selected food items.

Further, detailed personal and family medical history was elicited. Information was sought mainly with regard to acquired disorders affecting the immune system such as chronic infectious diseases—i.e. tuberculosis, pyelonephritis, syphilis, mononucleosis, chronic bronchitis or any parasitic infection, such as malaria—chronic inflammatory diseases—i.e. gout, non-tropical sprue, ulcerative colitis, rheumatic heart disease and biliary tract diseases, excluding gall stones—autoimmune diseases—i.e. systemic lupus erythematosus, scleroderma, Sjogren's disease, pernicious anemia, idiopathic thrombocytopenia, dermatomyositis, rheumatoid arthritis, myasthenia gravis, Hashimoto's diseases and Grave's disease—and allergic conditions—i.e. drug and food allergies, asthma, and eczema. These conditions do not obviously represent a comprehensive listing of all diseases in each of these categories, but rather the more frequently occurring disorders. A positive history was defined as previous occurrence of at least one of the disorders listed in each of these categories. Vaccinations, tonsillectomy and radiation exposure for medical purposes were also explored. Finally, patients were asked to indicate, in addition to their occupational history, whether they had ever been exposed to 20 potentially cancerogenic chemical or physical agents, including asbestos, glass fibers, coal, coke, petroleum, tar, metal dust, plastic products, resins, glue, dyes, wood dusts, benzene, solvents, electric fields, ultra-violet rays, herbicides and pesticides, either on their job or for other activities (farming is frequently a secondary activity in individuals employed in industries or other jobs in the area where the present study was conducted).

Data analysis and control of confounding

Relative risks of non-Hodgkin's lymphoma, together with their 95% approximate confidence interval (CI) [8]

were computed from data stratified for sex and age in quinquennia by means of the Mantel–Haenszel procedure [9]. Significance was assessed by the linear trend described by Mantel [10]. To account simultaneously for all potential confounders on which data were available, e.g. education, smoking habits, marital status, time period, etc., multiple logistic regression, with maximum likelihood fitting [11], was used. Since results did not differ from Mantel–Haenszel estimates, these were chosen for presentation.

RESULTS

Social factors and smoking

Cases of NHL and controls were very similar as regards various socio-demographic factors such as years of education and main life-time occupation (Table 2). No trend of increasing risk was seen with the increase of body weight (Table 2). Cases used to drink alcoholic beverages as frequently as control subjects. On the contrary, fewer cases than controls were life-long non-smokers (RR associated with ever smoking = 1.5; 95% CI = 1.0–2.3) and the RR estimates tended to be elevated for heavier smokers and for those who had started smoking at younger age (Table 2).

Part medical history

Table 3 takes into consideration the relation between non-Hodgkin's lymphoma and various diseases related to the immune system. Whereas chronic inflammatory diseases and allergic conditions did not seem to be associated with the development of lymphoma, positive past history of chronic infectious diseases was more frequently reported by cases than controls (RR = 1.8, 95% CI = 1.1–2.9). Such excess was chiefly due to higher percentages of cases, in comparison with controls, having had diagnosis of tuberculosis (5.8 vs 2.7%), pyelonephritis (1.9 vs 0.7%), chronic bronchitis (6.7 vs 4.2%) and malaria (6.3 vs 2.0%). Among autoimmune disorders, which were not overall associated with NHL, rheumatoid arthritis was reported slightly more often by cases than controls (3.0 and 2.0%, respectively) (Table 4). No significant difference emerged as regards past history of diabetes, tonsillectomy, exposure to radiation for diagnostic or therapeutic purposes as well as practice of most common vaccinations, including BCG vaccination (not shown in Tables).

