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ORIGINAL ARTICLE

Incidence and survival of gastric non-Hodgkin's lymphoma: A population-based study from the Association of the French Cancer Registries (FRANCIM)

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Abstract

Background. Most epidemiological studies on gastric lymphomas (GL) were carried out before changes in therapy were introduced. The aim of the study was to measure the incidence of GL and to estimate survival. *Material and methods.* Data were provided by the Association of the French Cancer Registries database. Age-standardized incidence rates were calculated for 786 incident cases diagnosed between 1978 and 2002. Crude and relative survival were calculated for 361 cases diagnosed between 1989 and 1997. Effects specific to sex, age at diagnosis, year of diagnosis, and grade of malignancy were estimated in multivariate analysis. *Results.* Incidence was stable during the study period. However, high-grade GL frequency increased whereas low-grade and not otherwise specified (NOS) GL frequencies were respectively stable and decreased. At 5 years, relative survival was 63% in men and 60% in women. Patients aged 75 or older had a five-year relative survival of 33%. Age at diagnosis was the only significant prognostic factor in multivariate analysis. Time trend improvement in prognosis was observed. *Discussion.* Results in elderly patients show that therapeutic regimens should be specifically designed and assessed for them. The prognosis improvement trend is probably related to the implementation of changes in management of patients and has to be confirmed by more recent data.

The stomach is the major site of gastrointestinal non-Hodgkin's lymphomas (NHL) and accounts for 7.1 to 10.5% of adult NHL [1–4]. Gastric Lymphoma (GL) harbours many features distinctive from nodal NHL. The observation that low-grade GL have morphological features similar to those of Peyers' patches has led to the concept of MALT-type lymphoma, and it has been shown that in most cases, low-grade MALT-type GL are associated with *Helicobacter pylori* infection. There have been numerous biological and clinical studies of GL. By comparison, epidemiological data are scarce. Population-based studies have shown that NHL incidence is increasing in many developed countries and that NHL relative survival has risen in recent years [5,6]. Such information provided by these studies is lacking for GL specifically. Additionally, there have been substantial changes in GL therapy over the past 20 years. Firstly, the role of surgery has declined. Secondly, low-grade MALT-type GL have been increasingly treated with antibiotics for *Helicobacter pylori* eradication. Thirdly, the treatment of high grade GL is now based on poly-chemotherapy. Most of the well conducted population-based studies of GL were performed before the aforementioned changes in therapy were introduced [1–4,7].

The aims of this study were to measure the incidence of GL and to estimate crude and relative

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survival by sex, age, grade of malignancy and period of diagnosis using the data base of the French network of cancer registries FRANCIM. The trends of relative survival over time were also evaluated.

Material and methods

Data were provided by the database of the French Association of cancer registries FRANCIM which covers 15% of the French population and includes patients diagnosed between 1978 and 2003. The FRANCIM Association includes all registries which have obtained accreditation and legal authorizations by national committees. Accreditation is renewed every four years by a committee that assesses the completeness and quality of data as well as the scientific production of the registries. Registries follow standard rules in accordance with the recommendations of the International Agency for Research on Cancer (IARC) and the European Network of Cancer Registries [8,9]. The registries include all the invasive tumour cases diagnosed in patients residing in the "*départements*" (a French geographic entity) they cover. The main data sources are public and private pathology and cytology laboratories, hospitals and clinics as well as the records of the National Health Insurance Service. The French registries do not include cases only registered from death certificates because of legal considerations. Cases were selected from topography code C16 and morphology code between 9590/3 and 9714/3 of the International Classification of Disease for Oncology, 2nd revision (ICDO-2) [9]. The classification of lymphomas changed during the study period. For this reason, there is a broad range of pathological diagnoses in this study of GL. To make tumour types homogeneous and comparable, the diagnoses were categorized in three grades of malignancy (low-grade, high-grade and not otherwise specified (NOS) GL) using tumour morphology code with the advice of clinicians (Eric Deconinck and Franck Carbonnel) and pathologists (Anne Clairotte). Table I shows each type of GL and corresponding grade.

Table I. Definitions of grades (codes from the International Classification of Diseases for Oncology, second edition) and corresponding number of cases included in the survival study (1989–1997).

