

Factors affecting the incident juvenile bone tumors in an Austrian case–control study

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Abstract

This case–control study investigates etiologically important factors for juvenile osteosarcomas and possible reasons for the relative scarcity of their incidence in the population. Information on a variety of risk factors, psychosocial factors, and factors possibly occurring in early childhood was obtained by interviewing 88 patients (ages 8–25 years) with osteosarcoma, Ewing's sarcomas and other bone tumors, and three age- and sex-matched control groups (hospital, neighbour and family controls), and their mothers. For both sexes, children's diseases in their history, which increased the risk were measles (RR = 1.56, not significant) and mumps (RR = 1.81, 95% CI = 1.05–3.13), whereas clinically apparent chickenpox was associated with a significant decrease for bone tumors (RR = 0.46, 95% CI = 0.26–0.8). Dermal and respiratory allergies (without hay fever) were also inversely associated with bone tumors. Breast feeding for longer than 2 months was associated with low risk for bone tumors for boys, whereas for girls, paternal age was a risk factor; remaining stable in a multivariate model (RR = 2.36, 95% CI = 0.90–6.21). A change in the presence of an emotionally significant person or changes of residence were risk factors both in univariate and multivariate analyses. The strongest and most persistent risk factor was difficulties in school, indicative of emotional disturbances (RR = 2.58, 95% CI = 1.39–4.78). Considering such host factors as possibly important modifiers of risk in addition to exogenous carcinogenic agents, these factors were consistent and statistically significant for both sexes and despite the small numbers recruited for this study, thus predicting susceptibility. The factors may become relevant for preventive psychotherapy applied to susceptible persons for improvement of prognosis after surgical therapy in preventing recurrences.

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1. Introduction

Research into the causes of bone tumors in children and adolescents has focussed primarily on radiation and accelerated skeletal growth, although it remains unclear why few exposed individuals develop the mostly fatal diseases osteosarcoma and Ewing's sarcoma considering the ubiquitous occurrence of risk factors [1].

The present study included questions on such factors that could produce particularly strong effects on the limbic system of children and young adults to add evidence to the unexplained cause of rare tumors in young patients.

The study was designed to test the hypothesis of whether patients are different from control subjects in factors influencing self-regulation, in particular extended inhibition or suppression of regulatory competence by long-lasting difficulties in coping with negative events.

The project was part of an interdisciplinary effort of central European clinicians and epidemiologists that focused on an integrated investigation of bone tumor pathology and etiology and was inspired by Lent Johnson [1]. The international group's activities included a concept for etiologic research, which to that point had not been conducted. Because of the existence of a population-based bone tumor registration scheme established between 1973 and 1980 in Germany [2], the case-reference approach was one of the objectives of the international activity [3,4]. A biological model and

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the concept of this analysis is given in more detail in a preceding publication [5].

2. Subjects and methods

For demonstration of a purposeful use of registry data as a tool for epidemiologic research to investigate the distribution of risk factors responsible for the clinical manifestation of several types of juvenile bone tumors, registries were established to study the increased incidence of rare bone neoplasia in Germany and Austria and for systematic surveillance of incidences. Northern and Eastern Austria (including Vienna) had been fully covered in the registry, therefore, this data formed the main basis of this incidence-based study.

2.1. Cases

Incidences were obtained from independent sources (surveys of the Pathological Institutes in the Northern Region and of the Vienna Bone Tumor Registry) were compared with mortality statistics for Austria from the Central Office of Statistics, Vienna, and showed a fairly representative and unbiased case collection.

The study included all incident and prevalent cases from 1978 onward. The peak age of cancer development in boys was 15 years and 13–14 years in girls (combined average, 14 years). All 88 patients in the age group between 8 and 25 years between the years 1978 and 1988 were included in the study. One pathologist at the diagnostic center (AK) reviewed all diagnoses (M.S.-K.); she had either established the diagnoses herself or re-evaluated each case's histology for identical criteria and complete histology. This allowed unequivocal classification for comparisons of the main histologic groups.

The three types of bone tumors were osteosarcomas ($n = 61$, 35 males, 26 females), Ewing's sarcomas ($n = 14$, 4 females, 10 males), and 13 others (Table 1). During the study, a decline in the occurrence of osteosarcomas led to the study being halted in 1988. The reasons for exclusion of cases were foreign nationality ($n = 3$), death within the time

interval from becoming eligible until the interview ($n = 3$), and parents' refusal to participate ($n = 1$).

2.2. Controls

Three control groups were matched for age and sex for assessment of expected prevalences. Neighborhood controls either were selected randomly based on the proximity to the last residence of the case or indicated by the cases' mothers. Family controls were either siblings or cousins. During the interviews, the mothers provided the name of a relative of the same sex and similar age to the patient, who would agree to be interviewed as a healthy volunteer. Hospital controls, selected from the same wards as the study patients, were hospitalized for orthopedic ailments and diseases such as fractures, malformations for surgical correction, or osteomyelitis. The control patients were chosen by the chief physicians of the respective wards and were interviewed at about the same time the index patients were interviewed. In cases in which a patient's mother had died, the next of kin was asked to fill in; however, controls were not eligible if their mothers had died.

A complete matched set of 87 controls (50 male case/hospital control patients and 38 and 37 female case and hospital controls) was consecutively interviewed. Only 69 of the neighborhood controls (36 males and 33 females) and 53 family controls (24 males and 28 females) agreed to the interviews. The distribution of the 208 controls by group and mean age is shown in Table 1.

