

Fluoride exposure in public drinking water and childhood and adolescent osteosarcoma in Texas

Natalie P. Archer¹ · Thomas S. Napier² · John F. Villanacci²

Received: 19 November 2015 / Accepted: 7 May 2016
© Springer International Publishing Switzerland 2016

Abstract

Purpose The purpose of this study was to examine the association between fluoride levels in public drinking water and childhood and adolescent osteosarcoma in Texas; to date, studies examining this relationship have been equivocal. Using areas with high and low naturally occurring fluoride, as well as areas with optimal fluoridation, we examined a wide range of fluoride levels in public drinking water.

Methods This was a population-based case–control study, with both cases and controls obtained from the Texas Cancer Registry. Eligible cases were Texas children and adolescents <20 years old diagnosed with osteosarcoma between 1996 and 2006. Controls were sampled from children and adolescents diagnosed with either central nervous system (CNS) tumors or leukemia during the same time frame. Using geocoded patient addresses at the time of diagnosis, we estimated patients' drinking water fluoride exposure levels based on the fluoride levels of their residence's public water system (PWS). Unconditional logistic regression models were used to assess the association between osteosarcoma and public drinking water fluoride level, adjusting for several demographic risk factors.

Results Three hundred and eight osteosarcoma cases, 598 leukemia controls, and 604 CNS tumor controls met

selection criteria and were assigned a corresponding PWS fluoride level. PWS fluoride level was not associated with osteosarcoma, either in a univariable analysis or after adjusting for age, sex, race, and poverty index. Stratified analyses by sex were conducted; no association between PWS fluoride level and osteosarcoma was observed among either males or females.

Conclusions No relationship was found between fluoride levels in public drinking water and childhood/adolescent osteosarcoma in Texas.

Keywords Childhood osteosarcoma · Fluoridation · Cancer epidemiology · Public drinking water

Introduction

Osteosarcoma is a rare malignant bone tumor which affects primarily the long bones, the incidence of which peaks around puberty [1]. Ionizing radiation is the only environmental risk factor consistently shown to be associated with osteosarcoma [2]. However, it is biologically plausible that exposure to fluoride could be associated with osteosarcoma, since fluoride is deposited in bone and is known to increase cell division [3, 4].

Drinking water is the most significant source of fluoride exposure in the USA [3], due in large part to fluoridation of public water systems (PWSs). Community water fluoridation is considered to be an effective public health strategy for preventing tooth decay [5]; however, some opponents have suggested a relationship between fluoridation and adverse health outcomes, including osteosarcoma. Several studies have examined the association between exposure to fluoride in drinking water and osteosarcoma, and results have been inconsistent. A majority of these studies did not

✉ Natalie P. Archer
natalie.archer@dshs.state.tx.us

¹ Office of Program Decision Support, Texas Department of State Health Services, P.O. Box 149347, Austin, TX 78714-9347, USA

² Environmental Epidemiology and Disease Registries Section, Texas Department of State Health Services, P.O. Box 149347, Austin, TX 78714-9347, USA

find an association between exposure to low levels of fluoride (such as the amount added to fluoridated public water systems) and increased risk of osteosarcoma [6–10]. However, two ecologic studies [11, 12] and one case–control study [13] found associations between fluoridated drinking water and osteosarcoma in male children.

The purpose of this study was to examine the association between fluoride levels in public drinking water and osteosarcoma among children and adolescents 0–19 years of age (childhood osteosarcoma) in Texas. Because Texas contains both areas with high and low naturally occurring fluoride, as well as areas that optimally fluoridate [14], it is an ideal location to examine a wide range of fluoride levels in public drinking water systems.

Methods

Study design and selection criteria

This was a population-based case–control study. Eligible cases included Texas children and adolescents (0–19 years of age) reported to the Texas Cancer Registry (TCR) who were diagnosed with primary malignant osteosarcoma (International Classification of Childhood Cancer (ICCC) group VIIIa) between 1 January 1996 and 31 December 2006, and who had sufficient residence address information for geocoding. This study was approved by the Texas Department of State Health Services (DSHS) Institutional Review Board (IRB#1).

