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A Case-Control Study of Fluoridation and Osteosarcoma

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Abstract

Public health policy decisions in the United States have resulted in 62.4% of the population having access to fluoridated water. The purpose of this study was to examine the association between community water fluoridation and osteosarcoma. A secondary data analysis was performed with data collected from 2 separate but linked studies. Patients for phase 1 and phase 2 were selected from US hospitals via a matched case-control study design. For both phases, cases included patients diagnosed with osteosarcoma, and controls were patients diagnosed with other bone tumors or nonneoplastic conditions. In phase 1, cases (n = 209) and controls (n = 440) were patients of record in the participating orthopedic departments from 1989 to 1993. In phase 2, cases (n = 108) and controls (n = 296) were incident patients who were identified and treated by orthopedic physicians from 1994 to 2000. This analysis included all patients who met eligibility criteria on whom we had complete data on covariates, exposures, and outcome. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association of community water fluoridation with osteosarcoma. A modestly significant interaction existed between fluoridation living status and bottled water use (P = 0.047). The adjusted OR for osteosarcoma and ever having lived in a fluoridated area for nonbottled water drinkers was 0.51 (95% CI, 0.31 to 0.84; P = 0.008). In the same comparison, the adjusted OR for bottled water drinkers was 1.86 (95% CI, 0.54 to 6.41; P = 0.326). Findings from this study demonstrated that community water fluoridation is not associated with an increased risk for osteosarcoma.

Keywords: oral health, health policy, cancer, fluoride, epidemiology, orthopedics

Introduction

Community water fluoridation is considered one of the most important public health policies of the 20th century (Centers for Disease Control and Prevention [CDC] 1999). The initial policy recommendation was to adjust community water systems to include fluoride in the water at a range of 0.7 to 1.2 ppm to minimize tooth decay and dental fluorosis (Galagan and Vermillion 1957), which was based on the assumption that individuals residing in warmer climates consume more water than those in cooler climates (Sohn et al. 2001). Recent research demonstrated that there was little variability in water consumption in the United States due to climate differences; thus, the CDC recently recommended an optimal level of 0.7 ppm (Sohn et al. 2001; Beltrán-Aguilar et al. 2015). Accordingly, the majority of fluoridated communities served by public water systems adjusted the fluoride content of their drinking water to 0.7 ppm as recommended by the CDC (US Department of Health and Human Services 2015). Community water fluoridation continues to be associated with reduced tooth decay in the US population (Slade et al. 2018). In 2016, 62.4% of the US population had access to fluoridated water (CDC 2016).

Fluoride exposure from drinking water has been examined as a risk factor for osteosarcoma (McGuire et al. 1991; Gelberg et al. 1995; Moss et al. 1995; Bassin et al. 2006; Kim et al. 2011; Blakey et al. 2014; Archer et al. 2016). Of the 7 fluoride and osteosarcoma case-control studies, 6 reported that fluoride in drinking water was not associated with osteosarcoma (McGuire et al. 1991; Gelberg et al. 1995; Moss et al. 1995; Kim et al. 2011; Blakey et al. 2014; Archer et al. 2016). Only 1

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A supplemental appendix to this article is available online.

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study collected bone specimens (Kim et al. 2011); that study did not find any association between bone fluoride levels and risk for osteosarcoma.

Osteosarcoma—a rare, painful primary malignant bone tumor—accounts for about 2% of childhood cancers. Of the approximately 850 new cases diagnosed annually in the United States, about 400 occur in persons <20 y old (American Cancer Society 2020). The age-specific incidence is bimodal: the first peak in adolescence (ages 11 to 15 y) and the second after age 60 y (Miller et al. 1996). Cases of osteosarcoma occurring later in life (50 to 60 y) are generally secondary to radiation therapy or transformation of a preexisting benign tumor, such as Paget's disease (Miller et al. 1996). Among adolescents, osteosarcoma tends to occur about 1.5 times as frequently in males than females (Homa et al. 1991). Rates are slightly higher in African Americans than in Caucasians (Gurney et al. 1999). Ionizing radiation is the single environmental exposure known to increase risk for osteosarcoma (Steiner 1965; Tucker et al. 1987). Conditions such as Li-Fraumeni syndrome, retinoblastoma, bone trauma, and rapid skeletal growth, particularly during the time of puberty (Operskalski et al. 1987; Gelberg et al. 1997; Buckley et al. 1998), have been suggested as risk factors for osteosarcoma. The findings of a pooled analysis of more recent studies of height and birthweight suggest that rapid bone growth during puberty and in utero contributes to osteosarcoma etiology (Mirabello et al. 2011).

