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TRENDS IN CHILDHOOD AND ADOLESCENT CANCER SURVIVAL IN SWEDEN 1960 THROUGH 1984

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The temporal changes in childhood and adolescent cancer survival in Sweden 1960–1984 were analyzed. Complete follow-up through 1986 of 6 262 patients younger than 20 years at diagnosis revealed that the overall 5-year survival rates increased from 36.1 to 65.7% in males and from 43.6 to 73.6% in females. The temporal trends differed markedly between age groups and tumour sites and types. Over the study period, 5-years, survival for testicular cancer increased from 46.9 to 87.2%, kidney cancer, predominantly Wilms' tumour from 35.5 to 77.1% (with a higher rate of 89.1% in 1975–1979), Hodgkin's disease from 61.2 to 91.9%, non-Hodgkin's lymphoma from 32.5 to 76.6%, and all leukemias from 8.9 to 58.7%. Only a moderate improvement was noted for tumours of the bone, muscle and connective tissue, and survival rates for tumours of the nervous system remained largely unchanged. Our data reflect the remarkable therapeutic improvements that have occurred for cancer in the young and indicate that these improvements have rapidly become available in Sweden.

Key words: Childhood cancer, prognosis, temporal trends.

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Multidisciplinary co-operation has brought about important advances in the treatment of childhood and adolescent cancer over the last decades (1, 2). These achievements have been documented mainly in clinical trials of selected patients (3), but declining mortality rates (4) despite a stable or increasing incidence (5) have indicated that survival from childhood cancer has also increased in the population at large. However, the temporal trends in cancer survival have been analyzed in only a few population-based studies (6–9). Some of them were based on small numbers of patients (8), covered short periods of time (7) or did not reflect the most recent years (6). One study failed to show any further overall improvement after the first part of the 1970s (8).

Our aim was to describe trends in childhood and adolescent cancer survival on a national scale. We took advantage of the nationwide cancer registration in Sweden and included the most recently diagnosed patient cohorts for whom a reasonable length of follow-up has been attained. By this means, the impact of improved treatment could be assessed in virtually all 6 262 patients younger than 20 years and diagnosed as having cancer in Sweden during the period 1960 through 1984.

Material and Methods

Study population

The investigation was based on cases of malignant disease notified to the Swedish Cancer Registry. According to regulations, every physician in all establishments for medical care under public as well as private administration have to report all cases of diagnosed cancer to the registry. Pathologists report separately to the registry every cancer diagnosis

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(basal-cell carcinomas of the skin are not reported). Thus, the majority of cases are notified with two reports (10). After the establishment of the Swedish Cancer Registry in 1958, the extent of underreporting, although difficult to assess, was presumably highest during the first years of registration, but it has been judged to be close to zero in recent years (10).

For the purpose of this study, the first two years of cancer registration were excluded. Persons younger than 20 years and diagnosed as having a malignant disease during the period 1960 through 1984 were thus eligible for case selection. Patients with preinvasive cancers and rare benign lesions, who have to be reported according to the regulation, were excluded. All remaining patients in the cancer registry file were linked through their individually unique national registration number to three nationwide registries—the Death Registry, the Registry of Population Changes (emigration register) and an updated registry of all living persons in Sweden on December 31, 1984. In this way all patients who had died or emigrated and who were lost to follow-up could be identified.

A total of 6 784 patients were potentially eligible for the study. Patients diagnosed at autopsy and lost to follow-up were excluded and those with multiple primaries were included only from the date when the first malignant disease was diagnosed. The numbers in the various categories are specified in Table 1. A total of 391 patients were excluded from the study since it was impossible from the register data to settle whether they were diagnosed in an advanced stage shortly before death or whether the disease was detected only at autopsy. In the former case, these patients—46% of whom were younger than 5 years—might have biased the survival trends if they were unevenly distributed over the period of study. Of them 31% were diagnosed in 1960–1964, 31% in 1965–1969, and only 21, 11 and 6% respectively during the following 5-year periods. Most of the excluded cases were leukemias (46%), brain tumours (21%), and non-Hodgkin's lymphomas (8%). Hence, for these types and sites, the early survival estimates—notably from the 1960s—might become slightly exaggerated and the temporal improvement accordingly underrated.

Table 1

Definition of study population comprising all patients younger than 20 years and diagnosed as having cancer in Sweden 1960–1984 with complete follow-up through 1986

Category	Number
Total number in Cancer Registry life	6 784
Diagnosed at autopsy	463[1)]
Multiple primaries	41
Lost to follow-up	18[2)]
Study population	6 262

[1)] Seventy-two were coded as diagnosed at autopsy, whereas 391 patients were diagnosed and deceased within the same month.
[2)] Three patients had an erroneous code for gender (compared with the national registration number) and 15 patients could neither be identified as alive nor as dead on December 31, 1984.

A total of 6 262 patients were eventually included in the study cohort—3 395 males and 2 867 females. The distribution of the patients by age at diagnosis and site or type of cancer is shown in Table 2.

Diagnostic ground

The basis of the diagnosis is routinely coded in the cancer registry file. With two exceptions, virtually all diagnoses during the whole time period were based on microscopic examination of a tissue specimen or a fine-needle aspiration biopsy. However, the diagnosis of tumours of the nervous system (ICD code 193)—during various 5-year periods—was based on clinical data alone in 0.6 to 3.5% of the cases and on x-ray examination in 4.8 to 14.1%.

Classification of leukemia was based on clinical examination alone in a proportion which decreased from 66.0 to 8.4% over the study period. It is, however, likely that the treating pediatrician/hematologist in most cases had examined bone marrow samples without consulting any pathologist/cytologist and not reporting to the cancer registry that the sampling had been done. At present, this classification is largely dependent upon cytochemical, immunological and/or cytogenetic analysis (11–13). Therefore, even if classification and coding into various types was done throughout the period in question, it is not appropriate to base analyses of subtypes of leukemias on registry data alone. For this reason all patients reported as having leukemia (ICD-7 code 204–207) were combined in the analysis. The relative proportions of lymphocytic (ICD 204) and non-lymphocytic leukemias (ICD 205, 206, 207) seen during 1980–1984, 79 and 21% respectively, are consistent with reports from specialized centers (14, 15).

