Fluoride Exposure and Childhood Osteosarcoma: A Case–Control Study

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ABSTRACT

Objectives. This study tests the hypothesis that fluoride exposure in a nonoccupational setting is a risk factor for childhood osteosarcoma.

Methods. A population-based case–control study was conducted among residents of New York State, excluding New York City. Case subjects (n = 130) were diagnosed with osteosarcoma between 1978 and 1988, at age 24 years or younger. Control subjects were matched to case subjects on year of birth and sex. Exposure information was obtained by a telephone interview with the subject, parent, or both.

Results. Based on the parents' responses, total lifetime fluoride exposure was not significantly associated with osteosarcoma among all subjects combined or among females. However, a significant protective trend was observed among males. Protective trends were observed for fluoridated toothpaste, fluoride tablets, and dental fluoride treatments among all subjects and among males. Based on the subjects' responses, no significant associations between fluoride exposure and osteosarcoma were observed.

Conclusions. Fluoride exposure does not increase the risk of osteosarcoma and may be protective in males. The protective effect may not be directly due to fluoride exposure but to other factors associated with good dental hygiene. There is also biologic plausibility for a protective effect. (*Am J Public Health.* 1995;85:1678–1683)

Introduction

Although the benefit to dental health of fluoride exposure has been clearly established, the release of the National Toxicology Program study in which a dose–response relationship for osteosarcoma was indicated for exposure to sodium fluoride among male rats has provoked criticism of water fluoridation programs.[1] In response, the Department of Health and Human Services conducted a review of fluoride's benefits and risks and recommended that analytical epidemiologic studies of osteosarcoma be conducted to determine the risk factors associated with its development.[2]

Osteosarcoma is the fourth most common cancer in persons under 25 years of age[3] occurring most often around puberty.[4] The only known etiological agent is radiation[5]; other suggested risk factors include a rapid rate of bone growth, previous bone trauma, and viruses.[6–8] Persons with the hereditary form of retinoblastoma or with the Li–Fraumeni cancer family syndrome are at high risk for osteosarcoma.[9,10]

Fluoride is deposited directly into the bone, with about 99% of fluoride in the body contained in the skeleton.[1,2] Children, who are actively forming bone, have a higher amount of uptake of fluoride into the bone matrix than adults.[1,2] Fluoride uptake into bone results in an increased rate of osteoblast proliferation and bone formation.[11] Bone in the areas of the knees, ankles, shoulders, and wrists, where childhood osteosarcomas most often occur, shows a high response to fluoride.[12]

Toxicological studies of sodium fluoride have yielded mixed results.[1,13–15] In in vitro studies fluoride appears to be mutagenic and can induce chromosome aberrations, sister chromatid exchanges, cytotoxicity, and neoplastic transformation in cultured mammalian cells.[1,13,14] The recent study conducted by the National Toxicology Program found equivocal evidence for a carcinogenic effect among male F344/N rats, but there was no evidence for carcinogenicity in female F344/N rats, nor in male or female mice.[1] Another study sponsored by the Procter and Gamble company found no carcinogenic evidence in Sprague–Dawley rats.[16]

Ecological studies generally have found no relationship between fluoride levels in drinking water and osteosarcoma and bone cancer incidence or mortality rates.[17–23] Individual exposures were examined in only two small studies.[24,25] One study based on only 20 males found that males under age 20 years who resided in communities with fluoridated water at the time of diagnosis had a higher osteosarcoma rate than those who resided in communities with nonfluoridated water.[24] The other study had only 22 matched case–control pairs and found no associa-

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tion between osteosarcoma and lifetime fluoride exposure from drinking water.[25]

Within New York State, average annual osteosarcoma incidence rates from 1976 to 1987 in fluoridated areas were found not to differ from rates in nonfluoridated areas.[23] To further investigate the potential association of fluoride exposure with childhood osteosarcoma in New York State, excluding New York City, we conducted a population-based case–control study. All sources of fluoride except dietary sources were examined separately and were combined to estimate total lifetime fluoride exposure. Because deleterious effects were limited to male rats in the National Toxicology Program study, additional analyses were conducted by gender.

