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Original Paper

Small Influence of Parental Educational Level on the Survival of Children with Leukaemia in The Netherlands between 1973 and 1979

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We studied the effect of parental educational level (PEL), an indicator of socio-economic status (SES), on survival of children with acute lymphoblastic (ALL) and non-lymphoblastic leukaemia (ANLL). All children with ALL and ANLL diagnosed in The Netherlands in the period 1973–1979, registered by the Dutch Childhood Leukaemia Study Group and followed until 1991 were included. Bone marrow and blood smears had been uniformly classified in a central laboratory; cases with acute lymphoblastic leukaemia (ALL) were subdivided into standard risk (SR) and high risk (HR). PEL, assessed as a risk indicator in a separately conducted population-based case-control study of the same children (response rate: 88%), was divided into low, when neither of the parents had more than elementary school or lower vocational education, and high when either had more. Children with SR ALL of high PEL parents had a slightly higher 10-year survival rate than of low PEL parents (58% versus 54%, $P = 0.25$), whereas survival for the latter increased more ($P = 0.06$) from a lower level in the period 1973–1975. However, children of low PEL parents with HR ALL and ANLL had a higher 10-year survival rate compared with children of high PEL parents ($P = 0.10$ and 0.22, respectively). Children without information on PEL, non-responders, migrants and with missing values exhibited slightly worse survival rates. The influence of PEL on survival of acute leukaemia in children in The Netherlands during 1973–1979 appeared small or even equivocal. Small differences in SES and optimal geographic and financial access to care, delivered through national treatment protocols, may be responsible for these results.

Key words: childhood leukaemia, survival, parental educational level
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INTRODUCTION

In the 1970s, survival of childhood acute lymphoblastic leukaemia (ALL) was observed to be superior in caucasian children in the U.S.A [1–3]. and South Africa [4] compared with black children. After the introduction of 'total therapy' in 1967 [5], survival appeared to improve faster among caucasian children with ALL, which also became apparent from a differential decline in mortality from childhood leukaemia [6]. Furthermore, in Australia, caucasian children of high social status had a better survival rate compared to children of low social status [7]. These discrepancies in survival are, to a small extent, attributed to differences in disease characteristics or access to adequate therapy, whereas host factors such as nutritional status and compliance with maintenance treatment and hygienic advice may also be important.

We were able to study differences in survival according to socio-economic status (SES) among a population-based group of children with ALL and acute non-lymphoblastic leukaemia (ANLL) in The Netherlands diagnosed between 1973 and 1980. Two highly accurate population-based data sets were available: one comprised disease and treatment parameters [8] while the other, drawn from a case-control study among the parents of these children, consisted of a large number of then putative risk factors and indicators including parental educational level (PEL) [9]. Taking the age of parents into

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account, PEL is considered a reliable indicator of SES in The Netherlands [10]. At the time, access to treatment facilities was relatively good both geographically and financially, and guidelines had been developed for diagnosis and treatment within the Dutch Childhood Leukaemia Study Group (DCLSG), a collaborative group of all paediatricians.

PATIENTS AND METHODS

Since 1972, the diagnosis of leukaemia in children has been reviewed in the central laboratory of the DCLSG. Data on disease features, treatment and regular follow-up are registered centrally. Bone marrow and blood smears from all children with (suspected) leukaemia are classified according to FAB criteria [11]. A survey carried out among all paediatricians in 1980 revealed that incompleteness during the period 1973–1979 was less than 5% and could largely be corrected [12].

All 714 children (age $\leq$ 14 years) with ALL and ANLL, diagnosed in the period 1973–1979, were followed up to 1991, through either the hospitals or the virtually complete municipal population registries. Of all patients, 81% had ALL and 14% ANLL; due to small numbers, patients with acute unclassifiable and chronic myelocytic leukaemia (n = 38) were excluded from this analysis. Causes of death, known for all deceased patients, were always related to the underlying leukaemia. Except for 14 patients, ALL was classified as standard risk (SR) (72%) and high risk (HR) (28%), the latter on the basis of the presence of mediastinal enlargement, a white blood cell count (WBC) of $\geq 50 \times 10^9/l$ or central nervous system involvement. Children with SR ALL were mainly treated according to DCLSG protocols, adapted over time [13, 14] while children with HR ALL and ANLL were treated according to a variety of institutional schedules.