Because three different control groups were used to facilitate the study of associations during several comparisons, the possible heterogeneity between the groups was analyzed. Risk estimates as derived from a comparison of the case with the control groups were considered valid only if the different groups were representative of the general population and reflect prevalences of factors in unaffected populations.

2.3. Questionnaire-based interviews

The questionnaire was designed based on knowledge on the major risk factors for bone tumors during the preparation

Table 1
Age distribution of cases by histological type and controls (1979–1989)

Sex	Cases			Controls		
	Osteo-sarcoma	Ewing-Sarcoma	Other	Hospital	Neighbour	Family
Male						
<i>N</i>	35	10	5	50	36	24
Age ^a	16.5	15.4	17.4	17.1	15.9	16.8
S.E. ^b	0.6	1.1	1.0	0.6	0.6	0.8
Female						
<i>N</i>	26	4	8	37	33	28
Age ^a	15.8	13.3	14.4	15.5	15.6	16.0
S.E. ^b	0.6	1.7	2.0	0.5	0.7	0.9

^a Mean.

^b S.E.: standard error.

of the pilot study. It included all factors that were relevant for the increased risk of tumors of the bony and soft tissue [6,7].

The question concerning difficulties at school was included because of evidence from prospective epidemiologic research that chronic emotional stress and understimulation causing masked depression could result in a higher risk for manifest cancer compared with well-regulated, unstressed groups [8].

All interviews of patients and controls were carried out by one trained senior female interviewer who appointed the family and neighborhood controls.

2.4. Statistical analysis

The evaluation was carried out using univariate analysis and multivariate conditional logistic regression models. According to statistical practice, 95% confidence intervals are presented without adjustment for multiple comparisons indicating the observational nature of a case–control study [9].

For 49 cases (55.7%) three controls were matched, missing were for three patients the neighborhood, for 20 patients the family, and for 15 patients the neighborhood and the family controls. For categorical variables, a chi-square test for homogeneity in contingency tables was used. We primarily used the simple conditional logistic regression model for the relative risk (RR) approximated by the odds ratio (OR) estimation in which the three control groups were merged. For a few variables when large differences within control groups were found an appropriate logistic regression model was used that accounted for those differences [10]. This model requires a priori propositions about the preferred control group for certain variables.

The representativeness of different control groups for subsequent relative risk (RR) estimation was analyzed for homogeneity between control groups because of the consequences of any associations. For all variables, the results of the appropriate tests were arranged according to the *P* values.

Results based on a model that included one variable are described as univariate analysis in the tables. In all analyses, the individual matching was kept.

For multivariate analyses, relevant risk factors were included in the order of improvement of fit as obtained by the reduction of the deviance/deviation (goodness of fit statistics).

Finally, analyses were carried out separately for the different morphologic types of osteosarcoma and other bone neoplasms as a subgroup (Table 9).

3. Results

The multivariate analysis in a model of factors found relevant follows their presentation as univariate results.

Difficulties in school were most frequently reported by hospital (23%) compared with family (15.4%) and neighborhood controls (8.7%). In addition, the number of daughters as offspring of parents differed from 69% of mothers with more than one daughter (hospital controls) to 76.8% in neighborhood and 82.7% in family controls.

3.1. Number of residences

More cases of both sexes (31.6%) reported a higher number of former residences than the three control groups, thus frequent change of residence was a risk factor (RR = 2.76 for boys and 2.43 for girls), but only statistically significant for both sexes combined (RR = 2.41; 95% confidence interval (CI) = 1.06–5.49).

3.2. Paternal occupation

The fathers were engaged in blue collar occupations in 68.0 and 68.2%, respectively, at birth of male cases and controls. At the time of the interview, however, 74.0 and 59%, respectively, of the fathers of the patients and the controls were blue collar workers; 71.0% of the fathers of the female patients were blue collar workers both at birth and currently; for the controls the percentages were 76.5 and 73.5%, respectively. The distribution did not show a particular effect in the analyses.

3.3. Neonatal period and parental factors

Male patients had been nursed about half a month less than controls in general, with an even greater difference for neighborhood controls (Table 2).

The low RR of 0.11 (95% CI = 0.02–0.6) for males who had been breastfed for more than 2 months' indicates a quasi-protective effect of breast-feeding (age-adjusted, statistically confirmed *P* < 0.05). No difference was discernible in girls.

The ages of the mothers at birth of the proband did not differ (average, 25 years in all compared groups, Table 2).