Grade	ICDO-2 codes	N
High-grade	9673/3: lymphocytic, intermediate differentiation, diffuse	4
	9674/3 : centrocytic	7
	9676/3 : centroblastic-centrocytic, diffuse	5
	9680/3 : large cell, diffuse NOS	82
	9681/3 : large cell, cleaved, diffuse	1
	9682/3 : large cell, non cleaved, diffuse	6
	9683/3 : centroblastic diffuse	34
	9684/3 : immunoblastic	17
	9687/3 : Burkitt's lymphoma, NOS	1
	9697/3 : centroblastic, follicular	3
	9698/3 : large cell follicular, NOS	2
	9702/3 : peripheral T-cell lymphoma NOS	1
	9714/3 : large cell (K-1 +) lymphoma	1
Total		164
Low-grade	9670/3 : small lymphocytic, NOS	35
	9671/3 : lymphoplasmacytic	13
	9672/3 : small cleaved cell, diffuse	3
	9675/3 : mixed small and large cell diffuse	17
	9686/3 : small cell, noncleaved, diffuse	1
	9690/3 : follicular, NOS	2
	9691/3 : mixed small cleaved and large cell, follicular	4
	9692/3 : centroblastic-centrocytic, follicular	2
	9693/3 : lymphocytic, well differentiated, nodular	1
	9695/3 : small cleaved cell, follicular	2
Total		80
Not Otherwise Specified (NOS)	9590/3 : malignant lymphoma NOS	98
	9591/3 : malignant lymphoma, non Hodgkin's, NOS	18
	9592/3 : lymphosarcoma NOS	1
Total		117
Total		**361**

Incidence

Data were provided from six general registries (*départements* of Doubs, Hérault, Isère, Bas-Rhin, Somme, Tarn) and one specialized haematology registry (Côte-d'Or) which cover the whole study period. Age-Standardized incidence Rates (ASR) per 10^5 person-year using world population as reference [10] were calculated for 5-year periods (1978–1982, 1983–1987, 1988–1992, 1993–1997, 1998–2002) with a 95% confidence interval assuming a Poisson distribution for the number of cases [11]. The estimated annual percent change was calculated between the first and the last period incidence with a 95% confidence interval using the delta method.

The evolution of GL grade distribution was described for three study periods 1989–1991, 1992–1994, 1995–1997 using the survival study database (see below). Changes in distribution were tested using the χ^2 test.

Survival

Survival data were provided by the first population-based cancer survival study including all French

registry data [7] involving 205 562 incident cases diagnosed between January 1, 1989 and December 31, 1997 from 11 registries. Vital status was obtained on January 1, 2002 using a standardised administrative procedure.

Relative survival was estimated using an excess rate model [12]: the observed mortality rate was divided into two mortality rates: the expected mortality rate (i.e., the natural mortality rate) and the excess mortality rate (i.e., mortality rate due to cancer). The method used to obtain relative survival estimates was described in a previous publication [13].

Univariate analysis

Briefly, the excess mortality rate was modeled with a flexible and continuous function of time among several candidate functions using the Akaike Information criterion [14]. Estimates of the excess mortality rate make it possible to obtain one, three, five-year crude and relative survival through the relation between rate and survival. Crude survival was estimated using the same approach with the expected mortality rate set at zero. Crude and relative survivals are given with their 95% confidence interval.

Multivariate analysis

Effects specific to covariates on the excess mortality rate (sex, age at diagnosis, year of diagnosis, and grade of malignancy) were estimated using the same flexible function of time for the baseline rate function and with proportional effects of covariates on the mortality rate. The statistical significance was calculated using the likelihood ratio test. The covariates of age at diagnosis and year of diagnosis were analysed as continuous covariates.

Results

Incidence and evolution of grade distribution

Seven hundred and eighty six incident cases of GL were included in the FRANCIM registries between 1978 and 2002. The trends of age-standardized incidence rates per 100 000 person-years are given in Figure 1 for males and females. Rates were higher in men than in women, respectively 0.57 [0.39; 0.75] and 0.25 [0.14; 0.36] per 100 000 person-year for the 1978–1982 period and 0.51 [0.4; 0.61] and 0.29 [0.21; 0.36] for the 1998–2002 period. Between these two time periods, there was no significant increase or decrease of incidence rates in either sex. From 1978 to 1992, incidence rates increased to a maximum of 0.66 and 0.52 for men and women respectively, and decreased thereafter.

The distribution of lymphoma grades varied according to study periods as shown in Table II. A significant decrease in NOS GL with a concomitant increase in high-grade GL ($p = 0.006$) was observed. There was no significant link between grade and age class distributions.