Survival analysis

Each patient contributed years of observation until the date of death, date of emigration or the closing date of this follow-up, December 31, 1986. Dates of death were obtained from the Death Registry and dates of emigration through 1984 from the Register of Population Changes. The observed survival rates for all causes of death were calculated by means of the actuarial (life table) method (16) and the cancer-specific mortality was estimated by calculating the relative survival rate (17, 18). Relative survival is the ratio of observed to expected survival rate, the latter based on individuals in the general population corresponding to the patient group with respect to 5-year age group, gender, and calendar year of observation. As the impact of causes of death other than cancer is

Table 2

Number of patients by site or type of malignant disease and age at diagnosis

ICD 7-code	Site or type	Age (years) at diagnosis			
		0-4	5-9	10-14	15-19
178	Testis	42	7	8	119
180	Kidney	245	80	14	15
192	Eye	195	36	16	19
193	Nervous system	348	217	177	151
196	Bone	36	59	171	210
197	Connective tissue, muscle	83	34	62	85
200, 202	Non-Hodgkin's lymphoma	110	123	106	154
201	Hodgkin's disease	14	42	84	245
204-208	Leukemia	779	427	275	275
	Other	180[1]	105[2]	224[3]	689[4]
Total		2 032	1 130	1 137	1 963

[1] Biliary passages and liver (33), endocrine glands (53), other (94).
[2] Colon (16), ovary (16), thyroid gland (9), other (64).
[3] Colon (66), ovary (26), melanoma (18), other (114).
[4] Colon (121), breast (10), cervix uteri (12), ovary (114), mediastinum (11), urinary organs (33), melanoma (122), thyroid gland (98), other (168).
Number of patients within parentheses.

negligible at the ages concerned in this study, the difference between the observed and relative survival rates did not exceed 0.5 percentage points in any age group or at any period of follow-up. Only relative survival rates will be presented in the following.

Results

Overall results

The overall relative survival by 5-year age groups for the entire study period is shown in Fig. 1. The excess death rate was fairly similar in the various age groups during the first year of follow-up. After that year, however, patients aged 15-19 years did best, whereas those aged 5-9 years showed the lowest survival rate. In neither of the age groups could a cured fraction be reliably identified earlier than 10 years after diagnosis, as indicated by the leveling-off of the curves (Fig. 1). Separate analyses of the overall survival rates for males and females revealed that females generally had a more favorable course than males. This difference apparently increased at older ages (Table 3) as recently described in detail (19).

Trends in survival by age and gender

The 5-year relative survival between the period 1960-1964 and 1980-1984 showed an overall change from 36.1 to 65.7% in males and from 43.6 to 73.6% in females (Table 3). This corresponds to a reduction in excess mortality by 46 and 53% respectively.

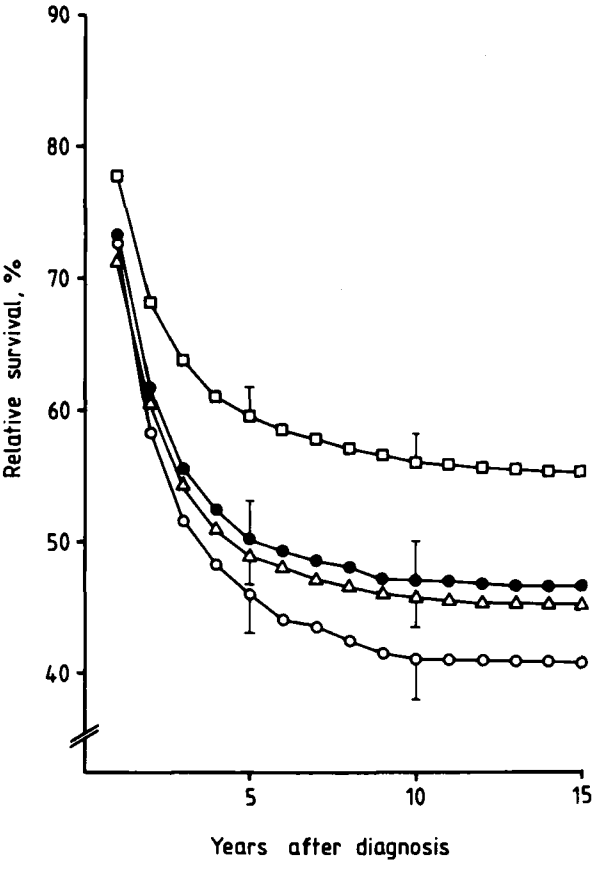

Fig. 1. Relative survival in all patients younger than 20 years and diagnosed as having a malignant disease in Sweden in 1960 through 1984, by 5-year age group. Vertical lines show the 95% confidence interval. △—△ 0-4 y.; ○—○ 5-9 y.; ●—●10-14 y.; □—□ 15-19 y.