Table 2
Mean and standard error (in parentheses) of duration of breastfeeding and age of parents at birth of proband

	Cases	Controls		
		Hospital	Neighbour	Family
Duration of breastfeeding (months)				
Males	1.8 (0.2)	2.3 (0.3)	2.5 (0.5)	2.1 (0.5)
Females	2.3 (0.3)	2.3 (0.5)	2.3 (0.3)	2.1 (0.4)
Age of father at birth of proband				
Males	28.4 (0.9)	27.3 (0.9)	28.8 (1.1)	28.0 (1.3)
Females	28.8 (0.8)	31.1 (1.7)	29.1 (1.0)	28.4 (1.2)
Age of mother at birth of proband				
Males	25.1 (0.9)	24.1 (0.7)	25.8 (0.9)	25.9 (1.2)
Females	25.2 (0.8)	26.8 (1.0)	25.8 (1.1)	24.3 (1.0)

Table 3
Familial factors (%)

		Cases	Controls		
			Hospital	Neighbour	Family
No. of spouses of mother					
Males	1	90.0	92.0	94.4	95.8
	2+	10.0	8.0	5.6	4.2
Females	1	94.7	91.9	97.0	96.4
	2+	5.3	8.1	3.0	3.6
No. of spouses of father					
Males	1	88.0	86.0	91.7	91.7
	2+	12.0	14.0	8.3	8.3
Females	1	97.4	78.4	93.9	96.4
	2+	2.6	21.6	6.0	3.6
Stepparents or change of emotionally important person					
Males	No	88.0	94.0	91.7	95.8
	Yes	12.0	6.0	8.3	4.2
Females	No	89.5	91.9	100.0	100.0
	Yes	10.5	8.1	0.0	0.0

For girls, the fathers' age was an average 30 years. However, an estimated RR of 2.1 (univariate) became 4.55 (95% CI = 1.17–17.68) for paternal age above 30 and remained after age-adjustment in the multivariate model, in that an estimated RR for both sexes combined by paternal age above 30 of 2.11 (95% CI = 1.14–3.90) was found (Table 9).

The number of spouses of parents was found to be higher among male cases in that 10% of patients' mothers had a second husband compared against 8.0, 5.6, and 4.2% among the controls (Table 3). Stepparents and a change of emotionally important persons, respectively, were found twice as frequently in males and female cases, if all controls were considered together (Table 3).

Table 4
Univariate analysis (estimates of relative risk for diseases)

Disease	Males		Females		Total	
	RR ^a	95% CI ^b	Rr ^a	95% CI ^b	RR ^a	95% CI ^b
Chickenpox	0.32*	0.15–0.71	0.72	0.30–1.73	0.46*	0.26–0.80
Measles	1.81	0.61–5.33	1.30	0.40–4.18	1.56	0.71–3.44
Mumps	1.18	0.59–2.34	3.70*	1.37–10.01	1.81*	1.05–3.13
Rubella	0.85	0.42–1.70	1.27	0.61–2.65	1.02	0.62–1.70
Skin allergy	0.69	0.26–1.88	0.84	0.31–2.31	0.76	0.37–1.55
Asthma/Bronchitis	0.43	0.16–1.16	1.06	0.34–3.24	0.61	0.29–1.28
Hay fever	1.66	0.64–4.34	1.07	0.19–6.02	1.49	0.65–3.43
Hay fever/skin allergy	0.97	0.43–2.17	0.89	0.35–2.28	0.94	0.51–1.73
Hay fever but no skin allergy	1.54	0.52–4.56	1.30	0.12–14.51	1.49	0.55–4.02
Skin allergy but no hay fever	0.45	0.12–1.64	0.83	0.27–2.53	0.63	0.27–1.44
Intestinal diseases	0.87	0.31–2.45	0.54	0.16–1.77	0.70	0.32–1.52
Hepatitis	1.62	0.31–8.41	–	–	0.92	0.22–3.81
Kidney diseases	0.78	0.14–4.43	0.90	0.09–8.68	0.82	0.20–3.27
Bone diseases	0.45	0.09–2.17	0.45	0.09–2.17	0.45	0.15–1.37
Ever had an injury or accident	1.97	0.94–4.14	0.82	0.38–1.77	1.30	0.78–2.17
Ever had a bone injury	1.61	0.85–3.02	0.62	0.24–1.61	1.18	0.71–1.97

^a RR relative risk.

^b CI, confidence interval.

* $P < 0.05$.

3.4. Children's diseases

The children's past medical experiences were analyzed in three categories: previous typical childhood illnesses, typical immunizations against the childhood diseases, and previous clinical diseases, such as asthma and bronchitis, trauma, and bone injuries.

The prevalence of medical episodes and childhood and other diseases among patients and controls are shown in Tables 4 and 5.

For boys, there was a strong negative relation between clinically apparent chickenpox and bone tumors (Table 4); and because of the strong influence of male patients, the RR of 0.46 was statistically confirmed for both girls and boys.

Measles and mumps showed increased RR, although the RR of 1.81 was statistically significant only for mumps; the RR of 3.70 for having a history of mumps was statistically confirmed for females. Most RR estimates, however, were not significant, and the above mentioned extreme findings must be interpreted in the light of the high number of estimates.

Trauma and accident carried an increased risk of borderline significance with a RR of 1.97 (95% CI = 0.94–4.14) for boys (RR = 0.82 for girls), whereas bone injury and trauma had a RR of 1.61 for boys (95% CI = 0.85–3.02) and a decreased risk for girls (RR = 0.62).

For diseases such as hay fever and allergic reactions without dermal allergy the RR was 1.49, but not statistically significant. Dermal allergy and allergy without hay fever were inversely associated with bone tumors (RR = 0.76 and 0.63).

