Association Between Fluoride in Drinking Water During Growth and Development and the Incidence of Osteosarcoma for Children and Adolescents

A Thesis Presented by

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INTRODUCTION

Osteosarcoma is an uncommon but highly lethal primary malignant tumor of bone (Dorfman and Czerniak, 1995) associated with a median survival of approximately three years (Homa et al., 1991). The etiology of osteosarcoma is essentially unknown (Link and Eilber, 1997). It develops from primitive bone-forming mesenchyme within bone and is characterized by the production of osteoid tissue (Link and Eilber, 1997). Although osteosarcoma is very rare, it is the most common tumor of bone and one of the principal malignant neoplasms in children, adolescents and young adults (Homa et al., 1991; Dorfman and Czerniak, 1995; Link and Eilber, 1997), with an incidence rate of 5.6 per million per year for Caucasian children under 15 years old (Link and Eilber, 1997). Males are affected 1.5 to 2 times as frequently as females (Link and Eilber, 1997; Dorfman and Czerniak, 1995) and their survival from time of diagnosis tends to be shorter than for females (Homa et al., 1991). The age-incidence distribution of osteosarcoma is bimodal raising the possibility of different risk factors contributing to the incidence of osteosarcoma at different ages. The first and larger peak incidence occurs in the second decade of life (Fraumeni, 1975; Link and Eilber, 1997; Dorfman and Czerniak, 1995). Most but not all evidence suggests osteosarcoma is associated with

growth (Johnson, 1953; Price, 1958; Tjalma, 1966; Fraumeni, 1967; Operskalski et al., 1987; Link and Eilber, 1997; Henderson et al., 1997; Gelberg et al., 1997; Buckley et al., 1998; Re et al., 1998). Since fluoride acts as a mitogen (increasing the proliferation of osteoblasts) and its uptake in bone increases when skeletal growth is more rapid, (Gruber and Baylink, 1991; Ganong, 1995; Kleerekoper, 1996; Whitford, 1996), it is biologically plausible that fluoride exposure during specific periods of growth is associated with the subsequent development of osteosarcoma, and fluoride could either increase or decrease the rate of osteosarcoma.

There are conflicting data regarding the association between fluoride exposure and the incidence of osteosarcoma. Several animal studies have been conducted, but only one has shown that exposure increases osteosarcoma formation, specifically in male rats (Bucher et al., 1991). Human studies also show conflicting results. The majority of epidemiological studies found no association between fluoride and osteosarcoma (Hrudey et al., 1990; Mahoney et al., 1991; Freni and Gaylor, 1992; Operskalski et al., 1987; McGuire et al., 1991; Moss et al., 1995; Gelberg et al., 1995). However, an association between fluoride in drinking water and osteosarcoma was noted in males under age twenty in two prior studies (Hoover et al., 1991; Cohn, 1992), while no association has been observed in females or among cases occurring at older ages. Furthermore, prior studies have primarily evaluated fluoride exposure at the time of diagnosis or as an average lifetime exposure and have not evaluated exposure at specific ages during growth and development when cell division is occurring rapidly.

Therefore, we use data from the Harvard Fluoride Osteosarcoma Study (McGuire

et al., 1995) to explore age-specific effects and evaluate exposure to fluoride in drinking water at ages when growth is more rapid. Specifically, based on prior studies suggesting on [sic] effect of fluoride limited to males under age twenty, we limited our analysis to the first two decades of life and evaluated effects in males and females separately.

METHODS

Setting

We used data from a hospital-based, matched case-control study which evaluated lifetime exposure to fluoride from drinking water and self-administered fluoride products (McGuire et al., 1995). Subjects were identified through the orthopedic departments at eleven teaching hospitals across the United States. Up to four matched controls were sought for each case. Medical records were abstracted and information collected included date of birth, date of diagnosis, sex, race and current address. Telephone interviews were conducted between January 1992 and January 1995 with the parent or subject (over 18 years old) or with a proxy if subjects were deceased or incapacitated. Interviewers collected information which included a complete residential history, use of fluoride supplements and self-administered fluoride products.