Information on past episodes of herpes zoster infection and skin warts and condylomata acuminata was also elicited. Whereas at no time cases seemed to have been more prone than controls to develop lesions induced by human papillomavirus, a slight, non significant, excess of episodes of herpes zoster infection was seen (RR = 1.4, 95% CI: 0.7–2.6),

TABLE 2. DISTRIBUTION OF 208 CASES OF NON-HODGKIN'S LYMPHOMA AND 401 HOSPITAL-CONTROLS ACCORDING TO VARIOUS SOCIO-DEMOGRAPHIC FACTORS AND LIFE-STYLE HABITS, ITALY, 1984-88

	Non-Hodgkin's lymphoma		Controls		Relative risk*	95% Confidence interval
	No.	(%)	No.	(%)		
Education (yr)						
≤5	136	(65)	252	(63)	1	
6-8	41	(20)	74	(18)	1.46	(0.90-2.38)
≥9	31	(15)	75	(19)	1.25	(0.74-2.11)
X ₁ ² (trend)					1.10	p = 0.29
Occupation						
Clerical/Professional	54	(26)	113	(28)	1	
Manual worker	78	(37)	158	(39)	1.06	(0.68-1.65)
Farmer	29	(14)	56	(14)	0.87	(0.46-1.62)
Other	47	(23)	74	(19)	1.05	(0.55-2.01)
Body mass index†						
≤23	62	(30)	108	(27)	1	
24-25	65	(31)	132	(33)	0.83	(0.53-1.31)
≥26	81	(39)	161	(40)	0.78	(0.50-1.22)
X ₁ ² (trend)					0.67	p = 0.41
Alcohol consumption (standard drinks/day)						
≤2	81	(39)	162	(40)	1	
3-5	67	(32)	120	(30)	1.02	(0.63-1.63)
≥6	60	(29)	119	(30)	1.06	(0.58-1.96)
X ₁ ² (trend)					0.06	p = 0.81
Smoking habit						
Never smoker	79	(38)	182	(45)	1	
Ex-smoker	64	(31)	100	(25)	1.44	(0.85-2.45)
Current smoker						
≤14 cigarettes/day	29	(14)	45	(11)	1.57	(0.87-2.83)
≥15 cigarettes/day	36	(17)	74	(19)	1.52	(0.86-2.71)
X ₁ ² (trend)					2.78	p = 0.10
Age at starting smoking‡§						
Never	79	(55)	182	(61)	1	
≥20 yr	30	(21)	61	(20)	1.45	(0.82-2.55)
≤19 yr	34	(24)	58	(19)	1.50	(0.83-2.70)
X ₁ ² (trend)					4.41	p = 0.04

* Adjusted for age and sex by means of the Mantel-Haenszel procedure.

† Weight (kg)/height (m²).

‡ Figures do not add up to the total because of a few missing values.

§ Ex-smokers excluded.

especially in the ten years preceding neoplastic diagnosis. When a separate analysis of different histologic grade was performed, high-grade lymphomas showed the strongest associations with chronic infectious diseases (RR = 2.4, 95% CI: 1.1-5.3), herpes zoster infection episodes (RR = 2.2, 95% CI: 0.9-5.4) and also autoimmune diseases (RR = 2.0, 95% CI: 0.6-6.5).

Occupation

Nearly half of the patients which were included in the present investigation were manual workers or

farmers but few of them reported any specific exposure to chemical or physical agents. Table 4 provides RR estimates for all those industrial occupations or exposures which involved at least ten cases. There appears to be an excess of chemical and petrochemical workers among cases in comparison with controls (RR = 1.6 and 1.8, respectively), but no RR estimate was significantly above unity. Employment in food manufacturing industries (not in Tables) was reported by seven cases and eight controls. A tentative search for a duration of employment-risk relationship did not show substantially

TABLE HIS

Diseas

Chron
cases
Non
≥1

Chron
disease
Non
≥1

Autoir
Non
≥1

Allerg
Non
≥1

Herpe:
No
Yes

≤2 y
diag
inter

3-
diag
inter

≥
diag
in

Skin w
condit
No
Yes

≤2 y
diag
inter

3-
diag
inter

≥
diag
in

Tonsill
No
Yes

* Ad

elevat
been
indust

The

TABLE 3. DISTRIBUTION OF 208 CASES OF NON-HODGKIN'S LYMPHOMA AND 401 HOSPITAL-CONTROLS ACCORDING TO HISTORY OF VARIOUS ACQUIRED DISORDERS AFFECTING THE IMMUNE SYSTEM AND TONSILLECTOMY, ITALY, 1984-88