Table 3

Relative 5-year survival (with 95% confidence interval) by gender, age, and period of diagnosis

Age at diagnosis, years	Period of diagnosis					
	1960–64	1965–69	1970–74	1975–79	1980–84	1960–84
0–4						
Males	33.8 (26.5–41.1)	30.6 (24.7–36.5)	44.7 (38.4–51.0)	61.4 (55.1–67.7)	64.1 (56.6–71.5)	47.1 (44.1–50.2)
Females	28.2 (20.9–35.5)	41.3 (34.0–48.5)	48.8 (41.9–55.7)	63.1 (55.6–70.5)	72.8 (65.7–79.9)	51.2 (47.8–54.6)
5–9						
Males	38.6 (28.7–48.6)	39.1 (30.3–47.9)	39.4 (31.2–47.5)	42.2 (33.5–51.0)	63.4 (54.3–72.4)	44.5 (40.5–48.6)
Females	32.6 (22.5–42.7)	24.8 (15.8–33.7)	38.8 (29.0–48.7)	63.0 (53.7–72.3)	74.6 (66.6–82.5)	48.6 (44.1–53.1)
10–14						
Males	30.6 (21.5–39.6)	33.1 (24.1–42.2)	45.2 (36.6–53.7)	48.2 (39.5–56.9)	72.0 (63.6–80.4)	45.7 (41.6–49.9)
Females	44.7 (35.3–54.1)	46.9 (36.7–57.1)	51.9 (40.9–62.9)	59.0 (49.9–68.2)	70.8 (61.8–79.7)	55.4 (51.1–59.8)
15–19						
Males	39.5 (32.8–46.3)	46.5 (39.5–53.6)	56.6 (49.9–63.3)	54.5 (47.4–61.6)	65.4 (58.5–72.4)	52.6 (49.5–55.7)
Females	59.2 (52.3–66.2)	66.0 (58.8–73.7)	65.8 (58.2–73.3)	72.7 (66.2–79.3)	76.1 (69.4–82.7)	67.6 (64.5–70.8)
0–19						
Males	36.1 (32.1–40.1)	37.2 (33.6–41.1)	47.3 (43.6–50.9)	53.4 (49.7–57.2)	65.7 (61.8–69.7)	
Females	43.6 (39.4–47.8)	47.3 (43.0–51.5)	52.4 (48.1–56.7)	65.3 (61.4–69.3)	73.6 (69.8–77.4)	

The survival curves for each 5-year age group and period of diagnosis are shown in Figs 2a–d and the 5-year relative survival rates calculated from these figures are summarized in Fig. 3. A substantial improvement over time occurred in all age groups. The increase in survival rate was more pronounced in patients younger than 15 years compared to those aged 15–19 years at diagnosis and it started later in patients aged 5–14 years at diagnosis. As a result, all age groups showed a similar prognosis during the last study period (1980–1984), with a 5-year survival close to 70% (Fig. 3).

The temporal trends are shown separately for males and females in Table 3. A considerable variation in 5-year survival between groups defined by age and gender was noted during the earlier periods of diagnosis. In recent years, however, a more homogeneous pattern emerged, all groups having a 5-year survival in the range 63.4 to 76.1% during the last period of analysis.

Temporal trends by site and type

The trends in relative survival after 5 years of observation are illustrated for some major cancer sites and types in Figs 4–6. In all these malignant diseases (except Hodgkin's disease, see below), the 5-year survival was a good approximation of the cure rate, since the further decrease in the cumulative rate after 10 and 15 years of follow-up was mostly in the order of a few percentage points only. Dates when new treatments became available are indicated in Figs 4–6 and further explained in footnotes. This information was derived from the scientific literature, from Swedish treatment protocols and from personal communications.

Testicular cancers were dominated by malignant teratomas, which accounted for 157/176 (89%) of all cases, followed by seminomas (6%). Apart from a plateau during the 1970s, there was a steady increase in relative survival after 5 years of observation from 46.9 (28.6–65.2)% in patients diagnosed in 1960–1964 to 87.2 (77.1–97.3)% in those diagnosed in 1980–1984 (Fig. 4).

Cancer of the kidney is almost equivalent to nephroblastoma (Wilms' tumour) under the age of 15. The rapid improvement in 5-year relative survival from 35.5 (23.6–47.6)% in 1960–1964 to 89.1 (81.2–97.0)% in 1975–1979 was followed by a decrease to 77.1 (66.4–87.8)% during the last period of diagnosis. The difference between the relative

