

Height at diagnosis of malignancies

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SUMMARY Studies of the presenting height of children with malignancies have produced conflicting results, from an excess of taller patients to an excess of shorter patients. The problems of measurement bias, inadequate comparison populations, small numbers of patients, subgroup analyses, and overreliance on simple significance tests are all possible reasons for the variation in results. To clarify this issue, we studied heights at diagnosis of 3657 children and adolescents aged under 18 years. Their malignancies included acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute non-lymphoblastic leukaemia, osteosarcoma, retinoblastoma, neuroblastoma, Wilms' tumour, rhabdomyosarcoma, and Ewing's sarcoma. Compared with published standards for the heights of children in control populations, no significant deviation from population norms was found for patients in any of the 10 disease categories after proper adjustment for multiple significance testing.

Intrigued by Tjalma's observation of an increased risk of bone sarcoma in larger breeds of dogs,¹ Fraumeni investigated the relation between stature and malignant bone tumours in children and adolescents.² He found that children with osteosarcoma or Ewing's sarcoma were significantly taller at diagnosis than the control group, who had non-osseous cancers, and suggested that development of these malignant tumours was related to accelerated skeletal growth. After studying 236 children with newly diagnosed acute lymphoblastic leukaemia Broomhall *et al* reported that these children were significantly taller than normal children, which implied involvement of growth hormone or somatomedin in the development of acute lymphoblastic leukaemia.³ Hancock *et al* observed a taller stature associated with Hodgkin's disease in adults and suggested it was a constitutional factor.⁴ Subsequent studies of children with osteosarcoma,⁵ Ewing's sarcoma,⁶ or acute lymphoblastic leukaemia⁷⁻¹¹ have yielded conflicting results. We studied a large number of patients with newly diagnosed malignant diseases to determine if any relation existed between unusual height and childhood malignancies.

Patients and methods

Our study included 3657 patients aged under 18 years with newly diagnosed malignancies who were admitted to St Jude Children's Research Hospital

between 1962 and 1985. Patients were excluded if their heights were not measured within one month of diagnosis. The 2101 boys and 1556 girls were segregated into 10 categories of disease; acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute non-lymphoblastic leukaemia, osteosarcoma, retinoblastoma, neuroblastoma, Wilms' tumour, rhabdomyosarcoma, or Ewing's sarcoma (Table). There were too few patients with brain tumours referred to our centre during this period for them to be included in the analyses.

In general, standing height was used for children aged over 5 years and recumbent length for those under 5.¹² Standing height was measured with the child standing erect with closed heels, buttocks, upper part of the back, and occiput against a two metre measuring scale; the head was positioned so that the external auditory meatus and the lower border of the orbit were on a plane parallel to the floor. Recumbent length was measured with the child lying on a firm table with the soles of feet held firmly against a fixed upright placed at the zero mark; a movable upright was then brought firmly against the vertex.

Heights at diagnosis of these children and adolescents were compared with normal values produced by the National Center for Health Statistics (NCHS).¹³ The 5th, 10th, 25th, 50th, 75th, 90th, and 95th centile heights for boys and girls up to 18 years

Table Standard deviation scores of presenting height of children with malignancies

Disease		No of patients	Mean of SD score	SE	p Value
Acute lymphoblastic leukaemia	Boys	901	0.082	0.036	0.02
	Girls	690	0.043	0.042	0.30
	Total	1591	0.065	0.027	0.02
Non-Hodgkin's lymphoma	Boys	212	0.049	0.073	0.51
	Girls	83	0.254	0.108	0.02
	Total	295	0.106	0.061	0.08
Hodgkin's disease	Boys	156	-0.089	0.078	0.32
	Girls	104	0.237	0.084	0.005
	Total	260	0.048	0.058	0.41
Acute non-lymphoblastic leukaemia	Boys	242	-0.151	0.079	0.06
	Girls	186	-0.009	0.079	0.91
	Total	428	-0.089	0.056	0.12
Osteosarcoma	Boys	84	0.132	0.115	0.25
	Girls	66	0.087	0.118	0.47
	Total	150	0.112	0.083	0.18
Retinoblastoma	Boys	53	-0.408	0.273	0.14
	Girls	48	0.100	0.152	0.51
	Total	101	-0.167	0.162	0.31
Neuroblastoma	Boys	172	-0.003	0.089	0.97
	Girls	143	-0.064	0.083	0.44
	Total	315	-0.031	0.061	0.62
Wilms' tumour	Boys	105	-0.072	0.097	0.46
	Girls	106	0.030	0.107	0.78
	Total	211	-0.021	0.072	0.77
Rhabdomyosarcoma	Boys	111	-0.063	0.093	0.50
	Girls	82	0.106	0.114	0.36
	Total	193	0.009	0.072	0.90
Ewing's sarcoma	Boys	65	0.044	0.142	0.76
	Girls	48	-0.078	0.153	0.61
	Total	113	-0.008	0.104	0.94
Total	Boys	2101	0.006	0.024	0.82
	Girls	1556	0.054	0.027	0.05
	Total	3657	0.026	0.018	0.15

were obtained from cubic spline equations. These equations were produced at NCHS from charts based on data collected from 1962 to 1975.

