Gender and Time Differences in Initial Location and Histological Grade of Non-Hodgkin's Lymphomas in Southern Sweden

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In accordance with international data, non-Hodgkin's lymphomas (NHL) in the Southern Health Care Region of Sweden were more common in men than in women and there was an inreasing incidence for both genders in the 1980s and 1990s. A study of the years 1983 and 1992, i.e. the beginning and the end of a 10-year period, was carried out. Case records for 94% of all adults diagnosed in 1983 and 1992 (220 men and 171 women) were reviewed. The sites of the lymphomas and malignancy grade (Kiel classification) were recorded. Comparisons were made between the genders and between the two years studied. Among 170 men with nodal lymphomas, 49 were localized (stage I–II) in lymphoid tissue regional to the respiratory tract, 18 were localized elsewhere and 103 were generalized (stage III–IV). The corresponding sites in 138 women were 28, 33 and 77, respectively ($p = 0.002$), implying a predominance of stage I–II lymphomas regional to the respiratory tract in men and a larger number of localized lymphomas elsewhere, mostly abdominal/retroperitoneal with or without inguinal engagement in women. High-grade nodal lymphomas were more common in 1992 (54%) than in 1983 (34%, $p = 0.01$), suggesting an increasing number of mainly high-grade lymphomas. For extranodal lymphomas (50 in men and 33 in women), no clear differences were observed for gender and the years studied. Risk factors, e.g. occupational hazards, are probably different for men and women. The gender differences in initial nodal location suggest that initial lymphoma sites may be related to different risk factors. Epidemiologic studies where both malignancy grade and initial lymphoma locations are taken into account may be helpful in defining risk factors.

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The incidence of non-Hodgkin's lymphoma (NHL) is higher for men than for women, a difference that is marked both in Scandinavia (1–3) and in other populations (4–6). It is not known if this is entirely due to constitutional differences between genders or whether a more pronounced exposure to some environmental risk factors, e. g. occupational hazards, among men might contribute.

An increasing incidence of non-Hodgkin's lymphoma (NHL) affecting both genders has been reported in recent years from various parts of the world (1–8). It is not known if this pattern is due to increasing numbers of lymphomas with some particular locations. In some studies of incidence trends, histological characteristics have been recorded (1, 4, 5, 8) but because of the different classifications used, it is not entirely known whether there is an ongoing increase in aggressive or indolent lymphomas or in both subgroups.

According to annual registry data presented by the National Board of Health and Welfare in the 1980s and 1990s, the common gender difference in incidence was also characteristic in the Southern Health Care Region of Sweden. Increasing incidence rates were also reported for both genders (see Fig. 1.). In the present study initial lymphoma locations and histological malignancy grades were recorded for each patient in 1983 and 1992. These years were selected because they represented the beginning and the end of a 10-year period. The aim was to detect possible gender differences in initial location and histological malignancy grade of the lymphomas. The selection of these years also offered an opportunity to trace possible changes in lymphoma locations and malignancy grade.

MATERIAL AND METHODS

Population

Sweden is divided into health care regions and each of them has a regional tumour registry to which all patients with a recent diagnosis of malignancy are reported. In 1983 the Southern Health Care region of Sweden had 1.58 million inhabitants and in 1992 1.53 million.

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Patients

All patients aged 15 years or older with NHL reported to the Southern Swedish Regional Tumour registry in 1983 and 1992 were identified. The 12 hospitals that had participated in the diagnostic and staging procedures were visited. The case record for each patient was scrutinized and only those with a diagnosis based on biopsy material were included in the study. The results of the staging procedures and the histological type were recorded.

In 1983, 199 adult patients with an unequivocal diagnosis of NHL were reported to the registry. Case records containing sufficient information on biopsy diagnoses and results of staging procedures were available for 185 patients (93%). Using the same diagnostic criteria, 215 adults were identified in 1992 and for 206 (96%) of them, the case records were sufficient. In the total material of 391 patients there were 220 men and 171 women giving a sex ratio of 1.3. The mean age at diagnosis in 1983 was 67 years for men and 71 years for women, and in 1992 65 and 70 years, respectively.