Methods

Study Population

Cases of osteosarcoma newly diagnosed from January 1978 through December 1988 were identified from the New York State Cancer Registry. Case subjects who were 24 years of age or younger and residing in New York State, excluding New York City, at the time of diagnosis were eligible for inclusion in the study. Case subjects with preexisting cancers were excluded, resulting in a case population of 171.

Control subjects were pair-matched one-to-one to case subjects by year of birth and sex. Potential control subjects were randomly selected from live birth records maintained by the New York State Department of Health. All children born in New York City were excluded. Control subjects were assigned the same age at diagnosis as the corresponding case subjects as a reference date to provide equal time periods at risk. Control subjects had to survive until their matched case subject's age at diagnosis.

Case and control subjects and their parents were traced to determine their vital status and to locate their current address and telephone number. Although it was easier to trace the case subjects than the control subjects because more current information was available, an exhaustive search was made for each potential control subject before another one was selected as a replacement. An average of 2.10 birth certificates were searched before an adequate control subject was located and interviewed.

TABLE 1—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables (Parents' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	*P*
Tablets, mg					.03
0	110	104	1.00	. . .	
1–250	3	4	0.81	0.18, 3.66	
251–550	7	4	1.72	0.50, 5.91	
551–3500	2	10	0.11	0.01, 0.88	
Mouth rinses, mg					.43
0	110	111	1.00	. . .	
1–7	5	2	4.02	0.44, 36.75	
8–50	4	4	1.03	0.23, 4.57	
51–1005	3	5	0.60	0.14, 2.65	
Toothpaste, mg					.06
0–433	38	23	1.00	. . .	
434–862	26	35	0.43	0.20, 0.92	
863–1425	30	31	0.54	0.25, 1.19	
1426–2235	28	33	0.49	0.23, 1.06	
Dental treatments, mg					.06
0	88	91	1.00	. . .	
15	25	17	1.52	0.75, 3.08	
30–60	4	6	0.75	0.21, 2.72	
75–390	5	8	0.64	0.18, 2.21	
Water, mg					.61
0	40	57	1.00	. . .	
1–1850	32	16	4.13	1.65, 10.35	
1851–3385	26	23	1.84	0.81, 4.20	
3386–6100	24	26	1.40	0.60, 3.29	
Total fluoride, mg					.24
0–1235	31	31	1.00	. . .	
1236–2161	31	29	1.04	0.50, 2.14	
2162–4101	34	27	1.20	0.56, 2.57	
4102–8433	26	35	0.67	0.29, 1.54	

Note. Odds ratios were estimated from conditional logistic models.

Interviews

A telephone interview was requested from all living study subjects who were at least 18 years of age. Permission to interview the subject's parent was requested during the interview. If a case subject refused the interview, permission was requested to interview the case subject's parent. If permission was not granted, the parent was not interviewed. If the subjects were deceased or too young for an interview (<18 years old), the contact letters were sent directly to the parents. If a control subject did not allow us to contact his or her parents (n = 3), or if the parents refused to be interviewed after the control subject was interviewed (n = 6), the control subject was replaced.

The interview focused on the subjects' sociodemographic, medical, and exposure histories before the date of diagnosis or reference date. Fluoride exposure information was obtained from questions about the use of fluoridated products (toothpastes and mouth rinses) and fluoride supplements (drops, tablets, vitamins, and dental treatments). In addition, a complete residential history from birth until the age of diagnosis or reference age was taken. This history included complete addresses, the years of residence at each address, the water source (public supply or private well) at each address, and whether the water at each address was fluoridated.