Survival

The survival analysis was conducted in 361 incident cases of GL (200 in women) diagnosed between 1989 and 1997. Number of cases by sex, age and grade of malignancy is shown in Table III. There

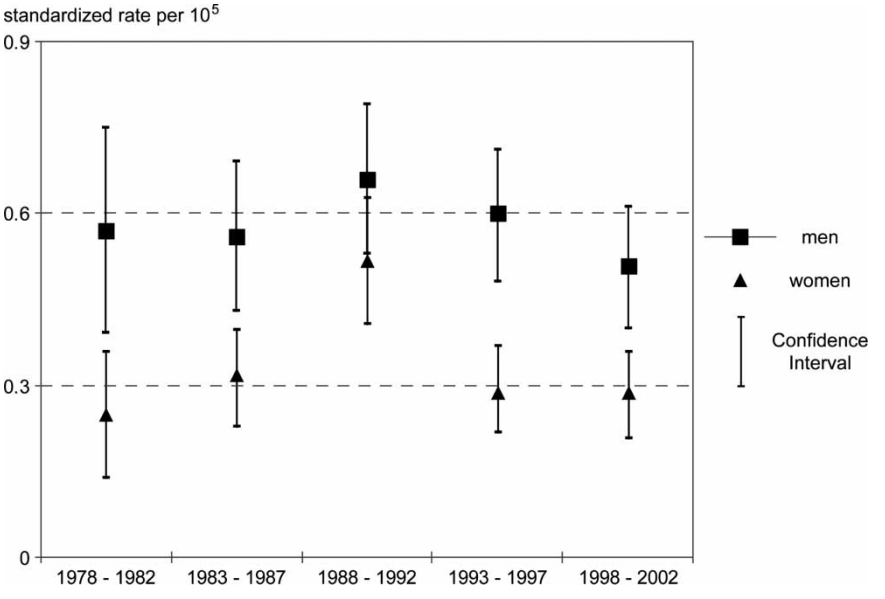

Figure 1. Age-standardized incidence rates per 100 000 in men and women from 1978–1982 to 1998–2002.

Table II. Evolution of lymphoma grade distribution during the three study periods.

Grade	[1989–1991]	[1992–1994]	[1995–1997]
Low-grade GL (n = 80)	22%	29%	17%
NOS grade GL (n = 117)	41%	31%	27%
High-grade GL (n = 164)	37%	40%	57%

were 164 high-grade, 80 low-grade and 117 NOS GL (Table I). These GL represented 5.7% of NHL cases included in the FRANCIM registries between 1989 and 1997.

Univariate analysis

One-year, three-year and five-year relative survival were respectively 69%, 63% and 61% (Table IV). Figure 2 shows relative survival curves in men and in women. One-year relative survival was 71% (64–76%) in men and 65% (57–72%) in women. After three years, relative survival was 65% (57–72%) in men and 60% (52–68%) in women and after five years, they were 63% (55–70%) in men and 60% (51–68%) in women.

The relative survival curves for five age groups are shown in Figure 3. Patients aged 75 or more had poor survival as compared to the other age groups: five-year relative survival and CI were 33% (23–43%) and 68% (55–79%) respectively. The highest five-year relative survival was observed in the 45–55 age group (87% (74–94%)). The two other age groups had similar relative survival: 74% (55–87%) and 73% (59–82%) respectively for the 15–45 and 55–65 age groups.

Low-grade GL had a higher survival than high-grade GL; NOS GL had an intermediate survival (Table IV). Five-year relative survival was 68% (55–78%), 58% (49–65%) and 62% (52–71%) respectively for low-grade, high-grade and NOS grade.

Additionally, as shown in Table IV, five-year relative survival tended to be better in the late study period as compared to the early one (68% (56–77%) for the 1995–1997 period vs. 58% (46–67%) for the 1989–1991 period).

The analysis of survival by age group, grade category and period could not be performed because of a too low number of cases in each category.

Multivariate analysis (Table V)

Estimate of covariate effect for sex, age, year of diagnosis and grade of malignancy showed that age was the only prognostic factor significantly associated with survival ($p < 0.001$). A patient one year older than the mean age (66.6 years) had a mortality rate related to GL multiplied by 1.05 compared to the mean age. Year of diagnosis, taken as a continuous covariate, was not significantly associated with survival (Hazard ratio of 0.98 [0.91; 1.05]).

Discussion

This is the first population-based study on GL issued from the database of the French network of cancer registries. It shows that global GL incidence was stable over the 1978–2002 period. However, from 1989 to 1997, a significant change in GL grade distribution was observed with an increase in the relative frequency of high-grade GL and a concomitant decrease of NOS GL. GL prognosis tended to improve during the study period despite the increasing frequency of high-grade GL. However, in multivariate analysis, the only significant prognostic factor was age at diagnosis.

