

THE EPIDEMIOLOGY OF NON-HODGKIN'S LYMPHOMA: COMPARISON OF NODAL AND EXTRA-NODAL SITES

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International population-based cancer incidence data, coded according to the International Classification of Diseases for Oncology (WHO, 1990), were used to describe geographical patterns of incidence of extra-nodal non-Hodgkin's lymphomas. Incidence data from the USA were also used to describe age and sex distribution of lymphomas at different extra-nodal sites. The percentage of all non-Hodgkin's lymphomas coded as being of extra-nodal origin is between 25% and 35% in most countries, with the stomach, skin and small intestine being the most common extra-nodal sites. In general, the pattern of incidence rates for extra-nodal lymphomas tends to reflect that of other lymphomas. For example, the age incidence curve of each site-specific extra-nodal lymphoma is similar to that of nodal lymphomas, and in countries where total lymphoma incidence is high the incidence of lymphomas at each extra-nodal site also tends to be relatively high. Although specific factors are known to increase the risk of lymphomas at certain anatomical sites, these data suggest that the aetiology of extra-nodal lymphomas is not entirely independent from that of nodal lymphomas. *Int. J. Cancer* 72:923–930, 1997.

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Non-Hodgkin's lymphomas arise either in lymph nodes and in other lymphatic tissues, such as the tonsils, spleen, Waldeyer's ring and thymus ("nodal" lymphomas), or in lymphatic cells in other organs ("extra-nodal" lymphomas). Differences in presentation, behaviour and survival between non-Hodgkin's lymphomas at different primary sites have led several authors to suggest that nodal and extra-nodal disease should be considered as distinct entities with differing aetiologies (Freeman *et al.*, 1972; Otter *et al.*, 1989; D'Amore *et al.*, 1991). Furthermore, there is compelling evidence that specific local factors may play an aetiological role in the development of lymphomas at certain extra-nodal sites *e.g.*, *Helicobacter pylori* infection is associated with primary gastric lymphoma, but not with lymphomas at other sites (Wotherspoon *et al.*, 1993; Parsonnet *et al.*, 1994).

For the purposes of cancer registration, non-Hodgkin's lymphomas have generally been coded according to the International Classification of Diseases (ICD-9, 1975 revision; 200 and 202. WHO, 1977), with no reference to primary site of the tumour. With the introduction of the International Classification of Diseases for Oncology in 1976, however, lymphomas were coded according to morphology and to topography (ICD-O; WHO, 1990). The primary site of non-Hodgkin's lymphoma has been coded in several routinely collected, population-based, cancer registry series. These data were used to describe the epidemiology and geographical distribution of non-Hodgkin's lymphoma at different anatomical sites.

METHODS

Site-specific information on non-Hodgkin's lymphoma was available for 39 centres in 14 countries (see "Acknowledgements" for a list of centres, with registration years to which the data refer), at the International Agency for Research on Cancer, in Lyon, France [ICD-O morphology codes: 959–970, excluding 965–966 (Hodgkin's disease); site codes C01–C80]. Registries that had recorded details of at least 300 lymphomas were included. Inci-

dence rates were then calculated with the corresponding person-years at risk from the registries and age-standardized to the "world standard" population (Parkin *et al.*, 1992). When data were available from several registries within the same country, the numbers of tumours and person-years at risk were summed and rates calculated to provide a pooled estimate of incidence for that country. Lymphomas at any given site were rare, and the population structure (in terms of age and sex distribution) was similar for most of the countries included here (Parkin *et al.*, 1992), so data for men and women were combined to lend greater stability to the results.

The definition of what constitutes an extra-nodal (ICD-O topography codes C01–C76) or nodal lymphoma (ICD-O topography code C77) can be ambiguous for certain anatomical sites such as blood, bone marrow, and spleen (collectively known as the reticulo-endothelial and haematopoietic system; ICD-O topography code C42) and so these have been examined separately here.

When considering age, sex and ethnic distribution of lymphomas at specific extra-nodal sites, the largest single data set was used. This included information from the Surveillance, Epidemiology and End Results (SEER) program in the USA (SEER, 1994), together with data from Los Angeles.

RESULTS

The incidence rate for all non-Hodgkin's lymphomas combined (Table I), varies from a low of 2 per 100,000 per year in Thailand (based on 723 cases), to about 10 per 100,000 in whites in the USA (based on 30,855 cases). Across Europe, there is a roughly 2-fold difference in incidence, from about 4 per 100,000 in Slovakia (based on 1156 cases), to about 8 per 100,000 in The Netherlands (based on 2582 cases).

As a proportion of the total incidence rate of non-Hodgkin's lymphoma, the greatest variation by anatomical site is seen for tumours coded to blood, bone marrow and spleen (reticulo-endothelial and haematopoietic origin). Only 1 to 2% of all non-Hodgkin's lymphomas are coded to this site in the USA, 11% in England and Wales and 36% in Italy; this variation may be due to reporting differences. The total proportion coded as being of extra-nodal origin shows much less variation, ranging from 22 to 25% of all lymphomas in the USA to 33% in Denmark and 34% in Israel. Only France (42%) and Kuwait (52%) have particularly high relative frequencies.

