Pergamon

European Journal of Cancer Vol. 31A, No. 5, pp. 771–782, 1995

0959-8049/95 $9.50+0.00

0959-8049(94)00534-6

Patterns of Childhood Cancer Mortality: America, Asia and Oceania

F. Levi, C. La Vecchia, F. Lucchini, E. Negri and P. Boyle

Age-standardised mortality rates for childhood cancers for the calendar period 1950–1989 were reviewed for 22 countries (Canada, U.S.A., 10 Latin American countries or territories, Egypt, seven countries or territories from Asia, Australia and New Zealand) using data from the World Health Organization database. The highest mortality rates (between 6 and 7.5/100 000 boys, between 5 and 6/10 000 girls) for all childhood neoplasms were registered in Latin American countries (Uruguay, Cuba, Argentina, Costa Rica), Kuwait, New Zealand and Singapore. Rates were low in most developed countries, such as Canada, U.S.A., Australia, Japan and Israel (3.5 to 4.5/100 000). The pattern was similar for leukaemias, which account for approximately 50% of all childhood cancer mortality. From the 1960s onwards, a 50% decline in childhood cancer mortality was observed in the U.S.A. and Canada, and substantial declines were also observed in other developed countries, such as Australia, Israel and Japan. The pattern was much less favourable for other areas of the world, including Latin America and a few countries from Asia for which there were data. These declines in childhood cancer mortality are essentially attributable to improved management of the disease. The delay observed in the decline in mortality for most developing countries emphasises the scope and the importance of extending adequate treatments for childhood cancers to these areas of the world.
Eur J Cancer, Vol. 31A, No. 5, pp. 771–782, 1995

INTRODUCTION

PATTERNS AND trends in childhood cancer have been reviewed for 24 European countries and, even within Europe, appreciable differences in trends emerged [1, 2]. In fact, several countries of central and eastern Europe tended to have less favourable recent trends in childhood cancer mortality, thus suggesting that the impact of newer therapeutic advancements for most childhood neoplasms has probably been limited in these areas [1, 3]. Only scattered data are available on the issue from other areas of the world, including the U.S.A. [4].

It is, therefore, useful to systematically analyse trends in other areas of the world for which data are available, bearing in mind the international variation in registered childhood cancer incidence [5, 6].

MATERIALS AND METHODS

Cancer death certification data and estimates of the resident population at age 0–14 years (further subdivided in three quinquennia of age, 0–4, 5–9, 10–14 years) for the period 1950–1989 were derived from the World Health Organization database.

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Revised 16 Dec. 1994; accepted 20 Dec. 1994.

Table 1. Average annual population (×1000; age 0–14 years) in 22 selected American, Asian and Oceanian countries (1985–1989)

Country	Males	Females
Canada	2780	2643
U.S.A	26827	25571
Argentina	4899	4752
Chile	1934	1859
Colombia	5415	5273
Costa Rica	522	501
Cuba	1284	1226
Mexico	17439	16823
Panama	436	417
Puerto Rico	537	517
Uruguay	417	404
Venezuela	3677	3539
Egypt	10211	9648
Hong Kong	659	609
Israel	721	684
Japan	12607	11993
Kuwait	349	339
Philippines	11290	10754
Singapore	318	294
Sri Lanka	2899	2785
Australia	1888	1795
New Zealand	402	384

This included meaningful information for all leukaemias and all childhood neoplasms in Canada, the U.S.A. (all races combined), 10 Latin American countries or territories, Egypt, seven countries or territories from Asia, Australia and New

