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Patterns of Occurrence of the Leukaemias

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Despite a proliferation of epidemiological studies during the past two decades, aetiologies of the leukaemias remain poorly understood, and characterisation of descriptive patterns has been limited. Recent publications of international mortality and incidence data, along with the expanding U.S. database, make a comprehensive assessment of leukaemia patterns particularly timely. Total leukaemia mortality has dramatically declined among children and increased among the elderly, while incidence has declined somewhat (for Caucasian and African-American females) or remained stable (for African-American males) during the past two decades in the United States. Population-based 5-year relative survival for total leukaemia has risen substantially among children since the mid-1970s, and improved slightly among other age groups in the U.S., where survival is consistently higher among Caucasians than African-Americans, but differs little by gender. In a detailed assessment by leukaemia subtype, some important differences in geographic, racial/ethnic, age and trend patterns are identified, suggesting that the subtypes may have different aetiologic factors. Proven and suspected risk factors cannot explain more than a small fraction of the observed geographic and temporal variation in incidence. Several noteworthy subtype-specific characteristics or trends warrant further investigation: for acute lymphoid leukaemia (ALL), increasing incidence, with higher rates in Spanish and Latino populations; for chronic lymphoid leukaemia (CLL), declining incidence, with dramatically low rates among Asians; for acute myeloid leukaemia (AML), increasing incidence among African-American males; and for chronic myeloid leukaemia (CML), declining rates among Caucasian but not among African-Americans.

Key words: leukaemia, myeloid, lymphoid, incidence, mortality, survival, trends
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INTRODUCTION

THE AETIOLOGIES of the leukaemias remain largely obscure since the few known risk factors explain only a small fraction of the incidence. There have been few descriptions [1–3] of leukaemia patterns by subtype in different populations. Yet, examples of aetiological diversity by subtype include the specificity of association between benzene [4] or alkylating agents [5] and acute myeloid leukaemia (AML), and between rubber industry solvents and chronic lymphoid leukaemia (CLL) [6].

Leukaemias have been characterised according to newer classifications by a few specialised registries in relatively circumscribed regions [7–10]. Trends in international age-specific and age-adjusted incidence and mortality have been presented in several recent publications [11–12]. The expanding U.S. database and recent publications of international cancer mortality and incidence data make it particularly timely to assess in detail the descriptive patterns for the leukaemias by subtype. We do not attempt to discuss or relate the observed patterns to the known or suspected risk factors for leukaemia, which have been succinctly reviewed in the accompanying editorial by Alexander (pages).

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MATERIALS AND METHODS

The four major subtypes recognised by most registries are acute lymphoid leukaemia (ALL), CLL, AML and chronic myeloid leukaemia (CML). The remaining leukaemia cases are other rare subtypes or have inadequate type specification. The five categories (four corresponding to specific subtypes and the fifth category designated other/NOS (not otherwise specified)) and the clinicopathological codes from the International Classification of Diseases for Oncology (ICD-O) [13] are shown in Table 1. (Most population-based cancer registries continue to consider ALL and CLL as leukaemia subtypes, although a recent proposal for classification of the lymphoid neoplasms suggests combining ALL and CLL with non-Hodgkin's lymphomas (NHL) and myeloma [14].)

Data sources utilised were international [15] and U.S. (National Center for Health Statistics) mortality data and international incidence data [16]. Cancer incidence registries selected generally had a minimum 20 years of registry operation, at least 100 leukaemia cases during the 5-year reporting interval, the five-category classification, and geographic representativeness. These stringent criteria excluded all African, many Asian and Latin American, and some European and North American registries.

More detailed investigation of age-specific patterns, time trends, survival rates, and occurrence by racial/ethnic group, by cell type, utilises 1973–1990 incidence data from the U.S. Surveillance, Epidemiology, and End Results (SEER) Program, including five states and four cities, or approximately 10% of the

Table 1. *Leukaemia morphology codes*

Subtype	Codes
ALL	9821.
CLL	9823, 9825, 9940.
AML	9840, 9841, 9861, 9866, 9867, 9870, 9880, 9891, 9910, 9932.
CML	9863, 9865.
Other and NOS Leukaemias:	9800, 9801, 9802, 9803, 9804, 9810, 9820, 9822, 9824, 9860, 9862, 9864, 9890, 9892, 9894, 9930.
Total Leukaemia:	9800–9940, excluding the following: 9830 (plasma cell leukaemia); 9842 (chronic erythraemia); 9850 (lymphosarcoma cell leukaemia); 9868 (chronic myelomonocytic leukaemia); 9893 (chronic monocytic leukaemia); 9900 (mast cell leukaemia); 9920 (megakaryocytic myelosis) and 9932 (acute myelofibrosis).

U.S. population [17–18]. Incidence and mortality rates are expressed per 100 000 person-years at-risk, and were age-adjusted using the world standard population. U.S. SEER Program 5-year relative survival rates, expressed as percentages, were adjusted for general population mortality.

RESULTS

International age-standardised mortality

For total leukaemia, relatively high age-standardised mortality rates, ranging from 4.8 to 7.4 per 100 000 person-years for males and from 3.2 to 4.6 per 100 000 person-years for females, occurred in the populations of Western Europe, Oceania and North America (Figure 1). Lower rates, ranging from 3.7 to 4.5 per 100 000 for males and from 2.8 to 3.5 per 100 000 for females, were observed in Asia and Latin America. It is noteworthy that male and female rates in Israel and Costa Rica closely paralleled those of the industrialised countries of Europe, Oceania and North America.