Referents were sampled from Texas children and adolescents (0–19 years old) reported to the TCR who were diagnosed with either central nervous system (CNS) tumors (ICCC Group III) or leukemias (ICCC groups I a and b) during the same time frame. These cancers were selected as referents/controls because an association between fluoride exposure and either of these cancers does not seem to be biologically plausible, and no literature could be found linking fluoride exposure with either cancer. Referents were sampled at a 4:1 control/case ratio; two childhood CNS tumor controls and two childhood leukemia controls were randomly selected for each childhood osteosarcoma case. Density (or risk-set) sampling was used to select referents from the TCR, which involved selecting controls that were at risk of being diagnosed with osteosarcoma for at least as long as a corresponding case [15]. For example, if a case patient was diagnosed at age 9, density-sampled referents for this case were randomly selected from all potential referent patients diagnosed at age 9 or later.

For both cases and referents, the tumor of interest (osteosarcoma for cases, CNS tumors or leukemias for referents) had to be either the first or only incident of cancer in

order for the child or adolescent to be included in the study. Children or adolescents with these tumors occurring as second or later tumors were excluded from the study, as were children and adolescents with multiple primary tumors.

Study data

Geocoded address information at the time of diagnosis for both osteosarcoma cases and CNS tumor and leukemia referents were mapped onto certificates of convenience and necessity (CCN) water service area boundary shapefiles, which helped to determine the PWS servicing each residence. Additional information on PWS locations were obtained from the Texas Commission on Environmental Quality (TCEQ) Water Utility Database (WUD). Average and highest fluoride levels for each PWS during some or all of the time frame of interest (1996–2006), depending upon availability, were then determined using data from CDC's Water Fluoridation Reporting System (WFRS). Because many PWSs had multiple fluoride values associated with them over the time period of interest, average fluoride values were calculated for each PWS. The highest fluoride value for each PWS was also obtained.

Each patient's fluoride exposure level was estimated based on the fluoride level of their residence's PWS. Cases and referents who resided in an area outside the boundaries of any PWS (e.g., on well water) were excluded from analysis. For public water systems that fluoridated (added fluoride to the drinking water) during the time period of interest, cases or selected referents diagnosed less than 5 years after fluoridation started at their residence were excluded from analysis, in order to fulfill the criterion of temporality.

Statistical methods

Demographic characteristics of the two different cancer referent groups (childhood CNS tumor patients and childhood leukemia patients) were first compared, to determine whether any significant demographic differences existed between these two control groups. The T tests were used for continuous variables, and Chi-square tests were utilized for categorical variables. Demographic characteristics of childhood osteosarcoma cases were also evaluated.

The exposure variable of interest in our analysis was patients' average PWS drinking water fluoride level. The highest PWS fluoride value for each residence was also examined as a secondary exposure variable. Average and highest PWS fluoride levels were examined as categorical variables, with the following categories: low or sub-optimal fluoridation (0.0–0.6 ppm); optimal fluoridation (0.7–1.2 ppm, determined by CDC's fluoridation

recommendations during the time period of cancer diagnosis in this study); and above-optimal fluoridation (≥ 1.3 ppm).

The proportion of cases and referents within each fluoride level category (sub-optimal, optimal, above optimal) was first compared, using a Chi-square test, for both average and highest fluoride levels. The relationship between the source of fluoride in public drinking water (natural fluoridation vs. artificial fluoridation with fluorosilicic acid) and osteosarcoma was also assessed using a Chi-square test. Next, unconditional logistic regression analyses were conducted to determine the association between average PWS fluoride level and diagnosis of childhood osteosarcoma. Both crude and adjusted analyses were performed, and odds ratios (ORs) and corresponding 95% CIs were calculated. In the adjusted logistic regression models, covariates included age as a continuous variable, and sex, race/ethnicity (White, Black, Hispanic, and Other), and percent of census tract below poverty index (<5, 5–9.9, 10–19.9, and ≥ 20 %) as categorical variables. Because of previously reported sex differences in the association between fluoride and osteosarcoma [11, 13], we also conducted adjusted logistic regression analyses stratified by sex.