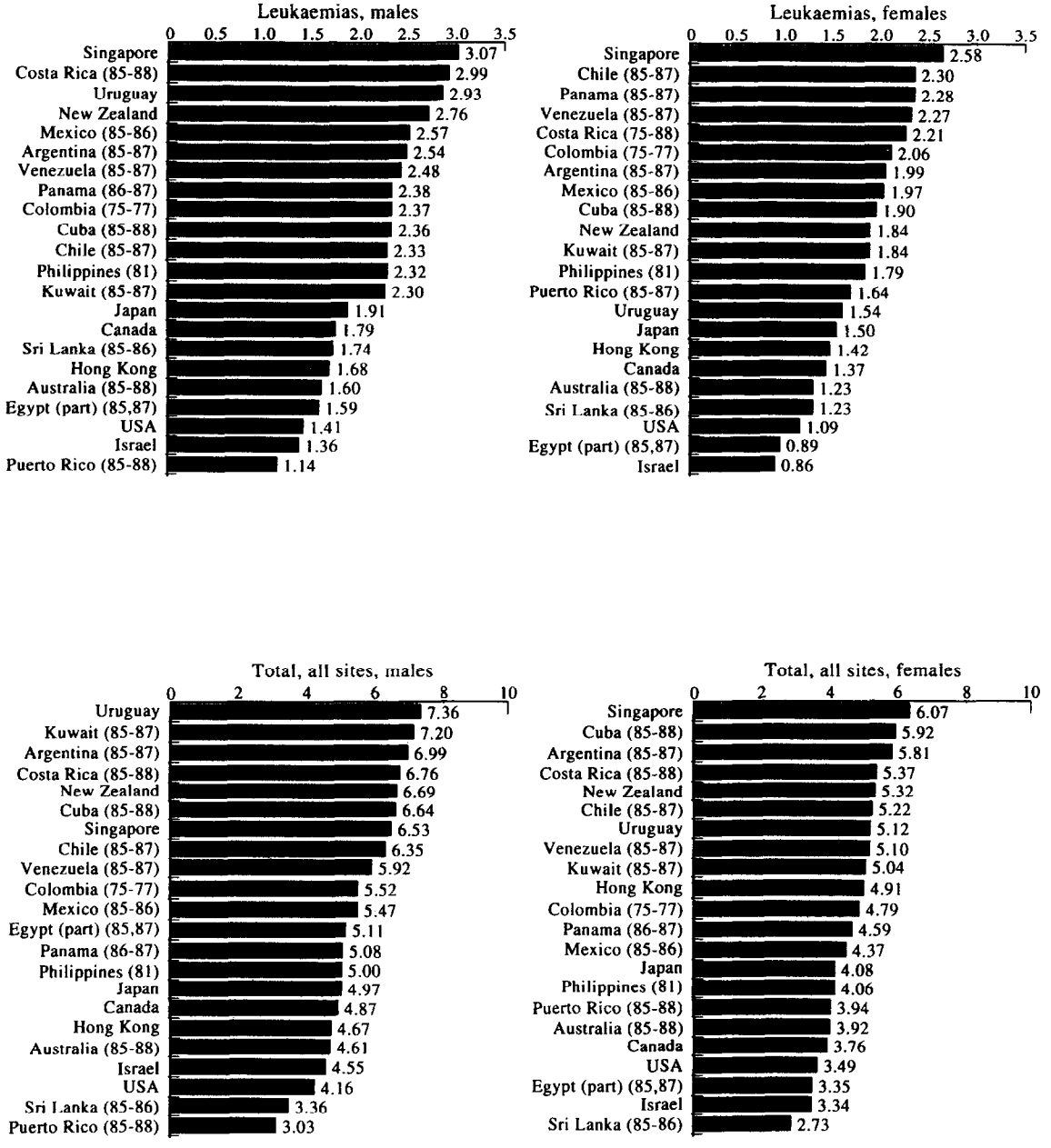

Figure 1. Age-standardised (0–14 years on the world standard population) death certification rates per 100 000 from leukaemias and all childhood cancers in selected American, Asian and Oceanian Countries. Period 1985–1989 unless specified.

Zealand. For other childhood neoplasms considered (malignant bone neoplasms, kidney cancer—mostly Wilms' tumour, eye neoplasms—mostly retinoblastoma, Hodgkin's disease and non-Hodgkin's lymphomas) meaningful mortality data were available for six countries only, i.e. Canada, U.S.A., Hong Kong, Japan, Australia and New Zealand. Table 1 gives the average annual population at ages 0–14 years for the 22 countries considered.

It was not possible to obtain reliable death certification data for neoplasms of the nervous system because of difficulties in histopathological classification and of changes in classification of neuroblastoma, which is coded partly for the organ affected (chiefly, the adrenal gland, i.e. with cancers of the endocrine system), partly for the connective and soft tissue sarcomas, and partly for the nervous system. During the calendar period considered, four different revisions of the International Classification of Diseases (ICD) were in operation. Nonetheless, there were no major changes in the classification or coding of these cancers or groups of cancers between the sixth and the ninth revision of the ICD [7–10].

From the matrices of certified deaths and resident population, age-standardised (0–14 years) mortality rates were derived on the basis of the world standard population [11]. In a few countries, data were missing for part of one or more calendar periods. When a single year was missing within a quinquennium, numerators and denominators were interpolated linearly from the previous and subsequent calendar year. No extrapolation was made for missing data at the beginning or the end of the calendar period considered, or when data on one or more quinquennia were not available.

RESULTS

The main results are summarised in Figures 1–3. Figure 1 is a histogram of the most recent available mortality rates for

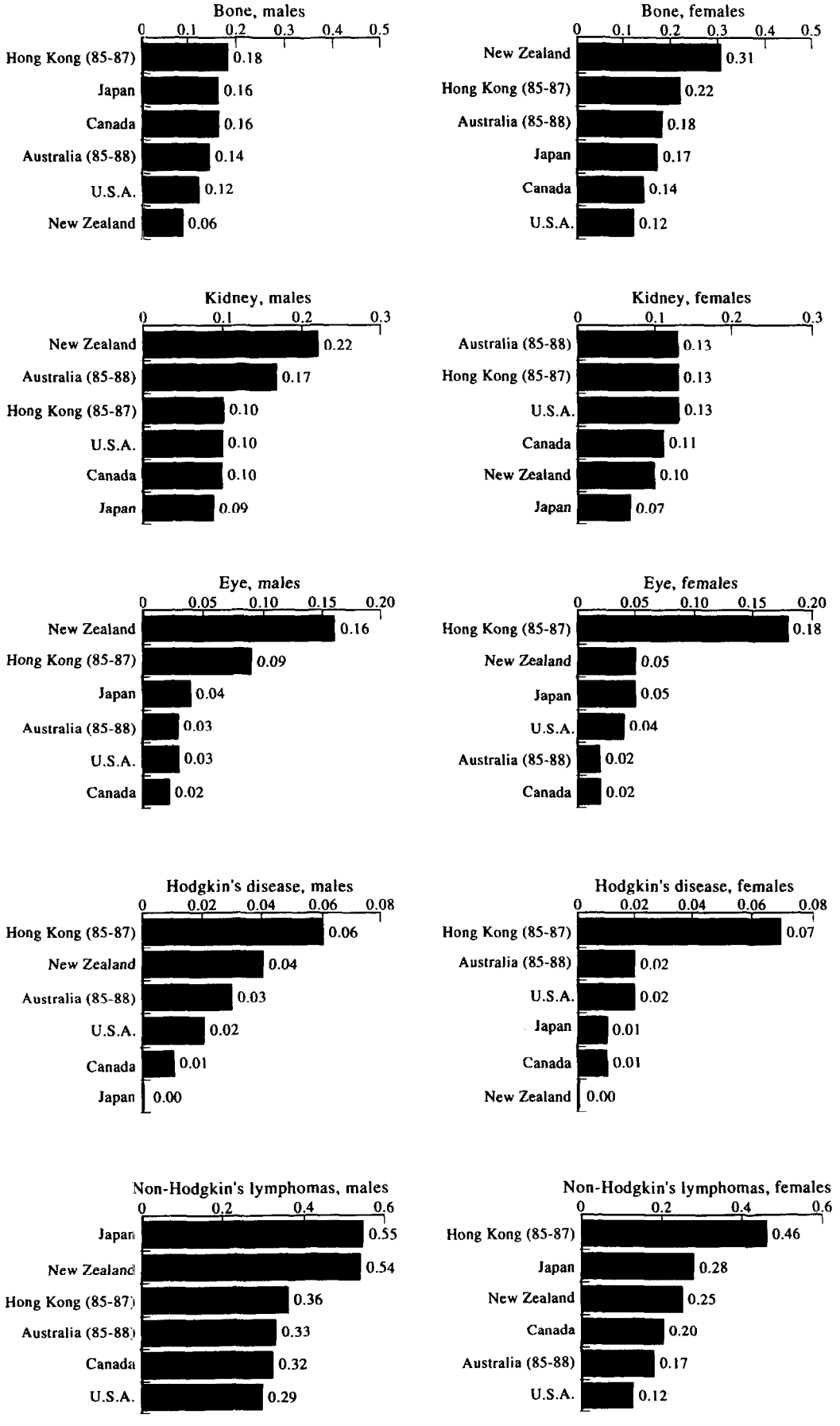

Figure 2. Age-standardised (0–14 years on the world standard population) death certification rates per 100 000 from tumours of bone, kidney, eye, Hodgkin's disease and non-Hodgkin's lymphomas in selected American, Asian and Oceanian countries. Period 1985–1989 unless otherwise specified.

