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The incidence and distribution of leukaemia and lymphoma within Northern Ireland in the period 1989-1993

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SUMMARY

This is the first attempt to systematically record haematological malignancies in Northern Ireland. The methods are identical to a similar effort in other parts of the UK,[1] except that an independent cross check with a cancer registry source was not possible. In addition problems with the census may create differences. Generally, the rates for the leukaemias are slightly lower than in England and Wales, except for acute lymphoblastic leukaemia whilst non-Hodgkin's lymphoma rates are higher. It remains to be seen how stable this situation is as further data are accumulated.

INTRODUCTION

The Northern Ireland Leukaemia Research Fund Data Collection Study started in 1989 as an independent collection system. At that time there was no Health Service cancer registration scheme in Northern Ireland. The aim was to give an accurate picture of the descriptive epidemiology of haematological malignancies in Northern Ireland. The data come from a special collection of material from the diagnostic laboratories of collaborating haematologists and histopathologists around the province. The method of collection was the same as that used in parts of Great Britain.[1] A previously published study in Northern Ireland[2] (the Podar report) concentrated on those leukaemias which are associated with ionising radiation, and used several incomplete registration sources to retrospectively obtain incident cases.

Using these data, variations in the incidence of disease by age, sex and area can be described. This is of intrinsic interest and may also be of value in generating hypotheses about the causes of the diseases studied.

Incidence rather than death certificate data are used because there is concern over both the accuracy of death certificates and their validity as a measure of disease incidence. Therapeutic advances have led to marked changes in the survival pattern of both leukaemias and lymphomas, with greater survival rates leading to marked decline in mortality.[3] Death certificates were used in the Podar report[2] to examine mortality in the leukaemias linked with ionising radiation.

METHODS: Background

Seven disease groupings were used, namely:–

(1) Acute Myeloid Leukaemia (AML),
(2) Chronic Myeloid Leukaemia (CML),
(3) Myelodysplasia (MDS),
(4) Acute Lymphoblastic Leukaemia (ALL),
(5) Non-Hodgkin's Lymphoma (NHL),
(6) Hodgkin's disease (HD), and
(7) Multiple Myeloma (MM).

These groupings were chosen because they provided sufficient numbers of cases for a critical statistical analysis.

Incidence data are reported in 5-year age groups up to 79 years.[4] In common with the GB Leukaemia Research Fund atlas,[1] no incidence data on the over 80's are reported because of lack of diagnostic accuracy and ascertainment problems. Further detail is given in the full report.[4]

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Local government district populations from the 1991 census were used in the analysis.[5] However, since no post-enumeration survey was carried out, the quality of data is likely to be poor in certain areas and certain age-groups due to under-enumeration.[6]

METHODS: Data Collection

Hospitals likely to diagnose or treat haematological malignancies were identified and the help of their haematologists and histopathologists sought. A central hospital in each area whose consultant staff were prepared to oversee the activity of a Belfast based, Northern Ireland Leukaemia Research Fund funded clerical officer, was identified. The clerk's duty was to collect and record information on every new case falling within the agreed diagnostic groups presenting at the hospitals. Each clerk had a limited number of hospitals to visit to collect data. This was recorded on standard forms and was completed for all new registrations after 1st January, 1989. Included for each patient were full name, sex, date of birth, home address and postcode at diagnosis, exact diagnosis and the date it was made. Copies of relevant haematology or histopathology reports were sent with the registration form to the Leukaemia Research Fund centre in Leeds. All the haematologists and histopathologists in Northern Ireland were involved in this study.

The exact system for case identification from each hospital laboratory was adapted to local practices relating to the reporting and storage of diagnostic information. Whenever there was doubt regarding the validity of a registration, the information was sent to Leeds for a decision. In addition the returns made by each clerk were relayed back for subsequent rechecking and for the addition of missing data. The work of the data collection clerks was controlled by regular contact with Leeds. Also, detailed procedures have been compiled hospital by hospital and kept up to date.

On receipt, the identification information was checked and the address postcode confirmed. A matching and identification program enabled the personal details to be checked to discover if the patient had been registered already. If not, or if the previous registration related to another diagnosis, the registration was completed. A second diagnosis was normally registered only if a malignant progression appeared to be ruled out.

The computer software has numerous logical checks. Also, all new input data are proof read by two clerks. Cases with missing information are reviewed, duplicate registrations are checked for discrepant information and decisions about registration made.

Unfortunately, as there was no formal cancer registration scheme in Northern Ireland when the study was set up it has not been possible to perform cross-checking for this time period.

STATISTICAL ANALYSIS

Since cancer incidence rates show marked variation with age and sex, it is necessary to standardise the rates so as to ensure that regional differences are not merely a reflection of differences in the age-sex structure of the population. In computing figures for the entire Northern Ireland study area (see Tables 1, 2 and Figures 1 of the full report[4]), the direct method of standardisation has been used, and overall incidence rates standardised to a uniform population are presented.

Elsewhere in the full report,[4] indirect standardisation is used, because we are seeking to make comparisons between the 26 Northern Ireland districts, and such comparisons are subject to smaller random variation when this method is used. Age-sex specific rates for the entire area of Northern Ireland are computed and used to generate expected numbers of cases for each district. The ratio of observed to expected for the district is its Standardized Morbidity Ratio (SMR), which is given as a percentage.

A district with an SMR of 100 has the same number of cases as if the provincial age and sex-specific rates had applied. Any process of computing a standardised ratio involves calculating an average of the ratios applicable to individual age-sex strata. This will not be appropriate if geographical changes of risk themselves show age or sex variation. Differences between the observed case counts, and the expected values are reported in terms of "p-values".[4]

If age-standardised rates, or SMR's, are mapped, then there is a tendency for those areas with few events to yield extreme values owing to Poisson variation. These areas are then given undue prominence. One proposed solution is to include some measure of statistical significance in the information to be mapped.[7] Indeed, most atlases have exclusively mapped p-values. However, this confuses statistical significance with biological importance and gives undue prominence to areas of high population in which quite modest deviations of the rate from the overall value may achieve a high level of statistical significance.