U.S. mortality trends. For both U.S. Caucasians (Figure 2a) and non-Caucasians (Figure 2b) (the latter including African-Americans, Asian-Americans and Native Americans), mortality rates decreased dramatically in children and adolescents (aged <19 years) from 1950–1954 to 1985–1989, especially from the early 1960s. A smaller decline occurred among young adults (aged 20–44 years), while there was little change in mortality among middle-aged persons (aged 45–64 years). Rates increased among the elderly (aged 65 years and above), particularly in non-Caucasians.

Mortality data, available at the national level (Figure 1) and over long periods (Figures 2a and b), cannot be used to estimate incidence by subtype because of improvements in survival among young people and because the specific type of leukaemia is frequently not mentioned on the death certificate.

International age-standardised incidence

Total. Figure 3 presents age-adjusted total leukaemia incidence rates per 100 000 person-years by sex for selected registries, ordered by decreasing rates among males on each continent. Within virtually all populations, total leukaemia incidence rates

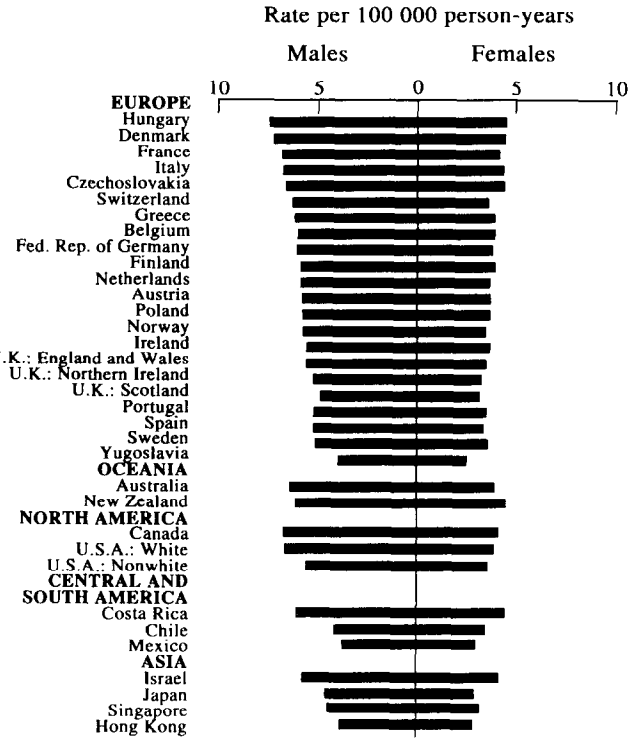

Figure 1. International variation in leukaemia mortality (age-adjusted, world standard) by sex, 1983–1987. Data from [15].

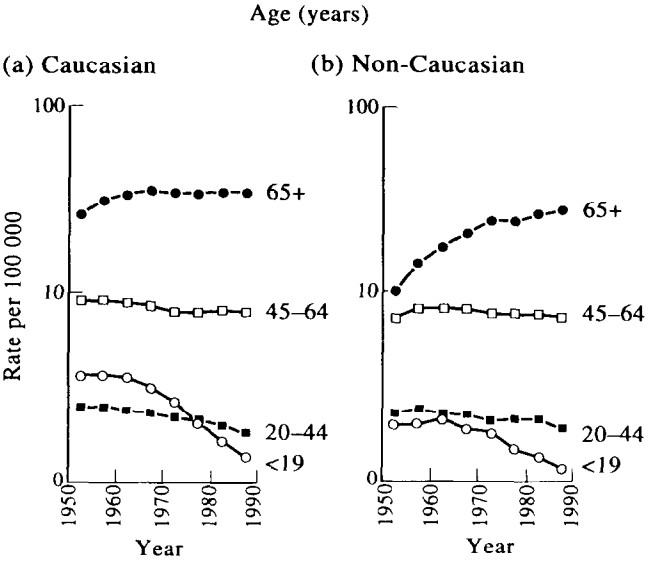

Figure 2. U.S. trends in leukaemia mortality (age-adjusted, world standard) by age group among Caucasians and non-Caucasians, 1950–1954 to 1985–1989.

were higher for males than for females. There was a distinct racial and geographic gradient, with the highest rates (6.1–12.4 per 100 000 person-years for males; 4.1–7.9 per 100 000 person-years for females) among Caucasians in North America, Oceania and Northern and Western Europe, and progressively lower rates (3.9–8.1 per 100 000 person-years for males; 2.8–6.3 per 100 000 person-years for females) in Southern and Eastern Europe, African-Americans, Central and South America, and Asia.