Results

The TCR contained 397 childhood and adolescent primary malignant osteosarcoma patient records over the study time frame. Records for 345 of these cases (87 %) were geocodable. We then selected four times as many geocodable referent cancer patient records (1,380 records; 690 from childhood brain cancer patients and 690 from childhood leukemia patients). Out of a total of 1,725 geocodable case and control records, 1,663 (96.4 %) were able to be assigned to a corresponding PWS with a known fluoride level. An additional 153 patients were excluded because the date of cancer diagnosis occurred either before or less than 5 years after their corresponding PWS's fluoridation start date. Therefore, a total of 1,510 individuals were included in analyses; these included 308 childhood and adolescent osteosarcoma cases, 604 childhood CNS tumor referents, and 598 childhood leukemia referents.

Characteristics of the childhood CNS tumor and childhood leukemia referents are displayed in Table 1. There were significant differences in age, race, sex, and poverty index between the two referent groups. Because of these differences, crude and adjusted regression analyses were first conducted comparing osteosarcoma cases to each referent group separately. However, the relationship between fluoride levels and osteosarcoma did not differ based on the referent group used; therefore, analyses

presented are for both referent groups combined. Demographic characteristics of the childhood osteosarcoma cases in the analysis are also shown in Table 1 and are compared with characteristics of all cancer referents (childhood CNS tumor and childhood leukemia referents combined).

Average fluoride levels for PWSs analyzed ranged from 0.1 to 5.5 ppm. A Chi-square test showed no significant differences between the proportion of cases and the proportion of referents within each of the fluoride level categories, when either using average PWS fluoride levels or highest PWS fluoride levels as the exposure of interest ($X^2 = 1.05$, $p = 0.59$ and $X^2 = 0.73$, $p = 0.69$, respectively). We also found no significant difference in the odds of childhood osteosarcoma due to fluoride source ($X^2 = 1.64$, $p = 0.20$) (Table 2).

In crude logistic regression analyses, PWS fluoride level was not associated with osteosarcoma, regardless of the measure used (average or highest fluoride level). Controlling for age, sex, race, and poverty did not change these results (overall p value for average PWS fluoride level = 0.60). Crude and adjusted odds ratios (ORs) of childhood osteosarcoma for optimal and above-optimal average PWS fluoride level categories, compared to the referent low/sub-optimal average fluoride level category, are shown in Table 3.

Stratified analyses by gender indicated no statistically significant association between average fluoride levels in public drinking water and osteosarcoma among either males or females (Table 4). A slight increase in odds of childhood osteosarcoma was observed at above-optimal PWS fluoride levels of 1.3 ppm or greater (compared to low/sub-optimal fluoride levels) among boys, but this association was not statistically significant. Among girls, a nonsignificant decrease in odds of osteosarcoma was associated with optimal and above-optimal fluoride levels (compared to the odds of osteosarcoma at sub-optimal fluoride levels) (Table 4).

Discussion

No evidence of an association between PWS fluoride levels and childhood osteosarcoma was observed in this study. Overall, odds of childhood osteosarcoma did not increase with increased PWS fluoride levels. Our finding of no association between fluoride levels in public drinking water and childhood osteosarcoma is consistent with a preponderance of case–control and ecologic studies on this topic [6–10, 16, 17].

Although results shown focus on logistic regression models with average PWS fluoride level (as a categorical variable) as the exposure variable of interest, models were also constructed using each PWS's highest fluoride level

Table 1 Demographic characteristics of childhood CNS tumor referents, childhood leukemia referents, and childhood osteosarcoma cases

	Childhood CNS tumor referents (<i>n</i> = 604)	Childhood leukemia referents* (<i>n</i> = 598)	Childhood osteosarcoma cases (<i>n</i> = 308)	<i>p</i> value ^a (osteosarcoma cases vs. combined referents)
Mean age (years)	13.9	14.4	13.5	0.05
Sex (% male)	52.3	59.0	57.8	0.50
Race (%)				0.25
White	54.8	38.8	41.9	
Black	12.6	10.5	15.3	
Hispanic	28.2	47.8	39.0	
Other/missing	4.5	2.8	3.9	
Poverty index (%) ^b				0.62
<5 %	22.3	18.9	22.3	
5–9.9 %	22.9	17.7	23.1	
10–19.9 %	25.6	28.9	25.6	
≥20 %	29.2	34.5	29.1	