Lymphoma sites

Uniform programmes for staging were used in the two periods studied and included physical examination, chest- and abdominal CT scans and bone marrow biopsy. Using the Ann Arbor classification (9), the following categories of initial location of lymphomas were recorded:

Nodal localized NHL (Stage I–II). Stage I–II lesions located in lymphoid tissue adjacent or regional to the upper or lower respiratory tract. Patients with stage I–II disease affecting nodes in the neck, supraclavicular fossae or mediastinum were referred to this group, as were those with lymphomas located in Waldeyer's ring.

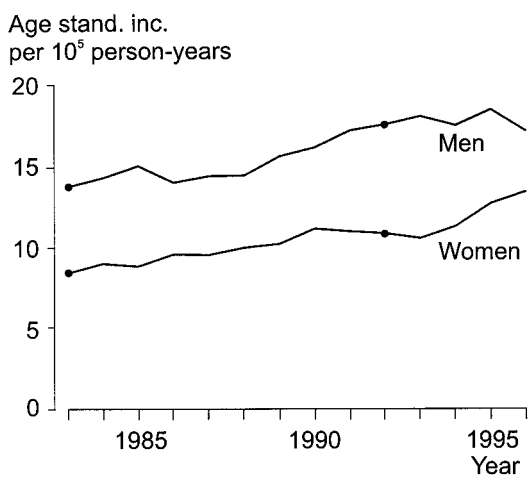

Fig. 1. Age standardized (Sweden 1970) incidence of NHL for men and women in the Southern Health Care Region of Sweden 1983--1996. The curves are presented using 3-year moving averages. The two years studied, 1983 and 1992, are indicated.

Stage I–II lesions in other sites, i.e. not associated with the respiratory tract. Patients with exclusively axillary manifestations, abdominal, retroperitoneal or inguinal lymphomas were referred to this group.

Generalized nodal lymphomas (Stage III–IV).

Extranodal lymphomas.

Histological grade

Diagnosis was based on biopsy material using the Kiel classification (10). For the present purpose the two histological malignancy grades used in this classification were recorded, i.e. high-grade or low-grade NHL.

Statistical methods

The development over time of the incidence of NHL in the Southern Health Care Region of Sweden is shown using an age-standardized incidence with the 1970 Swedish population as reference (2).

There were two study factors, gender and year (1983 and 1992), and site and histological malignancy grade were compared for these using Mantel-Haenszel's test stratified on year of diagnosis and four age groups ($< = 59$, 60–69, 70–79, $> = 80$ years) in the gender comparisons and on gender and age group in the year comparisons. Since site was classified into three groups, a generalized version of Mantel-Haenszel's test with two degrees of freedom (11) was used for this outcome.

RESULTS

Nodal vs. extranodal lymphomas in relation to sex and period

The initial locations and histological grade for nodal and extranodal lymphomas in 1983 and 1992 are presented in Table 1. In men, 50 out of 220 lymphomas were extranodal (23%), and in women, 33 out of 171 (19%). The difference is not significant (M-H's test, $p = 0.42$).

The proportions of extranodal lymphomas in 1983 and 1992 were similar, with 43 out of 185 (23%) and 40 out of 206 (19%), respectively (M-H's test, $p = 0.34$).

Sites of nodal lymphomas in relation to sex and period

The initial sites of all nodal lymphomas are listed in Table 1. Among men, including both years, 49 lymphomas were stage I–II regional to the respiratory tract, 18 stage I–II lymphomas had other locations and 103 were generalized at presentation. The corresponding numbers among women were 28, 33 and 77, respectively. The distributions in the two genders are significantly different (M-H's test, $p = 0.002$). Apparently, the difference was mainly due to a larger number of lymphomas regional to the respiratory tract in men and to a larger number of stage I–II lymphomas with other sites in women. The lymphomas not associated with the respiratory tract are subdivided in Table 2. There was a considerably larger number of ab-

Table 1

Initial sites and histological grade of lymphomas in 220 men and 171 women, 1983 and 1992

