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Growth and Development and Other Risk Factors for Osteosarcoma in Children and Young Adults

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Background. Risk factors for osteosarcoma in young people were investigated in a population-based case-control study among residents of New York State, excluding New York City.
Methods. Cases (n = 130) were diagnosed between 1978 and 1988 at ⩽24 years of age. Controls were randomly selected from birth certificates and were pair matched to cases on year of birth and sex. Exposure information was obtained by telephone interview with a subject and/or parent, and from birth certificates and school and medical records.
Results and Conclusions. A significant positive association was observed with height one year before diagnosis (*P*-value for trend = 0.02). No significant associations were observed between osteosarcoma and weight or body mass index one year before diagnosis, birth length, birthweight, gestational age, having reached puberty, having begun growth spurt, age at puberty, age growth spurt began, medical x-rays, antenatal exposures, family history of cancer, birth defects, or parental occupation.
Keywords: osteosarcoma, bone neoplasms, child development, growth, case-control study, height

Bone cancer is the fourth most common cancer in people under 25 years of age,[1] and osteosarcoma is the most common type of bone cancer in this age group. Very little is known about the aetiology of osteosarcoma in humans; the only known aetiologic agent is radiation.[2,3] Other factors suggested to be related to osteosarcoma include tall stature, previous bone trauma and viruses.[3–9] One case-control study observed an association between osteosarcoma and short length at birth.[9] Genetic factors have been identified in a small percentage of cases.[6,10,11]

Osteosarcomas are distributed throughout the entire skeleton, with the rapidly growing long bones of the extremities affected most often among young people.[12] An increase in osteosarcoma incidence around puberty has led many investigators to postulate that this cancer may be associated with the onset of puberty and may be a function of growth.[4–6] Animal studies have demonstrated an excess risk of bone sarcomas among larger breeds of dogs which suggests that a relationship may exist between human bone cancer and a large body size at the time of diagnosis.[13,14]

A number of antenatal environmental exposures such as infectious agents, drugs and radiation are capable of altering the normal development of an embryo which could contribute to the development of osteosarcoma in young people. Parental occupation is also of interest because parents can bring home chemicals or dusts from the workplace on their clothes, thus exposing their children.

The purpose of this population-based case-control study was to identify risk factors for osteosarcoma among people ⩽24 years of age. The specific aims were to investigate the relationship between osteosarcoma in young people and growth and development, radiation exposure, antenatal exposures, family history of cancer, birth defects, and parental occupation. In a previous publication using data from this study, the relationship between osteosarcoma in young people and fluoride exposure was investigated.[15]

METHODS

Cases and Controls

Details of the selection of cases and controls for this study have been described elsewhere.[15] Briefly,

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osteosarcoma cases who were <25 years of age and residents of New York State, excluding New York City, were retrospectively ascertained from the New York State Cancer Registry for the years 1978 through 1988. Seven cases with previous cancers were excluded, resulting in a case population of 171. Potential controls were randomly selected from live birth records in New York State, excluding New York City, and were one-to-one pair-matched to each case by year of birth and sex. Controls were assigned a reference age that was the age of diagnosis of the matched case, and they had to have survived until that reference age.

Interviews

Telephone interviews were requested from all study subjects (cases and controls) who were ⩾18 years of age and living. Interviews were also requested from parents of study subjects (including those <18 years of age). While subjects were able to provide some information about childhood exposures, their mothers or fathers were often able to provide more precise and detailed information.

The interview focused on the subjects' social, medical and exposure histories prior to diagnosis/reference. Issues regarding growth and development were addressed with questions about the subjects' heights and weights at various ages up to age 18, the age at which puberty occurred (age at menarche/voice change), and the age the growth spurt began. Questions were asked about exposure to x-rays, family history of cancer, and birth defects. Information on parental occupational exposures was obtained by asking whether either parent had worked in any of a list of occupations since the subject was born. In addition, parents were asked about maternal exposures during pregnancy.

Interviews were obtained from a case and/or a parent for 130 (76%) of the 171 osteosarcoma cases ascertained. Of the 130 cases for whom interviews were obtained, 64 (49%) were from the cases themselves and 126 (97%) were from parents. The low number of interviews from the cases themselves was due to 72 (42%) of the 171 ascertained cases being deceased. Thirty-five of the 130 cases participating in the study were born in New York City or outside of New York State (27%), making them not comparable to the controls with respect to place of birth.