* Statistically significant differences ($\alpha = 0.05$) were seen between CNS tumor referents and leukemia referents for all demographic characteristics shown: mean age: $p = 0.01$; sex: $p = 0.02$; race: $p < 0.0001$; poverty index: $p = 0.02$

^a *p* values shown are the result of either a *t* test (for mean age) or a Chi-square test (for sex, race, and poverty index) comparing values between childhood osteosarcoma cases and a combined referent group (childhood CNS tumor referents and childhood leukemia referents together)

^b Poverty index reflects percent poverty based on census tract

Table 2 Proportion of cases and referents within each fluoride level category (crude analysis) for average fluoride levels and highest fluoride levels seen within each public water system (PWS) and by fluoride source, with corresponding Chi-square test statistics and *p* values

	Osteosarcoma cases % (n)	CNS tumor and leukemia referents % (n)	X^2 value (<i>p</i> value)
Average PWS fluoride level			1.05 ($p = 0.59$)
Low/sub-optimal	70.1 (<i>n</i> = 216)	67.2 (<i>n</i> = 808)	
Optimal	22.7 (<i>n</i> = 70)	25.5 (<i>n</i> = 306)	
Above optimal	7.2 (<i>n</i> = 22)	7.3 (<i>n</i> = 88)	
Highest PWS fluoride level			0.73 ($p = 0.69$)
Low/sub-optimal	40.9 (<i>n</i> = 126)	39.3 (<i>n</i> = 472)	
Optimal	36.4 (<i>n</i> = 112)	39.0 (<i>n</i> = 469)	
Above optimal	22.7 (<i>n</i> = 70)	21.7 (<i>n</i> = 261)	
Fluoride source ^a (cases = 233, referents = 871)			1.64 ($p = 0.20$)
Fluorosilicic acid	49.4 (<i>n</i> = 115)	54.1 (<i>n</i> = 471)	
Natural	50.6 (<i>n</i> = 118)	45.9 (<i>n</i> = 400)	

^a Information on fluoride source was missing for 406 individuals (75 cases and 331 referents). Percentages shown are for the remaining 1,105 individuals (233 cases and 871 referents) with valid fluoride source information

(as a categorical variable) as well as continuous variables for average and highest fluoride levels as exposure variables. No significant association between PWS fluoride level and osteosarcoma was found for any of these models. In addition, given that PWS fluoride concentration was a group-level measure (not able to be measured at the individual level), we assessed the degree of spatial autocorrelation in our regression results by calculating Moran's *I* for Chi-square residuals. No significant spatial autocorrelation was observed ($Z = -0.94$, $p = 0.35$).

Our study found no significant association between PWS fluoride levels and odds of osteosarcoma among either boys or girls. One previous case-control study [13] reported a significant association between their high-exposure fluoride category in drinking water (>99 % of target fluoride content) and childhood osteosarcoma among boys 6–8 years of age, with a peak at 7 years of age (adjusted OR = 5.46; 95% CI = 1.50–19.90). Adjusted ORs for the high-exposure category among boys of different ages in Bassin et al. ranged from approximately 1.7–5.5. No significant

Table 3 Crude and adjusted odds ratios (ORs) for osteosarcoma for optimal and above-optimal average fluoride level categories, compared to the referent category (low/sub-optimal fluoride level), and corresponding 95% confidence intervals (CIs), and *p* values

Average PWS fluoride level	OR	95% CI	<i>p</i> value
Crude estimates			0.59 ^a
Low/sub-optimal (0–0.6 ppm)	1.00 (referent)	–	–
Optimal (0.7–1.2 ppm)	0.86	(0.63, 1.16)	0.31
Above optimal (\geq 1.3 ppm)	0.94	(0.57, 1.53)	0.79
Adjusted estimates ^b			0.60 ^a
Low/sub-optimal (0–0.6 ppm)	1.00 (referent)	–	–
Optimal (0.7–1.2 ppm)	0.85	(0.62, 1.16)	0.31
Above optimal (\geq 1.3 ppm)	0.96	(0.58, 1.58)	0.88

^a *p* value for the average fluoride level variable as a whole (type 3 analysis result, which is used to test significance of the overall categorical variable)

^b Adjusted for age, sex, race/ethnicity, and percent of census tract below poverty index