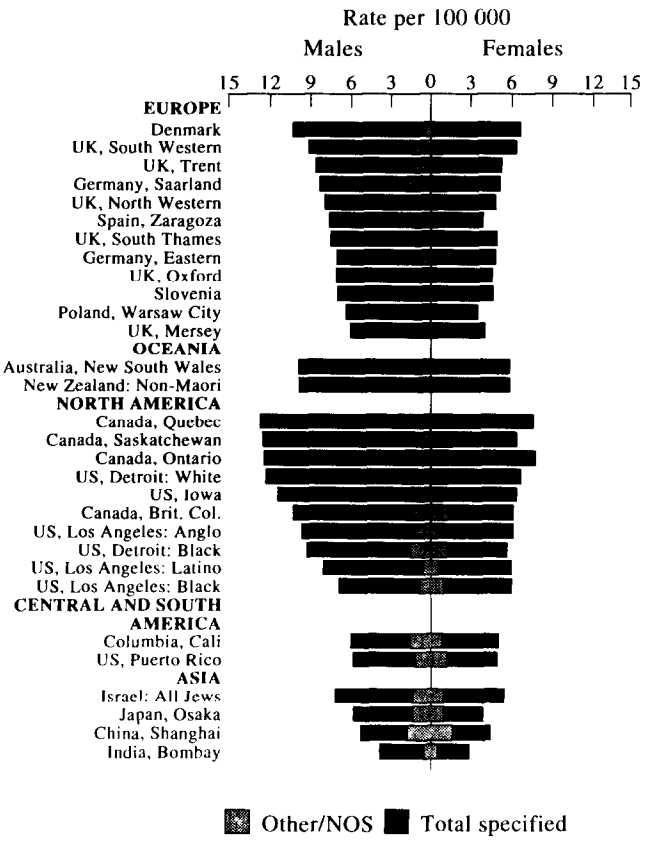

Figure 3. International variation in total leukaemia and other and non-specified leukaemia incidence (age-adjusted, world standard) by sex, 1983–1987. Data from [16].

NOS. Figure 3 also shows the rates of NOS leukaemias within the bars for total leukaemias. High NOS rates (greater than 15% of total) are reported from China (Shanghai), Colombia (Cali), Japan (Osaka), Canada (Quebec), Poland (Warsaw), and Germany (Saarland), whereas relatively low NOS rates (less than 5% of total) were seen in New Zealand (non-Maori), the United Kingdom (North-Western, South-Western, and Trent), Slovenia, Canada (Saskatchewan), and Denmark.

Subtypes. Internationally, lymphoid leukaemias accounted for 44% of all cases, myeloid and monocytic leukaemias accounted for 44%, and NOS for 12%. Figures 4a–d present the subtype-specific incidence rates for the same registries, ordered as in Figure 3.

Internationally, variation in incidence rates was greatest for CLL (10-fold differences between the highest and lowest rates) and least for CML (only a 4-fold gradient between the highest and lowest). Incidence rates for most subtypes were higher among males than females, except for AML in some registries.

Similar to total leukaemia, higher incidence rates for ALL, CLL, and AML occur among populations in Northern and Western Europe and North America, and lower rates in Asian and African-American populations. In parallel with the findings for total leukaemia, are the high rates of ALL, AML, and CML in Oceania. For ALL, but no other subtype, high rates are apparent in Spain, South America and U.S. Latinos; rates among Israeli Jews are low. Characteristic of CLL are the dramatically low rates among Asians and the zone of high incidence in the north central U.S. (e.g. Iowa and Detroit) and the contiguous central southern Canadian provinces (e.g. Saskatchewan, Quebec and Ontario). CML differs from the pattern for total leukaemia in that CML rates are elevated among African-American females in Detroit and Los Angeles, Los Angeles Latinos and East German males.

U.S. racial and ethnic variation. Similar to the international findings, the highest U.S. total leukaemia rates for both males and females occurred among Caucasians, followed by African-Americans, then Hawaiians, Filipinos and Hispanics; the lowest rates were in Japanese- and Chinese-Americans (data not shown) [18]. For lymphoid leukaemias, the pattern was similar, although rates were lowest and similar for Filipinos, Hawaiians and Japanese. In contrast, Hawaiians of both sexes had the highest myeloid leukaemia rates, followed progressively by Caucasians, African-Americans and Japanese; the lowest rates were in Filipinos, Hispanics and Chinese. Subtype was not specified for 10–29% of leukaemia cases.

U.S. age-specific incidence rates

Total. Although leukaemia is the most common malignancy among children and adolescents, the age-specific incidence rates are substantially higher in the elderly. Total age-specific leukaemia incidence rates show a bimodal age distribution, with a small peak in early childhood among Caucasians and African-Americans of both sexes and a high peak in the elderly (Figure 5). Among the youngest and oldest age groups, rates were higher in Caucasians than in African-Americans, but from ages 20–60 years they differed little by race. Males had higher rates than females at all ages except childhood.

NOS. The age-specific incidence curves for NOS leukaemias resembled those for total leukaemias (data not shown).

Subtypes. The early childhood peak is due almost entirely to ALL (Figure 6a). After ages 2–4 years, ALL rates decline rapidly with age, then begin to rise at age 40 years, increasing thereafter to almost the same level in the elderly as in children. Under the age of 20 years, ALL is the most common type (76%) of leukaemia [17], with AML comprising most of the remainder (Figure 6b). CML is quite rare and CLL non-existent (Figures 6c and d). After early adulthood, AML and CML increase exponentially and are predominant in middle age. CLL begins to increase rapidly after the age of 40 years, rises less rapidly after the age of 70 years, and is the predominant leukaemia type (39%) among persons aged 65 years and above.

The excess among Caucasians compared to African-Americans was more pronounced in older ages for all types except ALL, whereas CML rates appeared higher among African-Americans than among Caucasians for persons under the age of 70 years. Rates were higher among males than females at all ages for CLL, at most ages for CML, and only at older ages for AML. AML rates differed little by race or gender among persons aged 25–54 years.