The univariate analysis of vaccinations and repeated immunizations is shown in Table 5. Although there are some elevated RRs (e.g., for tetanus and polio vaccination

Table 5
Univariate analysis (estimates of relative risk for vaccinations)

vaccination	Males		Females		Total	
	RR ^a	95% CI ^b	RR ^a	95% CI ^b	RR ^a	95% CI ^a
BCG	0.75	0.24–2.35	0.64	0.19–2.13	0.70	0.30–1.59
BCG repeated	0.59	0.19–1.89	0.74	0.22–2.49	0.66	0.28–1.52
Chickenpox	1.79	0.36–8.86	0.68	0.18–2.55	1.04	0.39–2.77
Chickenpox repeated	0.62	0.28–1.39	1.02	0.42–2.46	0.77	0.43–1.41
Polio	0.55	0.11–2.83	0.48	0.06–3.60	0.52	0.15–1.86
Polio repeated	1.45	0.37–5.61	3.40	0.69–16.8	2.16	0.77–6.06
Tetanus	0.55	0.11–2.83	0.41	0.08–2.04	0.47	0.15–1.49
Tetanus repeated	1.09	0.35–3.38	1.75	0.47–6.56	1.35	0.58–3.15
Diphtheria	0.45	0.11–1.79	0.41	0.10–1.64	0.43	0.16–1.15
Diphtheria repeated	0.56	0.21–1.53	1.49	0.47–4.71	0.88	0.43–1.82
Pertussis	1.78	0.71–4.47	0.56	0.21–1.54	1.07	0.56–2.04
Pertussis repeated	1.16	0.53–2.56	0.33*	0.11–0.93	0.70	0.39–1.27
Reaction after vaccination	0.93	0.26–3.35	1.43	0.38–5.34	1.14	0.45–2.86

^a RR relative risk.

^b CI: confidence interval.

* $P < 0.05$.

consistently in both sexes) the results were never statistically confirmed, and often showed different results for both sexes.

The height at the time of the interview was used for descriptive comparisons, no difference was found between the cases and controls (Table 6).

When all data were compared together, the cases were on average 0.6 cm higher than the controls (Table 6). The subgroup with osteosarcoma alone had a 0.9 cm difference. In girls, the differences were 1.1 cm for all and 2.9 cm in the osteosarcoma group (as shown in Table 6). A growth spurt was seen in the girls aged 10–14 years. Although the data do not stem from a cohort, the cases between ages 7 and 10 were smaller (139.3 cm) compared with the controls

(144.9 cm); in the 11–13 age group, the 11 patients were taller (159.0 cm) than the 19 controls (153.5 cm), and in the 14–16 age group, the 11 patients were on average 168.5 cm tall, compared with 164.4 cm in the 30 controls. In boys, the biggest growth spurt occurred from age 14 onwards.

3.5. Psychosocial variables

A strong effect was found with difficulties in school versus faring well in school, because the univariate analysis showed that school problems occurred were more frequently in patients and contentment at school was found more frequently in controls (Table 7).

Table 6
Average height of cases and controls at time of interview, all cases included

Age group	Male				Female			
	Cases		Controls		Cases		Controls	
	<i>n</i>	cm	<i>n</i>	cm	<i>n</i>	cm	<i>n</i>	cm
7–10	3	137.7	6	134.0	3	139.3	9	144.9
11–13	6	148.3	23	156.8	11	159.0	19	153.5
14–16	19	173.2	27	174.1	11	168.5	30	164.4
17–18	8	177.8	20	176.1	5	162.2	20	166.7
19+	14	179.0	34	177.6	8	166.6	20	166.2
Total	50		110		38		98	
Mean height		170.3		169.7		162.5		161.4
Min		129.0		130.0		135.0		130.0
Max		188.0		193.0		180.0		181.0
S.E.		2.1		1.4		1.7		1.0
Average height of osteosarcoma patients and matched controls								
Mean height	33	170.4	81	169.5	26	165.5	66	162.6
Min		129.0		130.0		149.0		141.0
Max		188.0		190.0		180.0		178.0
S.E.		2.5		1.6		1.5		1.1

Table 7
Difficulties or contentment at school (%):

		Cases	Controls		
			Hospital	Neighbour	Family
Difficulties at school					
Males	Yes	38.0	28.0	13.9	29.2
	No	62.0	72.0	86.1	70.8
Females	Yes	26.4	16.2	3.0	3.6
	No	73.7	83.8	97.0	96.4
Contentment at school					
Males	Yes	82.0	88.0	91.7	79.2
	No	18.0	12.0	8.3	20.8
Females	Yes	94.7	83.8	93.9	100.0
	No	5.3	16.2	6.1	0.0

For cases, the emotionally important persons had changed more frequently than for the controls (Table 3).

3.6. Selected factors and their interaction

Multivariate analysis was used to search for interaction of individual risk factors. Table 8 contrasts univariate results for all types of tumors and both sexes with findings in a multivariate model including those results simultaneously, combining all cases. Including changes of residence, breast feeding, and paternal age in the analysis, a negative experience in school was consistently associated with an increased risk for bone tumors in boys (RR = 3.07) (Table 8),

and for girls a RR of 2.92, both statistically confirmed. For the subgroup osteosarcomas, the RR for boys was 5.29 and for girls 7.19. This result is consistent for both sexes and supports the theory that psychosocial factors may show an unconfounded effect.

Paternal age over 30 years at the birth of the proband became statistically confirmed in the multivariate approach, if four other risk factors were included. The variable “change of an emotionally important person” was not sufficiently strong to be confirmed by itself, but slightly enhanced the effect of other variables.