There were a total of 130 case–control pairs for which the subject or the parent or both were interviewed for both members of the pair. Sixty-four (49%) interviews were completed for the case subjects, 126 (97%) for the case parents, 119 (92%) for the control subjects, and 126 (97%) for the control parents. Ninety percent of the parents who were interviewed were biologic mothers. The primary reasons for not obtaining interviews

TABLE 2—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables for Males (Parents' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	*P*
Tablets, mg					.08
0	73	67	1.00	...	
1–250	2	2	1.00	0.14, 7.10	
251–550	1	3	0.33	0.03, 3.21	
551–3500	2	6	0.20	0.02, 1.71	
Mouth rinses, mg					.99
0	73	72	1.00	...	
1–7	2	2	0.90	0.05, 17.89	
8–50	2	2	0.81	0.09, 7.52	
51–1005	1	2	0.46	0.04, 5.81	
Toothpaste, mg					.01
0–433	12	27	1.00	...	
434–862	23	15	0.23	0.08, 0.70	
863–1425	19	21	0.41	0.14, 1.18	
1426–2235	24	15	0.25	0.09, 0.70	
Dental treatments, mg					.04
0	60	56	1.00	...	
15	14	11	1.00	0.39, 2.55	
30–60	1	5	0.20	0.02, 1.80	
75–390	3	6	0.50	0.12, 2.07	
Water, mg					.62
0	27	34	1.00	...	
1–1850	20	11	2.81	0.97, 8.09	
1851–3385	15	12	1.67	0.58, 4.77	
3386–6100	16	21	0.93	0.31, 2.83	
Total fluoride, mg					.02
0–1235	17	19	1.00	...	
1236–2161	17	23	1.14	0.46, 2.84	
2162–4101	17	19	0.78	0.27, 2.22	
4102–8433	27	17	0.41	0.14, 1.22	

Note. Odds ratios were estimated from conditional logistic models.

were the subject being deceased (42% of the case subjects), inability to locate the subject or parent (8% of the case subjects, 42% of the control subjects), and refusal by the subject or parent to participate in the study. Approximately 6% of the case subjects, control subjects, and control parents refused, and 12% of the case parents refused. Eleven case subjects and their matched control subjects were too young for interviews.

Fluoride Exposure Index

To analyze the relationship between fluoride exposure and osteosarcoma, the lifetime exposure to each source of fluoride was determined, and these were summed into a total lifetime fluoride exposure index. These sources included fluoride drops, tablets, and vitamins, fluoridated mouth rinses and toothpastes, dental fluoride treatments, and fluoride from drinking water and breast milk. It was not possible to measure fluoride from food, which ranges from 6% to 32% of total fluoride intake.[26]

For more than 96% of the addresses identified, the respondent indicated knowledge of whether the water supply was public or private. These data were validated by geocoding all addresses and matching them to census data. There was 96% agreement between the water source according to the 1990 census and the water source reported by interview.

The subjects or parents indicated knowledge of the fluoridation status of their water for only 40% of the addresses. Therefore, instead of relying on the interview information, all of the addresses were further investigated to determine fluoridation status. Natural fluoride levels are relatively low in New York State, so the water was considered not fluoridated for all addresses with private wells in New York. Because fluoridation often follows town boundaries, addresses identified to be within city limits were then compared with a fluoridation census.[27] Telephone calls were made to appropriate agencies to determine the fluoridation status of addresses that could not be classified with the aforementioned method.

The average amount of fluoride ingested by age for each fluoride source was determined from the literature. For example, the dose recommended by the American Dental Association for fluoride drops, tablets, and vitamins was 0.25 mg per day for an infant newborn to 2 years old, 0.50 mg for a 2- to 3-year-old, and 1.0 mg for a child 3 to 13 years of age for the time period of this study.[28–30]

Population-based estimates of tap water intake were used to determine the amount of water ingested by age and sex categories. The estimates were derived from the 1977 and 1978 US Department of Agriculture Nationwide Food Consumption Survey, and the mean estimates for the northeast geographic region (all seasons) were used.[31] The fluoride level in water was assumed to be 1.0 mg/liter for fluoridated areas and 0 mg/liter for nonfluoridated regions.