Fluoride ingestion has been suggested as a possible risk factor for osteosarcoma based on an animal study (National Toxicology Program [NTP] 1990). The 1990 report released by the NTP sparked renewed public interest in the relationship between fluoride and osteosarcoma. The study found that 4 of 130 male rats given high doses of sodium fluoride (100 ppm and 175 ppm) for 2 y developed osteosarcoma. However, female rats and male and female mice with similar levels of exposure did not. Other animal studies have been unable to provide evidence of an association between fluoride and osteosarcoma (Maurer et al. 1990), including a follow-up study by the NTP (1992).

Ecologic studies have failed to show any association or evidence of increased mortality after the introduction of fluoride into the water supply (Hoover et al. 1976; Newbrun 1977; Doll and Kinlen 1978). Time-trend studies of cancer in communities before and after the introduction of fluoridation have also shown no difference in osteosarcoma incidence rates between fluoridated and nonfluoridated areas (Hrudey et al. 1990; Mahoney et al. 1991; Freni and Gaylor 1992). Another ecologic study found that water fluoridation was not associated with increased incidence rates of osteosarcoma during childhood (Levy and Leclerc 2012). Similarly, an ecologic study from Great Britain did not find an association between osteosarcoma and fluoridation, as well as naturally fluoridated areas (Blakey et al. 2014).

The purpose of this study was to assess whether living in a fluoridated community in the United States is a risk factor for osteosarcoma. This is the first nonecologic study at the individual and not population level.

Methods

Data were collected from 2 linked studies: phase 1 data include patients treated between 1989 and 1993, and phase 2 data include patients treated between 1994 and 2000. Phase 1 was approved by the Institutional Review Boards of the hospitals and Harvard Medical School. Phase 2 was approved by the Institutional Review Boards of Harvard Medical School, the Medical College of Georgia, and the National Cancer Institute.

Enrollment

Study participants for phases 1 and 2 were recruited from US hospitals in academic medical centers per a case-control study design with all cases of osteosarcoma eligible (Table 1). All study participants provided consent prior to study enrollment. In both phases, controls were matched to cases on sex, age ±5 y, and distance from the hospital, a proxy for the effort and resources needed to obtain treatment. The Figure describes the study participants. Comparisons of cases and controls for the combined phases are shown in Table 2.

Case Definition

In phase 1, all patients diagnosed with osteosarcoma by the participating orthopedic departments from 1989 to 1993 were identified from the patient record files and recruited for telephone interviews. Cases had histologically confirmed osteosarcoma diagnosed between 1989 and 1993. In phase 2, incident cases of osteosarcoma were identified by orthopedic physicians in the participating orthopedic departments. All patients diagnosed and treated with primary osteosarcoma, confirmed by surgical pathology reports from 1994 to 2000, were considered eligible.

Control Definition

In phase 1, controls were patients of record from 1989 to 1993 with other bone tumors or nonneoplastic conditions identified from the same orthopedic surgery department as the cases. The phase 1 data set did not contain an indicator that allowed identifying the type of control. The controls in phase 2 were recruited from the same orthopedic departments as the cases in the years 1994 to 2000. The controls included patients from 2 categories: tumor and orthopedic. The tumor controls composed 13.3% of the controls and were patients with newly diagnosed malignant bone tumors other than osteosarcoma, such as Ewing's sarcoma, chondrosarcoma, and malignant fibrous histiocytoma. The orthopedic controls were patients with benign tumors and nonneoplastic conditions (inflammatory diseases, trauma, and sports injuries). The orthopedic controls included ambulatory orthopedic patients.