TABLE I

Age-specific incidence rates and uniform standardised incidence rates (per 100,000 person years) by disease grouping, pooled over both sexes. The number of cases is in parentheses.

Age	*AML*		*CML*		*MDS*		*ALL*		*NHL*		*HD*		*MM*	
0-4	1.4	(9)	0.0	(0)	0.0	(0)	7.4	(47)	1.3	(8)	0.0	(0)	0.0	(0)
5-9	0.2	(1)	0.0	(0)	0.0	(0)	2.9	(19)	0.0	(0)	0.9	(6)	0.0	(0)
10-14	0.6	(4)	0.5	(3)	0.2	(1)	1.7	(11)	0.3	(2)	0.6	(4)	0.0	(0)
15-19	0.8	(5)	0.0	(0)	0.2	(1)	1.9	(12)	1.1	(7)	2.2	(14)	0.0	(0)
20-24	1.1	(7)	0.2	(1)	0.0	(0)	0.6	(4)	1.1	(7)	2.9	(18)	0.0	(0)
25-29	0.8	(5)	0.0	(0)	0.2	(1)	0.5	(3)	1.3	(8)	2.5	(15)	0.0	(0)
30-34	1.2	(7)	0.4	(2)	0.2	(1)	0.7	(4)	0.9	(5)	3.2	(18)	0.2	(1)
35-39	1.0	(5)	0.4	(2)	0.4	(2)	0.6	(3)	2.4	(12)	1.2	(6)	0.8	(4)
40-44	1.6	(8)	0.4	(2)	0.4	(2)	0.2	(1)	5.9	(29)	2.0	(10)	0.2	(1)
45-49	1.1	(5)	0.2	(1)	0.4	(2)	0.2	(1)	9.8	(44)	1.1	(5)	2.9	(13)
50-54	1.6	(6)	1.3	(5)	1.3	(5)	0.3	(1)	13.3	(51)	1.3	(5)	2.9	(11)
55-59	4.5	(16)	2.5	(9)	2.0	(7)	0.0	(0)	16.0	(57)	1.7	(6)	5.6	(20)
60-64	4.6	(16)	0.9	(3)	5.3	(18)	1.2	(4)	22.8	(79)	2.6	(9)	10.7	(37)
65-69	7.4	(24)	0.9	(3)	10.5	(34)	1.2	(4)	34.8	(113)	3.1	(10)	11.7	(38)
70-74	4.6	(12)	1.2	(3)	15.0	(39)	1.2	(3)	37.2	(97)	0.8	(2)	21.1	(55)
75-79	8.4	(17)	0.5	(1)	18.9	(38)	0.0	(0)	45.7	(92)	2.5	(5)	21.8	(44)
Uniform Standardised Rate	2.6	(147)	0.6	(35)	3.4	(151)	1.3	(117)	12.1	(611)	1.8	(133)	4.9	(224)

A compromise is an "empirical Bayes" version of the SMR.[8] A probability model is adopted for the prior distribution of the true relative risks across the map. The influence of this model upon the estimation of the relative risks follows from "Bayes theorem". The method for estimating the parameters of this prior distribution is termed the "empirical Bayes" method

Two types of map are illustrated in the full report.[4] Both use "empirical Bayes" methods.[8] The first is a map of relative risk (RR) estimates which lie intermediate between the area-specific SMR and the mean of all the age-adjusted relative risks included in the map. Estimates are shrunk towards the mean; this shrinkage is substantial for RR's based upon small numbers of events while those based upon large numbers remain close to the corresponding SMR's. Using small areas, this approach may be modified so that shrinkage is towards a "local" mean based upon adjacent areas, and this method was used in the second map.[4] Comprehensive results are given in the full report.[4] GENSTAT V was used to carry out all analyses.[9]

RESULTS AND DISCUSSION

ACUTE MYELOID LEUKAEMIA

There were 147 cases. Age-specific incidence rates show higher rates in the first five years, followed by a decline (Table I). The pooled rates do not exceed those observed in cases aged 0-4 years until the 40's. There is a female excess in those aged 5-35 years roughly similar rates in both sexes between 35 and 55 yrs and a male predominance emerges in the over 55's. There is no evidence for a temporal trend. There is no evidence for between-district heterogeneity in the SMR's (Table II). There is not much variation in the "shrunk" RR's.

However, for the adjacency smoothed RR's, the highest rates tend to be concentrated in the South East of the province, particularly in the County Down area, Belfast Lough and the Mourne mountains. The lowest rates occur in the north of the province, and County Fermanagh.

CHRONIC MYELOID LEUKAEMIA

There were 35 cases. Age-specific incidence rates (Table I) show a female excess in the under 20's, a

TABLE II

SMR's by district of residence and disease grouping, pooled over both sexes. The number of cases is in parentheses. Significantly high or low SMR's are indicated by stars.[10]