All Neoplasms, Malignant and Benign

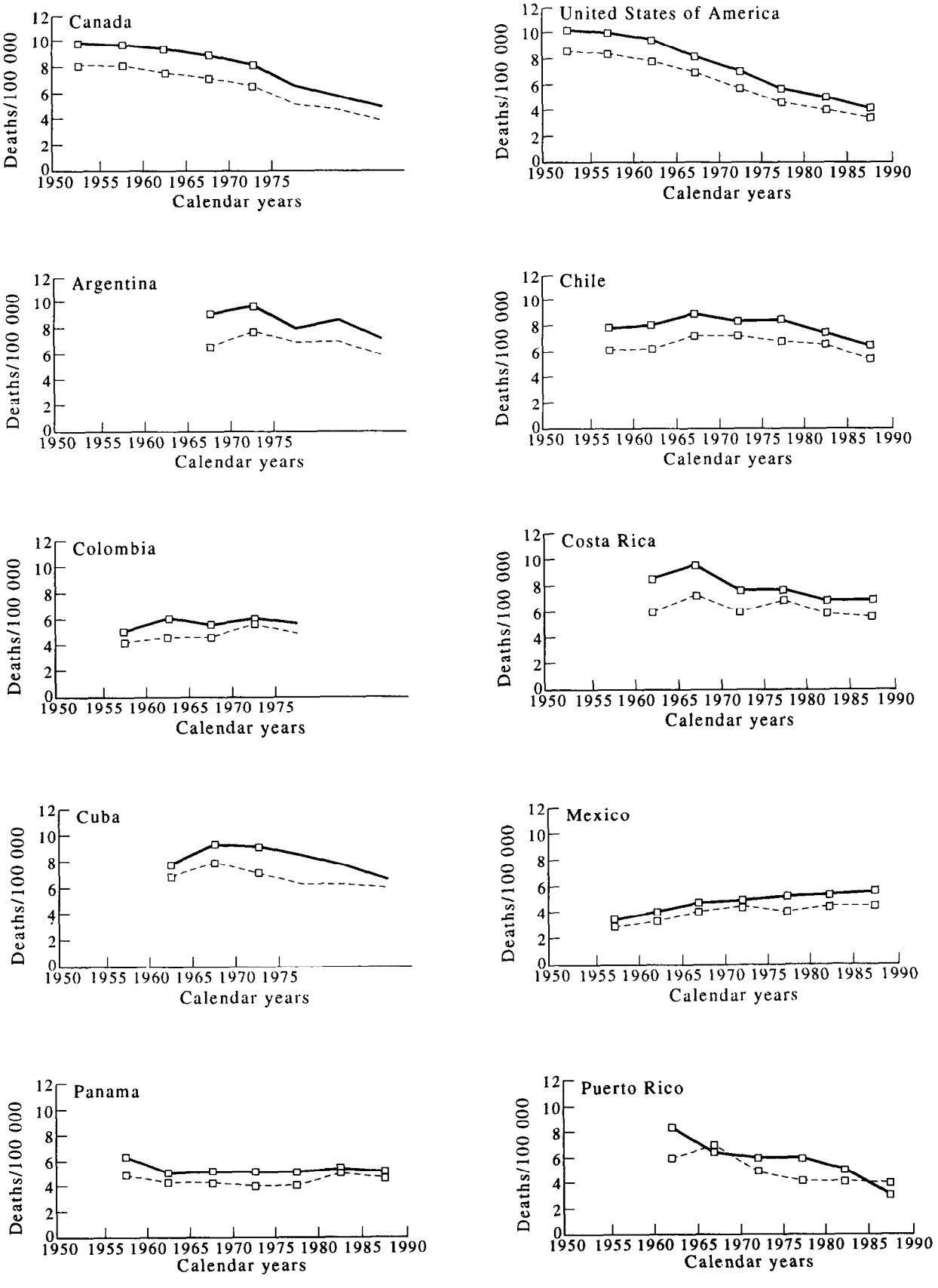

Figure 3

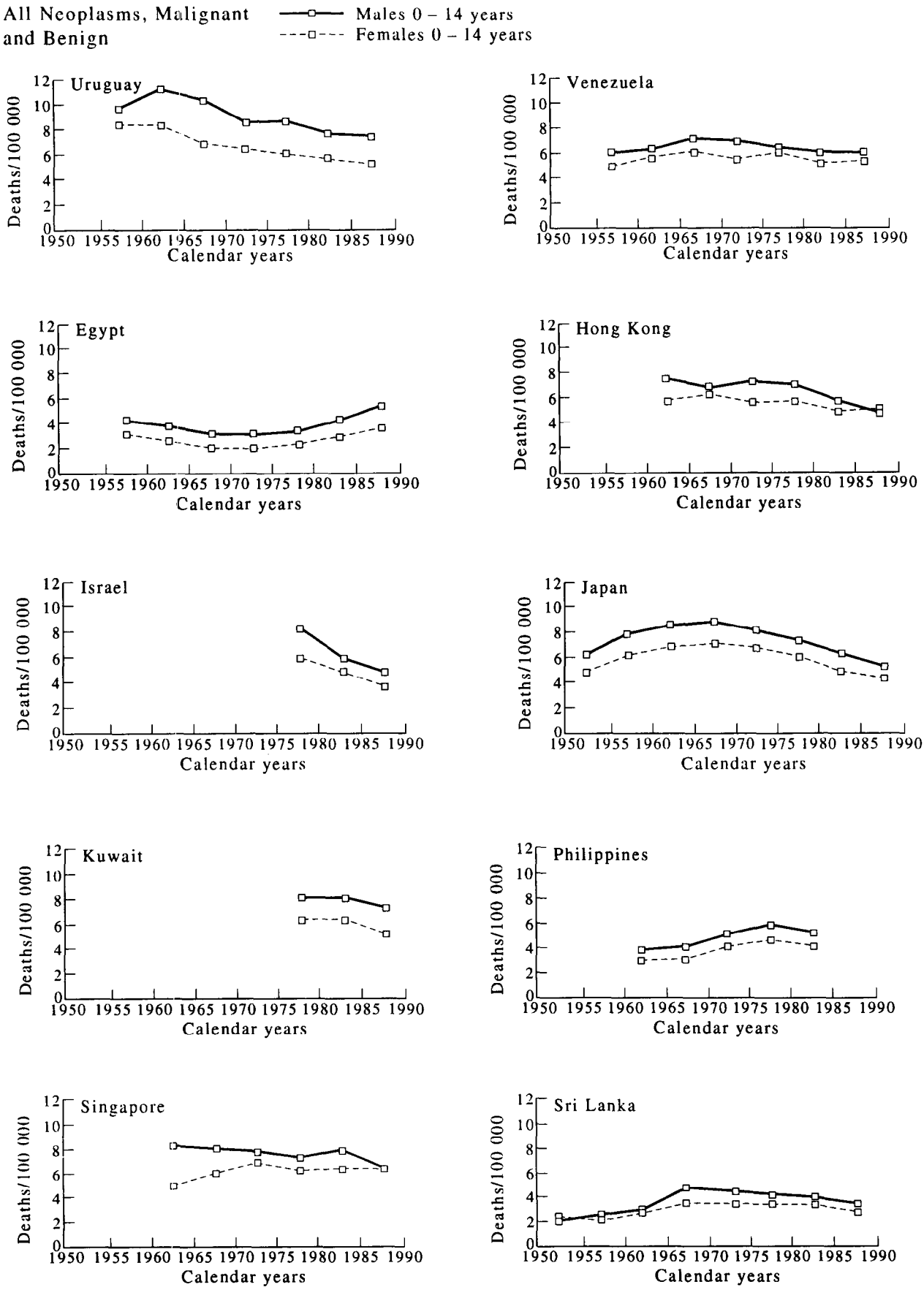
All Neoplasms, Malignant and Benign
Males 0 – 14 years
Females 0 – 14 years
Uruguay
Venezuela
Egypt
Hong Kong
Israel
Japan
Kuwait
Philippines
Singapore
Sri Lanka
Deaths/100 000
Calendar years
1950 1955 1960 1965 1970 1975 1980 1985 1990