Data on parental educational level (PEL) were derived from a questionnaire that was completed by parents of the same children in 1982, within the framework of an extensive population-based case-control study of risk factors among all children diagnosed in 1973–1979 [9]. The PEL was divided into two groups, using the highest level of either parent: elementary school or lower vocational training (low PEL) or more (high PEL). The study, which did not involve 30 immigrants (5%) for linguistic reasons, had a response rate of 88%, while data on PEL were missing in 11 cases (2%). Both groups of patients were evenly spread over the diagnostic period. The number of evaluable children with acute leukaemia and parents of known PEL was thus 575.

Analyses of actuarial survival according to PEL were carried out for all children with ALL, stratified for SR (n = 367), and HR ALL (n = 141), adjusted for WBC, and ANLL (n = 67). Survival rates were also computed for the groups of patients excluded from the present study. The periods of diagnosis considered were 1973–1975, 1976–1977 and 1978–1979. Differences in survival between groups were tested with the log-rank test [15]. Multivariate analyses were carried out using Cox-regression [16]. P-values less than or equal to 0.05 were considered significant.

RESULTS

The distribution of PEL did not differ for the various types of leukaemia, 39% of parents having received only lower education in 1973–1979. However, the proportion of children with ALL of low PEL parents declined from 45 to 25% in the course of time. During the first 6 months after diagnosis, there were no substantial differences in survival between children with various types of leukaemia according to PEL. At 5 and 10 years, the survival rate for all children of known PEL with ALL were 57 and 49%, repectively, with SR ALL 65 and 56% and with HR ALL 39 and 36% (Table 1). Since the survival rates for patients of unknown PEL (shown for the non-responders and being equal for migrant children) were clearly lower than for children of parents with known PEL, the rates for all patients appeared to be slightly worse than for patients included in this analysis. The survival rates for SR ALL children of high PEL parents were, better than for children of low PEL parents, but not significantly. In contrast, survival rates were worse, but not significantly, for children with HR ALL and high PEL parents compared to children of low PEL parents (P = 0.10); the same applied for children with ANLL (P = 0.22) (Table 1).

Over the time-periods considered, the survival for SR ALL

Table 1. Cumulative 5- and 10-year survival of children with acute leukaemia diagnosed in 1973–1979, according to parental educational level (PEL: low and high)

Type	Parental educational level	No. of patients	%	Survival (%) 5-year	10-year	(S.E.)*
ALL SR	low	145	(39)	60	54	(4)
	high	222	(61)	70	58	(3)
	low + high	367	(100)	65	56	(3)
	all†	438	(119)	63	54	(2)
ALL HR	low	54	(38)	48	45	(7)
	high	87	(62)	34	32	(5)
	low + high	141	(100)	39	36	(4)
	all†	176	(125)	37	33	(4)
ANLL	low	26	(39)	19	19	(8)
	high	41	(61)	12	10	(5)
	low + high	67	(100)	14	13	(4)
	all†	85	(127)	12	11	(3)

* Standard error of survival percentage. † Includes migrants (n= 30), non-responders to case-control study (n = 82) and missing values (n = 11). SR, standard risk; HR, high risk.

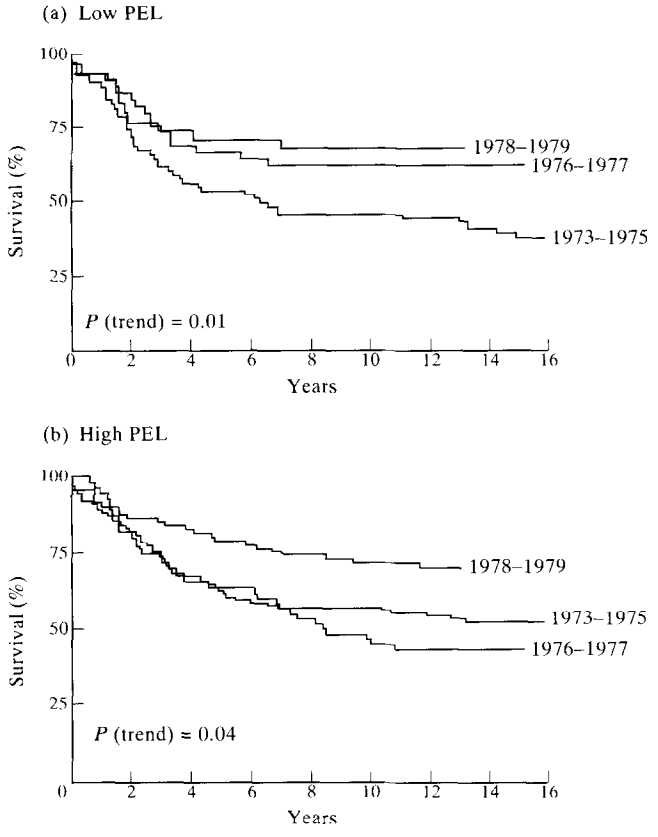

Figure 1. Survival for children with standard risk acute lymphocytic leukaemia (ALL) in The Netherlands, according to diagnostic period and parental educational level (low and high PEL).