In our study the height of each patient was converted to a standard deviation score, $(Y-\bar{X})/S$, in which Y is the patient's observed height in centimetres, \bar{X} is the 50th centile of normal subjects of the same age and sex, and S is an estimate of the standard deviation of normal heights. The value of S was obtained from the cubic spline equations for a subject of specified age and sex. If a normal statistical distribution is assumed, calculating $S_{\alpha}^2 = (X_{(1-\alpha)} - X_{(0.5)})^2 / Z_{\alpha}^2$, where $X_{(1-\alpha)}$ is the 100 $(1-\alpha)$ th centile height calculated from the NCHS equations and Z_{α}^2 is the $\alpha \times 100\%$ point of the normal distribution, for each centile ($\alpha=0.05, 0.10, 0.25, 0.75, 0.90, 0.95$) except the 50th then six different variance estimates are yielded. The estimate (S) of the standard deviation is simply the square root of the average of the six S_{α}^2 values. This

type of estimate is reasonable if the data are normally distributed and was necessary in this study because the sample standard deviation could not be calculated from the available NCHS data.

For each category of disease, a mean standard deviation score was computed for boys, girls, and both sexes combined (Table). A two sided t test was used to test whether or not the mean scores for patients in each disease-sex category were statistically different from zero.

As a result of the well known problems of multiple significance testing, some type of adjustment of the nominal p values in all of these tests was needed to avoid the spurious identification of 'significant' deviations from normality. A conservative approach is to divide the target significance level (say 0.05) by the number (k) of tests to get a level below which the nominal p value must fall to be declared significant.¹⁴ Unfortunately, in any data sifting analysis such as this one it is difficult to

identify the number of separate (but not independent) statistical tests that were actually conducted. As there were 10 categories of disease and we wished to examine the results for boys and girls separately we arbitrarily chose $k=20$ for a significant value—that is, an individual p value must be less than $0.05/20=0.0025$ to be declared significant at the 0.05 level—even though additional tests—for example, by age—were also performed.

A more important criticism of the significance testing approach is that it fails to consider the magnitude of the observed deviation from normality. With large numbers of patients, a significant difference may be clinically unimportant and, conversely, with a small number of patients, a large and potentially important difference may be missed. Accordingly, the actual differences (in cm) for a given category are of more importance than a simple 'significant' or 'not significant' result. These data are given for the category with the smallest nominal p value.

Results

No significant difference in average height from the controls was found for any of the patients with the 10 categories of disease based on the adjusted significance level (Table). Even when the analyses were performed after further dividing patients by age—for example, above or below 1 year for neuroblastoma—no significant difference was achieved. Few of the nominal p values were below 0.05.

The single category in which the nominal significance level was close to significance was that of girls with Hodgkin's disease (nominal p value=0.005). Figure 1 depicts the distribution of heights of the patients and the median values for normal controls by age at diagnosis. There was obviously no major deviation from normality, regardless of how the p

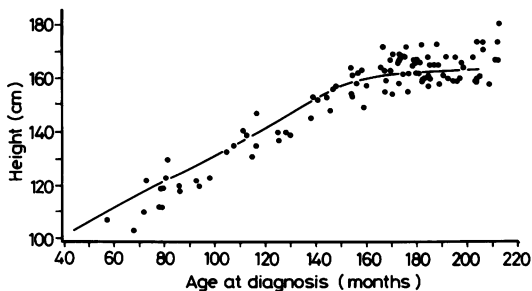


Fig. 1 Distribution of heights according to age in 104 girls with Hodgkin's disease. Each dot represents the value of a single patient. The solid line represents the median of normal controls by age.

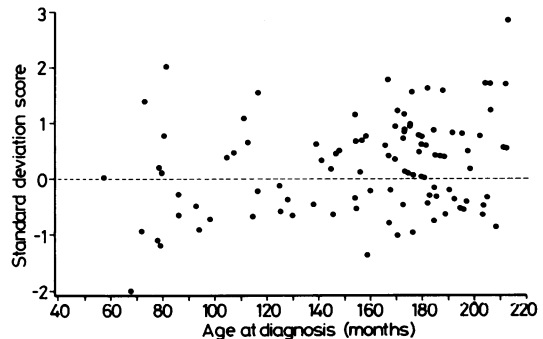


Fig. 2 Standard deviation scores according to age in 104 girls with Hodgkin's disease.

value was interpreted. Figure 2 shows the standard deviation scores of patients according to their ages at diagnosis. For example, the estimated mean (SE) increase in height for 12 year old girls with Hodgkin's disease was only 1.6 (0.7) cm.