Figure 3

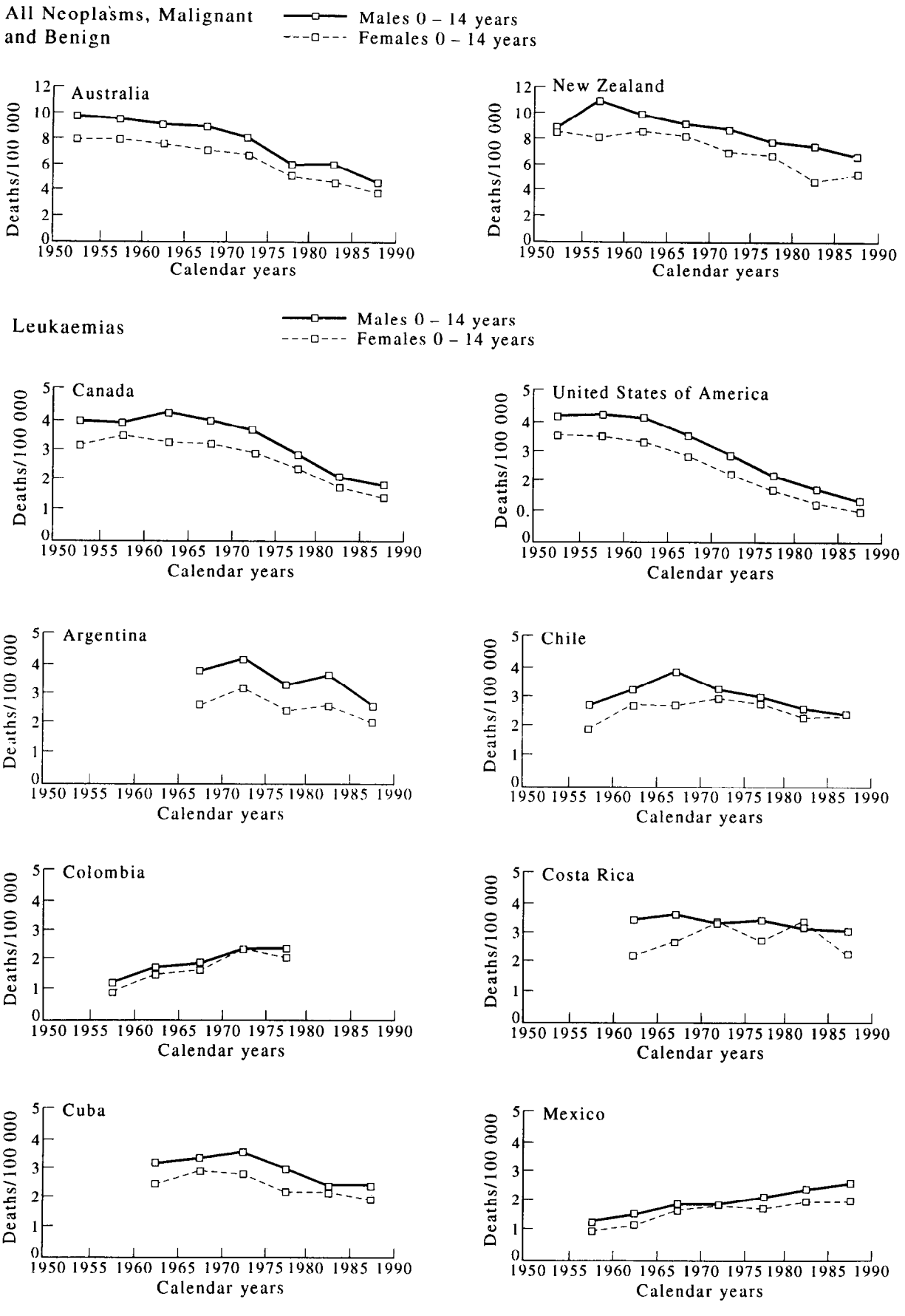
All Neoplasms, Malignant and Benign
Males 0 – 14 years
Females 0 – 14 years
Australia
New Zealand
Leukaemias
Males 0 – 14 years
Females 0 – 14 years
Canada
United States of America
Argentina
Chile
Colombia
Costa Rica
Cuba
Mexico
Deaths/100 000
Calendar years
1950 1955 1960 1965 1970 1975 1980 1985 1990