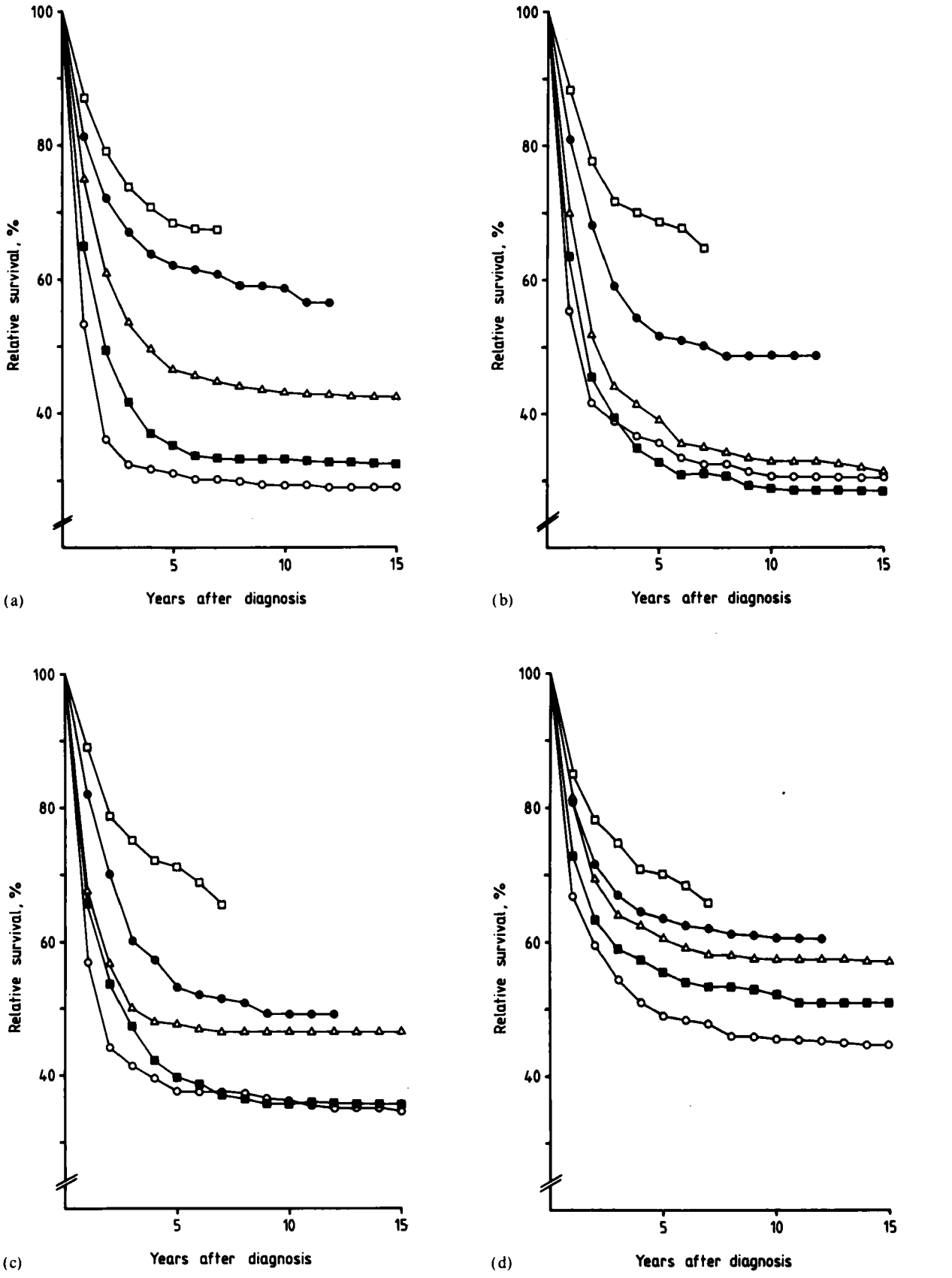

Fig. 2. Relative survival in males and females by period of diagnosis and age at diagnosis: a) 0–4 years, b) 5–9 years, c) 10–14 years, and d) 15–19 years. ○—○ 1960–64; ■—■ 1965–69; △—△ 1970–74; ●—● 1975–79; □—□ 1980–85.

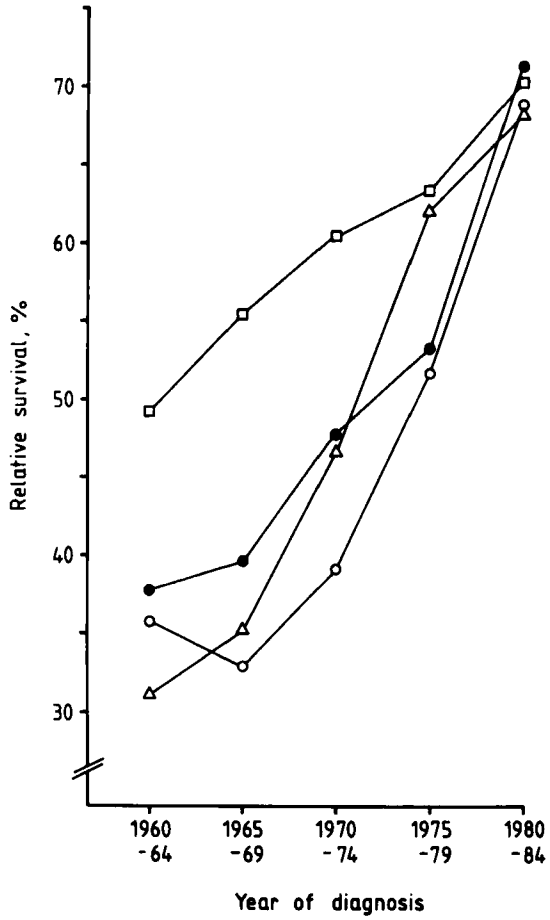

Fig. 3. Relative survival in males and females after five years of observation, by period of diagnosis and age at diagnosis. △—△ 0–4 y.; ○–○ 5–9 y.; ●—● 10–14 y.; □—□ 15–19 y.

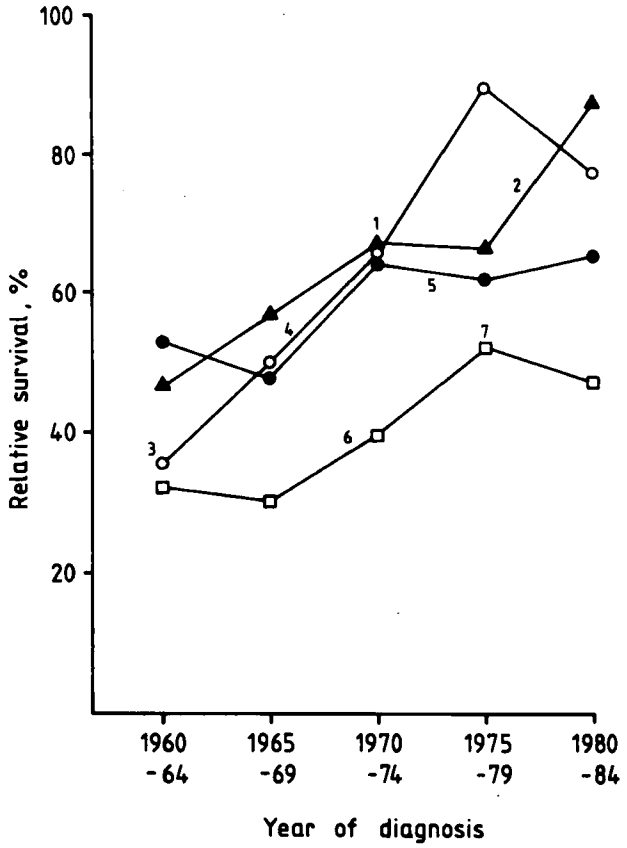

Fig. 4. Relative survival in males and females after 5 years of observation, by period of diagnosis in patients with cancer of the testis (ICD 178), kidney (ICD 180), bone (ICD 196), and connective tissue and muscle (ICD 197). ▲ testis; ○ kidney; ● connective tissue, muscle; □ bone. (For testicular cancer combination chemotherapy was introduced in 1972 and in 1978 cisplatinum was added. For cancer of the kidney single drug chemotherapy was first given in 1960 and supervoltage radiotherapy, as ^{60}Co, became generally available at about the same time; combination chemotherapy was introduced about 1970. For cancer of connective tissue/muscle combination chemotherapy became common about 1974. For sarcomas of bone single drug therapy was first used about 1971 and combination chemotherapy introduced about 1977.)

survival curves during these two latter periods was statistically significant ($p < 0.01$) (Fig. 4).

