THE AGE OF OSTEOSARCOMA PATIENTS IS INCREASING

AN EPIDEMIOLOGICAL STUDY OF OSTEOSARCOMA IN SWEDEN 1971 TO 1984

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We conducted an epidemiological study of osteosarcoma in Sweden from 1971 to 1984 to investigate whether the typical features of the disease had changed. Of 294 osteosarcoma patients reviewed, 249 had primary skeletal tumours, and for these the mean annual incidence was 2.1 per million, without any clear trend over time. The mean male/female ratio for the period was 1.6 again with no consistent pattern over time; nor was there any significant change in the distribution of tumours according to location. The only feature which showed a significant change over the 14-year period was the mean age of the patients, being at its lowest (19 years) in 1972 and at its highest (40 years) in 1981. Excluding the 22 patients with craniofacial tumours, the remaining 227 also showed a significant increase in mean age. Analysis of the annual age distribution disclosed an increasing fraction of patients older than those in the classical age peak between 10 and 29 years.

A large number of trials have shown improved survival in osteosarcoma over the last 15 years, which has been attributed mainly to adjuvant chemotherapy. The change we have observed in age distribution should also be taken into account in the evaluation of the results of treatment; it may be that older patients have a better prognosis.

Major studies on osteosarcoma consistently report a peak age incidence between 10 and 25 years; the occasional cases in elderly patients are often secondary to Paget's disease or irradiation (Price 1961; Dahlin and Coventry 1967; Larsson and Lorentzon 1974). Tumour location seems to display a constant pattern with a predominance of lesions about the knee (Dahlin and Coventry 1967; Broström 1979; Mirra 1980). The annual incidence of approximately two osteosarcoma cases per million has remained essentially unchanged over several decades (Larsson and Lorentzon 1974).

The only feature of osteosarcoma which shows a clear change is survival: improvement of five-year survival from about 20% to 50% has been reported from several centres over the last 15 years (Harvei and Solheim 1981; Rosen and Nirenberg 1985; Bacci et al 1986;

Simon et al 1986) and this has mainly been attributed to the introduction of adjuvant chemotherapy. However, the role of this treatment in osteosarcoma is still a matter of debate (Lange and Levine 1982; Souhami 1983; Carter 1984; Bertino 1987; Holland 1987) and although it is recognised that it does improve survival, there may be other contributory factors. Higher survival rates have been reported for osteosarcoma patients treated by surgery alone (Broström et al 1980; Gilchrist et al 1981) and there have been speculations about a change in the nature of the disease, questioning the validity of historical controls (Taylor et al 1978; Broström et al 1980; Giuliano, Feig and Eilber 1984; Lancet 1987). So far, however, no convincing evidence for a change in any of the characteristic features of osteosarcoma has been presented.

To analyse whether there has been a change in osteosarcoma with respect to age or location we conducted a nationwide study covering the period 1971 to 1984 based on the records of the Swedish Cancer Registry.

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0301-620X/90/1014 \$2.00
J Bone Joint Surg [Br] 1990; 72-B: 89-93.

MATERIAL AND METHODS

Pertinent data on all 335 osteosarcoma cases reported to the Swedish Cancer Registry from 1971 to the end of 1984 were collected. These included primary and secondary osteosarcomas of bone, parosteal variants, and primary osteosarcomas of the soft tissues.

Table I. Osteosarcoma in Sweden 1971 to 1984

	Number	Per cent	Age of patients			Sex ratio M/F
			Mean	Median	Range	
Primary skeletal	249	85	29	20	4 to 90	1.6
Secondary skeletal	9	3	71	74	41 to 93	0.5
Parosteal	18	6	43	40	13 to 77	0.8
Soft tissue	18	6	66	69	32 to 85	2.6

Fig. 1

Age distribution of patients with primary skeletal osteosarcoma in Sweden from 1971 to 1984.

To test the reliability of the reporting routine to the Cancer Registry, the operating lists for bone tumour cases at the Karolinska Hospital over the 14-year period were checked. Of the 81 osteosarcoma cases treated, five were missing from the Registry records. Two had not been reported by our department and three, although correctly reported, had been registered erroneously as carcinoma cases. Adding these five patients, the total series then comprised 340 cases. The failure of other hospitals to report osteosarcomas could not be assessed, nor the incidence of other errors in the Registry records.

The clinical and histopathological reports of all 340 cases were reviewed, and the histology of all the 74 cases diagnosed or treated outside the three established musculoskeletal tumour centres in Sweden was reassessed. An additional 63 cases with some discrepancy between clinical, radiological and histological features, so that they did not fit the classical description of osteosarcoma, were also re-assessed.

In 29 of the 340 cases, the diagnosis of osteosarcoma proved to be erroneous at histological review. In 15 other cases a different malignancy had been reported to the Registry, but had been incorrectly recorded as an osteosarcoma. The histopathological reports for two further cases were no longer available. These exclusions left 294 patients for analysis.