Disease	Non-Hodgkin's lymphoma		Controls		Relative risk ^a	95% Confidence interval
	No.	(%)	No.	(%)		
Chronic infectious diseases						
None	167	(80)	359	(90)	1	
≥1	41	(20)	42	(10)	1.81	(1.13-2.91)
Chronic inflammatory diseases						
None	195	(94)	375	(93)	1	
≥1	13	(6)	26	(7)	0.93	(0.47-1.82)
Autoimmune diseases						
None	198	(95)	388	(97)	1	
≥1	10	(5)	13	(3)	1.20	(0.52-2.76)
Allergic conditions						
None	164	(79)	315	(79)	1	
≥1	44	(21)	86	(21)	0.96	(0.63-1.46)
Herpes zoster						
No	187	(90)	375	(94)	1	
Yes						
≤2 yr before diagnosis or interview	4		3			
3-9 yr before diagnosis or interview	7		8			
≥10 yr before diagnosis or interview	10		15			
	21	(10)	26	(6)	1.39	(0.74-2.61)
Skin warts and/or condilomata acuminata						
No	190	(91)	363	(90)	1	
Yes						
≤2 yr before diagnosis or interview	0					
3-9 yr before diagnosis or interview	3		8			
≥10 yr before diagnosis or interview	15		7			
	18	(9)	38	(10)	0.95	(0.52-1.74)
Tonsillectomy						
No	161	(77)	311	(78)	1	
Yes	47	(23)	90	(22)	1.24	(0.81-1.90)

^a Adjusted for age and sex by means of the Mantel-Haenszel procedure.

elevated RR estimates in those workers who had been employed in chemical, petrochemical or food industries for longer periods of time (>10 yr).

DISCUSSION

The present study has some limitations common

to most hospital-based case-control investigations. Firstly, NHL cases may not be representative of all NHL cases in the population under study. A great effort, however, was made in order to contact all NHL patients admitted to the collaborating hospitals and to interview them as soon as possible after diagnosis. As a result of such procedure, very few cases

TABLE 4. RELATIVE RISK OF NON-HODGKIN'S LYMPHOMA ACCORDING TO A FEW SELECTED OCCUPATIONS AND EXPOSURES, ITALY, 1984-88*

Occupation or exposure	Non-Hodgkin's lymphoma No. of exposed	Controls No. of exposed	Relative risk†	95% Confidence interval
Chemical workers	20	27	1.64	(0.88-3.06)
Petrochemical workers	15	18	1.83	(0.87-3.84)
Dye and paint	14	38	0.72	(0.36-1.44)
Plastic resin and glue	10	21	1.01	(0.46-2.23)
Benzene and solvents	15	28	1.14	(0.57-2.28)
Wood and furniture workers	18	55	0.66	(0.37-1.19)
Metal and metal dust	19	37	1.10	(0.61-1.99)
Meat workers	26	36	1.11	(0.64-1.90)
Herbicides and pesticides	22	35	1.01	(0.58-1.77)

* Only occupations and exposure which involved at least ten cases.

† Adjusted for age and sex by means of the Mantel-Haenszel procedure.

had to be excluded because of death before interview, lack of histopathological material or refusal to collaborate. A good comparison of cases and controls should have been achieved by interviewing controls with a broad spectrum of conditions from all hospitals in the area under surveillance.

Geographical correlation studies have generally emphasized the presence of a socio-economic gradient in the risk of lymphomas [12]. In analogy with Hodgkin's disease [13], mortality rates from NHL showed in various countries of the United States a positive gradient with median income [14]. Similarly, higher frequency of lymphomas were reported among upper socio-economic groups and in whites as compared to blacks [14]. Differences in diagnostic practice and recording cannot, however, be discounted. The present case-control investigation, conducted within a homogeneous population having access to similar medical facilities and diagnostic standards, failed to confirm such socio-cultural gradient. Also, when the householders' education and occupation were considered, in addition to those of patients, cases and controls appeared very similar. Body weight and alcohol consumption did not seem to affect risk of NHL either.