Cumulative lifetime exposure for each fluoride source was estimated in milligrams by multiplying the amount ingested per exposure by the number of times per day exposed by the total number of days exposed. The lifetime exposures for each fluoride source were then summed to create a total lifetime fluoride exposure index.

Apart from dental fluoride treatments, for which there was a large amount of missing data (approximately 23% of the parents and 8% of the subjects), fewer than 5% of the parents' responses and fewer than 2% of the subjects' responses were missing. The percentage of missing responses did not differ between case and control subjects. A standard set of rules was established to impute values for missing data.

To measure intensity of exposure, each lifetime fluoride exposure variable was divided by the age at diagnosis or reference age to get an average annual exposure. Although matched pairs would still have the same within-pair association because of the matching by age, the relationship among pairs would change with this measure.

Analysis

Because recall could be different between the subjects and parents, separate data sets were created for each of these data sources, maintaining the matching. Sixty-four matched pairs were in-

cluded in the subjects' data set and 122 matched pairs were included in the parents' data set.

EGRET was used to analyze matched observations of each variable against disease status.[32] Odds ratios, 95% confidence intervals, and *P* values were computed by creating conditional logistic models. *P* values for trend were calculated by including the variables in models in their original, noncategorized continuous form. The *P* value for the likelihood ratio statistic reflecting the difference between the model with and the model without the continuous variable was interpreted as the *P* value for trend, which indicated whether the linear component of the trend was statistically significant. The *P* values do not necessarily appear to correspond to the trends of the categorical variables as presented because of the creation of arbitrary cutpoints in the continuous variables for presentation purposes. Extensive subgroup analyses were not conducted due to limitations presented by the relatively small number of subjects in the sample.

Results

Case subjects who were final study subjects (case subject and/or parent was interviewed) were not significantly different from case subjects for whom no interview was obtained (neither case subject nor parent was interviewed) with respect to race, vital status, age at diagnosis, year of diagnosis, stage of tumor, and anatomic location of tumor. However, a statistically significant higher percentage of case subjects not interviewed were male (61% vs 32%). Of the 130 case subjects who were final study subjects, 42 (32%) were male, 51 (39%) were deceased, and 96 (74%) were between ages 10 and 19 years. Eighteen case subjects (14%) but only 4 control subjects (3%) were non-White. This difference was statistically significant ($P = .002$).

The bivariate relationships between osteosarcoma and lifetime exposure to fluoride from tablets, mouth rinses, toothpaste, dental treatments, and drinking water, along with the total lifetime fluoride exposure index, are shown in Table 1 for the parents' data set. Because of the small number of affirmative responses, the fluoride from drops and the fluoride from vitamins were not analyzed separately. Fluoride from toothpaste and total lifetime fluoride exposure were categorized into quartiles. However, because so many individuals did not have exposure to the other fluoride sources, the lowest-level category for these variables included only those individuals with no exposure. Tables 2 and 3 present results for the same lifetime fluoride variables for males and females, respectively.

TABLE 3—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables for Females (Parents' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	*P*
Tablets, mg					.20
0	37	37	No convergence		
1–250	1	2			
251–550	6	1			
551–3500	0	4			
Mouth rinses, mg					.30
0	37	39	No convergence		
1–7	3	0			
8–50	2	2			
51–1005	2	3			
Toothpaste, mg					.85
0–433	11	11	1.00	...	
434–862	12	11	0.93	0.31, 2.80	
863–1425	12	9	0.65	0.17, 2.47	
1426–2235	9	13	1.80	0.45, 7.18	
Dental treatments, mg					.70
0	28	35	1.00	...	
15	11	6	2.25	0.69, 7.61	
30–60	3	1	3.00	0.31, 28.84	
75–390	2	2	1.00	0.06, 15.99	
Water, mg					.12
0	13	23	1.00	...	
1–1850	12	5	10.55	1.22, 91.04	
1851–3385	11	11	1.65	0.41, 6.59	
3386–6100	8	5	2.81	0.62, 12.69	
Total fluoride, mg					.24
0–1235	14	12	1.00	...	
1236–2161	12	8	0.74	0.20, 2.69	
2162–4101	10	15	1.81	0.56, 5.82	
4102–8433	8	9	1.34	0.32, 5.57	

Note. Odds ratios were estimated from conditional logistic models.