Exclusion Criteria for Study Entry

Patients >40 y of age at diagnosis and patients who reported prior radiation treatment for cancer or a history of kidney

Table 1. Participating Hospitals for Phases 1 and 2.

Hospital	In Phase 1	In Phase 2 and Dates of Participation
Massachusetts General Hospital, Boston, MA	Yes	Yes (Aug 1996 to Dec 2000)
The Cleveland Clinic Foundation, Cleveland, OH	Yes	Yes (Dec 1994 to Nov 2000)
University of Florida, Gainesville, FL	Yes	Yes (Dec 1994 to Dec 2000)
University of California, Los Angeles, CA	Yes	Yes (Nov 1994 to Jul 1996)
University of Chicago, Chicago, IL	Yes	Yes (Sep 1994 to Apr 2000)
Rush Presbyterian, Chicago, IL	Yes	Yes (Jun 1994 to Jul 1998)
Creighton University/St. Joseph's University, Omaha, NE	Yes	Yes (Apr 1994 to Jan 1999)
Children's National Medical Center, Washington, DC	Yes	Yes (Jan 1995 to Jun 1998)
Memorial Sloan Kettering, New York, NY	Yes	—
Case Western Reserve University, Cleveland, OH	Yes	—
Children's Hospital, Boston, MA	Yes	—
University of Nebraska, Omaha, NE	Did not provide records	Yes (Aug 1998 to Dec 2000)
Washington Hospital Center, Washington, DC	—	Yes (Oct 1996 to Jun 1998)

In phase 1, patients treated between 1989 and 1993 were identified from record files from orthopedic departments. In phase 2, patients treated between 1994 and 2000 were incident cases of osteosarcoma identified by orthopedic physicians.

dialysis were excluded in phase 1. The patients from phase 2 with kidney dialysis and radiation treatment were excluded in these analyses. In phase 2, no age restrictions or other exclusion criteria were placed on patients entering the study; thus, phase 2 attempted to enroll all cases. Additionally, in phase 2, patients were eligible if they were residents of the United States or were citizens temporarily living outside the United States (e.g., students, military, work assignment abroad). Foreign nationals who were in the United States solely for treatment were not eligible.

Data Collection of Covariates

A telephone interview was conducted in phase 1 between January 1992 and January 1995 with patients aged 18 to 40 y or with a parent if the patient was aged <18 y. If the patient was deceased at the time of the telephone interview, the interview was conducted with a family proxy. In brief, the questionnaire included demographic characteristics (age, sex, race/ethnicity, education) and residential history, including types of water consumed, use of toothpaste, and use of topical fluoride rinses and supplemental fluoride tablets (Bassin et al. 2006). Income was determined via a surrogate measure based on the zip code at the time of diagnosis, with data from the US Census Bureau.

In phase 2, all eligible patients were interviewed in person, during hospitalization or pre- or postadmission, by trained interviewers in English.