For the case-group osteosarcomas, most risk estimates remained or were enhanced (e.g., school problems, breast feeding in boys), and for girls the paternal age at birth became important (Table 9). Numbers became too small for a meaningful analysis of the other tumor types, and could only be carried out for a few variables in girls. Although paternal age emerged strongly (RR = 2.86), none of the associations was statistically confirmed.

Changes in behavior were observed in connection with puberty (as an explanation of the mother) in several cases (32%), among them there were, however, several cases with a pronounced observation of openly expressed difficulties after the birth of a younger sibling (6%) and observable depression (4%), whereas others expressed pronounced disagreement with “psychological reasons.”

Shocking events reported were death of a close persons because of cancer (2%), disappointment of a parent after divorce (4%), or overly sensitive interpretation of shocking

Table 8
Relative risk estimates for selected variables (univariate and multivariate analysis) for all tumors

Variable	Males		Females		Total	
	RR ^a	95% CI ^b	RR ^a	95% CI ^b	RR ^a	95% CI ^a
Univariate analysis						
No. of residences >1	1.93	0.89–4.21	1.52	0.66–3.52	1.73	0.98–3.06
Difficulties at school	2.35*	1.07–5.12	3.00*	1.10–8.17	2.58*	1.39–4.78
Single child	1.19	0.44–3.18	1.23	0.42–3.66	1.21	0.58–2.51
Proband has been breastfed >2 months	0.37*	0.15–0.90	1.65	0.68–4.01	0.74	0.40–1.34
Age of father at birth of proband >30	1.52	0.73–3.14	1.99	0.83–4.78	1.69	0.97–2.96
Change in emotionally important person	2.03	0.59–7.03	3.28	0.72–15.01	2.47	0.94–6.47
Multivariate model I ^c						
No. of residences >1	2.40	0.96–5.99	1.53	0.60–3.91	1.83	0.98–3.44
Difficulties at school	3.07*	1.24–7.63	2.92*	1.03–8.30	2.79*	1.44–5.40
Single child	0.88	0.26–2.98	1.80	0.51–6.34	1.29	0.56–2.98
Proband has been breastfed >2 months	0.28*	0.10–0.77	1.48	0.57–3.82	0.65	0.34–1.23
Age of father at birth of proband >30	1.61	0.72–3.63	2.42	0.92–6.36	2.02*	1.10–3.72
Multivariate model II ^c						
No. of residences >1	2.34	0.92–5.93	1.69	0.63–4.54	1.87	0.98–3.55
Difficulties at school	2.86*	1.15–7.14	2.74	0.93–8.13	2.65*	1.36–5.18
Single child	1.15	0.34–3.93	2.14	0.60–7.65	1.52	0.66–3.48
Proband has been breastfed >2 months	0.31*	0.11–0.85	1.83	0.67–5.01	0.71	0.38–1.36
Age of father at birth of proband >30	1.71	0.75–3.88	2.36	0.90–6.21	2.11*	1.14–3.90
Change in emotionally important person	1.59	0.32–7.77	4.23	0.68–26.22	2.38	0.78–7.31

^a RR: relative risk.

^b CI: confidence interval.

^c Additionally adjusted for age.

* $P < 0.05$.

Table 9
Relative risk estimates for selected variables (univariate and multivariate analysis) for osteosarcomas

Variable	Males		Females		Total	
	RR ^a	95% CI ^b	RR ^a	95% CI ^b	RR ^a	95% CI ^b
Univariate analysis						
No. of residences >1	2.08	0.86–5.04	2.17	0.78–6.05	2.12*	1.08A.14
Difficulties at school	3.06*	1.22–7.69	6.10*	1.59–23.40	3.89*	1.82–8.34
Single child	0.89	0.28–2.83	3.14	0.76–13.00	1.48	0.63–3.52
Proband has been breastfed >2 months	0.23*	0.06–0.82	1.36	0.48–3.87	0.59	0.27–1.25
Age of father at birth of proband >30	1.25	0.53–2.96	2.10	0.76–5.75	1.56	0.81–2.99
Change in emotionally important person	2.22	0.56–8.81	3.28	0.72–15.01	2.65	0.95–7.37
Multivariate model I^c						
No. of residences >1	2.80	0.91–8.59	2.34	0.60–9.08	2.26*	1.01–5.06
Difficulties at school	5.27*	1.67–16.67	7.19*	1.47–35.29	4.11*	1.80–9.42
Single child	0.46	0.09–2.41	9.27*	1.41–60.97	1.83	0.64–5.25
Proband has been breastfed >a months	0.10*	0.02–0.53	1.35	0.36–5.02	0.42*	0.18–0.99
Age of father at birth of proband >30	1.16	0.42–3.16	4.55*	1.17–17.68	1.96	0.93–4.13
Multivariate model II^c						
No. of residences >1	2.76	0.89–8.55	2.84	0.63–12.79	2.41*	1.06–5.49
Difficulties at school	4.88*	1.47–16.24	7.10*	1.27–39.61	3.80*	1.64–8.77
Single child	0.79	0.16–3.88	14.88*	1.85–119.81	2.26	0.79–6.51
Proband has been breastfed >2 months	0.11*	0.02–0.60	1.86	0.45–7.76	0.47	0.20–1.11
Age of father at birth of proband >30	1.25	0.45–3.47	4.75*	1.18–19.12	2.10	0.99–4.47
Change in emotionally important person	1.03	0.14–7.37	4.74	0.48–47.07	2.03	0.57–7.17

^a RR: relative risk.