Total lifetime fluoride exposure was not significantly associated with osteosarcoma among all subjects combined or among females. However, a significant protective trend was observed among males ($P = .02$). With respect to the individual sources of fluoride, a significant trend of decreasing risk with higher exposure was observed among all subjects for tablets ($P = .03$). The trends for toothpaste ($P = .06$) and for dental treatments ($P = .06$) were borderline significant and were also protective. The lowest exposure level for toothpaste was significantly protective for all subjects and for females; and the highest exposure level was significantly protective for tablets, further emphasizing the protective effect. Significant or borderline significant protective trends were also observed for each of these variables among males. The lowest exposure level for water had a significantly elevated odds ratio for all subjects and for females; however, trends were not significant.

The relationships between osteosarcoma and lifetime exposure to fluoride from the various sources, along with the total lifetime fluoride exposure index, are shown in Table 4 for the subjects' data set. Because of the small number of affirmative responses, fluoride from tablets was not analyzed separately. Although there appears to be an increasing risk with exposure, especially for the total fluoride intake, no significant trends were observed and all confidence intervals included 1.0. Models could not be run separately for each sex because of the small number of individuals in this data set.

For both the parents' and subjects' data sets, results of analyses controlling

TABLE 4—Number of Case and Control Subjects, Odds Ratios (ORs), and 95% Confidence Intervals (CIs) for Lifetime Fluoride Exposure Variables (Subjects' Data Set)

	No. Subjects				
	Case	Control	OR	95% CI	P
Mouth rinses, mg					.14
0	55	56	1.00	...	
1–35	3	2	1.50	0.25, 8.98	
36–150	2	4	0.55	0.10, 3.06	
151–950	4	2	1.83	0.33, 10.21	
Toothpaste, mg					.22
0–615	15	17	1.00	...	
616–1149	14	18	0.89	0.31, 2.61	
1150–1444	15	16	1.03	0.36, 2.97	
1445–3411	20	13	1.93	0.64, 5.84	
Dental treatments, mg					.52
0	45	45	1.00	...	
15	8	12	0.77	0.31, 1.96	
30–45	7	2	3.21	0.63, 16.50	
60–300	4	5	0.98	0.25, 3.93	
Water, mg					.48
0	21	29	1.00	...	
1–1950	15	11	2.31	0.74, 7.20	
1951–3350	14	12	2.07	0.53, 8.02	
3351–5650	14	12	1.76	0.59, 5.21	
Total fluoride, mg					.25
0–1250	14	18	1.00	...	
1251–2338	15	17	1.16	0.44, 3.04	
2339–3987	17	15	1.72	0.55, 5.39	
3988–9291	18	14	1.88	0.64, 5.55	

Note. Odds ratios were estimated from conditional logistic models.

for race and maternal age (which was found to be negatively associated with osteosarcoma in these data) were similar to the bivariate analyses. The results of the analyses for the average annual fluoride exposure variables were essentially the same as the lifetime exposure analyses in both data sets.