In general, for almost every country in the study, the most frequent extra-nodal sites are stomach and skin, followed by small intestine and tonsil. The percentage of all lymphomas found in the stomach ranges from 3% in Costa Rica to 10% in Kuwait, Italy and Spain. The percentage of all lymphomas in skin ranges from 1% in Thailand to 7% in blacks in the USA and the percentage in the small intestine ranges from 1% in Italy to 10% in Kuwait. The

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TABLE I - PERCENTAGE OF NON-HODGKIN'S LYMPHOMA OCCURRING AT SPECIFIC SITES,¹ IN DIFFERENT COUNTRIES

Site distribution of non-Hodgkin's lymphoma	Costa Rica	Puerto Rico	USA (whites)	USA (blacks)	USA (Latinos)	Israel	Kuwait	Philippines	Thailand	Slovakia	Denmark	France	Italy	Netherlands	Spain	England and Wales
Total incidence/100 000 (number) ²	4.67 (348)	5.08 (1742)	10.06 (30855)	5.54 (2120)	7.35 (10119)	8.02 (1762)	6.94 (315)	3.47 (682)	2.06 (723)	3.97 (1156)	6.66 (2664)	7.02 (2571)	6.53 (801)	7.62 (2582)	5.26 (1060)	6.13 (6281)
% nodal (C77)	69%	74%	77%	75%	73%	58%	43%	68%	68%	71%	63%	50%	35%	48%	59%	61%
% unknown primary site (C80)	0%	0%	0%	0%	0%	0%	4%	0%	0%	0%	1%	1%	1%	14%	15%	1%
% blood, bone marrow or spleen (C42)	9%	2%	1%	1%	2%	8%	1%	1%	5%	2%	3%	7%	36%	6%	2%	11%
% extra-nodal	22%	24%	22%	24%	25%	34%	52%	31%	27%	27%	33%	42%	28%	32%	24%	27%
% tonsil (C09)	3%	2%	1%	2%	3%	2%	3%	4%	3%	4%	3%	3%	3%	2%	2%	2%
% stomach (C16)	3%	6%	4%	6%	7%	8%	10%	5%	4%	9%	7%	8%	10%	7%	10%	4%
% small intestine (C17)	2%	2%	2%	2%	2%	3%	10%	3%	3%	2%	2%	2%	1%	2%	2%	2%
% skin (C44)	3%	2%	4%	7%	2%	5%	2%	1%	1%	4%	3%	6%	3%	5%	2%	3%

¹ICD-O (WHO, 1990). -²Incidence adjusted for age and sex.

percentage of lymphomas at different extra-nodal sites varies little between ethnic groups in the USA, although numbers in some categories are small.

The incidence rate for all extra-nodal lymphomas combined (Table II) varies from a low of less than 1 per 100,000 per year in Thailand (based on 189 cases), to around 3 per 100,000 in France and Kuwait (based on 1081 and 163 cases respectively). In general, the pattern of incidence rates for extra-nodal lymphomas tends to reflect that of other lymphomas: in countries where the incidence of extra-nodal lymphomas is high, the incidence of all other lymphomas also tends to be high (Figs. 1 to 4). There are, however, a few exceptions: whites in the USA have a particularly high incidence rate of lymphomas at nodal sites and, conversely, people in both Kuwait and France have relatively high rates at extra-nodal sites. The higher incidence rates for extra-nodal disease seen in France and Kuwait are due to higher rates at most individual sites, although in Kuwait the incidence of gastric and small-intestinal disease is especially high.

The male-to-female ratio for nodal lymphomas in North American whites was 1.4:1 and for all extra-nodal lymphomas combined was 1.5:1. This ratio varied by individual site (Table III), but only lymphoma of the thyroid was more common in women (0.4:1; excluding sex specific sites). The age distribution of nodal and extra-nodal lymphomas is shown in Figure 5, with individual extra-nodal sites shown in Figure 6. The proportion of lymphomas coded to extra-nodal sites is relatively consistent throughout most age groups.

DISCUSSION

We report geographical and ethnic differences in the incidence of extra-nodal lymphomas. Some interesting patterns emerge, but at this stage they should be interpreted with considerable caution. It is not clear how differences in coding practice, together with the relatively small numbers of tumours registered at some centres, may have affected the results. It appears likely that the large variation in the proportion of lymphomas recorded as being of "reticuloendothelial and haematopoietic" origin (blood, bone marrow and spleen; ICD-O, C42), is not real, but reflects differences in the way in which tumours are coded (or diagnosed) in different countries. Clearly, both lymphomas and leukaemias could be described as being tumours of 'haematopoietic and reticuloendothelial origin' (*i.e.*, deriving from cells of the blood or lymphatic system), leading to possible confusion. Otherwise, there is some consistency in the percentage of tumours being coded both to all extra-nodal sites combined and to individual sites, with only France and Kuwait standing out as having particularly high proportions and incidence rates of extra-nodal tumours. This suggests that the patterns of incidence for these sites reflect not only differences in coding practice, but rather true variation in the incidence of extra-nodal lymphomas, as such biases are unlikely to be the same between countries.