Case and Control Definitions

Cases had histologically confirmed osteosarcoma diagnosed between November 1989 and November 1992. Exclusion criteria were: age 40 years or older, any history of radiation therapy or a history of renal dialysis. Controls were patients of the same

hospital's orthopedics department, seen within ± 6 months of the case's diagnosis and matched with cases on age (± 5 yrs.), gender, distance from the hospital, with the same exclusion criteria applied to cases. Telephone area code rings defined distance from the hospital. Data on a total of 419 subjects, 139 cases, and their 280 matched controls, were available based on eligibility criteria, matching criteria and a completed interview. However, the current analysis is limited to 91 cases less than twenty years old and the 188 controls matched to these cases.

Exposure

For each subject, a complete lifetime residential history was obtained and a separate record created for each unique address at which the subject had ever lived. We obtained the primary type of the subject's drinking water (municipal, private well, bottled) and the subject's age(s) while at that address. From these data, we estimated the level of fluoride in drinking water for each subject at each age, and explored the effects of fluoride during their growth and development.

To estimate fluoride concentration for public water supplies, we obtained preliminary data from the 1985 CDC Fluoridation Census (CDC, 1998) and the 1992 CDC Fluoridation Census (CDC, 1993). We then contacted state agencies (State Dental Director's Office, State EPA Office of Drinking Water, Water Administrators Office) and local sources (county health departments, the town or city clerk's office and specific water systems) to confirm and supplement the CDC data. Specifically, we developed an empirically based method using source documentation which is described in more detail

in chapter 1 of this thesis. For subjects who drank well water, a sample was obtained from current or former residents for the specific appropriate addresses. Fluoride concentrations we measured at Harvard School of Dental Medicine using a Colorimeter (Model 41100-21, Hach Company, Ames, IA). Subjects who used bottled water as their primary source of drinking water were identified, but information about specific brand was not collected. We estimated fluoride levels to be 0.1 ppm in bottled water based on the weighted average of fluoride concentration in leading brands (thesis, chapter 2). Since subjects who used bottled water were also likely to consume fluoride from tap water in cooking, food and beverage preparation and use outside the home (e.g., school), we used the average of fluoride estimates for bottled water and municipal water for these residences.

Since average water consumption varies based on climate, we standardized fluoride exposure estimates based on CDC recommendations for optimal target levels of fluoride (Reeves, 1993). For example, for locations in warmer climates where the target fluoride level is 0.7 ppm, we divided fluoride levels by 0.7, while for locations in colder climates where the target fluoride level is 1.2 ppm we divided by 1.2. The standardization of fluoride exposure was done for all three types of primary drinking water.

Covariates

A proxy measure for socioeconomic status (SES) was determined by linking zipcode at the time of diagnosis with data from the Census Bureau which provide 1989

median family income for each zipcode. Median family income was categorized into quartiles based on the distribution for controls. We also used data from the Census Bureau to determine the 1990 population of the county where subjects resided at the time of diagnosis, categorized by approximate tertiles. We examined primary type of drinking water by including indicators for use of bottled water or well water at any time up to the exposure age. Since age matching allowed for a difference as large as five years, we included age (at diagnosis for cases and at hospitalization for controls) as a covariate. Lastly, since information was collected for use of self-administered fluoride products at home or in school-based programs, any use of these products was included as an additional covariate.

Statistical Analysis

We limited the present analysis to cases younger than twenty years old and their matched controls. Conditional logistic regression was used to estimate the odds ratio for the association between fluoride exposure and osteosarcoma, taking into account the matching between cases and controls. The dependent variable was an indicator identifying cases and the primary independent variables were measures of fluoride exposure. We fit two basic models. The first analysis included only the exposure measures as independent variables. The second model also included age, median family income, county population, use of private well water or bottled water, and any use of self–administered fluoride products as covariates.