The group of bone tumours was dominated by osterosarcomas (49.7%) and Ewing sarcomas (31.1%). The survival from bone tumours showed a moderate increase from around 30% in the 1960s to 50% from 1975 onwards. A variety of histo-pathological types constituted the group of tumours of connective tissue and muscle, with a predominance of alveolar sarcoma (21.8%) and fibrosarcoma (18.6%). Embryonal rhabdomyosarcomas accounted for 10.6%. The prognosis in patients with tumours of the connective tissue and muscle improved from a relative survival of about 50% after 5 years of observation in the 1960s to values between 62 and 65% after that period of time (Fig. 4). However, the survival curves did not differ significantly ($p > 0.05$).

Cancer of the bulb of the eye, i.e. retinoblastomas, were associated with 5-year relative survival rates exceeding 90% at all periods of diagnosis except in 1965–1969 (Fig. 5). During the last two periods almost all patients were cured, the relative survival in 1980–1984 being 96.4 (88.7–104.1)%.

For tumours of the nervous system—i.e. mainly astrocytomas (24.9%), medulloblastomas (24.0%) and neuroblastomas (21.9%)—the survival prospects were largely stable at around 40% over the study period, but they improved slightly during the last period of diagnosis to reach a level of 50.7 (41.8–59.6)%. This trend became more evident when tumours of the central nervous system (ICD code 193.0 + 193.1) were analyzed separately (Fig. 5). A more irregular pattern was observed for tumours of the peripheral nervous system dominated by neuroblastomas (196/222; 88%); the differences in survival between the periods of diagnosis were larger than could be expected from random variation alone ($p < 0.01$).

Hodgkin's disease showed a 5-year relative survival of 61.2 (50.4–72.0)% in 1960–1964. There was a marked improvement in 1980–1984 when the survival rate was 91.9

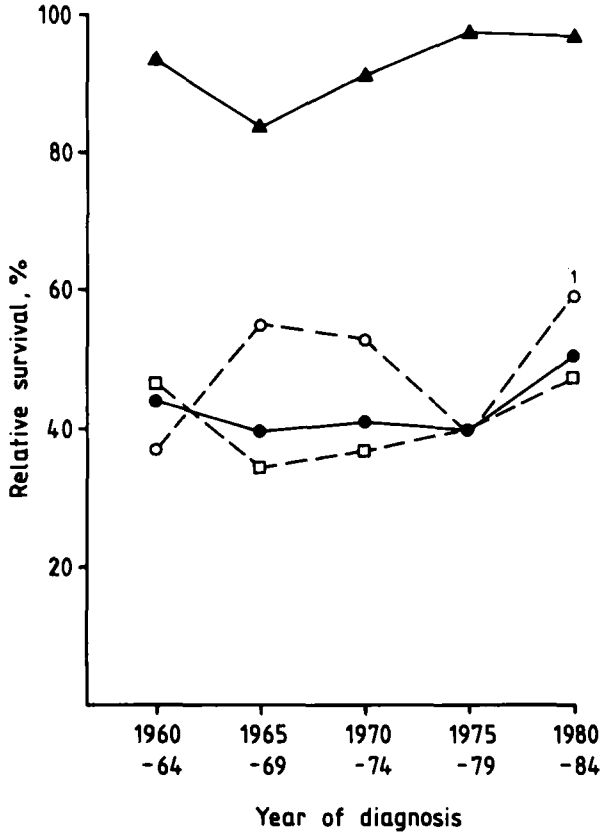

Fig. 5. Relative survival in males and females after 5 years of observation, by period of diagnosis, in patients with retinoblastoma (ICD 192, 0; bulb of the eye), tumours of the central nervous system (ICD 193.0 + 193.1), neuroblastoma (ICD 193.3; peripheral nerves), and nervous system (all) (ICDS 193). ▲ eyebulb; ● nervous system; □ CNS; ○ peripheral nerves. (Note! Tumours of peripheral nerves. 1: More intensive combination chemotherapy (OPEC) was introduced about 1982.)