District	*AML*		*CML*		*MDS*		*ALL*		*NHL*		*HD*		*MM*	
Derry	116	(9)	106	(2)	147	(10)	87	(7)	115	(34)	103	(8)	88	(9)
Limavady	124	(3)	358	(2)	188	(4)	42	(1)	55	(5)	122	(3)	94	(3)
Coleraine	63	(3)	173	(2)	20	(1)*	56	(2)	108	(22)	117	(5)	80	(6)
Ballymoney	88	(2)	0	(0)	0	(0)	56	(1)	63	(6)	196	(4)	58	(2)
Moyle	0	(0)	0	(0)	0	(0)	0	(0)	50	(3)	0	(0)	88	(2)
Larne	139	(4)	0	(0)	33	(1)	148	(3)	89	(11)	40	(1)	88	(4)
Ballymena	75	(4)	0	(0)	109	(6)	50	(2)	102	(23)	84	(4)	145	(12)
Magherafelt	32	(1)	0	(0)	32	(1)	69	(2)	95	(12)	167	(5)	108	(5)
Cookstown	111	(3)	0	(0)	112	(3)	119	(3)	120	(13)	118	(3)	172	(8)
Strabane	95	(3)	0	(0)	164	(5)	35	(1)	79	(10)	101	(3)	154	(7)
Omagh	125	(5)	108	(1)	227	(9)*	82	(3)	88	(14)	80	(3)	34	(2)
Fermanagh	78	(4)	250	(3)	147	(8)	268	(11)**	102	(22)	90	(4)	87	(7)
Dungannon	98	(4)	307	(3)	148	(6)	167	(6)	103	(17)	80	(3)	116	(7)
Craigavon	74	(5)	61	(1)	90	(6)	106	(6)	108	(30)	126	(8)	50	(5)
Armagh	43	(2)	90	(1)	64	(3)	75	(3)	110	(21)	70	(3)	116	(8)
Newry & Mourne	165	(12)	0	(0)	42	(3)	105	(7)	90	(26)	132	(9)	115	(12)
Banbridge	161	(5)	269	(2)	63	(2)	82	(2)	108	(14)	106	(3)	84	(4)
Down	115	(6)	323	(4)*	76	(4)	67	(3)	126	(27)	105	(5)	77	(6)
Lisburn	126	(11)	47	(1)	85	(7)	120	(9)	109	(38)	84	(7)	89	(11)
Antrim	53	(2)	0	(0)	86	(3)	123	(4)	118	(18)	106	(4)	75	(4)
Newtownabbey	128	(9)	0	(0)	58	(4)	97	(5)	79	(23)	78	(5)	104	(11)
Carrickfergus	133	(4)	272	(2)	67	(2)	170	(4)	104	(13)	143	(4)	67	(3)
North Down	126	(9)	118	(2)	113	(9)	148	(7)	77	(24)	83	(5)	86	(10)
Ards	97	(6)	135	(2)	123	(8)	67	(3)	87	(23)	73	(4)	187	(18)**
Castlereagh	46	(3)	194	(3)	125	(9)	76	(3)	78	(22)	167	(9)	38	(4)*
Belfast	98	(28)	61	(4)	116	(37)	96	(19)	114	(139)	87	(21)	117	(54)

* $p<0.05$
* * $p<0.01$

male predominance in the 20-50 year olds, and roughly equal rates in the over 50's, with a slow increase with age. There is no evidence of an increase with time. There is no evidence for between-district heterogeneity from the male and female SMR's, but possible evidence from the pooled SMR's (p=0.065 – Table II). In particular, Down has a significantly raised pooled SMR (p=0.05), and Dungannon has a significantly raised male SMR (p=0.02). However, these observations should be treated with caution, owing to the small number of cases.

The male shrunk RR's were much more heterogeneous than the female RR's. Highest rates occurred in Fermanagh, Dungannon, Banbridge, Down, Castlereagh, Carrickfergus and Limavady, whilst very low shrunk RR's were observed for Ballymena, Newtownabbey, Belfast and Newry and Mourne. The smoothed RR's were in general agreement with the shrunk RR's, particularly concerning the highest rates. However, the lowest rates appear to be concentrated in two distinct areas – the North East of the province and the Mourne region.

MYELODYSPLASIA

There were 151 cases (Table I). There is a marked predominance of males aged over 55, but below this a slight excess of females. There is no evidence of a time trend. There is marginal evidence for between-district heterogeneity from the SMR's (p=0.086 for pooled; p=0.110 for males; and p=0.097 for females). In particular, Omagh has a raised pooled SMR (p=0.03 – Table II) and Derry has a raised male SMR (p=0.05). As expected the smoothed RR's show far more variability than the shrunk RR's. This is particularly obvious for males.