Table 4 Adjusted odds ratios (ORs) and corresponding 95% CIs for childhood osteosarcoma, stratified by sex

Average PWS fluoride level	OR ^a	95% CI	<i>p</i> value
Boys (cases = 178, controls = 669)			0.71 ^b
Low/sub-optimal (0–0.6 ppm)	1.00 (referent)	–	–
Optimal (0.7–1.2 ppm)	1.03	(0.68, 1.55)	0.89
Above optimal (\geq 1.3 ppm)	1.31	(0.70, 2.46)	0.41
Girls (cases = 130, controls = 533)			0.16 ^b
Low/sub-optimal (0–0.6 ppm)	1.00 (referent)	–	–
Optimal (0.7–1.2 ppm)	0.68	(0.42, 1.09)	0.11
Above optimal (\geq 1.3 ppm)	0.58	(0.25, 1.36)	0.21

ORs shown for optimal and above-optimal average fluoride level categories are compared to the referent category (low/sub-optimal fluoride level)

^a Odds ratios adjusted for age, sex, race/ethnicity, and percent of census tract below poverty index

^b *p* value for the average fluoride level variable as a whole (type 3 analysis result, which is used to test significance of the overall categorical variable)

association was observed among girls, although adjusted ORs for the high-exposure fluoride category at different ages appeared to range from 1.0 to 2.5 [13]. Effect sizes observed for both boys and girls in our study were lower than the effect sizes reported in Bassin et al. Our highest PWS fluoride exposure category (above-optimal PWS fluoride levels) was associated with a protective effect among girls (OR = 0.58, 95% CI = 0.25–1.36), compared to sub-optimal drinking water fluoride levels, although this result was not statistically significant. The overall adjusted OR for our study's highest PWS fluoride exposure category among boys was 1.31 (95% CI = 0.70–2.46). We also conducted logistic regression analyses among older boys stratified by age category (6–8, 9–12, 13–15, and 16+); adjusted ORs for the above-optimal PWS fluoride level category for these age groups ranged from 0.5 to 1.6, with an OR of 1.2 observed among boys 6–8 years of age (data not shown). The effect sizes observed in our analysis were much lower than those reported among boys of comparable ages in Bassin et al. [13]. In addition, the findings of the

Bassin et al. study were based on preliminary results, and an analysis of bone fluoride concentrations (rather than drinking water fluoride) for a second set of patients from the same source yielded no significant association between bone fluoride levels and risk of osteosarcoma [18, 19].

Hoover et al. [12] analyzed SEER incidence data and found that childhood osteosarcomas appeared to be more prominent in fluoridated areas than in non-fluoridated areas; however, the increases in osteosarcoma observed in fluoridated areas were not related to the timing of fluoridation and were thus not thought to be due to fluoridation of public drinking water [12].

This study included a larger number of childhood osteosarcoma cases ($n = 308$) than any other case–control study of childhood osteosarcoma and fluoride in drinking water to date. Our inclusion of four times as many controls (1,202 individuals) resulted in a large sample size for this analysis, which helped increase precision of results and increased our power to detect potential differences in incidence of childhood osteosarcoma among the different

fluoride level categories. Also, the dataset included a wide range of fluoride levels in study participants' public drinking water, including naturally occurring levels above the optimal fluoride level. Because of this, our study was able to examine optimal and above-optimal PWS fluoride level categories separately, which has not previously been analyzed in other case-control studies of drinking water fluoride levels and osteosarcoma [9, 10, 13].

Limitations of this study include the assumption that fluoride levels of the public water systems serving the individuals' residences were indicative of fluoride levels in the water regularly consumed prior to being diagnosed with cancer. Since this study was a secondary data analysis, it was unknown how long each child had lived at their residence before being diagnosed with osteosarcoma or either of the referent cancers. We also did not have information on whether the children/adolescents in the analysis primarily drank tap water or bottled water.

This study used cancer referents, which had the potential to introduce bias; specifically, the exposures of the referent group(s) might not be representative of the general population. We attempted to detect/account for potential biases by examining two different cancer types as referents (childhood CNS tumors and childhood leukemias). The relationship between PWS fluoride levels and osteosarcoma was the same for both of the referent groups used.