Although lymphoma is not considered a tobacco-related cancer [15, 16], some epidemiological evidence [17] have suggested elevated risk in smokers in comparison with non-smokers. Such hypothesis is biologically plausible, since many carcinogenic agents, including benzene and radioactive elements, have been identified in cigarette smoke [18]. The present investigation, however, does not provide a conclusive answer since the risk estimates for smokers were only slightly above unity and showed a moderate (and non significant) dose-risk relationship.

Abnormalities of the immune system seem to be the best established risk factor for NHL: a more than 50-fold increased risk has been reported among renal transplanted patients and other immunosuppressed subjects [19]. Also persons with a variety of rare congenital immunodeficiency diseases and autoimmune disorders [20], including, most recently, acquired immune deficiency syndrome [21], seem to be at increased risk of NHL. Aetiological links with aspects of disturbed or aberrant immunity, in addition to genetic factors and infectious agents, were suggested in a very large case-control study in Yorkshire, U.K., which showed significant associations of NHL with past history of skin conditions, malignancies, kidney calculus, pneumonia, scarlet fever and diabetes [16]. Among the conditions affecting the immune system which were assessed in the present investigation, only chronic infectious diseases seemed to confer a significantly elevated risk of NHL.

An increased risk of mortality from lymphosarcoma was suggested in a British cohort of tuberculous patients (Peto J., personal communication). Tielch *et al.* [22] investigated the relationship between NHL and various acquired disorders potentially affecting the immune system but failed to find increased risk in patients with positive history of chronic infectious diseases. Apparent discrepancy may derive from different times of onset of such conditions. In the present series all cases of malaria and tuberculosis, reported in excess by NHL patients compared with control subjects, occurred prior to the 1950s—that is prior to the availability of effective treatment. Such infections may thus have produced, at the time, a truly persistent antigenic stimulus, whereas more recently such diseases may rather have to be considered acute infections.

It has been shown that immunosuppression can

facilitate
homavi
condyl
more 1
with c
zoster
cases,
neopla
risk ne
by Ca
found
herpes
The ex
sugges
may ei
or be
system
If not
associa
most s
which
of hun
the on
accura
excess
steroid
plex i
lymph
In t
culture
expos
solven
gested
failed
streng
have a
wood
[28].
design
half of
manua
chemic
to lym
appare
There
petroc
of the
vious r
did no
had b
period
Mor
presen
despite
investi

facilitate episodes of herpes zoster and human papillomavirus infections [23]. History of skin warts or condylomata acuminata was not, however, reported more frequently in the past by cases in comparison with controls. Conversely, past episodes of herpes zoster infection seemed to be more common among cases, at least in the ten years preceding the onset of neoplasia. A similar relationship, with the greatest risk near the time of NHL diagnosis, was reported by Cartwright *et al.* [16]. Paffenberger *et al.* [24] found that varicella, a childhood infection caused by herpes zoster, was predictive of NHL in adulthood. The excess of episodes of herpes zoster infection may suggest that the persistence of such slow-acting virus may either predispose to development of lymphoma or be favored by the impairment of the immune system possibly related to the early phases of NHL. If not due to chance, it is worth noting that all associations with immune-related diseases emerged most strongly among high-grade NHL, that are those which seem to have been increasing since the spread of human immunodeficiency virus [25]. Similarly, in the only previous epidemiological study in which an accurate subtype analysis was performed, the largest excesses of signs of poor or aberrant immunity, e.g. steroid and antihistamine use, eczema, herpes simplex infections, etc., were found in high-grade lymphomas [16].