Discussion

We found no significant difference between the heights of children with malignancies and the heights of normal children in the control population. This is in agreement with the studies of McWhirter *et al*, Robison *et al*, and Bessho for acute lymphoblastic leukaemia⁸⁻¹⁰ and that of Broström *et al* for osteosarcoma.⁵ Other studies have provided contradictory evidence. Broomhall *et al* found that children with acute lymphoblastic leukaemia were, on average, taller than normal controls.³ Berry *et al*, however, reported that significantly more boys with acute lymphoblastic leukaemia aged less than 4 years, were shorter at diagnosis,⁷ and Westphal *et al* found that their patients with acute lymphoblastic leukaemia were shorter and lighter.¹¹ Similarly, while Fraumeni reported that children with osteosarcoma or Ewing's sarcomas were taller,² a subsequent study by Pendergrass indicated that girls with Ewing's sarcoma were smaller.⁶

The contradictions in published results have several plausible explanations, which have nothing to do with accelerated skeletal growth, aberrations in growth hormone, or constitutional factors. The well known tendency to publish 'positive'—that is, differences are found—rather than 'negative'—that is, no differences are found—studies creates a bias toward publication of papers that confirm height differences, particularly when subgroup analyses by age, sex, and other categories are carried out. It is rare to find any adjustment to the statistical analysis caused by the multiplicity of tests carried out in a

subgroup analysis. For instance, if we had used the nominal significance level of 0.05, we would have concluded that girls with any malignancy, as a group, were taller at diagnosis (Table). We could also have reported that boys with acute lymphoblastic leukaemia or girls with non-Hodgkin's lymphoma or Hodgkin's disease were taller from this study. Obviously, however, no appreciable difference in height can be observed for girls with Hodgkin's disease in this study (Fig. 1).

The reliability of the actual height measurements for the study population are rarely discussed. These studies, including the present one, are usually retrospective analyses of height data that were routinely collected, and systematic bias is always a possibility. This is especially important in a small series because the observed average height differences, even if assumed to be real, are very small in absolute magnitude.

Control populations also need careful evaluation because any deviations from the average height of healthy children of the same age, race, and sex are critical in these studies. The use of accurate published norms may seem preferable to any internal control population, but the use of internal controls measured in the same way as patients can obviate any systematic bias in measurement, even though it would be difficult to ascertain selection bias in the controls. There is no simple 'best way' to proceed, but the possibility of inadequate or improper comparisons must be considered in evaluating the publications on this topic.

Another explanation for conflicting reports is variation in the number of patients studied. For example, we were more likely to detect a small deviation from normal heights in patients with acute lymphoblastic leukaemia (n=1591) than in patients with retinoblastoma (n=101). In fact, the observed average height of boys with retinoblastoma deviated most from the average height of any normal subgroup, but it was not significant because of the small number of patients (n=53). Caution is advised with respect to any conclusion drawn from small numbers of patients in these types of studies. A rough rule of thumb is that there should be at least 100 patients in the category under study. This would permit detection with a high probability (0.90) of any deviation from normality over 0.1 standard deviation in average height and would provide reasonable precision in the estimated distribution of heights.

A cautionary note should also be made about the interpretation of results of significance testing. Overreliance on these results impedes a balanced assessment of the magnitude and precision of the observed difference and the medical importance of

that difference. The significance tests normally used in these settings, even if proper adjustment for multiplicity is made, can only discriminate between the true difference and zero. Any observed difference will be declared significant if enough patients are included. An estimate of the magnitude of the differences is needed along with an estimate of its precision or standard error. For example, estimates and confidence intervals for the true height differences are more informative than simple significance tests.

Several investigators have suggested that growth hormone may influence the development and proliferation of acute lymphoblastic leukaemia.¹⁵ Increased serum growth hormone and somatomedin concentrations were found at diagnosis of childhood acute lymphoblastic leukaemia in one study.⁷ None the less any effect of growth hormone during the period of development of leukaemia seems to be clinically unimportant.

We conclude that there is no significant aberrant growth or stature associated with childhood malignancies at presentation. Future studies in this area should consider carefully the potential problems of measurement bias, inadequate comparison populations, small number of patients, subgroup analyses, and overreliance on simple significance testing.