U.S. incidence trends

Total. Age-adjusted total leukaemia incidence rates declined somewhat among U.S. Caucasians and among African-American females from 1973–1978 to 1985–1990 (Figure 7a); the decline was more pronounced among those over the age of 65 years. Rates did not change greatly among African-American males.

NOS. Age-adjusted incidence rates per 100 000 person-years for NOS leukaemias (Figure 7b) also showed slight downward trends in all four race/sex groups.

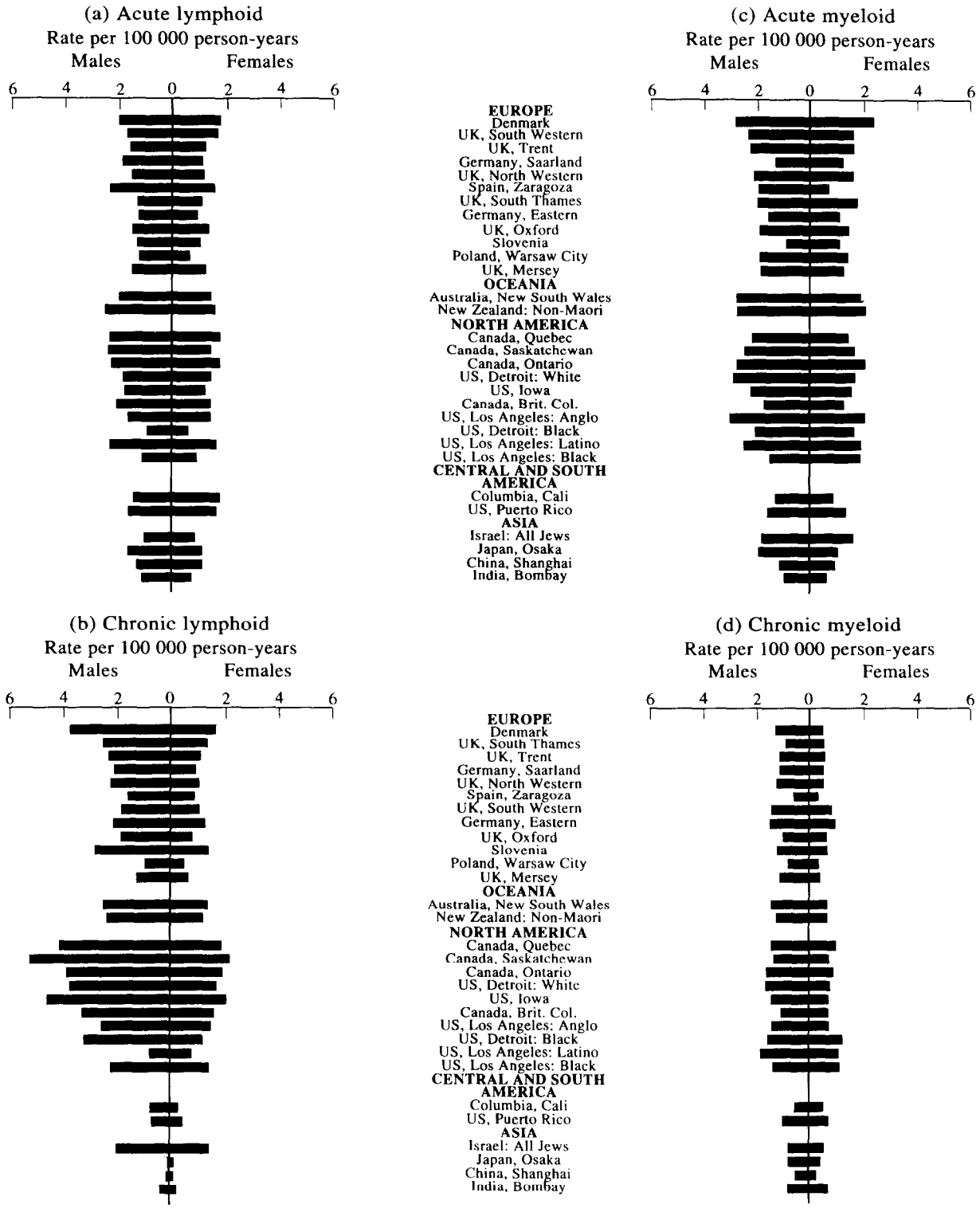

Figure 4. International variation in leukaemia incidence (age-adjusted, world standard) by cell type and sex, 1983–1987. Data from [16].

Subtypes. Between 1973–1978 and 1985–1990, rates per 100 000 person-years among Caucasians declined most rapidly for CML (Figure 7f), followed by CLL (Figure 7d), whereas the AML incidence (Figure 7e) decreased less rapidly among Caucasians and increased among African-American males. In contrast, ALL rates (Figure 7c) increased in all four race/sex groups. Rates for each of the subtypes have been higher among Caucasians than African-Americans, the major exception being the persistence since the mid-1970s of higher CML rates among African-Americans than among Caucasians.

U.S. survival trends

Total. Five-year relative survival rates for all leukaemia patients improved only slightly during 1973–1990 in the U.S.