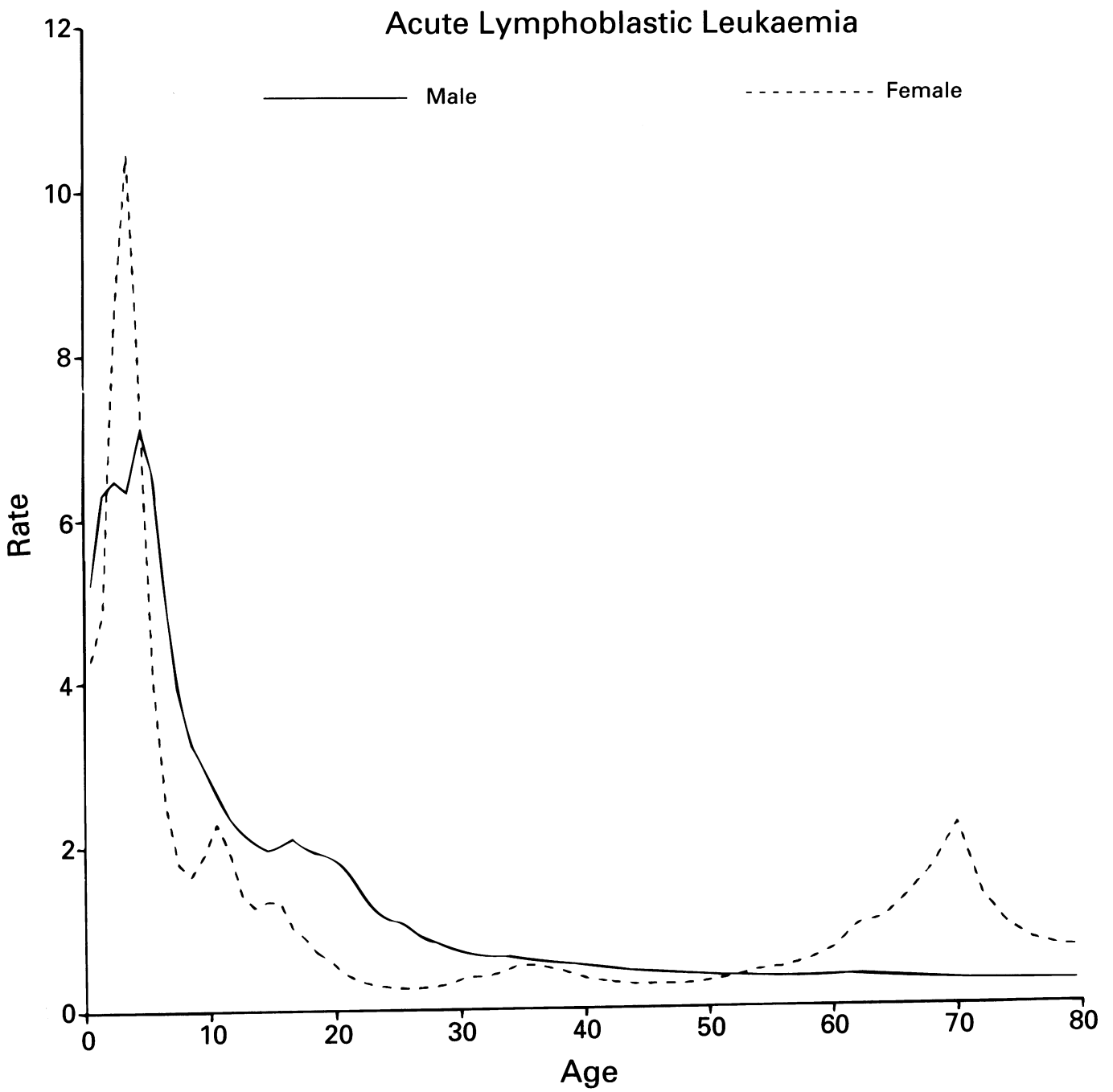


Fig 1. Age – specific incidence rates/100,000 population

There is a strong tendency for the highest rates to occur in the west of the province and the area comprising Belfast and the Ards/Strangford region. Lowest rates are observed in the North East and South East of Northern Ireland.

ACUTE LYMPHOBLASTIC LEUKAEMIA

There were 117 cases. The age-specific incidence rates show peaks in the first age quinquennium (Figure 1 and Table I). Subsequently there is a slight male excess in the under 50's and a female excess in the over 50's with a female peak around 70. There is no evidence of an increase with time.

There is a significant statistical interaction between sex and geographical distribution at district level (p=0.007). This indicates that the sex ratio of rates varies geographically. There is also marginal evidence for a statistical interaction between age and geographical distribution at district level (p=0.062). There is no evidence for between-district heterogeneity from either the pooled or female SMR's. However, there is strong variability between districts for males (p=0.011).

Fermanagh and North Down both have raised male SMR's (p=0.0007 and 0.020 respectively). Fermanagh has a raised pooled SMR (p=0.005), due to the excess of male cases (Table II).

Since there is a significant statistical interaction between sex and geographical distribution at district level, the maps of pooled rates may not be meaningful. Also, because there may be an interaction between age and geographical distribution, the male and female maps have to be treated with caution. (Accordingly, we only illustrate maps of male rates). These maps of male rates are illustrated (Maps 1 & 2) and show highest rates in the South West, particularly in County Fermanagh, and south of Lough Neagh, but also around Belfast Lough. Lowest rates are seen in the North and West of the province.

NON-HODGKIN'S LYMPHOMA

The study reports on 611 cases. Incidence is low in children but the incidence rates rise steeply from early adult life (Table I). There is a suggestion of an adolescent peak in males. There is a male excess at most ages. There is no evidence of an increase over time. Surprisingly, in view of English data suggesting the reverse (McNally et al – unpublished observations) there is some suggestion of a male decrease (p=0.036) over time.

There is no evidence for between-district heterogeneity in the SMR's (Table II). However, Belfast appears to have a raised SMR for males (p=0.048). Neither the shrunk RR's nor the female or pooled smoothed RR's show much variability. The male smoothed RR's show greater variability, the highest being observed in Belfast.

HODGKIN'S DISEASE

There were 133 cases of this condition. The age specific incidence curve shows a peak in young adults (Table I). After the modal values, which are similar in both sexes, there is a marked male predominance in older persons up to age 75. For the age group 75-79, there is a female excess. There is no evidence for a time trend.

There is no evidence for between-district heterogeneity in the SMR's (Table II). However, Ballymoney appears to have a raised SMR for females (p=0.04). There is not much variability in

TABLE III

MULTIPLE MYELOMA

Temporal variations (%) in standardised incidence rates

	MALE	*FEMALE*	*POOLED*
Year	*Rate (%)*	*Rate (%)*	*Rate (%)*
1989	5.4 (91.1)	3.8 (92.5)	4.4 (90.1)
1990	5.6 (95.0)	5.1 (124.3)	5.3 (109.7)
1991	5.7 (95.6)	4.8 (116.1)	5.2 (107.6)
1992	6.2 (104.4)	2.9 (70.1)	4.2 (86.5)
1993	6.8 (114.1)	4.0 (97.1)	5.2 (106.0)
Test for linear trend:	p=0.0141	p=0.5812	p=0.8374