In earlier reports, the proportion of lymphomas at extra-nodal sites has ranged from about 20% to 50%: Denmark 37% (D'Amore *et al.*, 1991), India 22% (Advani *et al.*, 1990), The Netherlands 41% (Otter *et al.*, 1989), Hawaii-Japanese 34% (Yanagihara *et al.*, 1989), Lebanon 44% (Salem *et al.*, 1986), Hong Kong Chinese 28% (Ho *et al.*, 1984), Japan 31% (Tokunaga and Sato, 1980), USA 25% (Freeman *et al.*, 1972), Israel 36% (Modan *et al.*, 1969), Finland 28% (Finnish Cancer Registry, 1966), Italy 48% (Banfi *et al.*, 1968) and East Germany 47% (Wilner and Umbreit, 1963). Many of these studies were based on histology series, rather than on population-based data, and they all included bone marrow, blood and spleen in the definition of extra-nodal site, in contrast to our method. Thus the proportion of extra-nodal tumours reported by others may be greater than reported here, but the studies cited also indicate no marked variation between countries or ethnic groups.

TABLE II – AGE- AND SEX-ADJUSTED INCIDENCE RATES PER 100 000 OF EXTRA-NODEL NON-HODGKIN'S LYMPHOMA BY SITE,¹ IN DIFFERENT COUNTRIES

Site distribution of extra-nodal non-Hodgkin's lymphoma	Costa Rica	Puerto Rico	USA (whites)	USA (blacks)	USA (Latinos)	Israel	Kuwait	Philippines	Thailand	Slovakia	Denmark	France	Italy	Netherlands	Spain	England and Wales
Incidence/100,000 of all extra-nodal sites combined (number)	1.07 (76)	1.22 (419)	2.20 (6768)	1.38 (518)	1.78 (250)	2.70 (594)	3.14 (163)	1.10 (210)	0.55 (189)	1.06 (311)	2.10 (869)	2.89 (1081)	1.83 (223)	2.34 (815)	1.24 (249)	1.63 (1685)
All oral sites (C00–14)	0.2 (14)	0.18 (65)	0.30 (954)	0.19 (68)	0.32 (43)	0.42 (91)	0.41 (19)	0.27 (50)	0.11 (38)	0.22 (64)	0.32 (138)	0.45 (164)	0.25 (36)	0.36 (125)	0.18 (36)	0.27 (290)
Tonsil (C09)	0.14 (9)	0.06 (34)	0.11 (309)	0.09 (32)	0.20 (28)	0.19 (43)	0.13 (8)	0.17 (29)	0.07 (22)	0.16 (45)	0.17 (68)	0.20 (78)	0.14 (21)	0.16 (55)	0.10 (20)	0.12 (114)
Stomach (C16)	0.15 (10)	0.30 (108)	0.41 (1356)	0.34 (133)	0.53 (70)	0.63 (139)	0.79 (33)	0.21 (35)	0.09 (30)	0.32 (99)	0.40 (176)	0.48 (195)	0.67 (84)	0.56 (188)	0.47 (101)	0.21 (220)
Small intestine (C17)	0.09 (7)	0.09 (28)	0.20 (561)	0.10 (38)	0.17 (25)	0.27 (56)	0.39 (31)	0.10 (23)	0.06 (20)	0.08 (20)	0.14 (50)	0.17 (60)	0.14 (11)	0.14 (42)	0.12 (18)	0.16 (152)
Colon (C18)	0.08 (6)	0.07 (24)	0.08 (238)	0.05 (18)	0.14 (19)	0.09 (19)	0.14 (12)	0.08 (15)	0.06 (23)	0.04 (11)	0.06 (24)	0.15 (51)	0.13 (15)	0.09 (32)	0.05 (7)	0.08 (74)
Bronchus and Lung (C34)	0.00 —	0.04 (11)	0.07 (193)	0.03 (9)	0.02 (2)	0.05 (10)	0.01 (1)	0.01 (2)	0.02 (4)	0.02 (4)	0.06 (21)	0.07 (29)	0.04 (3)	0.04 (13)	0.00 —	0.05 (46)
Bone, Joints and Articular Cartilage (C40-1)	0.02 (1)	0.05 (15)	0.06 (186)	0.04 (16)	0.09 (15)	0.08 (16)	0.11 (5)	0.04 (9)	0.01 (2)	0.04 (9)	0.03 (11)	0.12 (40)	0.00 —	0.1 (32)	0.1 (7)	0.05 (57)
Skin (C44)	0.15 (11)	0.11 (38)	0.37 (1081)	0.42 (152)	0.15 (17)	0.39 (84)	0.17 (5)	0.03 (5)	0.03 (89)	0.14 (41)	0.23 (90)	0.38 (145)	0.19 (23)	0.38 (140)	0.11 (24)	0.15 (158)
Connective, subcutaneous and other soft tissue (C49)	0.05 (4)	0.04 (11)	0.07 (214)	0.02 (5)	0.00 —	0.06 (11)	0.07 (7)	0.05 (11)	0.03 (7)	0.01 (1)	0.03 (8)	0.01 (37)	0.01 (1)	0.05 (21)	0.02 (4)	0.05 (52)
Eye and adnexa (C69)	0.02 (1)	0.01 (3)	0.08 (247)	0.03 (10)	0.07 (9)	0.06 (14)	0.00 —	0.01 (1)	0.03 (7)	0.02 (3)	0.05 (23)	0.05 (19)	0.03 (3)	0.06 (19)	0.01 (1)	0.05 (56)
Central Nervous System (C71-2)	0.01 (1)	0.06 (20)	0.16 (442)	0.04 (18)	0.10 (16)	0.17 (33)	0.11 (6)	0.03 (5)	0.02 (5)	0.07 (17)	0.12 (44)	0.11 (36)	0.03 (8)	0.18 (56)	0.06 (10)	0.09 (65)
Thyroid gland (C73)	0.00 —	0.04 (12)	0.08 (275)	0.01 (2)	0.03 (4)	0.03 (6)	0.13 (2)	0.03 (5)	0.01 (3)	0.02 (4)	0.07 (40)	0.02 (10)	0.05 (7)	0.07 (23)	0.01 (1)	0.10 (113)