Figure 3

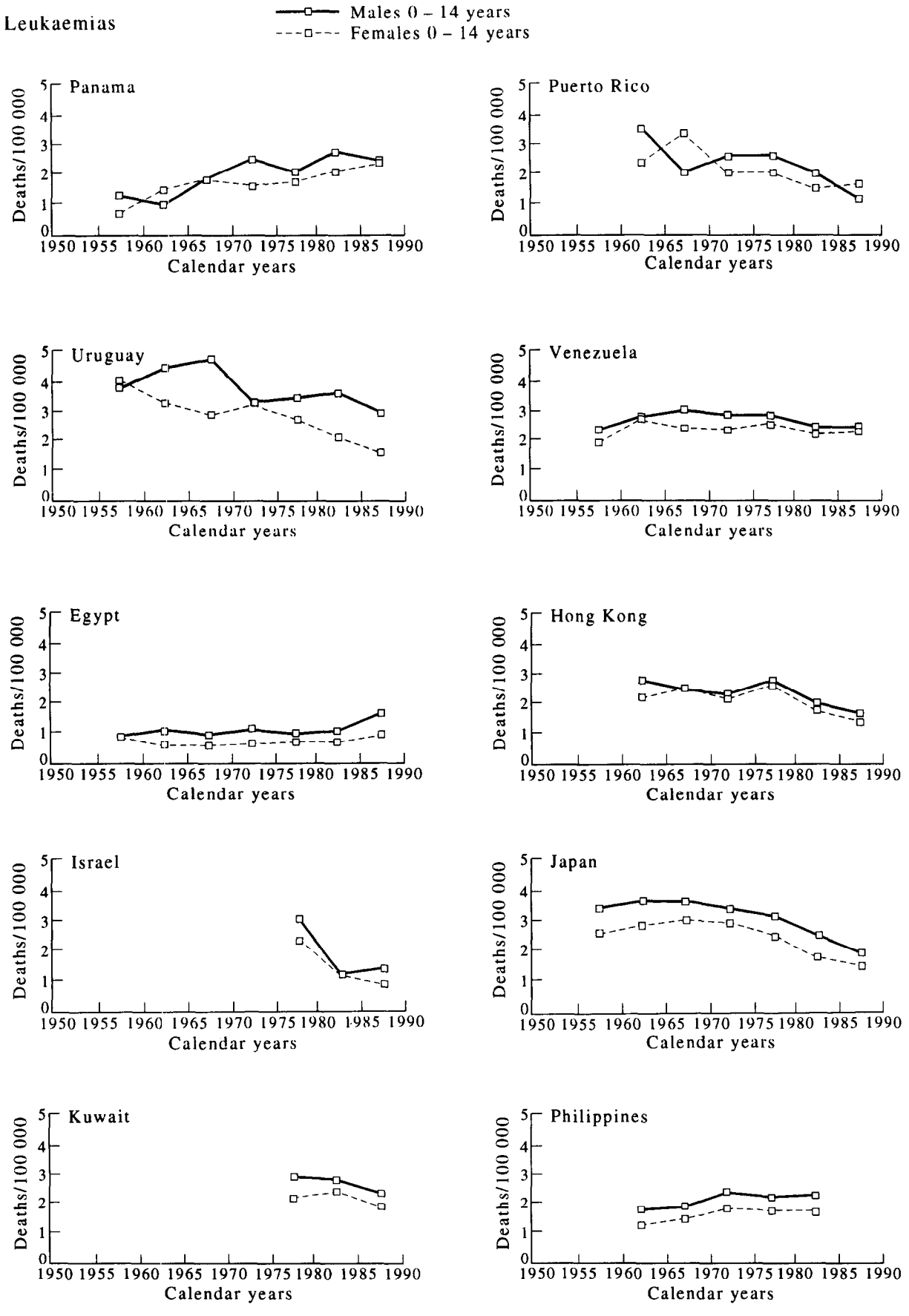
Leukaemias
Males 0 – 14 years
Females 0 – 14 years
Panama
Puerto Rico
Uruguay
Venezuela
Egypt
Hong Kong
Israel
Japan
Kuwait
Philippines
Deaths/100 000
Calendar years
0 1 2 3 4 5
1950 1955 1960 1965 1970 1975 1980 1985 1990

Figure 3

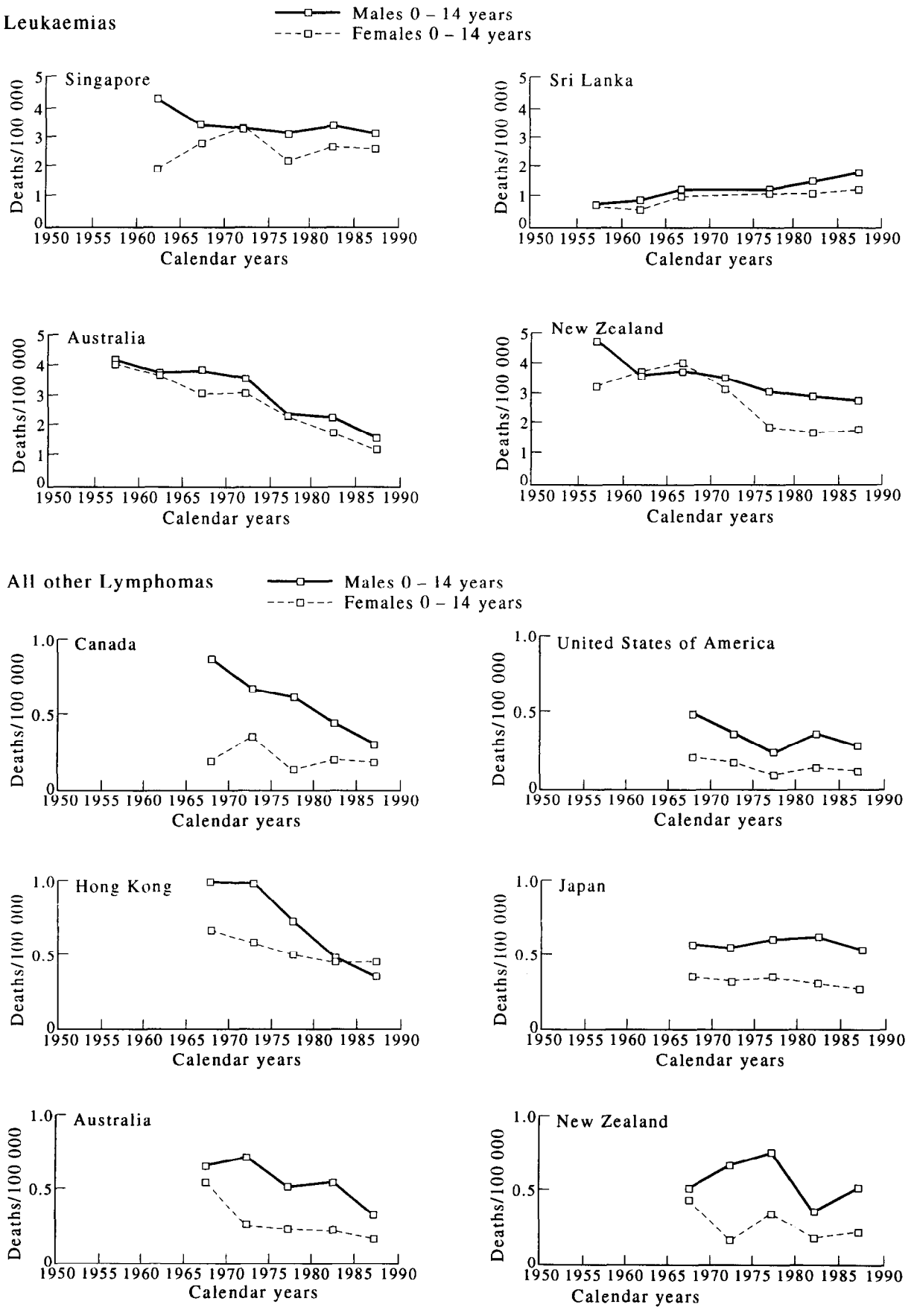
Leukaemias
Males 0 – 14 years
Females 0 – 14 years
Singapore
Sri Lanka
Australia
New Zealand
All other Lymphomas
Males 0 – 14 years
Females 0 – 14 years
Canada
United States of America
Hong Kong
Japan
Australia
New Zealand
Deaths/100 000
Calendar years
1950 1955 1960 1965 1970 1975 1980 1985 1990