We report the mean and standard deviation of fluoride levels in parts per million

(ppm) and proportion of target for each specific age. To examine the association between osteosarcoma and fluoride exposure at specific ages, we fit separate models for each age. Each model included the age-specific fluoride level and a sex-fluoride interaction term. For our primary analysis we categorized climate-standardized fluoride exposure into approximate tertiles based on the distribution among controls. We plot sex-specific estimates of the logarithm of odds ratio (i.e., beta) and 95 percent confidence intervals as a function of age. We also fit a model using fluoride exposure categorized without standardization by climate into three groups (less than 0.3 ppm, 0.3 ppm to 0.69 ppm, and 0.7 ppm or greater).

We performed a sensitivity analysis on our assumption that the fluoride content of bottled water is 0.1 ppm by fitting models using values as high as 0.5 ppm for bottled water (assuming that bottled water and municipal water each contributed half of the subjects' consumption). In addition, we conducted a sensitivity analysis separately evaluating the age and sex-specific effects of fluoride in drinking water among subjects that used any fluoride supplements or fluoride mouth rinses and those who did not.

RESULTS

There were a total of 91 cases less than 20 years of age and 188 controls matched to these cases. Characteristics of the 91 cases and 188 controls are presented in Table 3.1. The mean age ± standard deviation was 13.6 ± 3.5 years. There were 1.5 times as many male subjects, with white subjects comprising the greatest proportion. The mean number of residences was 2.6 ± 1.8. The 1989 median family income for zipcode

of residence, a proxy for socioeconomic status, was lower for cases than controls (P=0.02, Student t-test). Table 3.2 shows the average fluoride level and percent of climate-specific target in drinking water at each age for cases and controls.

Figure 3.1 shows the log of the odds ratio of osteosarcoma for the climate-standardized fluoride exposure at each age from 0 to 15 years, estimated using the conditional logistic regression models unadjusted for other covariates. Two plots are presented, one for males (Figure 3.1A) and another for females (Figure 3.1B). The green line shows the log odds ratios for the intermediate exposure category (30 percent to 99 percent of target fluoride level) and the red line shows the log odds ratios for the high exposure category (100 percent of target or greater), each relative to fluoride levels less than 30 percent of target. Among males, exposure to fluoride at or above the target level was associated with an increased risk of developing osteosarcoma (Figure 3.1A). The association was most apparent between ages 5-10 with a peak at six to eight years of age. The odds ratio for the high exposure group was 5.16 at 7 years of age with a 95 percent confidence interval of 1.64 to 16.20. Among females less than 20 years of age, no association between fluoride in drinking water and osteosarcoma was apparent at any age.

Next we fit models with all the covariates. As an example, Table 3.3 shows the model for subjects at 7 years of age. Figure 3.2 shows that the results continue to demonstrate an effect after adjusting for income by zipcode, county population, ever use of bottled or well water, age, and any use of self-administered fluoride products. For males, the odds ratio for the high exposure group was 7.20 at 7 years of age with a 95

percent confidence interval of 1.73 to 30.01. Sensitivity analyses, which assumed that the fluoride content of bottled was as low as 0.1 ppm or as high as 0.5 ppm yielded essentially identical results. A sensitivity analysis that categorized fluoride exposure based on the absolute fluoride concentration, not taking into account regional fluoridation targets, also showed essentially the same results. When separate analyses were conducted for subjects who used fluoride supplements or fluoride rinses and those who did not the results remain consistent (Figure 3.3). In these analyses the number of subjects was reduced due to lack of matched cases and controls in each group. Therefore, addition of other covariates was not feasible due to lack of convergence in the models.

DISCUSSION

Our exploratory analysis describes the association of fluoride level in drinking water and osteosarcoma at specific ages. It suggests that for males less than twenty years old, fluoride level in drinking water during growth is associated with an increased risk of osteosarcoma, demonstrating a peak in the odds ratios from ages six to eight years of age (OR=7.20, 95 percent CI 1.73-30.01 at age 7). All of our models are remarkably robust in showing this effect during the mid-childhood growth spurt, which, for boys, occurs at ages seven and eight years (Molinari et al., 1980; Tanner and Cameron, 1980; Berkey et al., 1983; Tanner, 1990). For females, no clear association between fluoride in drinking water during growth and osteosarcoma is shown in this study.