In the occupational field, employment in agriculture and forestry [26-28] and, in particular, exposure to phenoxy acid, chlorophenols and organic solvents [29] and insecticides [26], have been suggested as causative factors in NHL but other studies failed to confirm the association, at least at the strength originally suggested [30]. Increased risks have also been suspected among workers exposed to wood [16, 31], epoxy glues [16], food [14] and meat [28]. The present investigation was not specifically designed to explore occupational exposures and only half of the patients on study had been employed as manual workers or farmers. Specific exposures to chemical or physical agents suspected of being related to lymphoma risk were even rarer and none of them apparently resulted in a significant elevation of risk. There was a hint that employment in chemical and petrochemical industries may increase the probability of the onset of NHL, in agreement with a few previous reports [32, 33]. The elevation of risk, however, did not tend to be higher in those individuals who had been employed in such industries for longer periods.

Moreover, the absence of strong findings in the present investigation should be stressed. In fact, despite the large number of potential risk factors investigated, only one plausible and significant

association (with positive history of chronic infectious diseases) emerged, thus confirming the difficulties in studying epidemiologically the aetiology of lymphoreticular neoplasia.

Acknowledgements—The authors thank the Italian Association for Cancer Research for its support, Mrs Ilaria Calderan and Anna Redivo for editorial assistance, Mrs Tiziana Angelin and Maria Grazia Valentini for interviewing patients.

REFERENCES

1. Mezzanotte G., Cislighi C., Decarli A. & La Vecchia C. (1986) Cancer mortality in broad Italian geographical areas, 1975-77. *Tumori* **72**, 145.
2. Cislighi C., Decarli A., La Vecchia C., Laverda N., Mezzanotte G. & Smans M. (1986) *Dati, indicatori e mappe di mortalità tumorale, Italia, 1975-1977*. Pitagora, Bologna.
3. Decarli A. & La Vecchia C. (1986) Environmental factors and cancer mortality in Italy: correlational exercise. *Oncology* **43**, 116.
4. Barnes N., Cartwright R. A., O'Brien C., Roberts B., Richards I. D. G., Hopkinson J. M., Chorlton I. & Bird C. C. (1987) Variation in lymphoma incidence within Yorkshire Health Region. *Br. J. Cancer* **55**, 81.
5. Barnes N., Cartwright R. A., O'Brien C., Roberts B., Richards I. D. G. & Bird C. C. (1987) Spatial patterns in electoral wards with high lymphoma incidence in Yorkshire Health Region. *Br. J. Cancer* **56**, 169.
6. Barnes N., Beddall A. C., Bud C. C., Bradfield J. W. B., Brown I. L., Burnett A. K., Cartwright R. A., Davies J. D., Edwards M. S., Ellis I. O., Gillis C. R., Goepel J. R., Gorst D., Gough J., Hutchinson R. M., Al-Ismaïl S. A. D., Jones P. A. E., Lauder I., Lee F. D., Lucie N. P., Miller J. G., Nicholson C., Prentice A. G., Richards I. D. G., Roberts B., Rowe R. C. G., Southgate J., Turner D. R., Whittaker J. A., Winfield D. A. & Wood J. K. (1987) Distribution of leukemia, lymphoma, and allied disease in parts of Great Britain: analysis by administrative districts and simulations of adjacencies. *Leukemia* **1**, 78.
7. The Non-Hodgkin's Lymphoma Classification Project (1982) National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinic usage. *Cancer* **49**, 2112.
8. Breslow N. E. & Day N. E. (1980) Statistical methods in cancer research: the analysis of case-control studies. IARC Scientific Publication **32**. Lyon, France.
9. Mantel N. & Haenszel W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *J. natn. Cancer Inst.* **22**, 719.
10. Mantel N. (1963) Chi-square tests with one degree of freedom; extension of the Mantel-Haenszel procedure. *J. Am. Stat. Ass.* **58**, 690.
11. Baker R. J. & Nelder J. A. (1978) The GLIM system. Release 3. Numerical Algorithms Group, Oxford.
12. Correa P. & O'Connor G. T. (1971) Geographic pathology of lymphoreticular tumours: summary of survey from the geographic pathology committee of the