Figure 3

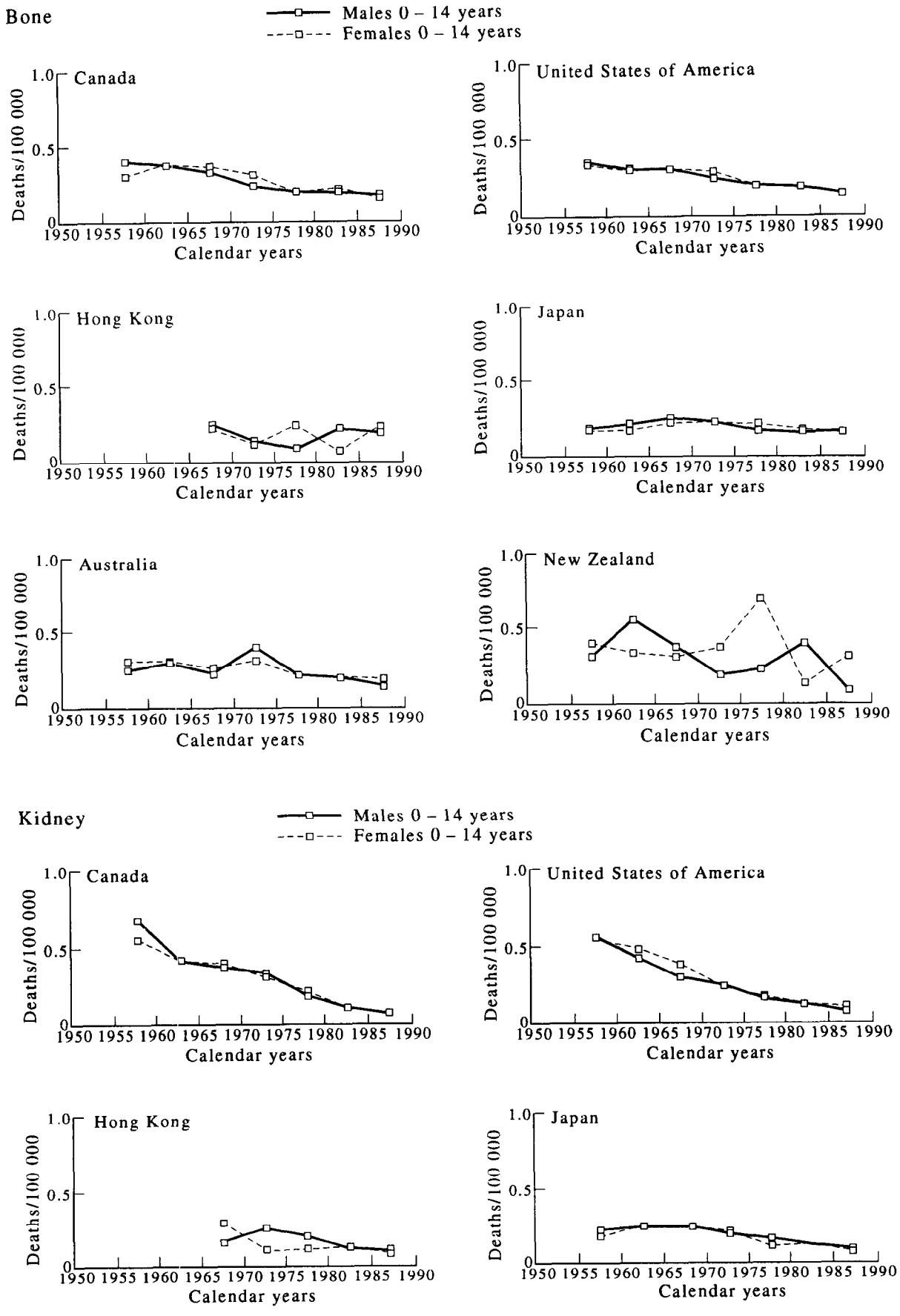
Bone
Males 0 – 14 years
Females 0 – 14 years
Canada
United States of America
Hong Kong
Japan
Australia
New Zealand
Kidney
Males 0 – 14 years
Females 0 – 14 years
Canada
United States of America
Hong Kong
Japan
Deaths/100 000
1.0
0.5
0
1950 1955 1960 1965 1970 1975 1980 1985 1990
Calendar years