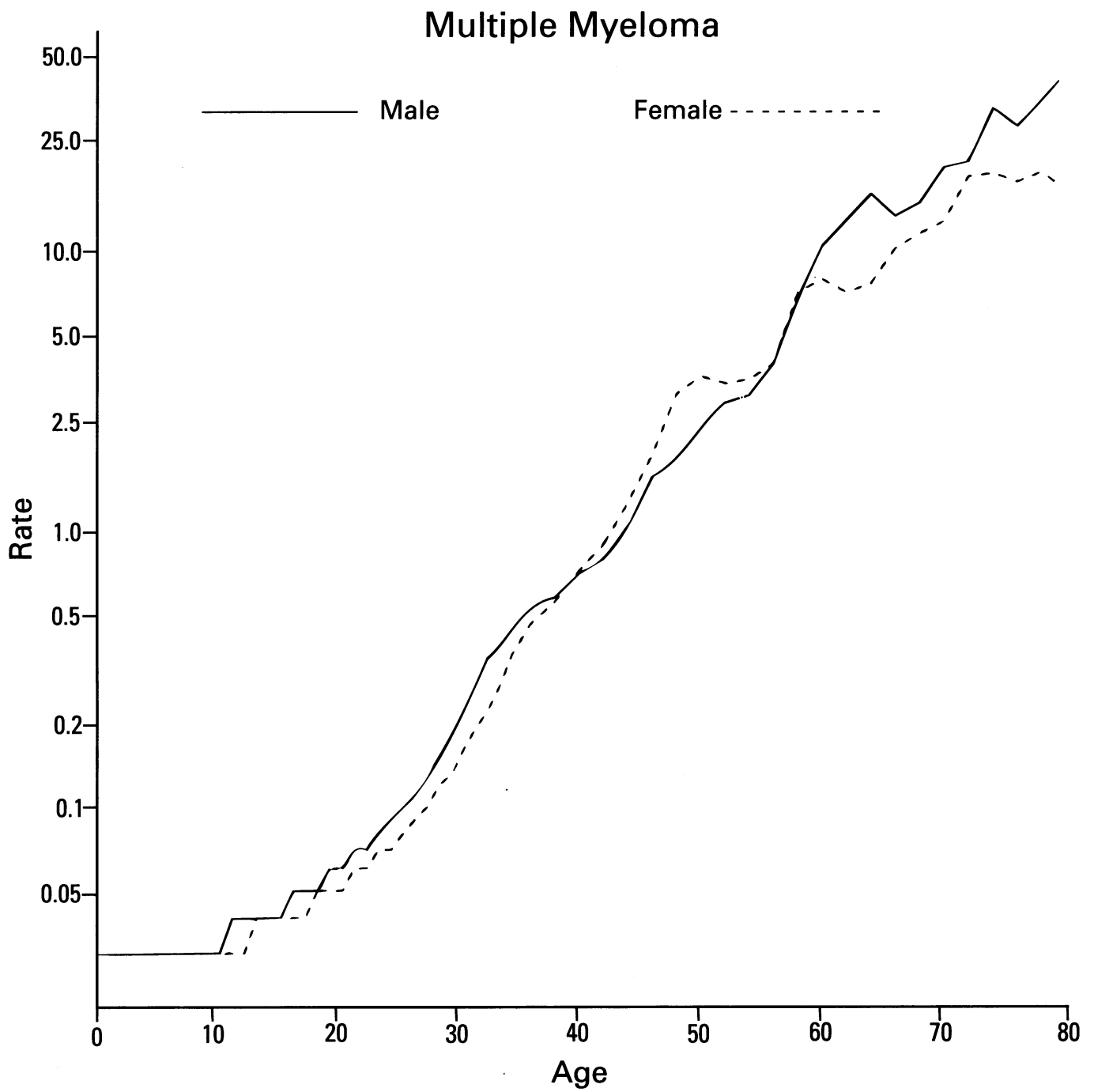
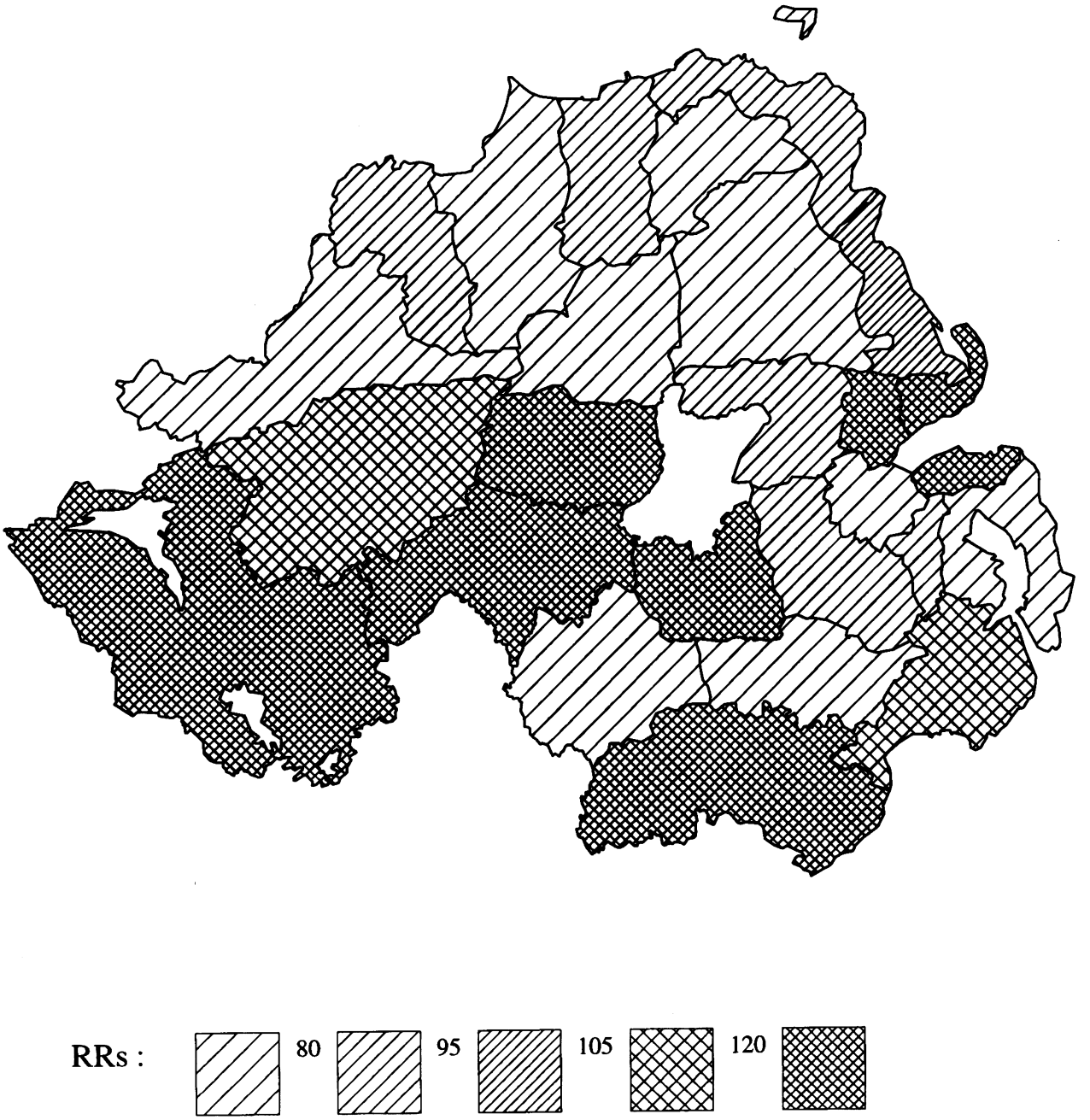