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References

- 1 Tjalma RA. Canine bone sarcoma: estimation of relative risk as a function of body size. *Journal of the National Cancer Institute* 1966;**36**:1137-50.
- 2 Fraumeni JF Jr. Stature and malignant tumors of bone in childhood and adolescence. *Cancer* 1967;**20**:967-73.
- 3 Broomhall J, May R, Lilleyman JS, Milner RDG. Height and lymphoblastic leukaemia. *Arch Dis Child* 1983;**58**:300-1.
- 4 Hancock BW, Mosely R, Coup AJ. Height and Hodgkin's disease. *Lancet* 1976;ii:1364.
- 5 Broström L-A, Adamson U, Filipsson R, Hall K. Longitudinal growth and dental development in osteosarcoma patients. *Acta Orthop Scand* 1979;**51**:755-9.
- 6 Pendergrass TW, Foulkes MA, Robison LL, Nesbit ME. Stature of Ewing's sarcoma in childhood. *Am J Pediatr Hematol Oncol* 1984;**6**:33-9.
- 7 Berry DH, Elders MJ, Crist WM, et al. Growth in children with acute lymphocytic leukemia: a pediatric oncology group study. *Med Pediatr Oncol* 1983;**11**:39-45.
- 8 McWhirter WR, McWhirter KM, Taylor D. Height and lymphoblastic leukaemia. *Arch Dis Child* 1983;**58**:839-40.
- 9 Robison LL, Nesbit ME Jr, Sather HN, Meadows AT, Ortega JA, Hammond GD. Height of children successfully treated for acute lymphoblastic leukaemia: a report from the Late Effects Study Committee of Children's Cancer Study Group. *Med Pediatr Oncol* 1985;**13**:14-21.
- 10 Bessho F. Height at diagnosis in acute lymphocytic leukaemia. *Arch Dis Child* 1986;**61**:296-8.
- 11 Westphal M, Morgan SK, Grush OC. Nutrition and growth in

- children with acute lymphoblastic leukaemia (ALL). *Clin Res* 1979;27:816.
- ¹² Vaughan VC III, Behrman RE. Assessment of physical growth and development. In: *Textbook of pediatrics*. Philadelphia: WB Saunders, 1983:26-37.
- ¹³ Hamill PV, Drizd TA, Johnston CL, Reed RB, Roche AF. NCHS growth curves for children birth-18 years. United States. *Vital Health Stat [III]* 1977;165:1-74.
- ¹⁴ Tukey JW. Some thoughts on clinical trials, especially problems of multiplicity. *Science* 1977;198:679-84.
- ¹⁵ Rogers PC, Komp D, Rogol A, Sabio H. Possible effects of growth hormone on development of acute lymphoblastic leukaemia. *Lancet* 1977;ii:434-5.

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Twenty five years ago

A study of growth promotion in children

Douglas Hubble and Duncan R MacMillan (Birmingham)—Arch Dis Child 1962;37:518-24

In this study 23 children with short stature of differing aetiology were treated by methandienone in doses of 0.08 to 0.73 mg/kg/day. At this time there was much interest in the new testosterone derivatives that were claimed to have a heightened effect on protein anabolism but a reduced androgenic effect. As the authors pointed out these protein anabolic drugs have complicated actions that were poorly understood, so they approached their use to promote growth with a conservative attitude. Their cases were placed into the following diagnostic categories: organic hypopituitarism (three cases), congenital hypopituitarism (four), Turner's syndrome (three), familial short stature (four), primordial dwarfism (five), dwarfism and obesity, mental and sexual retardation (four). All patients were given an initial course of treatment of three months' duration. This was continued if there was no evidence of virilisation and no appreciable advance in bone age. The presence of virilisation or of skeletal maturation proceeding faster than the rate of growth were regarded as indications for stopping treatment.

A satisfactory growth response was obtained in 10 of the 23 children, but the children in each group displayed a differing pattern of response. Six of the hypopituitary patients had a disappointing growth response and the one patient in this group who had a good response may not, in fact, have been a case of congenital hypopituitarism. The authors commented that protein anabolic agents were no substitute for the growth hormone. None the less they concluded that they should be used in hypopituitarism despite their poor effect on growth promotion and that it was safe to use them when skeletal maturation is retarded (especially in late maturing boys) and in primordial dwarfs with a retarded bone age.

Comment. Human growth hormone first became available in restricted amounts about the time of publication of this paper and in the ensuing 25 years has completely altered the outlook for children suffering from hypopituitarism. The advent of biosynthetic growth hormone is likely to result in further pronounced changes in the treatment of retarded growth provided adequate amounts can be marketed at reasonable cost. The place of anabolic steroids in the treatment of retarded growth is today even more problematical than it was in 1962. It is, indeed, very doubtful if they have any place in the treatment of children suffering from growth retardation from whatever cause.

(The senior author of this paper, Douglas Hubble, was a British pioneer in paediatric endocrinology and on a par with his American counterpart Lawson Wilkins. He was Chairman of the Academic Board of the British Paediatric Association from 1966-69 and James Spence Medallist in 1970. He had a remarkable command of the English language, both written and spoken, and great personal charm.)

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