- International Union Against Cancer. In *An International Survey of the Distribution of Lymphoreticular Tumours* (Correa P. & O'Connor G. T., Eds), p. 1609. Bethesda, Maryland.
13. MacMahon B. (1966) Epidemiology of Hodgkin's disease. *Cancer Res.* **26**, 1189.
 14. Cantor K. P. & Fraumeni F. J. Jr (1980) Distribution of non-Hodgkin's lymphoma in the United States between 1950 and 1975. *Cancer Res.* **40**, 2645.
 15. IARC Working Group on the evaluation of the carcinogenic risk of chemicals to humans: Tobacco smoking. (1985) IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans: tobacco smoking. IARC Scientific Publication 38, Lyon, France.
 16. Cartwright R. A., McKinney P. A., O'Brien C., Richards I. D. G., Roberts B., Lauder I., Darwin C. M., Bernard S. M. & Bird C. C. (1988) Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leukemia Res.* **12**, 81.
 17. Williams R. R. & Horm J. W. (1977) Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. *J. natn. Cancer Inst.* **58**, 525.
 18. Austin H. & Cole P. (1986) Cigarette smoking and leukemia. *J. Chron. Dis.* **39**, 417.
 19. Kinlen L. J., Scheil A. G. R., Peto J. & Doll R. (1979) Collaborative United Kingdom-Australian study of cancer in patients treated with immunosuppressive drugs. *Br. Med. J.* **ii**, 1461.
 20. Gatti R. A. & Good R. A. (1971) Occurrence of malignancy in immunodeficiency diseases. A literature review. *Cancer* **28**, 89.
 21. Ross R., Dworsky R., Paganini-Hill A., Levine A. & Mack T. (1985) Non-Hodgkin's lymphomas in never-married men in Los Angeles. *Br. J. Cancer* **52**, 785.
 22. Tielsch J. M., Linet M. S. & Szklo M. (1987) Acquired disorders affecting the immune system and non-Hodgkin's lymphoma. *Preventive Med.* **16**, 96.
 23. Boyle J., MacKie R. M., Briggs J. D. & Junor B. F. R. (1984) Cancer, warts, and sunshine in renal transplant patients. *Lancet* **i**, 702.
 24. Paffenberger R. S. Jr, Wing A. L. & Hyde R. T. (1978) Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias: Brief communication. *J. natn. Cancer Inst.* **60**, 89.
 25. Chase Boring C., Brynes R. K., Chan W. C., Causey N., Gregory H. R., Nadel M. R. & Greenberg R. (1985) Increase in high-grade lymphomas in young men. *Lancet* **i**, 857.
 26. Cantor K. P. (1982) Farming and mortality from non-Hodgkin's lymphoma: a case-control study. *Int. J. Cancer* **29**, 239.
 27. Pearce N. E., Smith A. H. & Fischer D. O. (1985) Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. *Am. J. Epidemiol.* **121**, 225.
 28. Pearce N. E., Sheppard R. A., Smith A. H. & Teague C. A. (1987) Non-Hodgkin's lymphoma and farming: an expanded case-control study. *Int. J. Cancer* **39**, 155.
 29. Hardell L., Eriksson M., Lennner P. & Lundgren E. (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br. J. Cancer* **43**, 169.
 30. Wiklund K., Dich J. & Holm L. E. (1987) Risk of malignant lymphoma in Swedish pesticide applicators. *Br. J. Cancer* **56**, 505.
 31. Grufferman S., Duong T. & Cole P. (1976) Occupation and Hodgkin's disease. *I. nam. Cancer Inst.* **57**, 1193.
 32. Li F. P., Fraumeni J. F., Mantel N. & Miller R. W. (1969) Cancer mortality among chemists. *J. natn. Cancer Inst.* **43**, 1159.
 33. Olén R. (1976) Leukaemia and Hodgkin's disease among Swedish chemistry graduates. *Lancet* **ii**, 916.

THE MA
(NHL)
are der
Most c
marker
ated wi
held vi
expansi
limited
a relativ
transfor
An opp
at a cl
bone-m
subsequ
varying
Evidenc
ecular

Abbre
chronic
trocytic;
immuno
lymphot
kb, kilo
Corre
Haemat
Pond St