Discussion

The total lifetime fluoride exposure index is the most important indicator of whether fluoride is significantly associated with osteosarcoma. In the parents' data set, a significant association was not observed among all subjects, but a significant protective trend was observed among males. Borderline significant or significant protective trends were also observed for lifetime fluoride exposure from tablets, toothpaste, and dental treatments among all subjects and among males only. In the subjects' data set, however, a protective trend was not observed for the total lifetime fluoride exposure index, nor for any of the individual lifetime fluoride exposure variables. Importantly, there was no statistically significant finding from either data set that fluoride exposure increases the risk of childhood osteosarcoma. This result is consistent with previous studies that found no association between fluoride exposure and osteosarcoma.[17–23,25]

The protective effects observed in the parents' data set may be due to concern for personal health and hygiene and not to fluoride exposure. Those individuals who use fluoride tablets, who brush their teeth more often with fluoridated toothpaste, and who receive dental fluoride treatments are possibly more involved with good health practices. The observed protective effects could be the result of healthy behavior practices or of correlates of health behaviors that protect against osteosarcoma, rather than a consequence of fluoride exposure, although it is unusual to find these practices more among boys. The fact that the protective effect was not observed for fluoridated water supports this argument. However, because fluoride is directly deposited into the bone and directly affects the bone structure, it is biologically plausible that the protective effect observed from fluoride exposure could, in fact, be real.

The only demographic variables significantly associated with osteosarcoma in this study were race and maternal age. In general, race is not considered a risk factor for osteosarcoma.[3,33–36] The procedure used to randomly select the control birth certificates did not produce the same percentage of non-White certificates as the percentage from the total live births for upstate New York (7.6% vs 12.8%). Of those certificates obtained for non-White control subjects, a substantially higher proportion did not contain the father's name compared with certificates obtained for White control subjects (33.3% among non-Whites vs 3.9% among Whites), making the non-White control subjects more difficult to trace. Neither race nor maternal age was observed to confound the osteosarcoma–fluoride relationship.

One major limitation in this study was that cases were identified retrospectively for the period 1978 to 1988. Problems with recall became exacerbated because of the long period of time that may have passed since the childhood exposures. Also, only 64 case subjects were directly interviewed because of deaths occurring after diagnosis. Despite this limitation, the case subjects, control subjects, and their parents were equally able to report on the fluoride-related exposures, with a low percentage of missing responses. Because neither the case nor the control group appeared to be more accurate in their reporting of exposures, any misclassification that occurred should be nondifferential and would therefore bias the results toward the null value.

The extent of nondifferential misclassification of fluoride exposure and resultant bias toward the null value are difficult to evaluate. We are confident that the water fluoridation information is accurate. There is no reason to suspect that residential histories were reported inaccurately, the water source information was validated by geocoding, and fluoridation status was objectively determined. However, subjects' and parents' accuracy in reporting exposure to other sources of fluoride could not be assessed.

The low response rate of 48% among control subjects (mainly due to an inability to trace them) was a concern. However, among study subjects, individuals who moved more than two times did not have significantly different total lifetime fluoride exposures than individuals who maintained one or two addresses up to the

diagnosis or reference age. This suggests that the nonparticipant control subjects who could not be traced because they moved often would not have differed from the participant control subjects with respect to total lifetime fluoride exposure.

A strength of this study was the relatively large sample size (122 case–control pairs for the parents' data set and 64 case–control pairs for the subjects' data set) compared with prior studies that examined individual fluoride exposures from drinking water.[27,28] Another advantage of this study was the inclusion of exposures to fluoride from sources other than drinking water.

The differences in results between the parents' and subjects' data sets are probably a reflection of differences in knowledge and recall. Parents were probably more aware of exposures that occurred at young ages, including use of fluoridated drops, tablets, vitamins, and toothpastes and exposure to dental treatments. Subjects probably provided more accurate information for exposures that occurred when they were older, particularly the use of fluoridated toothpastes and mouth rinses. Overall, the parents' data set is probably the more accurate one because of better knowledge of more types of fluoride exposure and when those exposures began.

Conclusion

In conclusion, this study provides no support for the hypothesis that fluoride exposure increases the risk for osteosarcoma. It contributes to the body of evidence that indicates that the public can continue to enjoy the dental health benefits of fluoride with no associated major risks. □

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