¹ICD-O, WHO 1990.

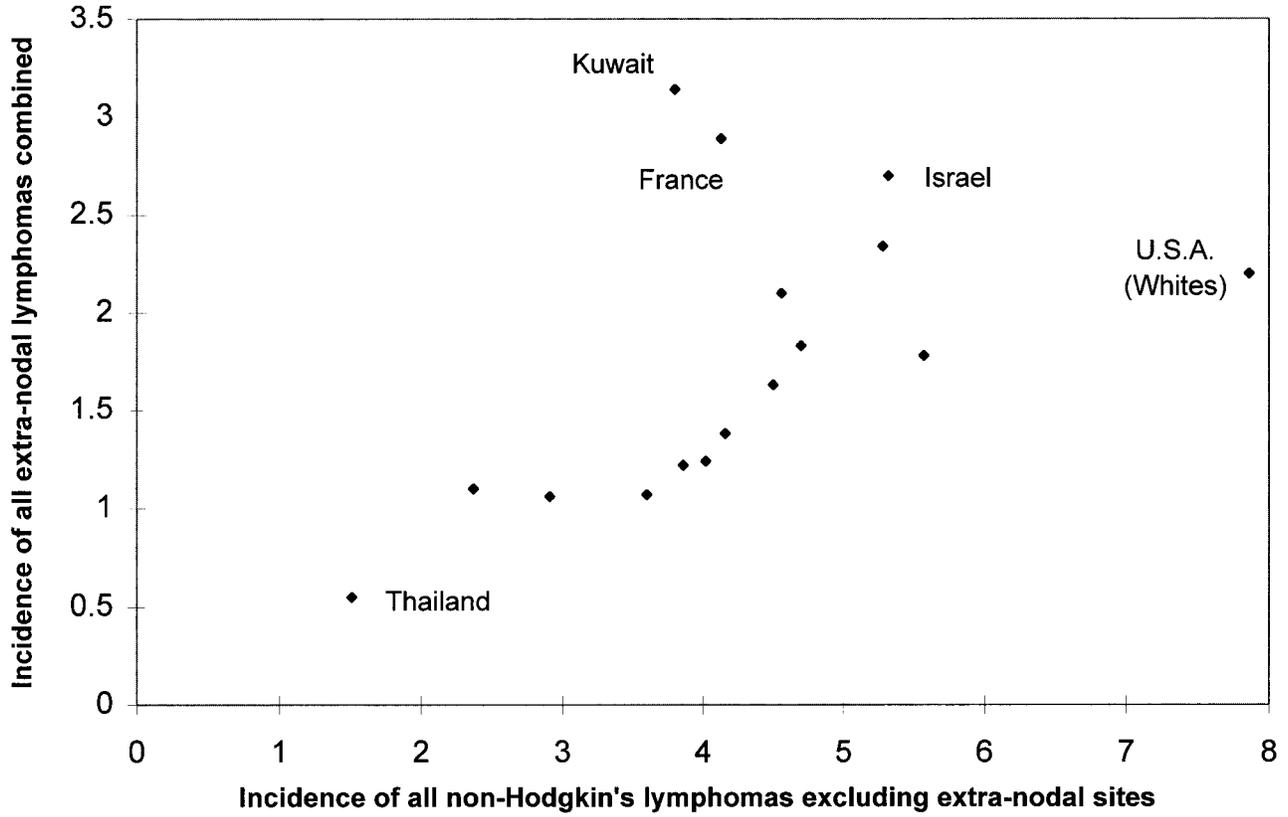


FIGURE 1 – Age- and sex-adjusted incidence rates of extra-nodal vs. all other non-Hodgkin's lymphomas (C42, C77 and C80).