Interviews were obtained from a subject and/or a parent for 130 matched controls, 118 (91%) from the controls themselves and 126 (97%) from the parents. An average of 2.1 birth certificates were selected before an adequate control was interviewed. Of the 143 birth certificates that were selected but did not result in a control interview, neither the control nor the parents could be located for 118 (83%) of these birth certificates. Nine controls resided in New York City or outside of New York State at the time of diagnosis of the matched case.

Collection of Data from Records

Birth certificates were acquired for 118 cases (91%) and all controls. Of the cases for whom no birth certificate was obtained, six were born outside of the US, and six were not found.

Height and weight information was obtained from medical and school records, in addition to the interviews. Information on the subject's primary physicians and the schools the subject attended was collected during the interview. Consent forms were mailed to all interviewed subjects or their parents, and were returned by 85% of the cases and 72% of the controls. The doctors and schools were then traced and asked to complete data forms on the subject's height and weight at various ages. Of the forms mailed, forms were returned with at least some information by 52% of the doctors and 82% of the schools. The per cent returned was similar for cases and controls.

Analysis

Odds ratios (OR), 95% confidence intervals (CI), and *P*-values were computed by creating conditional logistic models in EGRET.[16] *P*-values for trend were calculated for continuous variables by including the variables in a model in the continuous form. The *P*-value for the likelihood ratio statistic reflecting the difference between the model with and without that variable was interpreted as the *P*-value for trend.

To compare cases and controls with respect to height and weight one year before diagnosis/reference, a dataset was created that combined height and weight data from all available sources. This was necessary due to a large amount of missing data from records and the inability of subjects and parents to recall past height and weight. Since records were considered to supply accurate height and weight information, the primary source of information used was the school records. When this information was missing, the next source used was the medical record forms; then the subjects' interviews and finally the parents' interviews were used.

Height and weight data were converted to height-for-age and weight-for-age percentiles based on the age- and sex-specific growth standards of the National Center for Health Statistics using ANTHRO.[17] Body mass index (weight/height^2) was also calculated.

ANTHRO only calculates the height- and weight-for-age percentiles for ages ⩽17. For subjects aged >17, no meaningful increase in height after age 17 or 18 was

TABLE 1 *Number of osteosarcoma cases and controls, aged 3–24 years, odds ratios (OR), 95% confidence intervals (CI), and P-values for trend for height percentiles, weight percentiles and body mass index (BMI) one year before diagnosis, matched and unmatched,[a] New York State 1978–1988*

Variable	Matched					Unmatched				
	No. cases	No. controls	OR	95% CI	*P*-value for trend	No. cases	No. controls	OR	95% CI	*P*-value for trend
Height 1 year pre-diagnosis[b]					0.02					0.01
0–32.07%	14	23	1.00	–		18	30	1.00	–	
32.08–59.63%	14	18	1.29	0.48–3.52		22	28	1.32	0.58–3.00	
59.64–86.38%	19	13	2.85	0.93–8.69		24	21	2.02	0.86–4.72	
86.39–100%	20	13	2.29	0.91–5.74		27	17	2.68	1.14–6.30	
Weight 1 year pre-diagnosis[b]					0.21					0.39
0–30.22%	10	14	1.00	–		13	21	1.00	–	
30.23–60.21%	9	14	0.65	0.18–2.31		14	21	1.03	0.39–2.73	
60.22–80.96%	17	7	2.85	0.91–8.90		19	9	3.45	1.20–9.96	
80.97–100%	11	12	1.02	0.33–3.16		18	25	1.13	0.44–2.89	
Body mass index[c]					0.94					0.33
0–17.44	11	12	1.00	–		17	18	1.00	–	
17.45–19.72	11	11	1.12	0.34–3.70		16	16	1.06	0.39–2.88	
19.73–21.97	11	12	1.08	0.28–4.12		15	18	0.94	0.34–2.59	
21.98–29.72	12	10	1.38	0.35–5.41		16	21	0.84	0.31–2.30	

[a] Unmatched analyses controlled for year of birth and sex.
[b] Percentiles based on the age- and sex-specific growth standards of the National Center for Health Statistics[17]
[c] Both height and weight data were available for 45 matched pairs and 137 individuals (64 cases and 73 controls).

assumed, so the age 17 growth standard was applied. Because of the high likelihood that weight would continue to change with age, no extrapolations were made for the weight data. If height or weight was missing for the time one year before the diagnosis/reference age, but was available for the surrounding years, the mean of these two points was used as height or weight one year before the diagnosis/reference age.

Birthweight was abstracted first from the birth certificates, then from the parent interviews, and finally from the subject interviews. Birthweight was recorded in pounds/ounces and was converted to metric units. Birth length was obtained from the medical records, then from the parent interviews, and last from the subject interviews. Birth length was recorded in inches and was converted to metric units. Gestational age was obtained from the birth certificates.