In conclusion, this study found no association between fluoride levels in public water systems and risk of childhood osteosarcoma in Texas. This is consistent with findings from a majority of studies on this topic. Our results add to the body of evidence indicating that optimally fluoridated drinking water does not increase the risk of osteosarcoma in children.

Acknowledgments The authors would like to thank Dr. Melanie Williams, Ann Barnett, Dr. Erin Fox, Suzanne Jaster, Tracy Harbour, Paul Betts, Heather Powell, Dr. Heidi Bojes, and Emily Hall for their help. A special thanks to Dr. Noha Farag for her epidemiological expertise and help with analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

References

- Mirabello L, Troisi RJ, Savage SA (2009) Osteosarcoma incidence and survival rates from 1973 to 2004: data from the surveillance, epidemiology, and end results program. *Cancer* 115(7):1531–1543. doi:10.1002/ncr.24121
- Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W, Hoover RN, Fraumeni JF Jr (1987) Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med* 317:588–593. doi:10.1056/NEJM198709033171002
- National Research Council of the National Academies (NRC) (2006) Fluoride in drinking water—a scientific review of EPA's standards. National Academies Press, Washington
- Chavassieux P, Boivin G, Serre CM, Meunier PJ (1993) Fluoride increases rat osteoblast function and population after in vivo administration but not after in vitro exposure. *Bone* 14:721–725
- Centers for Disease Control and Prevention (CDC) (1999) Ten great public health achievements—United States, 1900–1999. *MMWR Morb Mortal Wkly Rep* 48:241–243
- Gelberg KH, Fitzgerald EF, Hwang S-A, Dubrow R (1995) Fluoride exposure and childhood osteosarcoma: a case-control study. *Am J Public Health* 85(12):1678–1683
- Hrudey SE, Soskolne CL, Berkel J, Fincham S (1990) Drinking water fluoridation and osteosarcoma. *Can J Public Health* 81:415–416
- Mahoney MC, Nasca PC, Burnett WS, Melius JM (1991) Bone cancer incidence rates in New York state: time trends and fluoridated drinking water. *Am J Public Health* 81(4):475–479
- McGuire SM, Vanable ED, McGuire MH, Buckwalter JA, Douglass CW (1991) Is there a link between fluoridated water and osteosarcoma? *J Am Dent Assoc* 122:39–45
- Moss ME, Kanarek MS, Anderson HA, Hanrahan LP, Remington PL (1995) Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979–1989. *Arch Environ Health* 50(3):235–241
- Cohn PD (1992) A brief report on the association of drinking water fluoridation and the incidence of osteosarcoma among young males. New Jersey Department of Environment Protection and New Jersey Department of Health
- Hoover RN, Devesa SS, Cantor KP, Lubin JH, Fraumeni JF (1991) Time trends for bone and joint cancers and osteosarcomas in the surveillance, epidemiology and end results (SEER) program. US Public Health Service, Washington
- Bassin EB, Wypij D, Davis RB, Mittleman MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes Control* 17(4):421–428. doi:10.1007/s10552-005-0500-6
- Hudak PF (1999) Fluoride levels in Texas groundwater. *J Environ Sci Health A* 34(8):1659–1676
- Checkoway H, Pearce N, Kriebel D (2004) Research methods in occupational epidemiology, monographs in epidemiology and biostatistics, vol 34, 2nd edn. Oxford University Press, New York
- Freni SC, Gaylor DW (1992) International trends in the incidence of bone cancer are not related to drinking water fluoridation. *Cancer* 70(3):611–618
- McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J, Misso K, Bradley M, Treasure E, Kleijnen J (2000) Systematic review of water fluoridation. *BMJ* 321:855–859
- Douglass CW, Joshipura K (2006) Caution needed in fluoride and osteosarcoma study. *Cancer Causes Control* 17(4):481–482. doi:10.1007/s10552-006-0008-8
- Kim FM, Hayes C, Williams PL, Whitford GM, Joshipura KJ, Hoover RN, Douglass CW, National Osteosarcoma Etiology G (2011) An assessment of bone fluoride and osteosarcoma. *J Dent Res* 90(10):1171–1176. doi:10.1177/0022034511418828