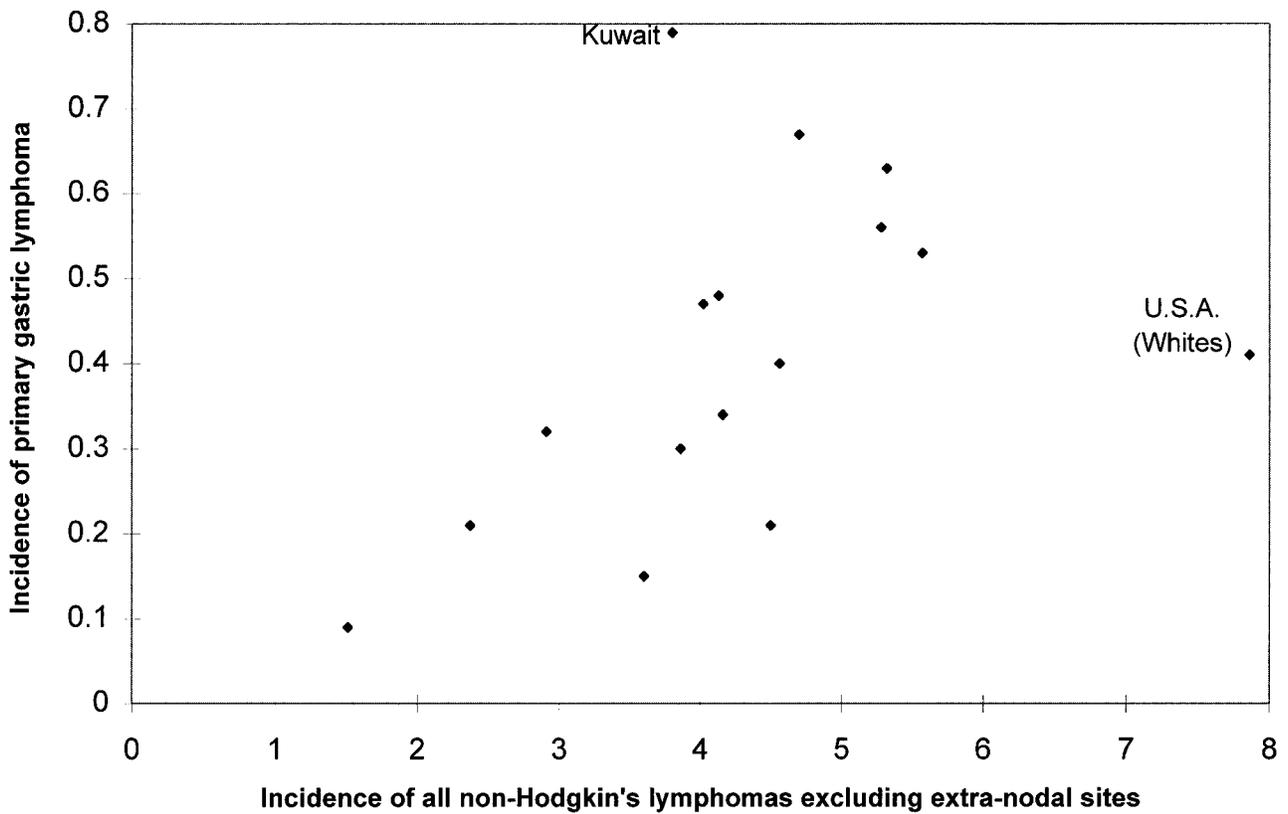


FIGURE 2 – Age- and sex-adjusted incidence rates of primary gastric vs. all other non-Hodgkin's lymphomas (excluding extra-nodal sites).