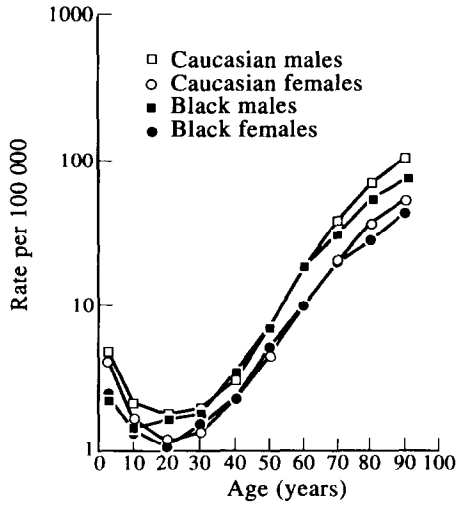

Figure 5. Age-specific incidence rates for total leukaemia by race and sex for nine SEER areas, 1973–1987.

SEER Program (Figure 8a); survival was consistently greater among Caucasians than African-Americans, with little gender difference. Survival among children, however, improved substantially [17].

NOS. In contrast, survival rates for patients with NOS leukaemias worsened over time (Figure 8b).

Subtypes. For each subtype, survival was somewhat better among Caucasian females than Caucasian males, whereas the gender difference was smaller among African-Americans (Table 2). Patients aged 65 years and older at diagnosis, regardless of cell type, have poorer survival than younger patients. Survival for all race/gender groups with ALL (Figure 8c) increased continuously from 1973–1978 to 1985–1990, with better survival among Caucasians than African-Americans, particularly among young patients. Although survival among children with AML also increased dramatically [17], rates for adults with AML and persons at all ages with the other two cell types did not change greatly during 1973–1990. Survival rates are most favourable for patients with CLL, followed by ALL, then CML; patients with AML have the worst prognosis.

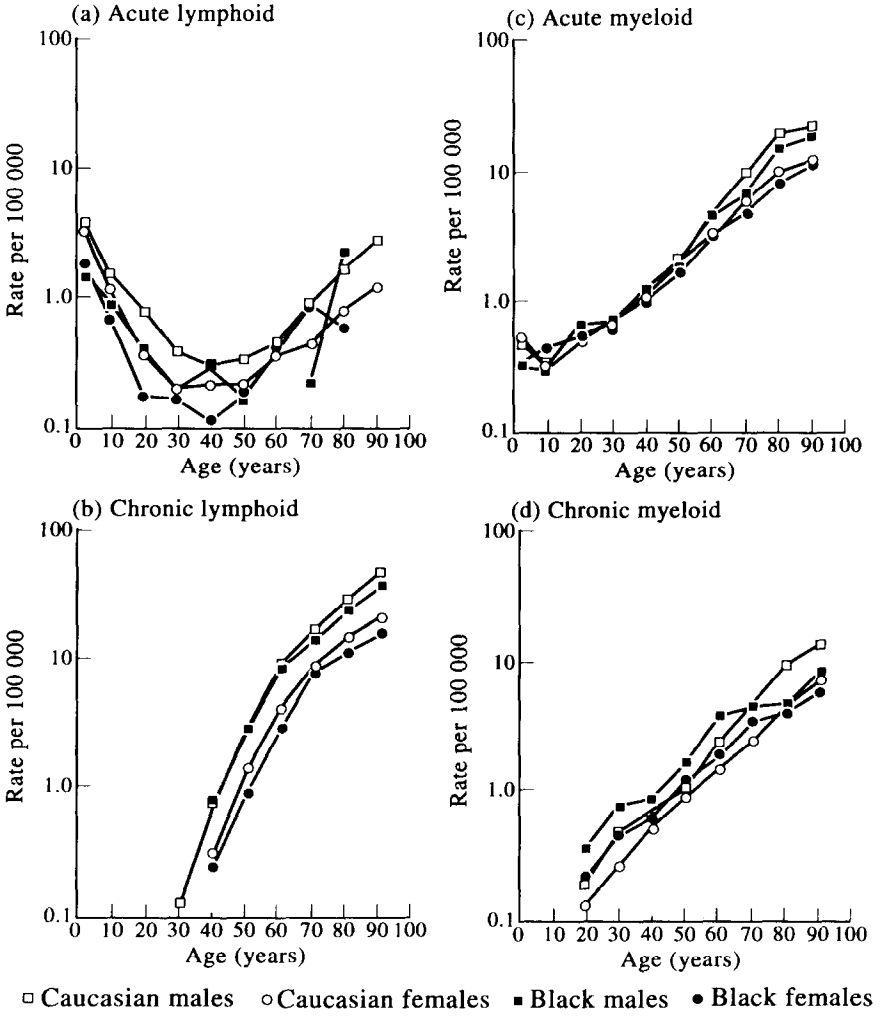

Figure 6. Age-specific incidence rates for leukaemia by cell type, race, and sex for nine SEER areas, 1973–1987.