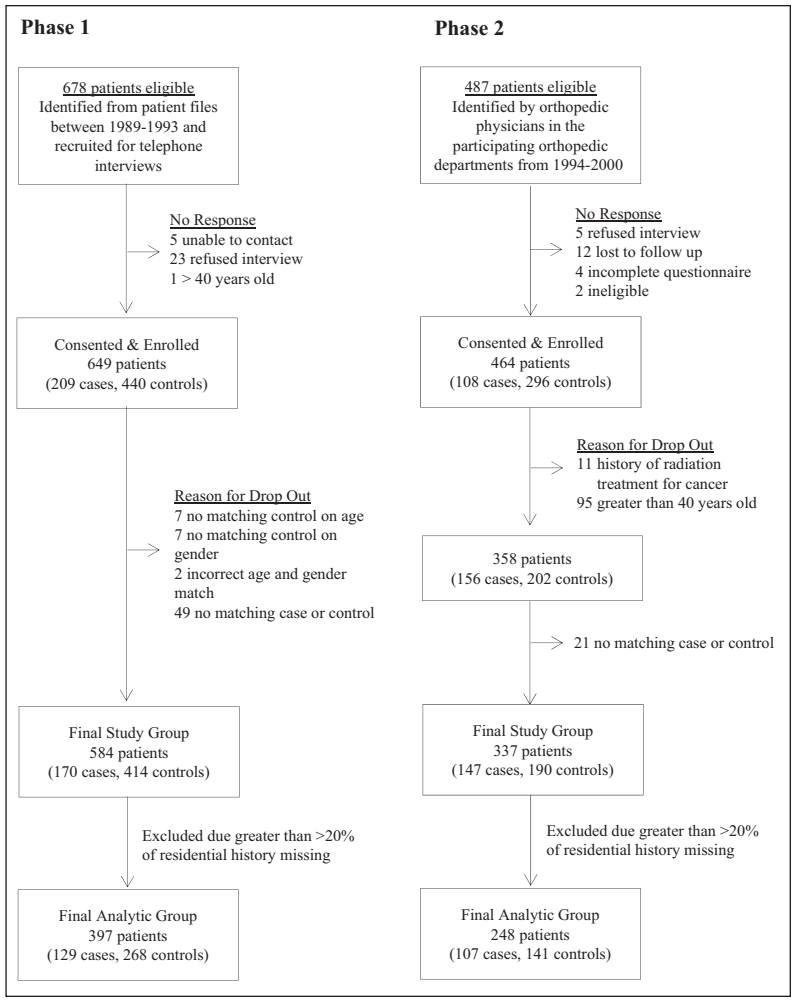

Figure. Patient recruitment.

Table 2. Univariable Associations Comparing Matched Cases and Controls for Phases 1 and 2 Combined.

	Patients, *n* (%)				
	All (*N* = 645)	Cases (*n* = 236)	Controls (*n* = 409)	Odds Ratio (95% CI)	*P* Value
Fluoride toothpaste use					
No	2	1 (0.4)	1 (0.2)	Reference	
Yes	641	234 (99.2)	407 (99.6)	0.58 (0.04 to 9.24)	0.696
Missing	2	1 (0.4)	1 (0.2)		
Age, y					
1 to 10	78	25 (10.6)	53 (13.0)	Reference	
11 to 20	386	150 (63.6)	236 (57.7)	1.35 (0.80 to 2.26)	0.259
21 to 30	142	45 (19.1)	97 (23.7)	0.98 (0.54 to 1.78)	0.956
31 to 40	39	16 (6.8)	23 (5.6)	1.48 (0.67 to 3.27)	0.339
Sex					
Female	255	94 (39.8)	161 (39.4)	Reference	
Male	390	142 (60.2)	248 (60.6)	0.98 (0.71 to 1.36)	0.907
Race					
Non-White	100	40 (17.0)	60 (14.7)	Reference	
White	545	196 (83.0)	349 (85.3)	0.84 (0.54 to 1.30)	0.441
Ethnicity					
Non-Hispanic	606	223 (94.5)	383 (93.6)	Reference	
Hispanic	39	13 (5.5)	26 (6.4)	0.86 (0.43 to 1.71)	0.664
Patient education					
Less than high school	328	132 (55.9)	196 (47.9)	Reference	
High school to some college	230	82 (34.8)	148 (36.2)	0.82 (0.58 to 1.17)	0.272
College degree or higher	85	21 (8.9)	64 (15.7)	0.49 (0.28 to 0.84)	0.009
Missing	2	1 (0.4)	1 (0.2)		
Income					
<$40,000	306	124 (52.5)	182 (44.5)	Reference	
$40,000 to $60,000	196	70 (29.7)	126 (30.8)	0.82 (0.56 to 1.18)	0.281
>$60,000	143	42 (17.8)	101 (24.7)	0.61 (0.40 to 0.94)	0.023
Ever lived in an urban area					
No	185	71 (30.1)	114 (27.9)	Reference	
Yes	460	165 (69.9)	295 (72.1)	0.90 (0.63 to 1.28)	0.550
Distance from hospital, miles					
0 to 100	394	136 (57.6)	258 (63.1)	Reference	
>100	251	100 (42.4)	151 (36.9)	1.26 (0.91 to 1.74)	0.172
Ever drank well water					
No	464	164 (69.5)	300 (73.4)	Reference	
Yes	181	72 (30.5)	109 (26.6)	1.21 (0.85 to 1.72)	0.294
Ever drank bottled water					
No	538	212 (89.8)	326 (79.7)	Reference	
Yes	107	24 (10.2)	83 (20.3)	0.45 (0.27 to 0.72)	0.001
Lived in a fluoridated area					
No	139	58 (24.6)	81 (19.8)	Reference	
Yes	506	178 (75.4)	328 (80.2)	0.76 (0.52 to 1.11)	0.156
Percentage of life lived in a fluoridated area					
None	139	58 (24.6)	81 (19.8)	Reference	
>0 to ≤50	108	27 (11.4)	81 (19.8)	0.47 (0.27 to 0.81)	0.007
>50 to <100	132	49 (20.8)	83 (20.3)	0.82 (0.51 to 1.34)	0.438
100	266	102 (43.2)	164 (40.1)	0.87 (0.57 to 1.32)	0.509