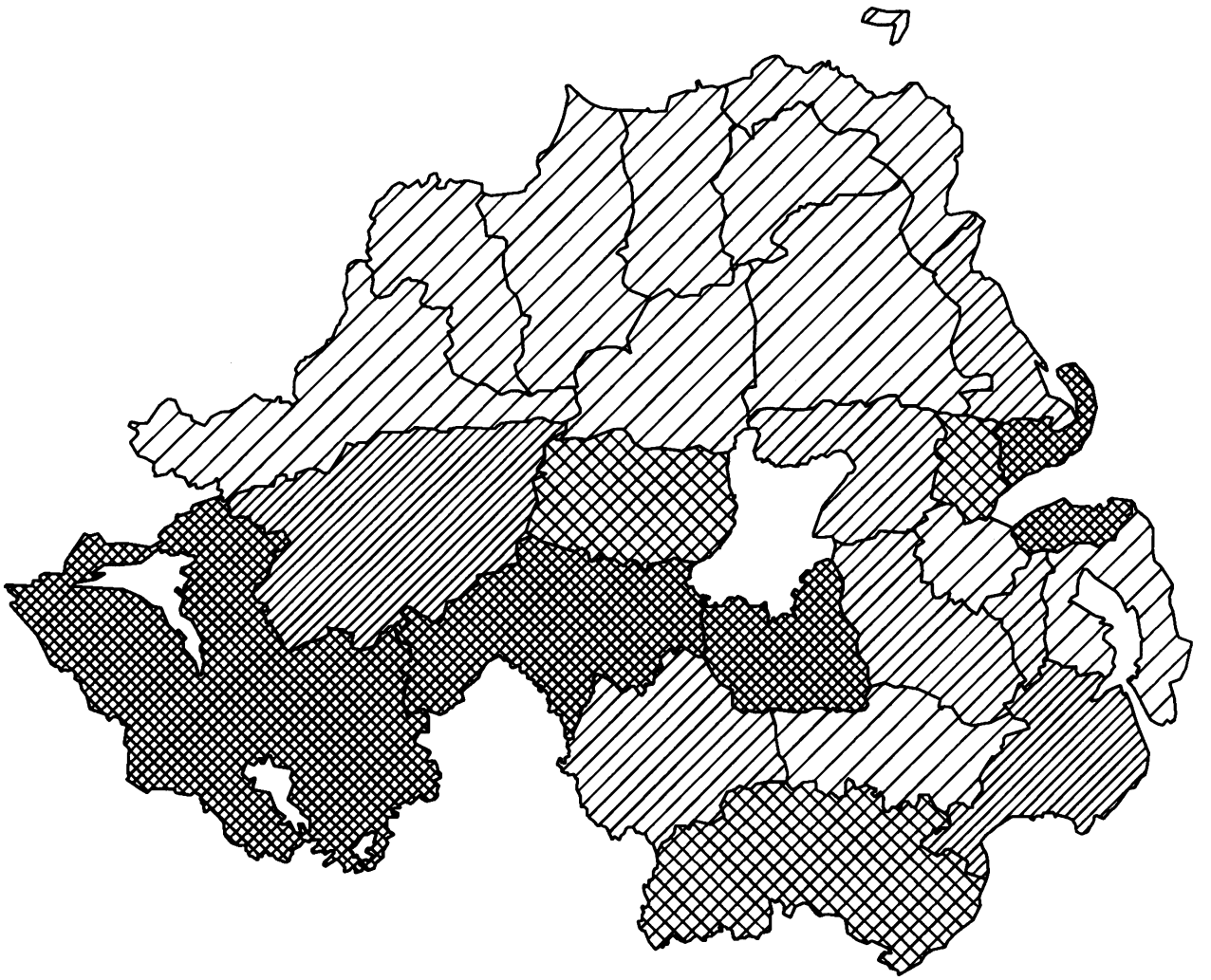
Fig. 2 Age – specific incidence rates/100,000 population

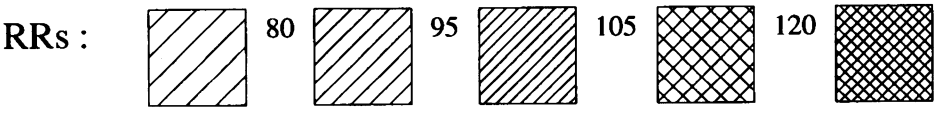
Map 1 ACUTE LYMPHOBLASTIC LEUKAEMIA
Incidence of disease (shrunk RRs) by district of residence. (Male)



NORTHERN IRELAND Local Government Districts.