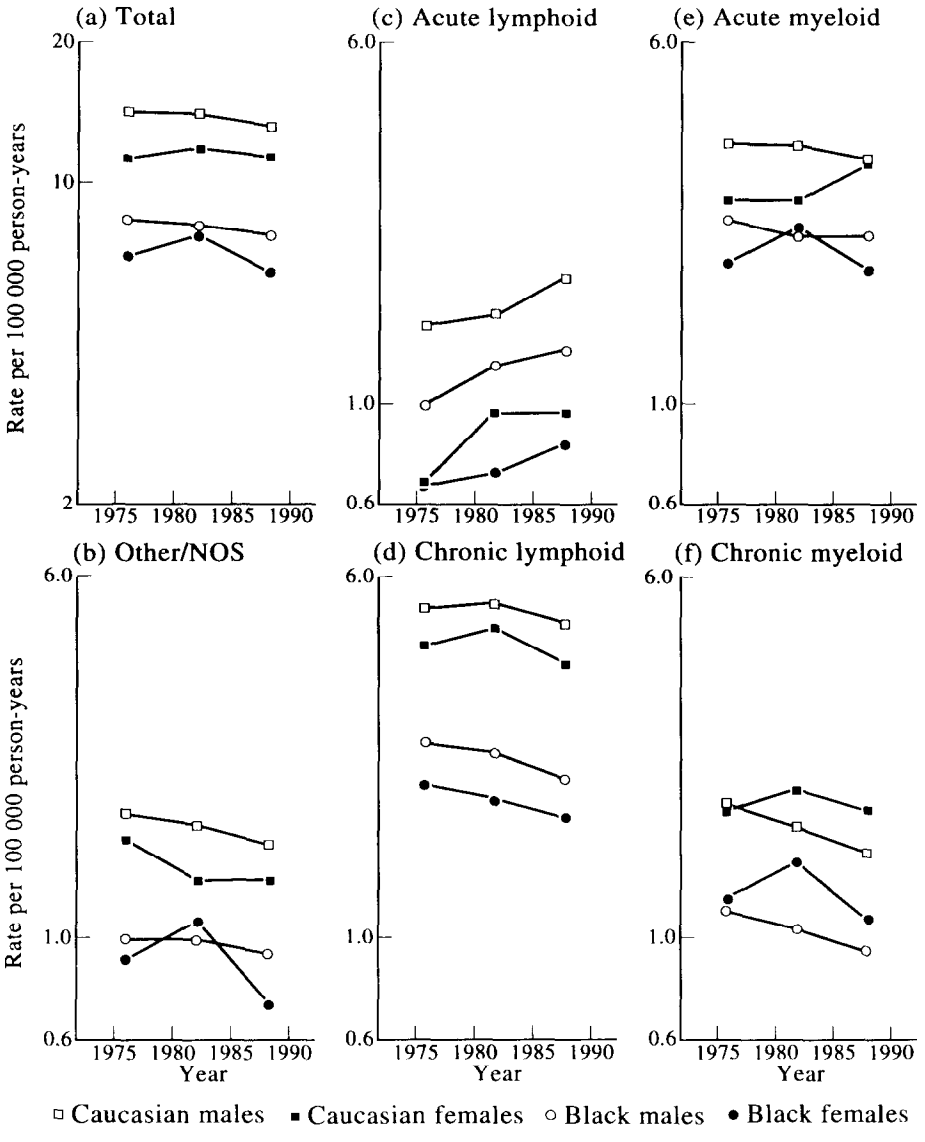

Figure 7. Trends in age-adjusted (world standard) incidence rates for leukaemia by cell type, race, and sex for nine SEER areas, 1973–1990.

DISCUSSION

Total leukaemia

Approximately 1.3% of males and 1.0% of females in the U.S., based on SEER estimates, will eventually develop some form of leukaemia [17]. Internationally, the highest total leukaemia incidence rates were found in North America and in Northern and Western Europe; incidence was lowest in Central and South America and Asia. In the United States, rates were highest among Caucasians and progressively lower among African-Americans, Hawaiian-Americans, and Hispanic-Americans; Asian-Americans had the lowest rates. Males had higher incidence and mortality than females, and a bimodal age distribution is characteristic. Similar to the patterns for the United States, mortality rates in many European countries slowly declined among adults under the age of 75 years [11], rapidly declined among children, but increased in the elderly [12].

Other and unspecified leukaemia (NOS)

The relatively high proportion of NOS leukaemias in several registries suggests that additional efforts are needed to characterise leukaemia cases by subtype. The decline in NOS leukaemia incidence in the SEER Program over time may reflect diagnostic improvements.

Acute lymphoid leukaemia (ALL)

Although the age-specific patterns for ALL and for total leukaemia were both bimodal, the highest peak for ALL occurred in early childhood and a lower peak among the elderly, whereas total leukaemia was characterised by a small peak in early childhood and a very high peak among the oldest age group. The notable ALL peak at ages 2–4 years was found in most populations [3]. Some authors have suggested that the early childhood peak, more characteristic of the common subtype of ALL, has emerged over time as socio-economic status has improved [19, 20]. The early childhood peak was seen among African-Americans (Figure 6a), but the T-lymphocyte and undifferentiated ALL subtypes accounted for a larger proportion of ALL in this population subgroup than among Caucasians [21–24].