Parental/guardian consent was required for participation in the interview as a corespondent if the participant was <21 y old. The personal interview collected information on demographic characteristics (age, sex, race/ethnicity, patient and parental education, and income), self-reported residential history (including types of water consumed, toothpaste, and topical and supplemental fluoride use), occupational history, medical history, family medical history, and growth and development (see Appendix for details on collection of residential history and other fluoride sources).

Statistical Methods

Baseline characteristics for cases and controls were summarized and compared with chi-square tests (Table 2). Conditional logistic regression models were used to account for matching.

Table 3. Adjusted Odds Ratios for Living in a Fluoridated Community and Risk of Osteosarcoma in Phases 1 and 2 per the Conditional Logistic Regression.

			Patients, *n* (%)			
	Patients, *n*	Ever Drank Bottled Water[a]	Cases	Controls	Odds Ratio (95% CI)	*P* Value
Ever lived in fluoridated area	645		236	409		
Yes	437	No	160 (75.5)	277 (85.0)	0.51 (0.31 to 0.84)	0.008
No	101	No	52 (24.5)	49 (15.0)	Reference	
Yes	69	Yes	18 (75.0)	51 (61.5)	1.86 (0.54 to 6.41)	0.326
No	38	Yes	6 (25.0)	32 (38.5)	Reference	
Percentage of life lived in fluoridated area						
None	139	Combined	58 (24.6)	81 (19.8)	Reference	
>0 to ≤50	108	Combined	27 (11.4)	81 (19.8)	0.41 (0.22 to 0.76)	0.005
>50 to <100	132	Combined	49 (20.8)	83 (20.3)	0.69 (0.40 to 1.21)	0.198
100	266	Combined	102 (43.2)	164 (40.1)	0.67 (0.38 to 1.18)	0.163

Analyses adjusted for race, ethnicity, income, ever lived in urban residence, distance from hospital, and ever drank bottled water (included only when bottled water × fluoridation exposure interaction was not significant).
[a]Analyzed separately for bottled water drinking status due to a significant interaction with fluoridation exposure.