Despite the use of multiple sources of information, there was still only a limited number of matched sets in which both the case and the control had information on height the year before diagnosis/reference (n = 67), weight the year before diagnosis/reference (n = 47), and birth length (n = 68). Consequently, in addition to the conditional logistic regression analyses using the matched pairs, unconditional logistic regression analyses were performed for the growth and development variables in which the matching was not maintained, allowing more subjects to be included. These analyses were performed adjusting for the matching variables, year of birth and sex.

RESULTS

Due to the matching, the cases and controls had the same distributions for sex (68% female), age at diagnosis/reference (mean ± s.d. = 15.1 ± 4.4) and year of birth (1966.9 ± 5.4). There were 18 non-white cases (13%) and four non-white controls (3%).

The height and weight percentiles and body mass indices one year before diagnosis/reference were each categorized into quartiles, based on the subjects included in the respective matched analyses (Table 1). A significant trend ($P = 0.02$) was observed of increasing risk of osteosarcoma with increasing height one year before diagnosis. Neither weight nor body mass index one year before diagnosis were associated with osteosarcoma.

The results of the analyses for height, weight and body mass index with the matching broken are also shown in Table 1. Again, a significant trend of increasing risk with increasing height was observed ($P = 0.01$). In this analysis, 91 cases were compared with 96 controls, as opposed to 67 pairs in the matched analysis.

The likelihood that the association observed between height and osteosarcoma could be explained by biases

TABLE 2 *Number of osteosarcoma cases and controls, aged 3–24, odds ratios (OR), 95% confidence intervals (CI), and P-values for trend for body size at birth and gestational age, matched and unmatched[a] analyses, New York State 1978–1988*

Variable	Matched					Unmatched				
	No. cases	No. controls	OR	95% CI	*P*-value for trend	No. cases	No. controls	OR	95% CI	*P*-value for trend
Birthweight[b]					0.44					0.41
<2500 g	9	5	1.00	–		9	5	1.00	–	
⩾2500 g	117	121	0.50	0.15–1.66		118	124	0.53	0.17–1.63	
Birthweight					0.44					0.41
1984–2977 g	29	36	1.00	–		29	36	1.00	–	
2978–3313 g	36	23	1.95	0.93–4.07		36	23	1.96	0.95–4.04	
3314–3664 g	32	29	1.20	0.61–2.37		33	30	1.38	0.68–2.79	
3665+ g	29	38	0.91	0.45–1.88		29	40	0.91	0.45–1.81	
Birth length					0.26					0.07
⩽48.26 cm	15	19	1.0	–		20	28	1.00	–	
50.8–53.34 cm[c]	41	40	1.30	0.59–2.89		56	57	1.46	0.72–2.95	
55.88+ cm	12	9	1.67	0.56–5.97		17	15	1.74	0.69–4.41	
Gestational age					0.61					0.59
<39 weeks	15	16	1.00	–		15	18	1.00	–	
39–41 weeks	80	83	1.01	0.48–2.12		83	95	0.99	0.46–2.14	
42+ weeks	15	11	1.58	0.52–4.80		15	14	1.29	0.47–3.54	

[a] Unmatched analyses controlled for year of birth and sex.
[b] Low birthweight is defined as <2500 g (ICD-9).
[c] This corresponds to birth lengths of 20 and 21 inches.

in the data was explored. Comparisons were made with respect to sex, age at diagnosis/reference, year of birth, race, and vital status between the subjects included in the matched and unmatched height analyses and the subjects excluded from these analyses. Compared to subjects not included in the analysis, those included were significantly older at diagnosis/reference (16.1 ± 4.2 versus 14.0 ± 4.3 matched data; 15.6 ± 4.2 versus 13.9 ± 4.6 unmatched data), had earlier years of birth (1966.4 ± 5.4 versus 1967.5 ± 5.5 matched data); (1966.6 ± 5.2 versus 1967.9 ± 5.9 unmatched data), and were borderline significantly more often white (95% versus 88% matched data; 94% versus 86% unmatched data). In the matched analysis, there was no differential selection of cases versus controls according to age or year of birth due to the matching. Furthermore, for those cases and controls included in the unmatched analysis, the ages at diagnosis/reference were similar (15.5 ± 4.2 for cases, 15.8 ± 4.2 for controls), as were the years of birth (1966.7 ± 5.3 for cases, 1966.4 ± 5.2 for controls). The trend of increasing risk of osteosarcoma with increasing height remained significant when non-whites were excluded from the analysis ($P = 0.01$, 60 matched pairs; $P = 0.03$, 82 cases, 93 controls unmatched).