Geographically, age-adjusted ALL incidence differed from total leukaemia in that the highest ALL rates occurred in Spain and among Latin Americans. ALL was the only leukaemia

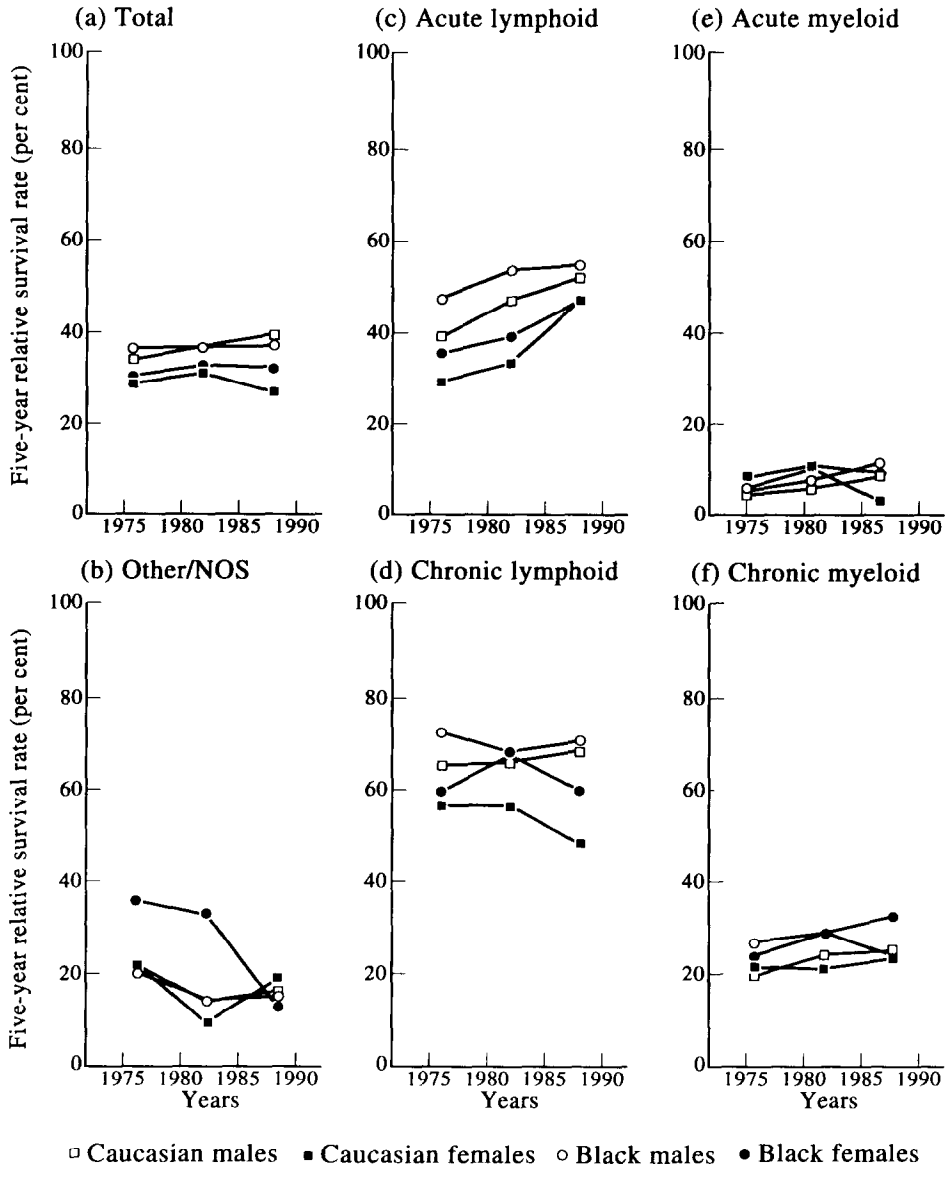

Figure 8. Trends in 5-year relative survival rates for leukaemia by cell type, race, and sex for nine SEER areas, 1973–1990.

subtype for which incidence increased (up to 0.26–0.40 per 100 000) in the SEER populations. Reasons for the high rates in Spain and in U.S. Latinos and increasing U.S. incidence are unknown, although some, but not all, of the increase may have been due to the decline (down 0.06–0.29) in NOS leukaemias. In the U.S., ALL was also the leukaemia subtype with the greatest improvement in survival, attributable to notable treatment advances [25].

Chronic lymphoid leukaemia (CLL)

In contrast to the bimodal age patterns for total leukaemia and ALL, CLL virtually never occurs prior to the age of 30 years [2]. CLL rates begin to exponentially increase around the age of 30 years and continue to rise at a slightly slower pace after the age of 70 years. The adult age-specific patterns for the four race/sex subgroups were similar for CLL as for total leukaemia.

Similar international patterns in age-adjusted rates were observed for CLL as for total leukaemia, although the rate ratios between populations with the highest and lowest rates (particularly the dramatically low rates among Asians) were substantially greater for CLL than for total leukaemia. In contrast with the high ALL rates in the Latin American and Spanish populations, CLL rates were low to mid-level in these populations.

Whereas ALL increased between 1973–1978 and 1985–1990, CLL displayed a continuing, although small, downward trend. The declining CLL incidence may reflect changing classification practices, such as previous misclassification (as CLL) of certain diffuse, well-differentiated NHL. The very low rates of chronic B-cell malignancies, including NHL and multiple myeloma as well as CLL, observed among Asians [2, 26], may be due to genetic and/or lifestyle factors that could be further evaluated in migrant studies. CLL survival remained unchanged.

Acute myeloid leukaemia (AML)

AML comprises 15–25% of total childhood leukaemias, with the highest rates among infants. After declining in early childhood, incidence then increases, beginning at age 10 years and is higher in males than in females older than the age of 60 years.