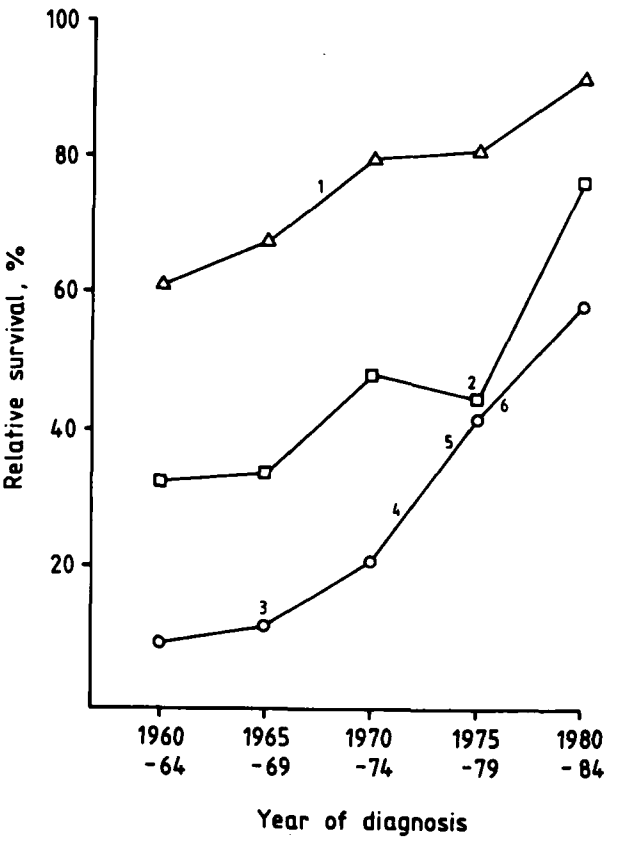

Fig. 6. Relative survival in males and females after 5 years of observation, by period of diagnosis, in patients with Hodgkin's disease (ICD 201), non-Hodgkin's lymphoma (NHL) (ICD 200 + 202) and leukemia (for specification, see text). △ Hodgkin's disease; □ NHL; ○ leukemia, all. (For Hodgkin's disease MOPP therapy was introduced in 1967–1968. For NHL combination chemotherapy was in use since beginning of the 1970s and more effective regimens were introduced about 1977. For leukemia single drug therapy was introduced in the beginning of the 1960s. In 1967, the first national program for childhood ALL was introduced and in 1973 the program was extensively revised; further revisions based on national and international experience were then made every second to third year.)

(85.3–98.5)%. Moreover, in Hodgkin's disease the survival curves departed from the general pattern by showing a continuing decrease during a longer period of follow-up. Thus, in patients diagnosed for instance in 1960–1964, the relative survival rates after 10 and 15 years of observation were 50.3 (39.2–61.5) and 45.6 (34.5–56.7)% respectively. This pattern disappeared, however, over the study period and the annual relative hazard (excess death rate) approached zero after about 7 years of observation in patients diagnosed in 1975–1979 and within 5 years in those diagnosed in 1980–1984. The trend towards improvement shown in Fig. 6 was accordingly underestimated, since the rates among recently diagnosed cases are better approximates of the cured fraction than those from the 1960s.

Non-Hodgkin's lymphomas (NHL) exhibited a much less favorable course than Hodgkin's disease, notably in the earlier years (Fig. 6). The temporal trends in survival from Hodgkin's disease and NHL were fairly similar with one exception, namely that a dramatic improvement in prognosis occurred among patients with NHL at the end of the study period. The 5-year relative survival increased from 45.1 (34.0–56.3)% in 1975–1979 to 76.6 (68.3–84.9)% in 1980–1984.

The prognosis for leukemias was very poor in the first period of the study with survival figures below 10%. A substantial increase occurred from 1970–1974 to 1975–1979, and the increase continued, to reach a 5-year survival rate of 58.7 (53.1–64.4)% during the last 5-year period (Fig. 6). Separate analyses for lymphocytic leukemias—predominantly acute lymphocytic leukemia (ALL)—and non-lymphocytic leukemias (predominantly acute myelogenous leukemia (AML))—during the last two periods revealed that this marked improvement in prognosis was mainly restricted to ALL (data not shown).

Discussion

The Swedish Cancer Registry provides unique opportunities to study trends in cancer survival (20). The favorable prerequisites are attributable to its population-based nature, the completeness of the registration (10), and the possibility of achieving almost complete follow-up with respect to survival. The registry started in 1958, and it therefore covers the entire period of important improvements in the treatment of cancer in the young (1, 2). Some underreporting during the first years of cancer registration should have affected mainly patients with advanced disease and a short survival time (21), which will imply underestimation of improvements over time. The aim of the present study was to describe the overall changes in survival. We have therefore in this context refrained from making a more detailed classification of childhood and adolescent cancers such as leukemias and tumours of the central nervous system (22). Analyses based on such subgrouping obviously can provide additional information.

Surprisingly few data have been published regarding survival trends in cancer in the young. So far, the most extensive and updated information comes from 2 965 patients younger than 15 years of age who were entered in the Manchester Children's Tumour Registry between 1954 and 1983 and followed up for at least two years (9). As patients diagnosed during one decade were combined into the same groups in this British study, recent improvements might have been concealed and direct comparison with the Swedish data is not possible. However, the overall 5-year survival rate in 1974–1983 of 49% (9) is lower than the Swedish male and female rates both in 1975–1979 and 1980–1984 (Table 3) in comparable age goups, indicating that new treatment modalities might have become available nationwide more rapidly in Sweden than in Great Britain. Rates slightly exceeding 50% without evidence of any overall improvement from 1973–1976 to 1977–1980 have been reported from Australia (8).

Testicular cancer. During the 1960s, there was an increase in awareness of the importance of the surgical technique for orchidectomy in case of a suspected testicular tumour, and uni/bilateral retroperitoneal lymph node dissection and adjuvant radiotherapy to the retroperitoneal lymph nodes became increasingly common (23). Even if each of these changes probably had only a minor impact on the prognosis of testicular teratomas, together they could have been responsible for the improvements observed from 1960–1964 to 1965–1969. Around 1970, single drug chemotherapy came into increasing use and this was followed within a few years by combination regimens. In 1978, cisplatinum was included in the chemotherapy combinations that were primarily used in many patients (24), thereby further improving the prognosis to an overall cure rate for all testicular tumours of close to 80% during the last 5-year period. This rate is considerably higher than that reported for non-seminoma patients of all ages in the United States in 1977–1979 (25) and for childhood germ cell tumours diagnosed in Great Britain in 1979–1983 (9).