Table 2. Five-year survival rates for acute childhood leukaemia diagnosed since 1971 *in the U.S.A., Britain, Australia (Queensland) and The Netherlands, according to diagnostic period*

Country/area	Leukaemia type	Period 1971–1973	1974–1976	1977–1979
U.S.A. (SEER) [20]	ALL	34%	53%	73%
	ANLL	5%	16%	26%
England and Wales [21, 22]	ALL	37%	47%	53%
	ANLL	4%	7%	18%
Australia [23]	ALL	—	46%	48%
	ANLL	—	17%	0%
The Netherlands	ALL	35%*	52%	62%
	ANLL	5%*	13%	11%

* Only 1972 and 1973.

children of low PEL parents improved just as well as that of children with high PEL parents, increasing from 45 to 65% and from 55 to 70%, respectively (Figure 1). After adjustment for age, sex and WBC at diagnosis, the improvement in survival for children with SR ALL of low PEL parents was more marked ($P = 0.06$). The survival rates for SR ALL children of high PEL parents diagnosed in 1976–1977 were unexpectedly lower. The 10-year survival rate increased for children with ALL HR from 33 to 42% ($P = 0.27$) without a difference according to PEL.

DISCUSSION

Slight and equivocal differences in survival of childhood ALL and ANLL were observed in relation to PEL in The Netherlands in the period 1973–1979. Survival of SR ALL children of high PEL parents was slightly better than for children of low PEL parents, especially in the early years 1973–1975, but the improvement in survival of SR ALL children of low PEL parents was more marked in agreement with the literature [3–7]. Mechanisms could be, for example, a better nutritional condition of children of high PEL parents who may have grasped the consequences of the new therapy, both initial and maintenance, more readily [17, 18].

If the declining proportion of low PEL parents among these children is largely due to increased opportunities for higher education in The Netherlands since the 1950s, less potentially high PEL parents were classified in the low PEL category. The observed initial difference in survival between SR ALL children of high and low PEL parents should then have been larger. Alternatively, the superior survival rates for HR ALL and ANLL children of low PEL compared with high PEL parents contradict the hypothesis that survival rates for children of parents with a low SES or PEL should be worse.

The inferior survival experience (Table 1) of the children without information on PEL-status may be explained as follows: children of the 12% non-responding parents in the case-control study had higher death rates [9], while the 30 migrant children not involved in the case-control study for linguistic reasons and the 11 children of parents with unknown PEL, also with lower survival rates, are more likely to have belonged to the low PEL group. The true difference in survival according to PEL could thus have been larger for SR ALL and smaller, but still the reverse, for HR ALL and ANLL.

The observed differences in survival according to PEL could not be explained by a difference in distribution of disease-specific prognostic factors, such as the WBC at diagnosis, neither by differential access to or adminstration of adequate therapy. Because the criteria for non-adherence to guidelines were not defined sharply enough, adequate documentation did not occur and the data were not usable. We cannot explain the temporary, albeit non-significant ($P = 0.44$) decline in survival of SR ALL children of high PEL parents in 1976–1977 in contrast to the clearly improved survival experience of children of low PEL parents ($P = 0.03$) (Figure 1), when the ALL III protocol was followed for these patients [19]. The smaller progress in survival for patients with HR ALL and ANLL, compared with SR ALL, is in agreement with experience in major cooperative groups. Compared with population-based rates for the U.S.A [20]., U.K [21, 22]. and Australia [23] in that era, survival rates for (all) children with ALL and ANLL in The Netherlands were relatively good (Table 2).

We conclude that the influence of PEL on survival of childhood leukaemia in The Netherlands may have been small and equivocal during the period 1973–1979. Relatively small differences in SES in previous decades and good access to diagnosis and treatment that were carried out with a high degree of national uniformity may be the most likely explanations.

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