The series was subgrouped into primary osteosarcoma of bone, secondary osteosarcoma associated with either Paget's disease or previous local irradiation, parosteal osteosarcoma and soft tissue osteosarcoma. For each patient the year of diagnosis, sex, age and tumour location were noted. The clinical features were analysed for the whole period of 14 years, and also for each year separately. The annual incidence per million of the total population and per 100 000 of specific age groups were calculated using data from the Swedish Central Bureau of Statistics. During the period 1971 to 1984 the Swedish population increased from 8 115 426 to 8 342 621.

Trends over time were determined by regression analysis. Student's *t*-test was applied to assess the significance of differences and *p* values < 0.05 were considered to be significant.

RESULTS

Data for the whole 14-year period. Of the total series of 294 cases, giving a mean annual incidence of 2.5 per million, 249 (85%) were primary skeletal osteosarcomas, 18 (6%) were parosteal variants, 9 (3%) were secondary and 18 (6%) were primary soft tissue osteosarcomas (Table I).

Considering only the 249 primary skeletal osteosarcomas, the mean annual incidence was 2.1 per million. The male/female ratio was 1.6 to 1. Long bones were involved in 187 cases (76%) of which only 14 were in the mid-shaft. More than half of all the lesions (130/249) were located about the knee (Table II), and almost two-thirds (154/249) were in 'typical' locations in distal femur, proximal tibia, proximal fibula or proximal humerus. Of the 95 tumours with an 'atypical' location, 22 were in the craniofacial bones.

The mean age of the 249 cases with primary osteosarcoma of the skeleton was 29 (median 19) years. The mean age of males was 29 years (range 4 to 88, s.d.

Table II. Location of 249 primary skeletal osteosarcomas

	Number	Per cent
Craniofacial bones	22	8.8
Vertebrae	4	1.7
Pelvis	23	9.2
Rib	6	2.4
Scapula	3	1.2
Humerus		
Proximal	24	9.6
Middle	3	1.2
Distal	1	0.4
Radius		
Proximal	1	0.4
Middle	1	0.4
Femur		
Proximal	15	6.0
Middle	5	2.0
Distal	70	28.1
Tibia		
Proximal	52	20.9
Middle	4	1.7
Distal	2	0.8
Fibula		
Proximal	8	3.2
Middle	1	0.4
Foot	3	1.2
Multifocal	1	0.4

Table III. Age-specific incidence of primary skeletal osteosarcoma in Sweden 1971 to 1984

Age in years	Number	Incidence per 100 000
0 to 9	10	0.07
10 to 19	112	0.71
20 to 29	40	0.25
30 to 39	29	0.18
40 to 49	10	0.08
50 to 59	12	0.08
60 to 69	16	0.13
70 to 79	12	0.14
80 to 89	7	0.23
90 to 94	1	0.39

Table IV. Age and sex ratio of primary skeletal osteosarcoma cases in Sweden 1971 to 1984

	Number	Age in years		Sex ratio M/F
		Mean	Range	
All sites	249	29	4 to 90	1.6
Location typical	154	24	4 to 88	1.9
atypical	95	39	4 to 90	1.4
Long bones	187	25	4 to 88	1.9
Pelvis	23	39	10 to 87	1.5
Craniofacial	22	42	22 to 82	1.0

21) and that of females 30 (6 to 90, s.d. 22). The age distribution showed the classical peak between 10 and 29 years (Fig. 1) and the fraction of patients of 30 years or older was 0.34. The highest incidence per 100 000 (0.70) was found in the 10- to 19-year age group and the lowest (0.07) for patients under nine years (Table III). The 154 cases with a 'typical' tumour location had a mean age of 24 years as compared with 39 years for the 95 patients with an 'atypical' location ($p = 0.001$). The age and sex of different subsets of patients according to the location of the tumour are shown in Table IV.

Year-by-year data. The annual number of primary skeletal osteosarcomas over the 14-year period varied from 10 to 27 cases per year, corresponding to an annual incidence from 1.2 to 3.3 per million; there was no clear trend over time. The annual male/female ratio varied from 0.4 to 3.0; in only one year, 1971, were there more females than males. These variations in sex ratio showed no consistent pattern over time, nor were there any significant change in the fraction of tumours in the long bones, or the proportion with a 'typical' or 'atypical' location.

However, the mean age of the patients (Table V) showed a significant increase over the 14-year period, regardless of whether we considered the whole series of 249 cases ($p = 0.01$), patients with lesions of the long bones ($p = 0.001$), those with a 'typical' location ($p =$

0.001), or excluded the 22 cases with craniofacial tumours ($p = 0.001$). The lowest annual mean age of patients with primary skeletal osteosarcoma was 19 years (in 1972) and the highest was 40 years (in 1981). For those with a 'typical' tumour location the corresponding figures were 13 years (in 1972) and 31 years (in 1982).

The age distribution over the 14-year period consistently showed that the highest incidence was between 10 and 29 years, but also showed a gradually increasing proportion of older patients. Thus, the fraction of patients aged 30 years or more increased significantly ($p = 0.05$, $r = 0.56$), being at its lowest (0.19) in 1972, and at its highest (0.57) in 1981. This increasing fraction in more recent years was still more pronounced when considering patients aged 40 or over ($p = 0.01$, $r = 0.67$) and those aged 50 or over ($p = 0.01$, $r = 0.78$) (Table VI).