Cases and controls were compared with respect to the source of height information, and were found to be fairly similar. In the matched analysis, height information came from school or medical records, as opposed to subject or parent interviews, for 81% of cases and 88% of controls. There were 48 pairs (72%) in which the height data came from the records for both pairs. The trend of increasing risk of osteosarcoma with increasing height was borderline significant when the matched analysis was restricted to these 48 matched pairs ($P = 0.08$). In the unmatched analysis, height information came from records for 84% of cases and 91% of controls. The trend of increasing risk of osteosarcoma with increasing height remained significant when the unmatched analysis was restricted to these subjects ($P = 0.045$; 76 cases, 87 controls).

Finally, it was considered whether the cases born in New York City or outside of New York State or the controls who resided in New York City or outside of New York State at the reference age introduced a bias. The trend of increasing osteosarcoma risk with increasing height remained significant after excluding these cases and controls from the matched analysis ($P = 0.015$; 50 pairs) and the unmatched analysis ($P = 0.02$; 71 cases, 94 controls), respectively.

No significant associations were observed between birthweight, birth length, or gestational age and osteosarcoma in the matched analyses (Table 2). In an

TABLE 3 *Number of osteosarcoma cases and controls, aged 3–24, odds ratios (OR), 95% confidence intervals (CI), and P-values for trend for puberty and growth spurt variables, information from subjects' interviews only[a], matched and unmatched[b] analyses, New York State 1978–1988*

Variable	Matched					Unmatched				
	No. cases	No. controls	OR	95% CI	*P*-value for trend	No. cases	No. controls	OR	95% CI	*P*-value for trend
Age of puberty[c]					0.79					0.52
9–12 years	9	10	1.00	–		15	19	1.00	–	
13 years	9	7	1.61	0.33–7.96		11	24	0.55	0.20–1.53	
14–21 years	11	12	1.11	0.28–4.43		14	25	0.75	0.27–2.09	
Age growth spurt began[d]					0.26					0.78
9–11 years	7	8	1.00	–		12	16	1.00	–	
12 years	5	11	0.57	0.12–2.74		5	21	0.29	0.08–1.04	
13 years	6	5	1.60	0.37–6.89		6	18	0.43	0.12–1.47	
14–21 years	12	6	2.79	0.52–15.09		16	23	0.89	0.31–2.59	
Reach puberty[e]					–					–
No	18	19	1.00	–		20	36	1.00	–	
Yes	38	37	1.13	0.43–2.92		40	68	1.07	0.48–2.38	
Began growth spurt[f]					–					–
No	12	9	1.00	–		13	18	1.00	–	
Yes	33	36	0.50	0.13–2.00		39	78	0.55	0.22–1.39	

[a] 64 case subjects and 118 control subjects were interviewed. There were 64 matched pairs for which subject interviews were obtained for both members of the pair.

[b] Unmatched analyses controlled for year of birth and sex.

[c] Includes those subjects who had reached puberty one year prior to the diagnosis/reference age or earlier. The matched analysis includes pairs in which both the case and control had reached puberty one year prior to the diagnosis/reference age or earlier.

[d] Includes those subjects who began their growth spurt one year prior to the diagnosis/reference age or earlier. The matched analysis includes pairs in which both the case and control began their growth spurt one year prior to the diagnosis/reference age or earlier.

[e] Reached puberty one year prior to the diagnosis/reference age or earlier. In the matched analysis, one or both members of eight pairs did not know when they reached puberty (age at menarche/voice change).

[f] Began growth spurt one year prior to the diagnosis/reference age or earlier. In the matched analysis, one or both members of 19 pairs did not know when they began their growth spurt.

unmatched analysis, however, there was a borderline significant trend of increasing osteosarcoma risk with increasing birth length ($P = 0.07$) (93 cases, 100 controls versus 68 pairs in the matched analysis). The primary source of information for birth length was the parents' interviews (80% of cases, 84% of controls). The primary source of birthweight information was the birth certificates (91% of cases, 100% of controls).

Subjects were better than their parents at providing information on puberty and growth spurt, as indicated by a lower percentage of 'don't know' responses; therefore, only information from the subjects' interviews was used for these analyses. In the matched analyses, age of puberty and age growth spurt began were examined for pairs in which both the case and control had reached puberty or began their growth spurt one year prior to the diagnosis/reference age or earlier (Table 3). No significant associations were observed between osteosarcoma and age of puberty or age growth spurt began.