^b CI: confidence interval.

^c Additionally adjusted for age.

* $P < 0.05$.

statements of important persons (2 boys made this observation), of diseases of close persons (4%), quarrels at home (2%), or of traumatic events (burns, falls, 4%). Because there are no comparable data from the control groups, assessment of these variables was difficult.

In conclusion, stable associations which were not explained by chance have been found for all tumors with difficulties in school, age of the father > 30 years for both boys and girls (statistically significant), number of residences > 1 and change of an emotionally important person (borderline significant) as well as being a single child (not significant). For boys, breast-feeding was strongly protective (statistically significant).

Increased risks for osteosarcoma were associated with the same factors, whereas only for girls the status single child showed a very high risk for osteosarcoma in the multivariate models, again accompanied by the increased risk of the father being above 30 years of age at birth of the probands, which implies an early loss of the father as emotionally important person.

4. Discussion

The findings in this study, may contribute to the awareness for some inherent indicators that may explain the low incidence of bone tumors, taking into account the large populations of children worldwide, at the same time often abundant

prevalence and density of recognized risk factors such as radiation exposure and exogenous toxic exposures but very rare incident disease. Studying risk factors also requires that the variables considered responsible for the promotion of progressive, overt clinical manifestations of tumors in a juvenile population are assumed identical even if the initiating agent may vary for the specific histologic type of tumor at a given site. This consideration was a major focus of the data analysis. If multiple events and the individual susceptibility may have to coincide, which seems to be a likely explanation, this is corroborated by some findings of this study.

These findings are preliminary because replication is needed to validate the most prominent associations relating to psychosocial effects and related disturbed self-regulation.

A comparatively strong effect of “soft” risk factors such as psychosocial indicators of stress and coping ability being identified, several sources of biases are to be controlled. If the individual risk is related to disturbing inhibition of central nervous processes involved in self-regulation, the increasing exposure of young populations to neurotoxic and brainstem-damaging agents becomes important as a risk factor in the future. A possible recall bias in the present study may not be entirely excluded but is not seen as a major source of misclassification, because it would have to occur in both sexes at equal frequency to be accountable for an influence, whereas the pertinent associations based on hard data were stable for both sexes. The number of questions and the often more intimate nature of the personal interview

caused the duration of one interview to last between 60 and 90 min. There were no differences between cases and controls except for the additional questions asked of patients about their own interpretation of the reason for the disease onset.

Significant differences ($P < 0.05$) between the control groups accounted for the observed heterogeneity. For example, the variable “contact with farm animals” was expected to have a lower prevalence in hospital than in rural controls. Because of the large number of variables considered in this study, a model was used first that included only one variable at a time. We concluded that the hospital controls must be considered as not entirely representative for most variables. One explanation is a different urban/rural distribution.

The small number of cases of each sex restricted the analyses to relatively simple models using only major risk factors and confounders, emphasizing control of all risk estimates for age and sex by design. Each significant result was checked for consistency to determine if it prevailed to the same degree when using data from one control group only. The age limit was chosen to assure that juvenile development and associated hormonal influences on growth after puberty would be different from adults. Around this age, the thyroid gland stops growing.

Medical history revealed the biggest contrasts in reported frequencies of apparent childhood diseases (in contrast to inapparent courses) in both chickenpox and mumps, in that more control mothers or relatives reported clinically apparent chickenpox than cases throughout all control groups in males and among neighborhood and family controls controls in girls. Mumps, however, was more frequent in its observable form in female patients, in boys only if compared with hospital controls (Table 4), which makes the finding less robust. Recall bias, though, presumably would be equally distributed in both mothers of patients and controls, because no information on the importance of this association has been published so far and thus the answering to this question was blind. This issue was investigated further in a separate small study in the Heidelberg pediatric hospital, in which correspondence of the antibody titers against childhood diseases with reported observation of parents of the same probands was found to be almost nonexistent [11].

It is noteworthy that in another case–control study mumps was found in a monovariate analysis to be associated with an increased risk for Ewing’s sarcoma (RR = 3.0), whereas after vaccination for mumps the RR was 0.23 (both statistically confirmed) [12]. After adjustment for other important risk factors in a multiple logistic model, however, the RR for mumps decreased (RR = 0.74, confidence intervals 0.2–2.5).

Those variables that indicated stable risk estimates in the univariate analysis were included in a multivariate model, by which the individual risk estimates not only remained equally important in general, but also some became enhanced.

The number of residences and problems in school (in males) and the paternal age over 30 at birth were consistently important for both boys and girls, and they require close consideration. In addition, in the multivariate models (Tables 8 and 9) the practical value of the separate analyses by histologic type of bone cancer is shown, and it became evident that effects are stronger and statistically confirmed (despite smaller numbers) for the subgroup of patients with osteosarcoma. This may indicate the justification of a specific rate-related approach in cancer epidemiology concerning biologic entities as well as biologic models of specific etiologic relevance.

Cancer incidence being related to toxic and carcinogenic exposures [13,14], these factors are obviously not sufficient as sole causes, since cancer in the older age groups increasingly becomes related to promoting factors such as social distress, chronic depression, and hopelessness associated with higher relative risks than “classic” carcinogens. It is a truism that carcinogenesis is a multivariate and multicausal process, but progression of neoplasia to clinically manifest disease in particular has been linked to deficient self-regulation due to depressiveness and hopelessness, occurring in children more often than documented.