Figure 3

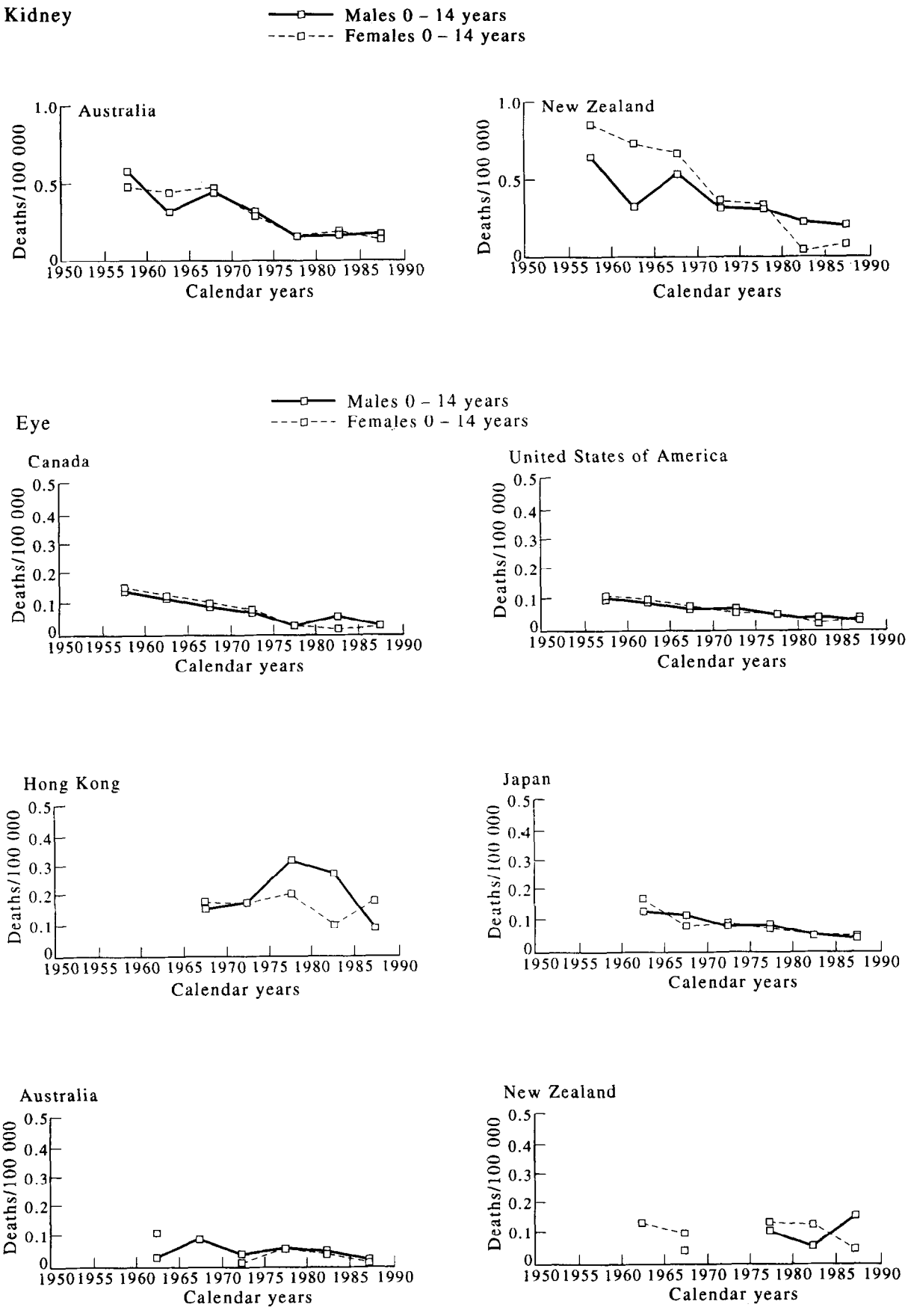

Figure 3. Trends in age-standardised (0–14 years on the world standard population) death certification rates per 100 000 from selected cancers in various American, Asian and Oceanian countries. Period 1950–1989.

leukaemias and all childhood neoplasms in 22 countries. Histograms for tumours of bone, kidney, eye, non-Hodgkin's lymphomas and Hodgkin's disease in six countries are shown in Figure 2, and trends in age-standardised (0–14 years) mortality rates from 1950 to 1989 for all childhood cancers, all leukaemias, Hodgkin's disease, non-Hodgkin's lymphomas, bone, kidney and eye cancers are indicated in Figure 3.

In the interpretation and discussion of these figures, due attention must be paid to random variation, particularly for smaller countries and rarer cancers, as well as to problems of reliability of death certification, particularly for some countries of Latin America and Asia, and for earlier calendar periods.

With these cautions in mind, the highest mortality areas for all childhood neoplasms were certain countries in Latin America (Uruguay, Cuba, Argentina, Costa Rica), as well as Kuwait, New Zealand and Singapore, with age-adjusted rates between 6.5 and 7.5/100 000 males and between 5 and 6.5/100 000 females. This may, at least in part, reflect a comparatively high incidence of childhood cancers in some of these countries, such as Costa Rica and New Zealand [6], but the pattern of incidence is only partly consistent with that of mortality, because of random variation of rates and different correlates of cancer mortality. Death certification rates were low in most developed countries, such as Canada, U.S.A., Australia, Japan and Israel (around 4.5/100 000 males and 3.5–4/100 000 females). Thus, the ratio between the highest and lowest country where death certification is reasonably reliable was approximately 1.8 in both sexes. Mortality rates were even lower in other countries, such as Sri Lanka and Puerto Rico, but the reliability and completeness of cancer death certification in these areas is open to serious criticism.

The pattern is similar for leukaemias, which account for about 50% of all childhood cancer mortality. Data for other neoplasms (bone, including Ewing's sarcoma, kidney—mostly Wilms' tumour, eye—mostly retinoblastoma, Hodgkin's disease and non-Hodgkin's lymphomas) were available and presented for only six countries whose data were considered reliable. Their pattern is more difficult to interpret because of small absolute numbers and thus substantial random variation. Nonetheless, New Zealand (and Singapore, not shown) tend to have among the highest rates for these neoplasms, thus contributing to their systematically high childhood cancer mortality rates.

With reference to trends in total childhood cancer mortality, substantial declines were observed in the U.S.A. (from 10.1/100 000 males in 1950–1954 to 4.2 in 1985–1989, from 8.6 to 3.5/100 000 females) and Canada (from 9.8 to 4.9/100 000 males, from 8.1 to 3.8/100 000 females). Some downward trend was already apparent in the 1950s, but the decline became steeper after the early 1960s. Among Latin American countries or territories, only Puerto Rico had a comparable fall in rates. Some recent declines were also observed in Argentina, Chile, Costa Rica, Cuba and Uruguay, but in all these countries mortality rates from all childhood cancers in the late 1980s were substantially higher than in North America (i.e. around 7–8/100 000 males, and 5–6/100 000 females). No evidence of decline was apparent for Colombia, Panama and Venezuela, and rates of all childhood cancer mortality increased in Mexico.