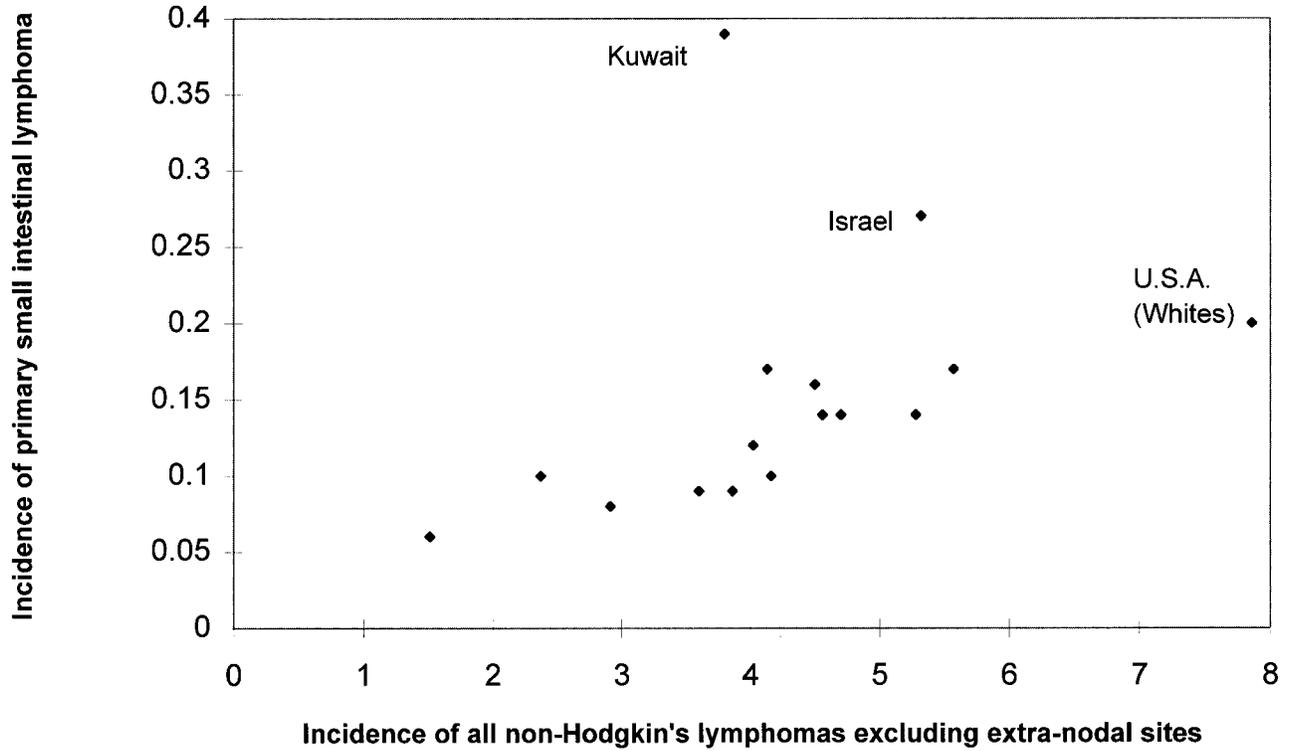


FIGURE 3 – Age- and sex-adjusted incidence of primary small-intestinal vs. all other non-Hodgkin's lymphomas (excluding extra-nodal sites).

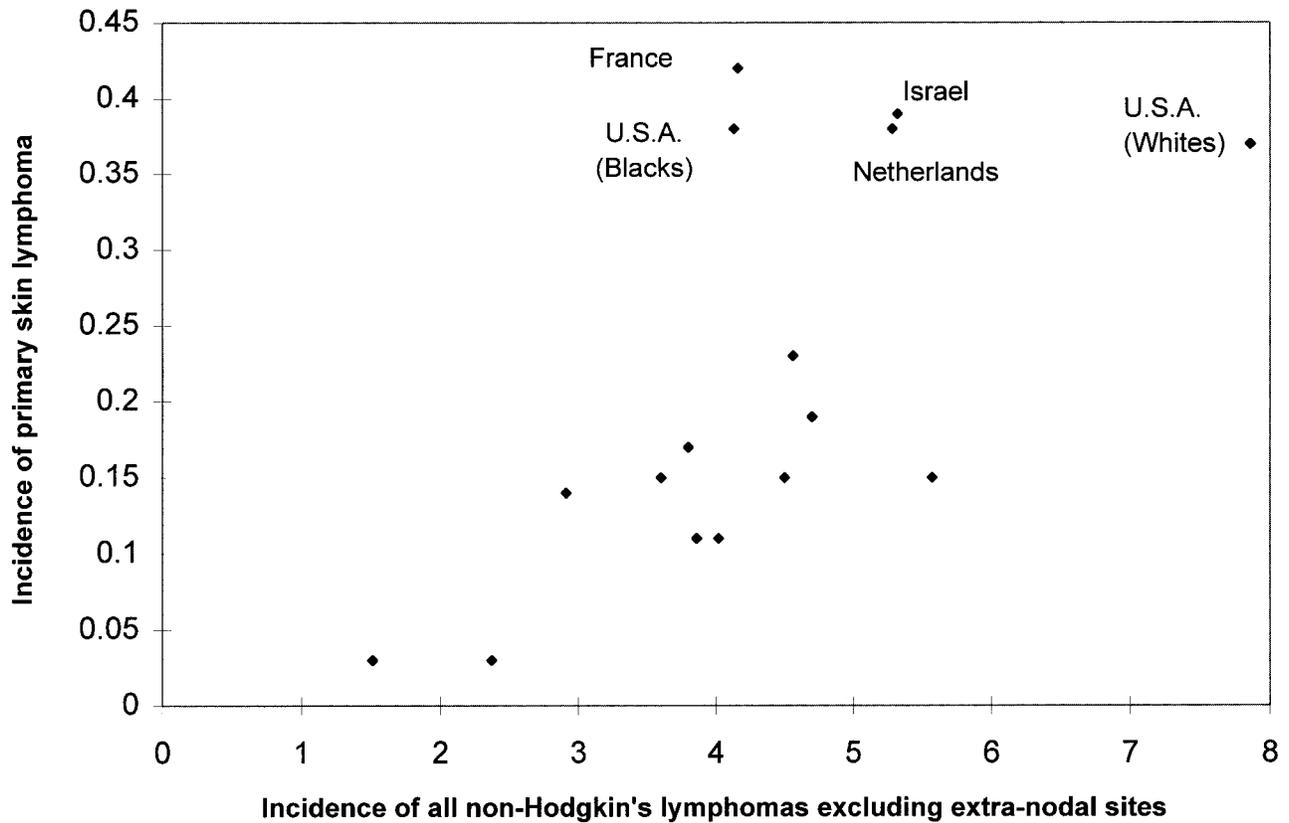


FIGURE 4 – Age- and sex-adjusted incidence of primary skin vs. all other non-Hodgkin's lymphomas (excluding extra-nodal sites).

It appears in these data, that the patterns of incidence and epidemiology of lymphomas at specific extra-nodal sites in part, reflect those of other lymphomas. There is very little geographic variation in terms of which extra-nodal sites are most frequent: primary lymphomas of the stomach and skin are the most common extra-nodal sites in almost all centres, followed by tumours of the small intestine and of the tonsil (Table II).