In the sarcoma entity of such neoplasias, however, which occur at an early age and only rarely, usual concepts would not apply [15]. Therefore, research is needed on further reasons why cancer becomes clinical and fatal in childhood, because regarding higher leukemia rates around nuclear power plants, the nevertheless inconsistent results need study of factors clearly unrelated to monocausal dose-response principles.

In 1952, Johnson reported on the growing suspicion that pregnancy may enhance the activity of some bone tumors as might be expected from the additive effects of growth hormone, estrogens, and androgens on osteoblastic activity [1]. When the study was designed, however, research into neuroimmunology and personality as important modifiers of outcome showed the strongest evidence of the influence of concomitant “social” factors was contributed by depressed mood and inhibited self-regulation [8]. This was recently supported by results from a prospective study on the synergistic effect of persistent depressed mood with a considerably higher risk of lung cancer in smokers [16].

The concept that chronic emotional stress and understimulation due to masked depression could result in a higher risk for manifest cancer compared with well-regulated, unstressed groups [17] was supported by findings on deficient DNA repair in lymphocytes after a radiation dose challenge in a highly distressed group when compared with a low-distress group [18].

Susceptibility, then, seems to depend on the functional differences of the organism that are summarized as host factors, including self-regulation and behavioral autonomy, topics of psychosocial research in childhood cancer, and increased acquired susceptibility [19]. Enhanced susceptibility

to exogenous etiologic agents is best described with effects of radiation exposure, for example.

The important concept of radiation as a cause of cancer is the one-hit effect theory together with the principle that the sensitivity of cells depends on their rate of mitotic activity, i.e. their proliferation activity. Hormonally induced increments of this rate increase the probability of somatic mutations occurring [20].

The observation within the case-group, was that the personality with a rational/antiemotional type of reaction to shocking events was over-represented, and—according to interview results—showed expression of strong disapproval of psychologic issues by the young patients, indicating denial and a tendency to rationalize (behaving in a controlled manner, instead of expressing sadness or complaint). This behaviour became evident in that the young patients either reacted rationally even after undergoing surgical interventions such as hemipelvectomy, by denying depression, or appeared inhibited about expressing sadness, agrees with the tendency to conform and adapt to expected behavior, such as self-control, which was found to be more prevalent in cancer candidates in prospective studies [21]. Only by the prospective approach, though, stable traits are assessed already before the proband develops the incumbent diseases. However, if the finding had been accompanied by questions about the effects of the event, that is, the degree of stress that the event produced in the affected individual, the results may have been more pronounced. This has been shown in a series of recently published studies on depressiveness and cancer risk, and even in a study using molecular genetic methods [18]. If intact self-regulation (low distress) versus stress without appropriate self-regulation (high distress) had been included, a modulating effect could be detected by Kiecolt-Glaser et al. [18] who showed that challenging human lymphocytes with a radiation dose (100 rad) and measurement of chromosomal repair resulted in delayed or damaged DNA repair only in persons classified as “highly distressed” compared with a “low-distress” reference group.

In this study, the emergence as a risk factor of such “hard” data as frequent changes of residence—an objective information unaffected by information bias—implies that loss of friends and close persons may become a sufficient reason for depressiveness in children.

Regarding the importance of duration of breast feeding for male infants, a Danish cohort study of juvenile diabetes demonstrated that breast feeding exerts a protective effect without explaining the complex psychology of this variable [22]. In this context, results of another case-control study showed considerable risk increments with specific parental occupations, which the authors found not entirely plausible from the point of view exogenous exposures, neither substantial nor measurable [13]. The only paternal occupation “social sciences” was associated with an odds ratio (OR) of 2.5 for osteosarcoma and an OR of 6.2 for Ewing’s sarcoma, and one maternal occupation with an OR of 3.1 was teaching, whereas high risks were associated with farm-

ing (OR = 7.8), managerial and administrative work (OR = 2.3), and product fabricating, assembling and repairing (OR = 2.0).

The common experience is that mothers and fathers with intellectual occupations often work longer, are more frequently absent from home, and are more absent-minded when at home, which may be shocking for single children who have no one to communicate. If these children are forced to leave their environment, friends, or relatives because the parents have to change residences to get to a new job, the loneliness and communication gap increase. Therefore, the findings of Hum et al. [13] are plausible with respect to these findings presented here. As mentioned above already in 1985, the influence of irreversibly stressful behavioral traits were found to be associated with disturbed repair after a radiation challenge by findings on deficient DNA repair in lymphocytes in a highly distressed group when compared with a low-distress group [18]. Also, after longlasting exposure to neurotoxic solvents, similar effects have been identifiable [23]. Stabler and Underwood [24] reviewed the pertinent literature linking disorders of mood and behavior, social inhibition and learning disability as results of afflicted cognitive and affective functions besides the somatic growth in children with growth hormone deficiency (“short” children). Young adults with impaired growth hormones are frequently found to have diminished quality of life, poor social relationships, and failed vocational pursuits, whereas growth hormone therapy can lead to improvements of the affective state, too. The authors hold that psychoeducational aspects should be adopted rather than to focusing mechanically on stature alone as a risk factor, since “although all need not receive growth hormone”, a therapy could be suitable and needed by all patients with delayed growth.