To determine whether associations varied by study phase, a phase indicator and phase × fluoridation exposure interaction term were added to the multivariable logistic regression model run on the combined data from both study phases. Neither term was statistically significant. The nonsignificant interaction term indicates that the association between fluoride exposure and osteosarcoma was not significantly different between the 2 phases, allowing them to be combined for analysis. Hence, all results reported in the tables are for models with the 2 phases combined. The Appendix contains tables with the "by phase" results. Due to missing fluoridation status for some residences, the exposure variables were calculated from the study participants' residential histories where >80% of their residential fluoride status is known. The main exposure analyzed is the dichotomous variable, ever versus never lived in a fluoridated community, stratified by bottled water consumption status. Also, percentage of life lived in residences within fluoridated communities was analyzed, where the denominator is the length of time lived in towns or cities with known fluoridation status. Percentage of time lived in fluoridated communities was categorized into 4 groups: 1) never lived in fluoridated communities; 2) lived in fluoridated communities ≤50% of time; 3) lived >50% of time in fluoridated communities but <100%; and 4) always lived in a fluoridated area. To test the association between fluoridation and osteosarcoma during possible child growth periods, age-specific multivariable analyses were run with the dichotomous exposure (ever/never) for 4 age periods (in years: 5 to 6, 7 to 9, 10 to 12, and 13 to 15), comparing those who lived in fluoridated communities at the specific ages with those who never lived in fluoridated communities.

The fluoridation exposure variable did not include information on the amount of water consumed at the residence, only whether the residence existed in a town or city where the water supply was fluoridated or not. Age and distance from the hospital were considered for inclusion in the models to adjust for possible residual confounding. Age was subsequently omitted because it did not have a significant effect in univariable or multivariable models. The final models included race, ethnicity, income, urban-living status, distance from hospital, and bottled water use as covariates.

Results are reported as odds ratios (ORs) and 95% CIs. All statistical analyses were performed with SAS software (version 9.4; SAS Institute), and *P* values <0.05 were considered significant. This study conforms to the STROBE guidelines.

Results

Table 2 shows the univariable comparisons for the matching factors used in the study design: age (groups in years: 1 to 10, 11 to 20, 21 to 30, and 31 to 40), sex (male and female), and distance from hospital (0 to 100 miles and >100 miles). As would be expected because of the matching, none of the matching factors were significantly different for cases and controls.

The ORs for household income showed a protective association for the highest income level and a nonsignificant negative linear trend across the income groups: <$40K (reference), $40K to $60K (OR = 0.82, *P* = 0.281), and >$60K (OR = 0.61, *P* = 0.023). While ever drinking well water showed no association with osteosarcoma (OR = 1.21, *P* = 0.294), the univariable comparison showed that drinking bottled water was associated with a lower risk of osteosarcoma (OR = 0.45 *P* = 0.001).

ORs for the combined analysis (phases 1 and 2) are shown in Table 3. Race (non-White and White), ethnicity (non-Hispanic and Hispanic), annual income (<$40K, $40K to $60K, and >$60K), urban versus rural living status, ever drinking well water versus never, and ever drinking bottled water versus never were evaluated as covariates.

Bottled Water Analysis

Bottled water use was included as an adjustment variable in the multivariable analysis since the univariable analysis showed a protective association for bottled water use and disease state.

To explore the association, we tested for the possibility of a bottled water use × fluoridation interaction. Multivariable conditional logistic regression was performed that included the bottled water indicator (OR = 0.16, $P = 0.001$) and an interaction term for drinking bottled water and ever/never fluoridation exposure (OR = 3.66, $P = 0.047$). Because of the significant interaction term, ORs for ever/never lived in a fluoridated community are reported for each level of the bottled water indicator. Note that the rate of consuming bottled water is low in this study (16.6%), likely attributed to the timing of the data collection (1994 to 2000); the multivariable analysis for ever/never fluoridation exposure and osteosarcoma among those who ever consumed bottled water includes 107 study participants, as compared with the 538 study participants who never consumed bottled water (Table 3). There was no significant interaction for percentage of life lived in a fluoridated community and bottled water use ($P = 0.104$).

Fluoridation

Table 2 shows the univariable comparisons for the 2 fluoridation exposure variables: ever/never lived in a fluoridated community and the percentage of time lived in a fluoridated area. While there was no significant univariable association shown for ever/never lived in fluoridation, there was a significant protective association for those who lived in a fluoridated community for less than half their lives as compared with the reference group, never lived in a fluoridated community (OR = 0.47, $P = 0.007$). The categories for larger percentages of time in a fluoridated community were not statistically significant, though in both instances the ORs were nominally <1.