To further examine whether puberty or growth spurt were associated with osteosarcoma, analyses were conducted on whether the subject had reached puberty or had begun their growth spurt at least one year before the diagnosis/reference age (Table 3). No significant associations were observed.

The remaining analyses reported here were only performed with the matching maintained, as there were few missing values. No significant associations were observed between osteosarcoma and exposure to medical x-rays, history of cancer in first-degree relatives, or birth defects (data not shown).

In order to examine the association between antenatal exposures and osteosarcoma, only information collected from the parents was used. This included maternal use of alcohol and cigarettes, exposure to dental and medical x-rays, intake of vitamin or mineral supplements, and intake of hormones (oestrogens, growth hormone, thyroid hormone, steroids, diethylstilboestrol [DES]) and drugs (tetracycline in particular) during pregnancy.

No significant associations were observed between maternal exposures during pregnancy and osteosarcoma (data not shown).

No significant associations were observed between parental occupations from birth of the subject to the diagnosis/reference age and osteosarcoma (data not shown). Parents were asked about work in various industries and whether they worked with various chemicals or materials. The number of affirmative responses for each occupation/exposure was quite small, with a maximum of eight affirmative responses to handling lead, mercury, chromium, or nickel.

It has been reported previously that race and maternal age are potential confounders in these data.[15] Adjustment for race and for maternal age did not materially change any of the results of the analyses reported here.

DISCUSSION

Because of the increase in osteosarcoma incidence around puberty, many investigators have postulated that osteosarcoma may be associated with the onset of puberty and may be a function of growth.[4–6] The shape of the age-incidence curve for osteosarcoma in young people bears a remarkable resemblance to the velocity curve for height,[18] with a shift to the right of several years. Females develop osteosarcoma at a younger age than males, consistent with the earlier skeletal development and maturation of females.[19] The increase in bone cancer incidence/mortality during the first 20 years of life is followed by a decline in incidence/mortality after the cessation of growth.[3] It is well known that rapidly growing tissue is particularly susceptible to carcinogenesis.[20]

In both the matched and unmatched analyses, a significant association was observed between height one year before diagnosis/reference and osteosarcoma. This association was found to be robust when various biases were considered. However, due to missing data, particularly in the matched analysis, the possibility that selection bias influenced the results cannot be completely ruled out.

Nevertheless, this finding was consistent with earlier reports that osteosarcoma cases are taller at the time of diagnosis than controls,[5,7] although a more recent study did not observe this association.[9] Weight, body mass index, age of puberty, age growth spurt began, having reached puberty, and having begun the adolescent growth spurt were not associated with osteosarcoma.

A previous study found an association between osteosarcoma in young people and short birth length.[9] In the present study, no association was found between osteosarcoma and birth length in the matched analysis. In the unmatched analysis, a borderline significant trend of increasing osteosarcoma risk with increasing birth length was observed. This association was in the opposite direction of that previously found.[9] Given these contradictory findings from two relatively small studies, the authors conclude there is presently no convincing evidence for an association between birth length and osteosarcoma.

No association was found between osteosarcoma and exposure to medical x-rays. Osteosarcomas have been reported to arise in a linear dose-response pattern after radiation therapy, but the amount of exposure received was orders of magnitude higher than the medical x-ray exposures experienced by the subjects in this study.[2,3]

One major limitation in this study was that cases were identified retrospectively for the period 1978–1988. Problems with recall became exacerbated due to the long period of time that may have passed since the exposures. The number of pairs analysed for a given variable was often diminished due to responses of ‘don’t know’ or to missing data from birth, medical or school records. Prior studies on risk factors for osteosarcoma in young people were also based on small sample sizes ranging from 64 to 85 cases.[5,9] Lack of power due to the small sample size could render it difficult to detect associations; biases in the selection of subjects included in a given analysis could result in spurious associations.

A second limitation of this study was the relatively large number of potential controls who were selected for the study but never located. These potential controls may have changed their address more frequently than controls who were located and participated in the study. If, in fact, the controls in the study were not representative of potential controls with respect to mobility, and if mobility was appreciably related to height or to other variables of interest (perhaps through a joint relationship with socioeconomic status), then results of this study would be influenced by a selection bias.

In summary, the association between height and osteosarcoma in young people observed in three of four studies, including the present study, is intriguing. However, as in previous studies, examination of the growth and development issues in this study relied on relatively small sample sizes. In addition, due to a substantial amount of missing data, the possibility that selection bias influenced the results cannot be ruled out. Strategies for investigating these issues with larger sample sizes and higher rates of information retrieval need to be developed.

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