Relatively high incidence rates of small-intestinal lymphoma have been reported before in the Middle East (Khojasteh *et al.*, 1983) and are a result of the presence of a distinct disease entity, immunoproliferative small-intestinal disease, or so-called Mediterranean lymphoma. This may partly explain the relative excess of small-intestinal lymphoma in Kuwait. Similarly, high rates of gastric lymphoma have been noted in parts of Northern Italy,

considerably higher than are seen in these data (Doglioni *et al.*, 1992), which may, in part, explain the relatively high rates of this disease in our data from Italy. The reasons for high rates of extra-nodal lymphomas in France are unclear.

The age distribution of extra-nodal lymphomas is very similar to that of nodal disease (Fig. 5) although data in the younger age groups are sparse. Furthermore, there appears to be little difference in the age pattern by individual site (Fig. 6), although the comparative excess of central-nervous-system lymphomas in young adults is probably a result of the prevalence of this disease in HIV-positive men in the USA.

There is considerable evidence that lymphomas at specific sites are preceded by the presence of local inflammatory processes at that site: *H. pylori*-associated gastritis and gastric lymphoma (Wotherspoon *et al.*, 1993; Parsonnet *et al.*, 1994), coeliac disease and small-intestinal lymphoma (Swinson *et al.*, 1983; Logan *et al.*, 1989), Sjögren's syndrome and lymphoma of the salivary gland (Hyjek *et al.*, 1988; Schmid *et al.*, 1982) and Hashimoto's thyroiditis and thyroid lymphoma (Hyjek and Isaacsou, 1988; Anscombe and Wright, 1985), for example. However, data presented here suggest that the epidemiological features of lymphomas at extra-nodal sites show relatively little variation. The age distribution of disease is roughly the same at all extra-nodal and nodal sites, and the variation in incidence, to a certain extent, reflects that of all other lymphomas combined (Figs. 1 to 4). There is little evidence in these data that suggests behaviour entirely independent from lymphomas at other sites. Certainly, the variation in terms of clinical course and survival between nodal and extra-nodal lymphomas (Otter *et al.*, 1989) can readily be explained by differences in the behaviour of the cell types from which they each develop, rather than reflecting separate aetiologies (Isaacson and Wright, 1984). Given the large body of evidence linking site-specific extra-nodal lymphomas with local inflammatory processes and the similar epidemiology of nodal and extra-

TABLE III – SEX RATIOS OF AGE-ADJUSTED INCIDENCE RATES FOR NON-HODGKIN'S LYMPHOMAS IN USA, BY SITE

Site distribution of non-Hodgkin's lymphoma ¹	Sex ratio in whites from the USA (M:F)
Total nodal lymphomas	1.4:1
Total extra-nodal lymphomas	1.5:1
All oral sites (C00–14)	1.4:1
Tonsil (C09)	1.9:1
Stomach (C16)	1.4:1
Small intestine (C17)	1.8:1
Colon (C18)	2.2:1
Bronchus and lung (C34)	1.2:1
Bone, joints and articular cartilage (C40-1)	1.4:1
Skin (C44)	1.9:1
Connective, subcutaneous and other soft tissue (C49)	1.3:1
Eye and adnexa (C69)	1:1
Central nervous system (C71-2)	1.8:1
Thyroid gland (C73)	0.4:1

¹ICD-O, WHO 1990.