The change in the relative proportion of young and old osteosarcoma patients over the period was explained by an increase in incidence for individuals aged 50 or more ($r = 0.72$, $p = 0.05$) as well as those aged 60 or

Table V. Annual incidence of primary skeletal osteosarcoma according to sex and age

Year	All locations			Atypical locations		
	Number	Mean age	Sex ratio M/F	Number	Mean age	Sex ratio M/F
71	10	24	0.4	5	17	0.7
72	16	19	3.0	12	13	3.0
73	21	22	3.2	15	22	4.0
74	25	26	1.3	13	19	1.6
75	19	33	1.4	10	19	1.0
76	27	31	1.2	14	25	1.8
77	15	23	2.0	10	23	2.3
78	16	30	1.3	11	24	1.7
79	20	26	3.0	15	26	2.7
80	21	37	2.5	11	30	1.7
81	14	40	1.3	8	25	1.7
82	10	38	1.0	8	31	1.7
83	10	31	2.3	8	26	1.7
84	25	31	1.5	14	30	1.3
	$r = 0.69$ $p < 0.01$			$r = 0.88^*$ $p < 0.01$		

*correlation coefficient relating mean age with time.

more ($r = 0.72$, $p = 0.01$). No clear decrease in incidence could be demonstrated for patients under 29 years.

The incidence of parosteal (18 cases) and of secondary osteosarcoma (nine cases) showed a fairly even distribution over the 14-year period, but eight of the 18 cases with primary osteosarcoma of the soft tissues were recorded during the last two years of the period.

DISCUSSION

The Swedish Cancer Registry, effective since 1958, offers unique possibilities for epidemiological investigations and, according to several control studies, provides reliable data (Mattsson 1984). Although some diagnostic mistakes, failures to report and false registrations occur, these errors altogether represent a low percentage (Mattsson 1984; Kreicbergs, Stark and Silfverswärd 1987). For rare malignancies like osteosarcoma, diagnostic mistakes may be assumed to be somewhat more frequent than for more common tumours. However, the relative number of diagnostic and registration errors for each year is presumably fairly constant and therefore should not affect the assessment of incidental changes over time.

Hence, it seems that a true increase in the age of patients with primary skeletal osteosarcoma has occurred in Sweden from 1971 to 1984. This finding cannot be

Table VI. Annual fraction of adults with primary skeletal osteosarcoma

Year	Fraction		
	≥ 30 years	≥ 40 years	≥ 50 years
71	0.30	0.20	0.10
72	0.19	0.06	0.00
73	0.24	0.05	0.05
74	0.32	0.20	0.16
75	0.47	0.21	0.21
76	0.37	0.30	0.22
77	0.20	0.13	0.07
78	0.19	0.19	0.19
79	0.30	0.15	0.15
80	0.48	0.43	0.33
81	0.57	0.43	0.36
82	0.50	0.40	0.40
83	0.40	0.30	0.30
84	0.40	0.28	0.24
	$r = 0.56^*$ $p < 0.05$	$r = 0.67^*$ $p < 0.01$	$r = 0.78^*$ $p < 0.01$

*correlation coefficient relating annual fraction with time.

explained by the increasing longevity of the Swedish population. The gradual increase in the mean age of osteosarcoma patients is mainly attributable to an increasing incidence among the elderly, which is not linked to an increasing proportion of tumours in atypical locations. The gradual change towards a higher mean age was found to apply to all the subsets of patients which permitted statistical analysis. Although the peak incidence was consistently between 10 and 29 years, it became gradually smaller because of the growing fraction of older patients.

Previous epidemiological reports on primary skeletal osteosarcoma consistently demonstrate an overwhelming predominance of patients in the age group 10 to 30 years with a distinct peak in adolescence (Larsson and Lorentzon 1974; Broström 1979). Another consistent finding, that girls afflicted by the disease are younger than boys, coinciding with the age of puberty, has nourished speculation about aetiological factors linked to the growth spurt (Broström 1979). Our findings do not invalidate this hypothesis, since we also found a peak age incidence among adolescents. However, since osteosarcoma is now almost as common in adults as in

adolescents, research should also be focused on host factors other than those related to growth.

The fact that more adults are developing osteosarcoma may prove to be important for the interpretation of the results of treatment. To our knowledge, no reports on survival in primary osteosarcoma of bone take into account the age distribution of the patients. Although a few studies on prognosis in osteosarcoma have dealt only with patients under 30 years of age, most have focused on tumour location and stage, surgical procedure and adjuvant chemotherapy without specifically considering the age of the patients. The improved survival figures which have been reported from several treatment centres during the last decade have mainly been attributed to adjuvant chemotherapy, although there have been few randomised trials (Edmonson et al 1984; Link et al 1986; Eilber et al 1987). As yet, it is uncertain whether the higher survival rates are also related to a change in age; it may be that older patients have a better prognosis than those who are younger.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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