Wilms' tumour. Better surgical techniques and increased use of postoperative radiotherapy had probably improved the prognosis even before 1960 for patients with Wilms' tumour. Single drug chemotherapy was introduced in Sweden in about 1960 (26). At the same time ^{60}Co-machines replaced the conventional radiotherapy equipment, increasing the possibilities of delivering a homogeneous dose to large volumes. In about 1970, combination chemotherapy replaced single drug treatment (27, 28). Also, the chemotherapy was more and more often given preoperatively rather than postoperatively (29). These changes occurred simultaneously with changes at major international cancer centers specializing in childhood cancer. Since the late 1970s, no more effective treatment has been added. Rather, the therapy has become more individualized and based on better understanding of the prognosis within subgroups, with the aim to obtain high cure rates with a lower risk of adverse effects. Whether, in certain cases this development may have resulted in suboptimal treatment which could have been responsible for the poorer prognosis among patients diagnosed in 1980–1984 compared with 1975–1979 is not known. Three-year survival rates of 80.9% and 95% have been reported from Australia for 1977–1980 (8) and from Great Britain 1979–1983 (9) respectively.

Sarcomas. Even though better surgical techniques and more sophisticated radiotherapy methods were introduced during the 1960s, this had no impact on the overall prognosis, either in soft tissue sarcomas or in bone tumours dominated by osterosarcomas and Ewing sarcomas. In the beginning of the 1970s, increased use of effective cytostatic drugs and—somewhat later—combinations of drugs developed for all major sarcoma types resulted in a significant but still relatively moderate improvement in the prognosis, starting about 1970 (30–33). Increasing survival rates have been shown also in other recent population-based analyses (9, 32).

Tumours of the nervous system. Although there have been improvements in the treatment of certain individual tumours in the central nervous sytem, such as medulloblastomas and ependymomas, the long-term survival changes have been relatively moderate, even at specialized centers (34, 35). Since these tumour types are less common than the astrocytic tumours, the treatment of which has not changed, the prognosis for the whole group has remained unaltered (36). A future improvement can be expected, as a result of the chemotherapy regimens which are inducing long-lasting complete remissions in a high proportion of patients with neuroblastomas that developed in the 1980s (37).

Hodgkin's disease. In Hodgkin's disease, the ability to deliver homogeneous radiotherapy doses to large volumes was markedly facilitated by the technical improvements

during the 1950s–1960s. The introduction of lymphangiography and explorative laparotomy improved the possibilities of accurately staging the patients, thereby giving more appropriate radiotherapy (38). Although chemotherapy was introduced in the early 1960s, there was no major change in prognosis until the MOPP regimen was introduced in 1967. Since then, no new and dramatically more effective treatments for children and adolescents have appeared, but better timing of the various modalities and earlier use of chemotherapy for certain stages can explain the continuous improvement (39, 40). Better diagnostic tools such as CT and ultrasonography may also have influenced the prognosis, since they have permitted more individualized therapy.

Non-Hodgkin's lymphomas. Effective combinations of drugs were introduced in the middle of the 1970s. Since then, there has been a continuous improvement (41, 42). This evolution may well explain the marked improvement seen during 1980–1984 compared with the preceding 5-year period. Better possibilities since the mid-1970s of discriminating non-Hodgkin's lymphomas from other disease entities and of identifying subgroups with different clinical behaviors may also have contributed to the improvement (43).

Leukemia. All register studies of leukemias involving long periods of time are hampered by the considerable improvement in the subclassification of these disorders. However, since the great majority of childhood leukemias are acute, this should not prevent an evaluation of changes in prognosis with time for the whole group of leukemias. There was a continuous change in the relative proportion of the various subtypes through all the 5-year periods of the present study. In the first 5-year period, acute blast- and stemcell leukemia was the predominant type. During the last period, 78% were ALL, 15% ANLL (virtually all AML) and only 4% were registered as acute non-specified. In Sweden the prognostic improvement started in about 1970, with a more marked improvement from 1975 (Fig. 6). In contrast, no improvement was achieved in a series of clinical trials of ALL carried out in the United Kingdom during the period 1972–1979 (44). Subanalysis during the last 5-year period, when the subclassification reached the present standard, revealed that the improvement was substantially better in ALL than in ANLL. Similar results have been reported from specialized centers (14, 15) and from population monitoring (9).

Conclusion

The main conclusion to be drawn from this population monitoring of cancer survival is that therapeutic achievements documented in clinical trials have rapidly became available nationwide in Sweden. As the overall survival rates were still increasing during the last period of the study, cure rates of 70–80% may now have been attained. We can therefore foresee a future in which further substantial improvements in cancer control at young ages require prevention rather than cure. In the clinical setting, the main challenges will be to monitor long-term consequences of the treatment and to maintain high therapeutic standards. The decrease in survival from Wilms' tumour during the last period of this study indicates that this goal is not reached without effort.

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REFERENCES

1. Levine AS. Perspectives on the biology and treatment of cancer in the young: The evolution of our understanding. In: Levine AS, ed. Cancer in the young. New York; Masson Publishing USA Inc, 1982: pp xii–xxiv.
2. Jones PM. Advances in managing childhood cancer. Br Med J 1987; 295: 4–6.
3. Hammond D, Chard RL Jr, D'Angio GJ et al. Pediatric malignancies. In: Hoogstraten B, ed. Cancer research: impact on the cooperative groups. New York: Masson Publishing USA Inc. 1980: 1–23.
4. Miller RW, McKay FW. Decline in US childhood cancer mortality—1950 through 1980. JAMA 1984; 251: 1567–70.
5. Parkin DM, Stiller CA, Draper GJ, et al. International incidence of childhood cancer. Lyon: IARC Sci Publ No. 87, 1988.
6. Myers MH, Heise HW, Li FP, et al. Trends in cancer survival among US white children, 1955–1971. J Pediatr 1975; 87: 815–8.
7. Ries LG, Pollack ES, Young JL. Cancer patient survival: Surveillance, epidemiology, and end results program, 1973–1979. JNCI 1983; 70: 693–707.
8. McWhirter WR, Siskind V. Childhood cancer survival trends in Queensland 1956–80. Br J Cancer 1984; 49: 513–9.
9. Birch JM, Marsden HB, Jones PH, et al. Improvements in survival from childhood cancer: results of a population-based survey over 30 years. Br Med J 1988; 296: 1472–6.
10. The Cancer Registry. Cancer Incidence in Sweden 1984. Stockholm: National Board of Health and Welfare, 1987.
11. Miller DR, Leikin S, Albo V, et al. Prognostic importance of morphology (FAB classification) in childhood acute lymphoblastic leukemia (ALL). Br J Haematol 1981; 48: 199–206.
12. Greaves MF, Janossy G, Peto J, et al. Immunologically defined subclasses of acute lymphoblastic leukemia in children: their their relationship to presentation features and prognosis. Br J Haematol 1981; 48: 179–97.
13. Baehner RL, Miller DR. Hematologic malignancies: leukemia and lymphoma. In: Miller DR, Baehner RL, McMillan CW, eds. Blood diseases of infancy and childhood. St Louis: Mosby, 1984: 619–721.
14. Creutzig U, Ritter J, Riehm H, et al. Improved treatment results in childhood acute myelogenous leukemia: a report of the German cooperative study AML-BFM 78. Blood 1985; 65: 298–304.
15. Riehm H, Gadner H, Henze G, et al. Acute lymphoblastic leukemia: treatment results in three BFM studies (1970–1981). In: Murphy SB, Gilbert JR, eds. Leukemia research:

advances in cell biology and treatment. Elsevier, Amsterdam, 1983: 251–63.
16. Cutler, S. Ederer F. Maximum utilization of the life table method in analyzing survival. J Chron Dis 1958; 8: 699–710.
17. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: A statistical methodology. Natl Cancer Inst Monogr 1961; 6: 101–21.
18. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. Comput Programs Biomed 1985; 19: 197–207.
19. Adami HO, Bergström R, Holmberg L, et al. The effect of female sex hormones on cancer survival: A register-based study in patients younger than 20 years at diagnosis. JAMA 1990; 263: 2189–93.
20. Adami HO, Sparén P, Bergström R, et al. Increasing survival after cancer in Sweden during 25 years. J Natl Cancer Inst 1989; 44: 1640–7.
21. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death-certificates in 1978. Acta Radiol Oncol 1984; 23: 305–13.
22. Birch JM, Marsden HB. A classification scheme for childhood cancer. Int J Cancer 1987; 40: 620–4.
23. Peckham T. Testicular cancer. Acta Oncol 1988; 27: 439–53.
24. Donohue JP, Einhorn LH, Perez JM. Improved management of nonseminomatous testis tumors. Cancer 1978; 42: 2903–8.
25. Li FP, Connelly RR, Myers M. Improved survival rates among testicular cancer patients in the United States. JAMA 1982; 247: 825–6.
26. Jereb B, Sandstedt B. Structure and size versus prognosis in nephroblastoma. Cancer 1973; 31: 1473–81.
27. D'Angio GJ, Evans AE, Breslow N, et al. The treatment of Wilms' tumor. Results of the National Wilms' Tumor Study. Cancer 1976; 38: 633–46.
28. D'Angio GJ, Evans A, Breslow N, et al. The treatment of Wilms' tumor: results of the second national Wilms' tumor study. Cancer 1981; 47: 2302–11.
29. Lemerle J, Voute PA, Tournade MF, et al. Effectiveness of preoperative chemotherapy in Wilms' tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial. J Clin Oncol 1983; 1: 604.
30. Rosen G, Caparros B, Huvos AG, et al. Preoperative chemotherapy for osteogenic sarcoma: Selection of post-operative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 1982; 49: 1221–30.
31. Nesbit ME, Perez CA, Tefft, et al. Multimodal therapy for the management of primary non-metastatic Ewing's sarcoma of bone: an intergroup study. Natl Cancer Inst Monogr 1981; 56: 255–62.
32. Flamant F, Hill C. The improvement in survival associated with combined chemotherapy in childhood rhabdomyosarcoma. A historical comparison of 345 patients treated in the same center. Cancer 1984; 53: 2417–21.
33. Donaldson SS. The value of adjuvant chemotherapy in the management of sarcomas in children. Cancer 1985; 55: 2184–97.
34. Pierre-Kahn A, Hirsch JF, Roux FX, et al. Intracranial ependymomas in childhood. Survival and functional results of 47 cases. Childs Brain 1983; 10: 145–56.
35. Bloom HJG. Medulloblastoma in children: increasing survival rates and further prospects. Int J Radiat Oncol Biol Phys 1979; 8: 2023–7.
36. Bloom HJG. Intracranial tumors: response and resistance to therapeutic endeavours, 1970–1980. Int J Radiat Oncol Biol Phys 1982; 8: 1083–113.
37. Shafford EZ, Rogers DW, Pritchard J. Advanced neuroblastoma: improved response rate using a multiagent regime (OPEC) including sequential cisplatin and VM-26. J Clin Oncol 1984; 2: 742–7.
38. Kaplan HS. Hodgkin's disease: Unfolding concepts concerning its nature, management and prognosis. Cancer 1980; 45: 2439–74.
39. Rosenberg SA, Kaplan HS. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodgkin's disease: 1962–1984. Int J Radiat Oncol Biol Phys 1985; 11: 5–22.
40. Kamps WA, Humphrey GB, Poppema S, eds. Hodgkin's disease in children. Boston: Kluwer Academic Publishers, 1989.
41. Anderson JR, Wilson JF, Jenkin RDT, et al. Childhood non-Hodgkin's lymphoma. The results of a randomized therapeutic trial comparing a 4-drug regime (COMP) with a 10-drug regimen (LSA2L2). N Engl J Med 1983; 308: 559–93.
42. Coleman M. Chemotherapy for large-cell lyphoma: Optimism and caution. Ann Intern Med 1985; 103: 140–2.
43. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. Cancer 1982; 49: 2112–35.
44. Medical Research Council: The working party of leukemia in childhood. Improvement in treatment for children with acute lymphoblastic leukemia. Lancet 1986; 1: 408–11.