Table 3 shows the combined-phases stratified multivariable results for those who ever lived in a fluoridated community as compared with those who never lived in a fluoridated community and for the comparison of percentage of life lived in a fluoridated community grouped into the following percentage groups: 0%, 1% to 50%, 51% to 99%, 100%. No statistically significant increased risk for osteosarcoma was demonstrated between ever and never having lived in a fluoridated community. In the multivariable model, having ever lived in a fluoridated community, including those who did not drink bottled water, showed a significant protective effect with osteosarcoma (OR = 0.51, $P = 0.008$). However, no statistical association was found between ever and never having lived in a fluoridated community with osteosarcoma in the multivariable analysis including those who drank bottled water (OR = 1.86, $P = 0.326$). Similar to the univariable comparison, the multivariable results for the comparison of the percentage of life lived in a fluoridated community showed a protective effect for those who lived 1% to 50% of their lives in a fluoridated community as compared with those who never lived in a fluoridated community (OR = 0.41, $P = 0.005$). The other 2 categories, >50% to <100% and 100% of life lived in a fluoridated community, were not significantly different from those who never lived in a fluoridated community. Last, we compared ever and never having lived in a fluoridated community for the combined phases where participants who lived in a fluoridated community during specific ages (5 to 6, 7 to 9, 10 to 12, and 13 to 15 y) were compared with those who never lived in a fluoridated community (Appendix Table A). Participants who lived in a fluoridated community but not during the specific ages were excluded from this subanalysis. None of the results for the age-specific multivariable analyses were significant. Results are found in Appendix Table A.

The univariable and multivariable results were similar for phase 1 and phase 2 when the phases were run separately (Appendix Tables B–E).

Discussion

These results indicate that residence in a fluoridated community is not related to an increase in risk for osteosarcoma, after adjusting for race, ethnicity, income, distance from the hospital, urban/rural living status, and drinking bottled water. This should not be surprising given that ingestion of fluoridated water is a common exposure and osteosarcoma remains a rare disease (Mirabello 2009).

Although residence in a fluoridated community does not provide a precise estimate for the amount of fluoride ingested, it is highly unlikely that a large-enough proportion of individuals who reside in such communities do not drink sufficient amounts of the community water supply to be considered nonexposed. In addition, many beverages bottled in fluoridated communities or served with ice made from fluoridated water contain optimal levels of fluoride.

Strengths of this study include the multicenter design ensuring a broad cross section of communities nationwide, the confirmation of diagnosis, the comparable selection and enrollment procedures for cases and controls, as well as the use of trained interviewers with a standardized intake procedure.

Potential limitations include the case-control study design, which is prone to selection and recall bias. However, it seems unlikely that selection bias played a role in these findings given that cases and controls were ascertained from the same hospitals and clinics and fluoridation status is a publicly documented decision. While recall bias is inherent in case-control studies, it is likely that any error regarding estimating exposure is a random error rather than a systematic error. The exposure was residence in a fluoridated community, which is a much broader variable than calculating specific exposures in parts per million and thus less prone to inaccurate assumptions. The bottled water variable was not quantified. Additional limitations include generalizability, since participants in this study were recruited from a sample of hospitals in 9 US cities, and the lack of individual fluoride exposure assessment. Other sources of fluoride, as found in processed foods and other beverages consumed (including filtered water), were not available.

The significant protective association found with some of the adjusted variables in the multivariable models—namely, higher income (and associated consumption of bottled water) and having a residence within 100 miles to the hospital—needs additional research designed to study the social determinants and the effects of bottled water.

These results show that residing in a community that reports fluoridating its water supply is not associated with an increased risk of osteosarcoma.

Author Contributions

F.M. Kim, C. Hayes, S.L. Burgard, D. Couper, contributed to data analysis and interpretation, drafted and critically revised the manuscript; H.D. Kim, contributed to data analysis, reviewed the manuscript; R.N. Hoover, contributed to design and data acquisition, reviewed the manuscript; C.W. Douglass, contributed to design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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