In Japan, childhood cancer mortality rates increased between the early 1950s and the late 1960s (from 6.0 to 8.4/100 000 males; from 4.1 to 6.8/100 000 females). This rise may be due, at least in part, to improved diagnosis and certification, although there is no simple explanation for this trend. Mortality rates declined thereafter to reach 5.0/100 000 males and 4.1/100 000 females in 1990. A consistent downward trend over the last decade was also observed in Israel, and more modest ones in Hong Kong and Kuwait, whereas no clear pattern was observed in Egypt and a few countries from Asia for which data were provided. Steady and consistent declines were observed in Australia (to reach 4.6/100 000 males and 3.9/100 000 females in 1985–1989), and , to a lesser extent, New Zealand (6.7/100 000 males and 5.3/100 000 females).

This pattern is broadly reflected in the trends for the main type of childhood cancer, i.e. leukaemia, although a clear decline in leukaemia mortality was evident only from the mid-1960s onwards in countries such as Canada, U.S.A. or Japan. Most trends were also favourable for other neoplasms considered, although several of these were more difficult to interpret due to low absolute numbers of cases. Only for non-Hodgkin's lymphomas in Japan was the decline relatively late, the disease still accounting for approximately 100 deaths per year in the late 1980s, i.e. only approximately 20% less than a decade earlier.

DISCUSSION

In conclusion, over the last three decades, the decline in childhood cancer mortality has been over 50% in the U.S.A. and Canada, corresponding to the avoidance of over 2000 deaths per year in the U.S.A. alone. Comparable declines were observed only in Puerto Rico, and in other developed countries of the world, such as Australia, Israel and Japan, and, to a lesser extent, New Zealand. The pattern was, however, much less favourable in other areas of the world for which data on childhood cancer were available, including South America and a few countries from Asia.

The declines in mortality from leukaemias and other childhood cancers were essentially attributable to improved management of the disease, including essentially newer multidrug chemotherapy schemes, but also improved radiotherapy and diagnostic techniques, as well as the introduction of supportive measures to overcome toxicity. This applies to acute lymphoblastic leukaemias, but also to most other childhood neoplasms, which appear to have responded much better to various therapies than have the majority of adult tumours [3, 12–15].

The observation that trends in mortality are still consistently downwards in developed countries indicates that further improvement in the management of childhood cancer is possible [3, 15]. The delay or the lack of noticeable declines in mortality in most developing countries emphasises the scope and importance of interventions needed to provide adequate treatment of childhood cancers in these areas of the world.

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Acknowledgements—This study has been made possible by a core grant of the Swiss (Aargau and St-Gall) League against Cancer. Supports were also received by the Italian Association for Cancer Research and the Italian League against cancer. This study was conducted within the framework of the CNR (Italian National Research Council) Applied Project 'Clinical Application of Oncological Research (contract no. 92.02384.PF39)' and of the 'Europe Against Cancer' Programme of the Commission of the European Communities.

Pergamon

European Journal of Cancer Vol. 31A, No. 5, pp. 782–784, 1995

0959–8049/95 $9.50+0.00

0959-8049(95)00092-5

Phase II Study of Rapid-scheduled Etoposide in Paediatric Soft Tissue Sarcomas

M. B. Phillips, F. Flamant, D. Sommelet-Olive and C.R. Pinkerton

Twenty three patients with paediatric soft tissue sarcomas who had relapsed or refractory disease were treated with a rapid schedule of intravenous etoposide (100 mg/m^2 daily on three consecutive days, weekly over 3 weeks). The regimen was well tolerated with predictable myelotoxicity. In 19 patients with rhabdomyosarcoma, there was a response rate of 42%. This appears to be better than previously reported with conventional three weekly schedules. These data indicate that for rhabdomyosarcoma, as for some other tumours, a divided dose regimen may be the optimal schedule and is worthy of further evaluation.

Key words: etoposide, rapid-schedule, dose intensity, rhabdomyosarcoma, sarcoma, childhood tumours
Eur J Cancer, Vol. 31A, No. 5, pp. 782–784, 1995

INTRODUCTION

THE SURVIVAL of children with soft tissue sarcomas has improved over the past decade with 5-year event-free survival for non-metastatic disease in the region of 70% for the major collaborative groups such as the American Intergroup Rhabdomyosarcoma Study Group (IRS) [1], International Society of Paediatric Oncology (SIOP) [2] and German Cooperative Soft Tissue Sarcomas Group (CWS) [3].

However, refractory disease (approximately 10% of cases) and local or metastatic relapse (30%) remain problems, and survival in those with metastatic disease remains less than 20%. Further efforts to improve chemotherapy regimens are thus warranted. The number of potential new drugs is limited and it is, therefore, important to optimise the scheduling and/or combinations of existing drugs.

Single-agent etoposide has previously been shown to have activity in relapsed rhabdomyosarcoma, although with conventional scheduling only comparatively low response rates are achieved (20%) in intensively pretreated children [4, 5].

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Revised 30 Jan. 1995; accepted 6 Feb. 1995.

The cytotoxic effect of etoposide shows marked dependence on schedule with *in vitro* studies demonstrating a clear direct relationship between duration of exposure of cells to etoposide and the degree of cell kill [6, 7]. In small cell lung cancer, the least effective way to give etoposide is as a single dose, and weekly divided dose administration has been shown to be a more effective schedule [8, 9]. In particular, high response rates were achieved with administration of a dose given divided over 5 days [10]. These studies provided the rationale to evaluate a weekly schedule in paediatric sarcomas. Potential advantages of this schedule also include allowing an increase in dose intensity and the rapid delivery of drugs in a minimum period.

PATIENTS AND METHODS

23 patients, 14 male, 9 female, with a median age of 4 years 9 months (range 8 months–18 years), were entered into this phase II study. The histopathological diagnoses in this group of patients with soft tissue sarcomas were 19 rhabdomyosarcoma, 2 fibrosarcoma, 1 synovial sarcoma and 1 undifferentiated soft tissue sarcoma. SIOP TNM stages at initial diagnosis were 2 stage I, 10 stage II, 5 stage III and 6 stage IV [11]. The indications for inclusion in the study were residual or progressive disease after first-line chemotherapy (9), relapse 3–24 months off treatment (13) and initial progressive disease (1). 11 patients had previously received etoposide and teniposide as part of their