	Men			Women		
	1983	1992	Total	1983	1992	Total
Nodal lymphomas						
Stage I–II resp. tract	19	30	49	17	11	28
Stage I–II other	11	7	18	14	19	33
Stage III–IV	46	57	103	35	42	77
Low grade						
Stage I–II resp. tract	8	8	16	8	4	12
Stage I–II other	8	3	11	5	6	11
Stage III–IV	33	35	68	24	21	45
High grade						
Stage I—II resp. tract	11	22	33	9	7	16
Stage I–II other	3	4	7	9	13	22
Stage III–IV	13	22	35	11	21	32
Extranodal lymphomas						
High grade	19	19	38	11	8	19
Low grade	4	8	12	9	5	14

dominal or retroperitoneal lymphomas with or without a concomitant engagement of inguinal lymph nodes in women (n = 25) than in men (n = 9).

In 1983 a total of 36 stage I–II lymphomas were located regional to the respiratory tract, 25 had other sites and 81 lymphomas were generalized. The corresponding numbers in 1992 were 41, 26 and 99, respectively (Table 1). The difference between the two years studied is not significant (M-H's test, p = 0.87).

Histological grade of nodal lymphomas in relation to gender and period

In men, 75 out of 170 nodal lymphomas were high grade (44%) and in women the corresponding proportion was 70 out of 138 (51%). The difference is not significant (M-H's test, p = 0.30).

In 1983, 56 out of 142 nodal lymphomas were classified as high grade (39%), and in 1992, 89 out of 166 (54%). The larger proportion of high-grade nodal lymphomas in 1992 is significant (M-H's test, p = 0.01).

Sites and histological grade of extranodal lymphomas in relation to gender and period

The number of men and women with low- or high-grade extranodal lymphomas in 1983 and 1992 is shown in Table 3. Obviously, the subgroups of patients with various extranodal sites were too small to permit meaningful comparisons between genders and between the two years studied.

In men, 38 out of 50 (76%) extranodal lymphomas were high grade and in women 19 out of 33 (58%). The difference is just significant at the 5% level (M-H's test, p = 0.04).

In 1983, 30 out of 43 (70%) extranodal lymphomas were high grade and in 1992 the corresponding proportion was almost identical, 27 out of 40 (68%) (M-H's test, p = 0.76).

DISCUSSION

Analogous to national and international data, the incidence of NHL is higher among men than among women in our region. Also in line with reports from Scandinavia and other parts of the world, the incidence in southern Sweden has been increasing for both genders in the 1980s and 1990s.

In the comparisons of initial lymphoma sites in the two years 1983 and 1992, a significant difference was observed: localized nodal lymphomas regional to the respiratory tract were more common in men than in women, whereas other localized lymphomas affecting abdominal or retroperitoneal lymph nodes with or without concomitant inguinal engagement were more common in women. Constitutional differences between the genders might be associated with different clinical manifestations of NHL. There are, however, no obvious reasons why initial locations of lymphomas should be governed by inherent sex qualities. Different exposure to some risk factors seems to be a more probable explanation of the clinical gender differences observed.

According to one model proposed for the pathogenesis of NHL, an increased proliferative activity in lymphocytes due to antigenic stimulation may increase the probability of oncogenic mutation (12–14). Exposure of mucous membranes in the upper and lower parts of the respiratory tract to some infectious agent(s) might then promote malignant transformation in adjacent lymphoid tissue. However, exposure to such agents are likely to affect men and

Table 2

Initial sites of nodal stage I–II lymphomas with locations other than regional to the respiratory tract