Consequently height as a risk factor for juvenile osteosarcoma was not identified in large case-control studies performed (Pendergrass, Pritchard and Robison, 1988, personal communication). In the context of proliferation, height at any age reflects the sum of all previous growth, and, therefore, data on stature alone are insufficient to assess the importance of skeletal growth and especially the influence of its increase or change on the pathogenesis of childhood bone cancer. The adequate study of a putative association by prospective follow-up is precluded by the low incidences of bone cancer, whereas the alternative approach by case-control study lacks valid data on height at earlier ages to appreciate growth spurts with desirable accuracy.

Compared with these drawbacks, personality was found to be a stable variable, and personality-related coping with adverse life events was described as having a stronger influence on the regulation of the psychoneuroendocrinology (regulation of the autonomous nervous system, the limbic system and hormonal homeostasis) than hitherto recognized [25]. Regulation of growth hormone by biogenic amines for release (dopamine) and inhibition (catecholamine-depletion) and chlorpromazine together with metabolic, endocrinologic, and behavioral aspects of beginning sexuality are of

particular importance during and after puberty, when vital functions may become inhibited for reasons originating in the social environment, which in rare cases leads to regulatory consequences such as masked or overt depression (considered to be directly related to dopamine suppression). Such cases are rare and occur in the fraction of the population that is unable to cope with adverse life events. Most studies reporting small or no effects related to shocking life events have suffered from an in-built defect because whereas life events are presumably occurring randomly to everyone, the reactions in response to the particular events (coping) differ by different personalities, leading to disappointment, help- and hopelessness in one fraction of the population, the so-called cancer candidates, with depression more often than in the fraction presenting with a fighting spirit, with anger and aggression as typical reactions [23,24]. In this study, however, typing of personality was not included since validated instruments for children were not available.

Somatomedin and significantly elevated growth hormone were measured by Goodman et al. [26] and called a “paraneoplastic syndrome”, i.e. the increased levels were thought to be related and due to secondary effects of the tumor. Measurements of height in a case–control study carried out ten years earlier by Fraumeni [27] only 1 month after diagnosis of bone tumors cannot exclude the possibility of a paraneoplastic syndrome, although these assessed measurements comparatively close in time to disease manifestation are an unlikely cause. Evain-Brion et al. [28] showed in 10 tall prepubertal children that growth hormone and somatomedin were elevated, suggesting a disorder of the hypothalamo-pituitary regulation, but unfortunately the children were not followed.

A marked pubertal rise of the levels of somatomedin was shown with peaks 2 years earlier in girls than in boys, directly related to the earlier spurt of height in girls [29]. If increased hormone levels which are responsible for normal growth occur in children who later develop bone cancer, especially in taller-for-age individuals with an accelerated growth rate, as suggested by Polednak, [6] the reasons for such increases may be worth investigating.

These may include stimuli that induce brainstem activity, as well as inhibit its normal function. Holly et al. [12] studied reasons for hormonal unbalance before such clinical developments by interviewing 43 patients with Ewing’s sarcoma and 193 control persons to identify paternal occupational and other exposures as causally associated with the disease. Adjusted RR estimates indeed suggested elevated prevalences of paternal agricultural occupations before conception of the subject (RR = 8.8, statistically confirmed). For children whose fathers had occupational exposures to herbicides, pesticides, or fertilizers, the RR was 6.1 (statistically confirmed).

Moreover, maternal use of thyroid hormone during pregnancy was associated with a statistically confirmed RR of 4.3 (RR = 3.4 if adjusted for other, such as paternal risk factors; 95% CI = 0.8–14.79), whereas exposure to cows and

living on or near a farm were also associated with increased risk but less important. Poison or a medication overdose was a risk factor (RR = 3.4), which remained also after adjustment (RR = 4.4).

These findings in a case–control study with a relatively small number of cases indicates an important influence of substances acting as toxicants on the central nervous system. Daigle et al. [14,30] confirmed these findings with another study including 204 cases of Ewing’s sarcoma interviewed all over the United States, aged 11 years on average (range, 8–21). The occupation of fathers in agriculture or farming showed a RR of 9.0 (statistically confirmed), but also smoking of both parents during pregnancy (RR = 2.17) and post-natal irradiation (RR = 2.05).

The degree of increase associated with maternal smoking during pregnancy was especially of concern and published in detail, [14] and interestingly the risks were lower and not significant in analyses using the region-matched controls. Patients more frequently had mothers who used tranquilizers during their pregnancy (RR = 7.0, statistically confirmed).

The phenomenon that the incidence of bone tumors is much higher among whites than blacks in the United States [14] has not been clarified, and for that reason the behavioral and emotional family interactions must be included in future research, taking into account the social structures of single child families and shocking events such as emotionally important losses, but also the inhibiting effects by endocrine disruption of neurotoxic compounds.

Studies investigating the efficacy of behavioral strategies or combinations of strategies to reduce side effects of medical procedures such as invasive chemotherapy in children with cancer seem to have yielded promising results. Carpenter [19] stressed the expansion of this concept to etiologic research and primary prevention in a systemic scientific approach.

Prevention has to include avoidance of neurotoxic exposures of all types as long as indices of susceptibility in children are not available, since a promoting effect of such exposures cannot be excluded in those having been exposed to carcinogenic initiation during pregnancy and early childhood, and suitable psychotherapy has not been validly introduced to prevent critical inhibition of self-regulation or progression of disease even after diagnosis.

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