Map 2 ACUTE LYMPHOBLASTIC LEUKAEMIA
Incidence of disease (smoothed RRs) by district of residence. (Male)

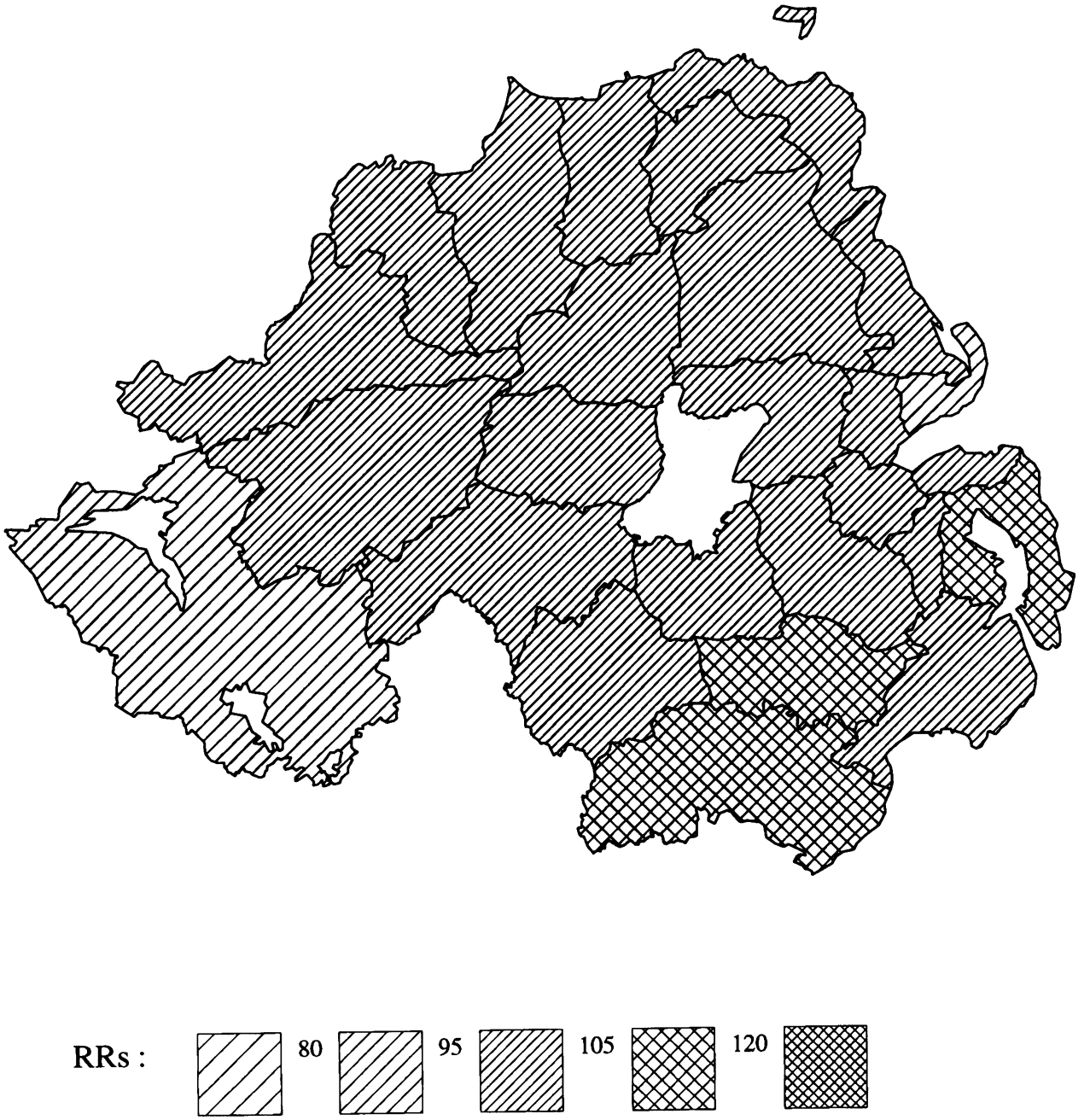




NORTHERN IRELAND Local Government Districts.