	Men			Women		
	1983	1992	Total	1983	1992	Total
Axillary only	4	1	5	1	2	3
Abdominal/retroperitoneal ± inguinal	4	5	9	10	15	25
Inguinal only	3	1	4	3	2	5

women to a comparable extent. It is therefore probable that other factors are responsible for the larger numbers of lymphomas regional to the respiratory tract observed in men. The present study was descriptive without information on exposure to possible risk factors and only speculative explanations of the gender differences are possible. Inhalation of some mutagenic agents, e.g. tobacco smoke, may be particularly common in men. However, in large cohort or case-control studies smoking has not been found to be a risk factor for NHL (15–17). Occupational inhalation of volatile organic solvents, a probable risk factor for NHL (18–23) is probably more common for men than for women and might be related to the particularly common initial location of lymphomas near the respiratory tract in men. There is some support for this supposition from a Swedish case-control study of 167 men with NHL (20). The odds ratio for daily occupational handling of organic solvents for at least one year was 3.3 (95% CI 1.9–5.8), but for a subgroup with supradiaphragmatic lymphoma presentation, the ratio was 6.5 (95% CI 3.2–13.3). Occupational inhalation of combustion residues of petrol products are also likely to be more common for men than for women. This is a probable risk factor for haematological malignancies other than NHL (24–26). This has also been reported to be associated with lymphatic malignancies, i.e. chronic lymphocytic leukaemia (27), hairy cell leukaemia (28, 29) and 'lymphoid leukaemia' (30).According to experimental animal studies, inhalation of diesel exhaust could induce malignant lymphoma (31).

An initial presentation of lymphomas in lymph nodes without anatomical relation to the respiratory tract was particularly common in women and mainly owing to a predominance of abdominal and/or retroperitoneal lymphomas with or without concomitant engagement of inguinal lymph nodes. Because antigenic stimulation of lymphoid tissue may increase the risk of mutagenic events, repeated infections of the urinary tract, known to be more common in women than in men, might cause such stimulation. It might also be speculated that some infectious agent(s) with a particular tendency to affect the female genital tract could cause a proliferative response in regional lymph nodes. There is evidence from animal studies that the deposition of spermatozoa (32) or seminal fluid (33) in the female reproductive tract will induce a transient activation of regional lymphoid tissue, with increased proliferation.

In 1992 the proportion of high-grade nodal lymphomas was larger than that in 1983. The biopsy specimens obtained in these two years have not been reviewed and it cannot be ruled out that pathologists in 1992 were more inclined to classify biopsied lymphoma tissue as high grade than in 1983. However, for extranodal lymphomas, high-grade histology was not reported more often in 1992 than in 1983. Hence, the larger proportion of high-grade nodal lymphomas in 1992 may reflect an increasing incidence especially of high-grade nodal lymphomas in the 10-year period 1983–1992. This hypothesis is in line with the results of a French study (5). Using the Working Formulation criteria for histological classification, a more pronounced increase of high-grade lymphomas in comparison with intermediate or low-grade lymphomas was observed in the period 1980–1989. In a comprehensive study in the

Table 3

Sites and histological grade of extranodal lymphomas in 50 men and 33 women 1983 and 1992

	Men 1983		Men 1992		Women 1983		Women 1992	
	High	Low	High	Low	High	Low	High	Low
Gastric	5	1	3	1	5	2	2	1
Intestinal	4	1	3	2	1	2	1	1
Cerebral	2	0	2	0	1	1	1	0
Skin	0	1	4	3	1	1	0	1
Testis	4	0	4	0	–	–	–	–
Ovary	–	–	–	–	0	0	1	0
Other	4	1	3	2	3	3	3	2
Total	19	4	19	8	11	9	8	5

USA, covering the period 1978—1995, high-grade NHL was also the most rapidly rising subtype (34).

Extranodal lymphoma sites are most heterogeneous. Consequently, the subgroups with various locations were very small in our material, precluding meaningful statistical comparisons between genders and between the two periods studied. There was a larger proportion of high-grade, extranodal lymphomas in men than in women, but this difference may largely be explained by constitutional differences; in men, there were 8 testicular lymphomas and it is well known that these are usually high grade.

The risk factors causing the increasing incidence of NHL observed internationally, nationally and in our region are unknown. The present results, and those presented by others, suggest that the increasing incidence is mainly due to rising numbers of high-grade lymphomas. Epidemiological studies of aggressive lymphomas may therefore be particularly important in order to reveal the causes of the rising incidence rates. The finding of gender differences in initial locations of nodal NHL suggests that initial lymphoma sites may be related to different risk factors. Epidemiological studies where initial lymphoma locations are taken into account may therefore be helpful in order to define such factors.

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