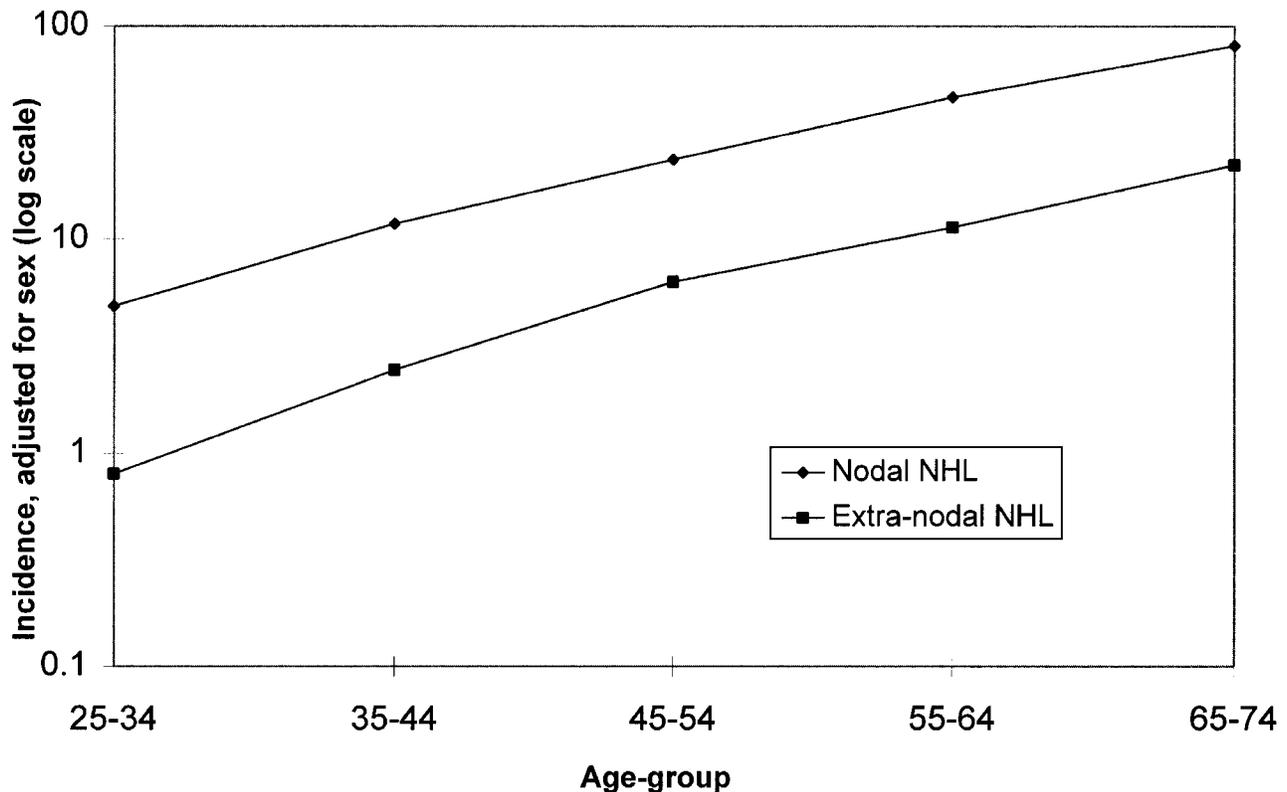


FIGURE 5 – Age-specific incidence per 100,000 of nodal and extra-nodal non-Hodgkin's lymphomas in the USA.

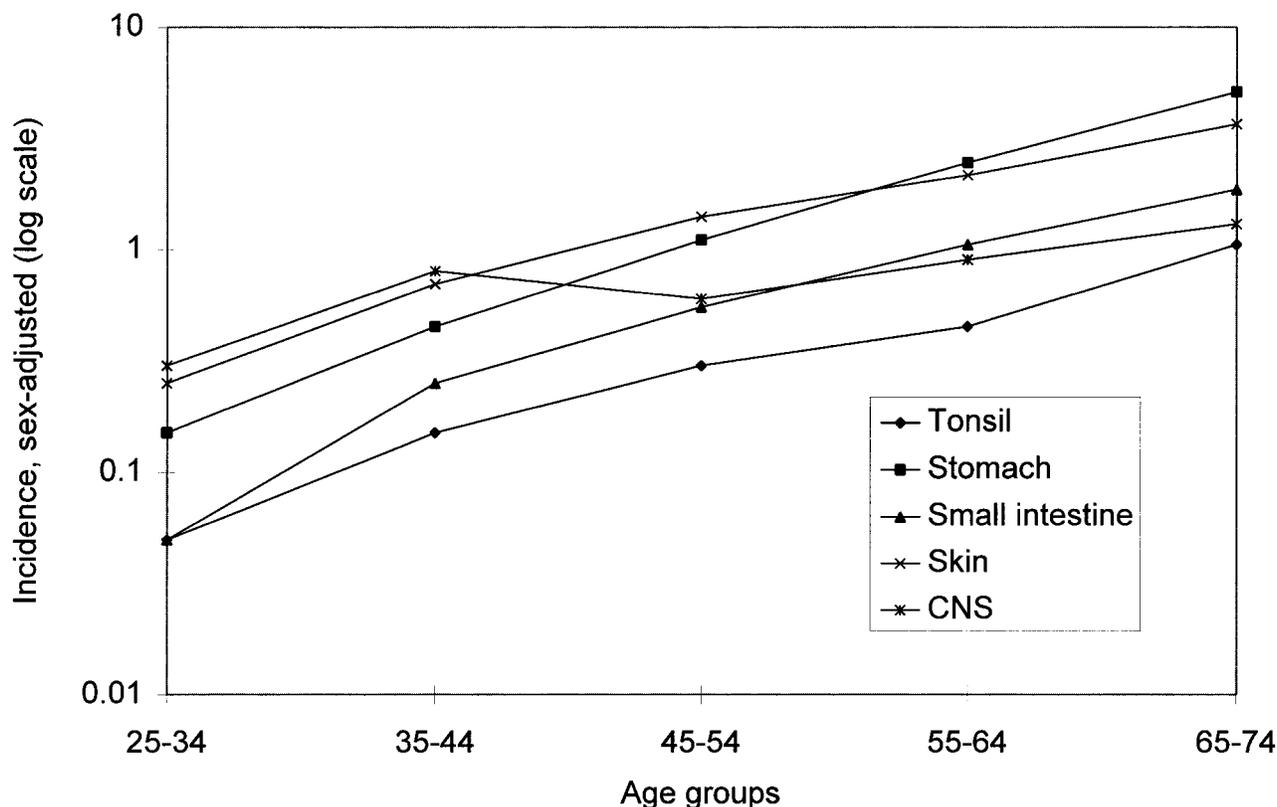


FIGURE 6 – Age-specific incidence per 100,000 of extra-nodal non-Hodgkin's lymphomas in the USA, by site.

nodal lymphomas, perhaps the same mechanism applies to nodal lymphomas. It may simply be that inflammation increases the rate of cell division of lymphocytes, thereby increasing the chance of a malignant clone developing.

In conclusion, although specific local factors are known to increase the risk of lymphomas at certain anatomical sites, our data suggest that the aetiology of extra-nodal lymphomas is not entirely independent of that of nodal lymphomas.

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