Although incidence has risen since 1973 among African-

Table 2. Five-year relative survival rates for leukaemia in the U.S. SEER Program by time period, race, sex, age and cell type

Period, age and race/sex group	Leukaemia cell type (%)				
	CLL	ALL	CML	AML	Total
1974–1976, All ages					
all races,					
both sexes	67.8	37.9	22.1	5.7	34.1
1983–1989, All ages					
all races,					
both sexes	68.1	51.5*	22.8	10.0*	37.6*
Caucasian males	66.8	51.0	21.6	8.8	38.9
Caucasian females	71.3	54.9	25.2	11.6	38.4
Black males	60.8	38.8	21.8	4.5	29.6
Black females	60.1	40.3	22.4	12.1	31.4
All races, both sexes					
Aged 0–14 years	N/C	72.4	N/C	31.1	64.6
Aged 0–64 years	74.4	55.8	31.7	16.7	42.9
Aged 65+ years	64.4	4.0	11.5	1.6	31.2

* $P < 0.05$ for 1983–1989 versus 1974–1976. N/C, not calculated because incidence is too low. Source: [17].

American males, rates remained stable or declined slightly among other race/sex groups. Five-year survival rates improved among children and adolescents, but the poor prognosis for AML remained unchanged, with population-based 5-year survival rates below 10% [17]. Recent improvements in selected clinical series [27] suggest that population-based relative survival may improve as increasingly efficacious treatment regimens become more widespread.

The similar rates among the four race/sex groups suggest that environmental or lifestyle factors may be more important than occupational exposures for onset of AML at ages 25–54, whereas the male excess at older ages might reflect prior occupational exposures.

Chronic myeloid leukaemia (CML)

CML is almost unknown before the age of 5 years, except for the rare juvenile CML in Caucasian males [28]. Incidence rises linearly with age. CML was the only subtype demonstrating higher incidence at ages 20–60 years among African-Americans than among other racial/ethnic groups in the United States [29]; this racial disparity increased over the past two decades as incidence declined among U.S. Caucasians, but not among African-Americans. There was less international variation for CML than for any other subtype, and 5-year survival rates for CML were essentially unchanged.

The declining rates of CML among Caucasians but not among African-Americans cannot be related to the only known risk factor, namely high doses of ionising radiation. While the relatively small differences observed internationally in age-adjusted rates suggest a smaller role for environmental factors than in other leukaemia subtypes, the racial differences in incidence which appeared in the U.S. during the past two decades point to the need for detailed case-control studies comparing possible risk factors between Caucasian and African-Americans.

DISCUSSION

Characterisation of the descriptive epidemiology of the leukaemias has been limited by the paucity of registries employing current classification schemes, variation in the proportion of NOS leukaemias among registries, lack of census data for certain populations, absence of long-term trend data for most populations and the rarity of the various subtypes, resulting in unstable rate estimates. In our detailed assessment of the leukaemias by subtype, we have identified some important differences in geographic, gender, racial/ethnic, age and trend patterns, suggesting that the subtypes may have different aetiologies. Proven and suspected risk factors cannot explain much of the observed geographic and temporal variation in leukaemia incidence.

We see no evidence of a leukaemia "epidemic", in that total leukaemia incidence rates, while increasing in some populations, have declined in others [11]. Total leukaemia incidence rates in the U.S. SEER populations declined from 1973–1978 to 1985–1990, while the only subtypes that increased were ALL in all groups and AML among African-American males.

Noteworthy findings warranting further investigation include: for ALL, the increasing incidence over time, the higher rates in Spanish and Latino populations and the bimodal age distribution; for CLL, the declining incidence over time, the dramatically low rates among Asians, the greater male predominance at all ages and the absence prior to the age of 30 years; for AML, the recent increase among African-American males and the similarity in incidence for all race/sex groups between ages 25 and 55 years; and for CML, the declining rates among Caucasians versus the lack of decline among African-Americans since the mid-1970s, the lack of international variation in age-adjusted rates and the virtual absence in childhood, except among Caucasian males.

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Striking Changes in Smoking Behaviour and Lung Cancer Incidence by Histological Type in South-east Netherlands, 1960–1991

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Changes in lung cancer incidence in south-east Netherlands between 1960 and 1991 were analysed, using data from the Eindhoven Cancer Registry, and related to previous changes in smoking habits. Male lung cancer incidence rates increased markedly from birth cohorts 1890–1899 to 1910–1919, followed by a decline. The peak incidences for both squamous cell carcinoma and small cell carcinoma were reached in 1978, while for adenocarcinoma it was 1985. A rising trend in female lung cancer incidence up to 1988 was found for each successive birth cohort and for every histological type. These changes in lung cancer incidence rates are most likely related to the pattern of past smoking habits: the percentage of male adult smokers in the southern part of the Netherlands decreased from 95% in 1960 to 40% in 1981 and the percentage of female adult smokers increased from 27% in 1960 to 40% in 1967, slightly decreasing only after 1979. In view of the trends in smoking behaviour, the incidence rates for male lung cancer will decline further, whereas female lung cancer incidence may decrease after the year 2000.

Key words: lung cancer, incidence, cancer registry, histology, trends
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INTRODUCTION

IN SOUTH-EAST Netherlands, male lung cancer incidence and mortality were among the highest in Europe from 1969 up to 1990, whereas female lung cancer incidence and mortality were among the lowest until 1980 [1–4]. Previous reports have suggested that the mortality rate for lung cancer among Dutch men has changed markedly: a decline is now apparent after a marked increase since World War II. In contrast, female lung cancer mortality has increased steadily [5, 6]. In this survey, temporal trends in the incidence of lung cancer in the south-east