Table III. Survival study population: Number of cases by sex, age and grade of malignancy.

Variable	Modality	Number of cases	Relative frequency (%)
Sex	Male	200	55.40%
	Female	161	44.60%
Age	[15; 45]	34	9.40%
	[45; 55]	41	11.40%
	[55; 65]	72	19.90%
	[65; 75]	88	24.40%
	[75; ++]	126	34.90%
Grade of malignancy	Low-grade	80	22.20%
	High-grade	164	45.40%
	NOS	117	32.40%

Table IV. Crude and relative survival at 1, 3 and 5 years. Relative survival by grade and by period of diagnosis (% and 95% Confidence Interval).

Survival	1 year	3 years	5 years
Crude survival	65 [60–70]	55 [50–60]	50 [45–55]
Relative survival	69 [64–74]	63 [57–68]	61 [55–66]
High-grade	67 [59–73]	61 [52–68]	58 [49–65]
Low-grade	74 [63–83]	69 [57–78]	68 [55–78]
NOS grade	66 [57–74]	62 [52–71]	62 [52–71]
[1989; 1991]	65 [55–73]	58 [48–68]	58 [46–67]
[1992; 1994]	70 [61–78]	61 [51–70]	59 [48–68]
[1995; 1997]	75 [65–82]	72 [62–80]	68 [56–77]

NOS: Not Otherwise Specified.

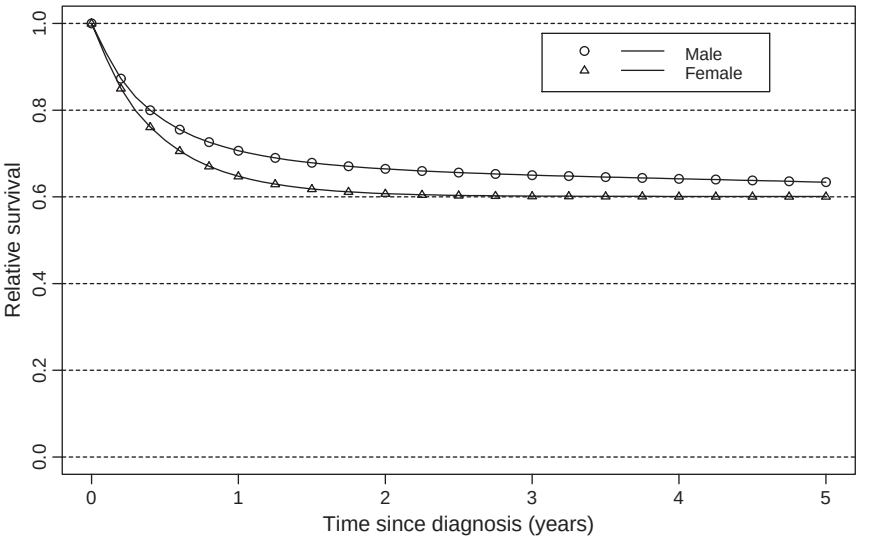

Figure 2. Curve of relative survival by sex for gastric non-Hodgkin's lymphoma diagnosed between January 1, 1989 and December 31, 1997.

Data quality

GL registration and coding methods in French registries follow international guidelines [8,9]. For extranodal NHL, the primary site is coded with the topography code of the organ (C16 for the stomach) and NHL is coded with the morphology code. However, confirming the primary site might be difficult even after examining clinical records. This difficulty in coding extranodal NHL is common to all cancer registries. Recently, new guidelines for haematological malignancies have been published by specialized registries and will contribute to improvement in data quality.

Incidence

Few population-based incidence data are available concerning GL (Table VI). Our incidence results appeared to be higher than those published for a similar period in a population-based study in England [1]. German incidence rates (study period 1993–1996) were lower than ours for men and higher for women [15]. Comparing our findings with Danish rates is not easy because of different reference populations and study periods [2].