Map 3 MULTIPLE MYELOMA

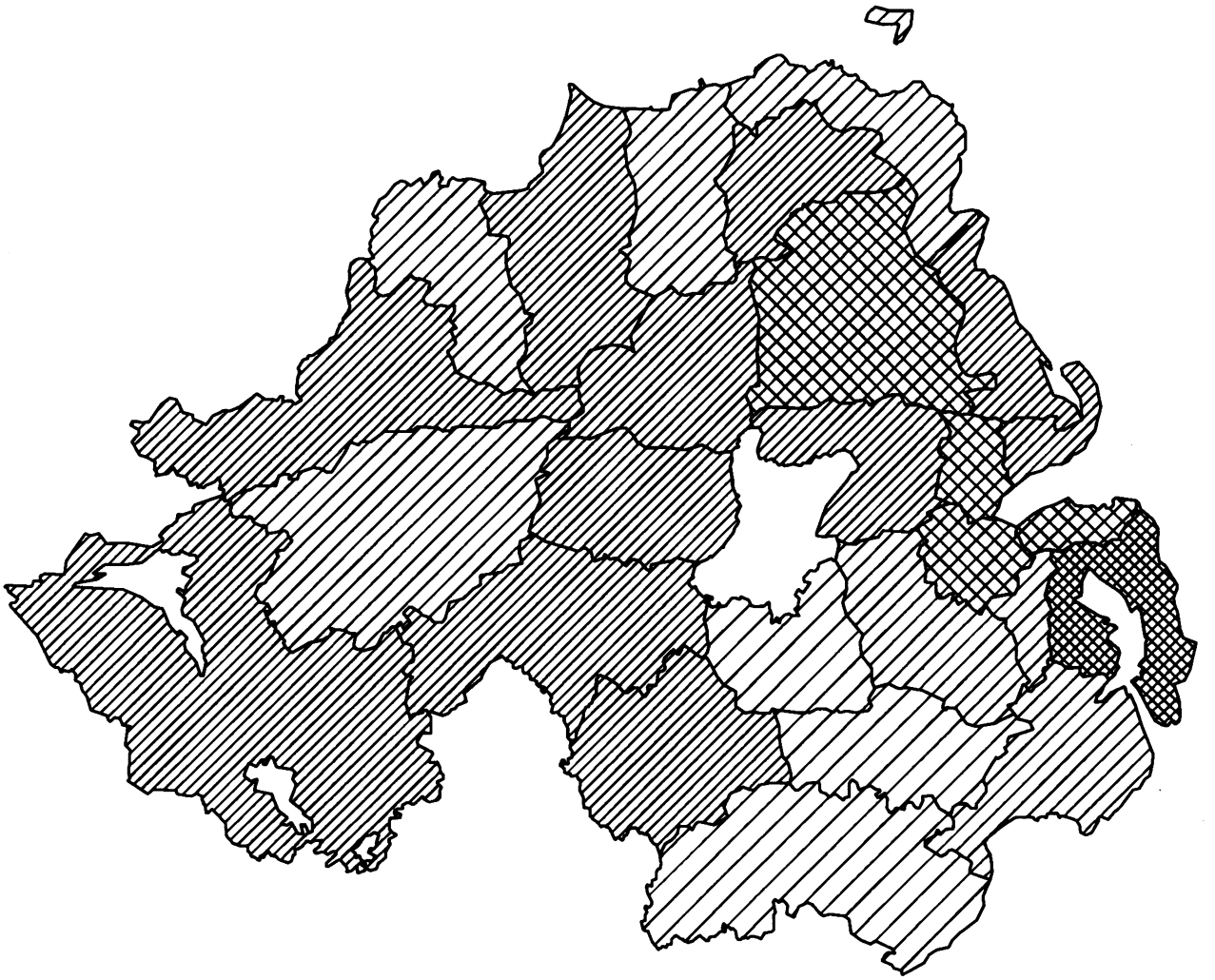
Incidence of disease (smoothed RRs) by district of residence. (Male)

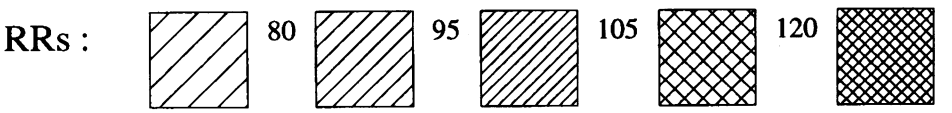


NORTHERN IRELAND Local Government Districts.

Map 4 MULTIPLE MYELOMA

Incidence of disease (shrunk RRs) by district of residence. (Female)





NORTHERN IRELAND Local Government Districts.

the shrunk RR's. No clear pattern emerges from the smoothed RR's. The highest female rates are in the North West and Mourne area. The highest male rates are in Castlereagh, Carrickfergus and Coleraine.

MULTIPLE MYELOMA

There were 224 cases. The disease is absent in children and young adults, but from the age of 30 onwards there is a steep rise with a marked excess in males over 60 (Figure 2 and Table I). There is evidence for an increase in the male rates (p=0.01), but the female rates were stable over the 5 year period (Table III).

There is a problem with under-registration of multiple myeloma, and so incidence rates are likely to be underestimates of the true rates.

There is no evidence for between-district heterogeneity from either the pooled or male SMR's. However, there is some evidence (p=0.083) of heterogeneity amongst the female SMR's. Ards has a raised pooled SMR (p=0.01 – Table II). The highest shrunk RR's occurred in the Belfast and Ards/Strangford areas. High smoothed RR's for males are observed in the Ards/Strangford area, and the Mourne district (Map 3). There were very low female smoothed RR's in the Armagh/South Down area (Map 4).

CONCLUSIONS

The authors regard this study as an important but initial step towards a careful and considered understanding of rates of disease in Northern Ireland. These early results will be supplemented by further work but they do not show unusual rates nor generate any major cause for concern. Indeed the results are quite similar to those from England and Wales.[1] The rates for the leukaemias except for ALL are slightly lower than in England and Wales whilst NHL rates are higher.

Possible under-enumeration in the census would affect district SMR's much more than overall province-wide age-specific incidence rates. This would have the consequence of artefactually raising SMR's in under-enumerated districts, and raising age-specific incidence rates in under-enumerated age groups. In particular the analysis of 35 cases of CML must be treated with caution. The most striking observation is the raised rates for ALL for males in County Fermanagh. This requires further investigation and explanation. The Podar report[2] examined the hypothesis that leukaemia incidence and mortality rates were higher in coastal than in inland areas of Northern Ireland. No significant coastal excesses were found.

The benefits of the data collection exercise are two-fold. For the first time, reasonably reliable estimates of the incidence of the leukaemias and lymphomas are available for Northern Ireland by age-group and local government district. These may be used in the planning of health services and may also be very useful in detecting any future excess occurrences of particular types of leukaemia and lymphoma.

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