Although nodal NHL incidence tends to increase over time, we did not observe a similar trend for GL. In comparison, GL incidence is increasing in

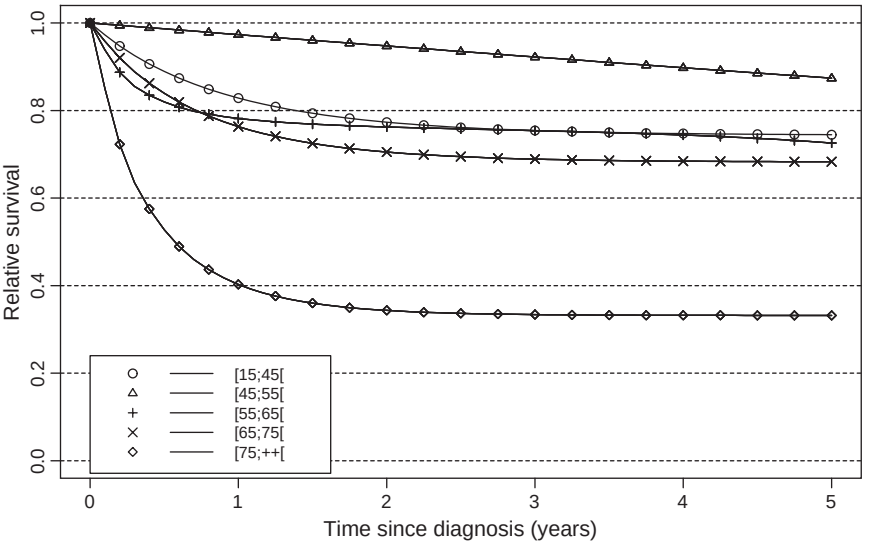

Figure 3. Curve of relative survival by age for gastric non-Hodgkin's lymphoma diagnosed between January 1, 1989 and December 31, 1997.

Table V. Multivariate analysis: Effect of covariates on the excess mortality rate (sex, age at diagnosis, year of diagnosis and grade) and 95% confidence interval (CI).

Covariates	Hazard ratio	95% CI lower limit	95% CI higher limit	P
Sex	1.04	0.73	1.50	0.815
Age at diagnosis	**1.05**	**1.04**	**1.07**	**<0.001**
Year of diagnosis	0.98	0.91	1.05	0.507
High-grade	0.78	0.78	2.04	0.345
NOS* grade	0.63	0.63	1.78	0.823

*NOS: Not Otherwise Specified.
Sex reference: male.
Grade reference: low.
Age at diagnosis and year of diagnosis are considered as continuous variables.

England [1] and is stable in Denmark [2]. In our study, however, when GL were categorized the relative frequency was stable in low-grade, decreased in NOS, and increased in high-grade GL. Improved diagnosis methods such as immunohistochemistry could well explain the decline in NOS and the proportional increase in high-grade lymphoma.

Survival

Our relative survival results for GL are similar to those obtained in Denmark [2], in the Netherlands [3] and in Copenhagen County [16]. These comparisons should be interpreted with caution because the study periods differed and possibly the distribution of high and low-grade GL cases differed as well. In our study, we observed a time trend increase in the survival of GL in univariate analysis; however in multivariate analysis, the increase was not statistically significant. The time trend improvement in prognosis cannot be attributed to an increase in the proportion of low-grade GL: on the contrary, an increase in high-grade lymphomas was observed. It is probably multifactorial and can be attributed to a better knowledge of the disease [17,18], less toxic chemotherapy regimens in the treatment of lymphomas [19] and decline in gastrectomy for GL [20–22], all of which appeared between 1989 and 1997. Addition of rituximab to the usual poly-chemotherapy cannot account for the time trend improved prognosis observed in this study, since it occurred after 1997.

As in NHL [6], age at diagnosis is an important prognostic factor. Patients older than 75 years have a worse prognosis than the other age groups. This suggests that these patients do not receive adequate treatment or die of its side effects. Specific treatments for elderly patients with GL should be designed.

In conclusion, this population-based study shows that the incidence rate of GL is stable over time. However, high-grade GL frequency is increasing whereas low-grade and NOS GL frequencies are, respectively, stable and decreasing. This study suggests that the changes introduced in the management of patients with GL since the end of the 1980s have improved its prognosis.

The relative survival of elderly patients is dismally low, compared with those of other age groups. Therapeutic regimens should be specifically designed and assessed for this category of patients.

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Table VI. Age Standardized incidence Rates (ASR) per 100 000 person-years in population based studies on gastric lymphomas.

Study [reference]	Country	Study period	Number of cases	ASR Male	ASR Female	Standard population
Gurney et al. [1]	England	1986–1993	650	0.29	0.20	World
Ullrich et al. [15]	Germany	1993–1996	94	0.51	0.38	World
D'Amore et al. [2]	Denmark	1983–1991	175	0.85	0.59	European
Our study	France	1988–1992	198	0.66	0.52	World
Our study	France	1993–1997	187	0.60	0.29	World

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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