We describe what appears to be a threshold effect, with similar effect magnitudes

in the intermediate and high exposure levels, as opposed to the expected dose-response gradient. One possible explanation is that this is due to misclassification of the primary exposure, for some artificially fluoridated systems. More specifically, Reeves (1996) reported that only 65 percent of fluoridated water systems routinely have optimal levels of fluoride maintained in the drinking water, which may result in our misclassifying up to 35 percent of the adjusted water systems, categorizing them in the highest group (100 percent of target or greater) when some truly belong in the middle group (30 percent to 99 percent of target). While nondifferential misclassification of exposure results in bias towards the null if the exposure is dichotomous, Birkett (1992) has shown that when there are three levels of exposure, the misclassified odds ratio for the highest exposure level is biased towards the null, but for the intermediate category the odds ratio can be biased in either direction. Hence, in our study the misclassification might mask an effect that increases with dose.

Our results are consistent with findings from the National Toxicology Program animal study which found "equivocal evidence" for an association between fluoride and osteosarcoma for male, but not female, rats (Bucher et al, 1991) and from two ecological studies that found an association for males less than twenty years old (Hoover et al., 1991; Cohn, 1992). Using data from the Surveillance, Epidemiology and End Results (SEER), Hoover et al. found an unexplained increase in osteosarcoma in males under 20 years of age in fluoridated versus non-fluoridated areas, but an analysis which took into account the duration of fluoride exposure failed to demonstrate a relationship between fluoride and osteosarcoma (Hoover et al., 1991). A similar, but much smaller study

conducted in New Jersey also showed an increase in osteosarcoma incidence rates for males less than 20 years old who lived in fluoridated areas compared to those living in non-fluoridated areas (Cohn, 1992).

A number of other case-control studies did not find an association between fluoride in drinking water and osteosarcoma (Operskalski et al., 1987; McGuire et al., 1991; Moss et al., 1995; Gelberg et al.; 1995). One possible reason for the lack of agreement may be related to the bimodal age-incidence distribution of osteosarcoma (Dorfman and Czerniak, 1995). When there are two distinct peaks in an age-incidence distribution, it has been suggested that two distinct sets of component causes should be considered (MacMahon and Trichopoulous, 1996). McGuire et al. (1991) and Moss et al. (1995) included cases up to age forty years and age eighty-four years, respectively, and if fluoride exhibits a different effect according to the age-specific distribution, detecting an effect would be unlikely. The study by McGuire et al. (1991) was also very small with only 22 cases of osteosarcoma. In another study of osteosarcoma in young people, researchers selected friends and neighbors as controls (Operskalski et al., 1987). Although this choice of selection might have been optimal for some exposures of interest, it resulted in inadvertently matching on fluoride exposure in drinking water, so as a result of overmatching, detecting a benefit or risk for fluoride would be unlikely.

Another potential explanation for the lack of similar findings reported in other studies which did not find an effect is that we evaluated age-specific effects. Rothman (1981) has pointed out that failure to identify the appropriate time window for exposure may result in misclassification which can adversely affect the ability to detect an

association. This might explain why the study by Gelberg et al. (1995) did not find an association between fluoride in drinking water and osteosarcoma since age-specific effects were not evaluated.

It is biologically plausible that fluoride increases the rate of osteosarcoma, and that this effect would be strongest during periods of rapid growth, particularly in males. First, approximately 99 percent of fluoride in the human body is contained in the skeleton with about 50 percent of the daily ingested fluoride being deposited directly into calcified tissue (bone or dentition) (Whitford, 1996). Second, fluoride acts as a mitogen, increasing the proliferation of osteoblasts (Gruber and Baylink, 1991; Ganong, 1995; Kleerekoper, 1996; Whitford, 1996) and its uptake in bone increases during periods of rapid skeletal growth (Whitford, 1996). This is not surprising, since in the young the hydroxyapatite structure of bone mineral exists as extremely small crystals surrounded by a hydration shell and bone is more hydrated in the young, providing a greater surface area for fluoride exchange to occur (Vauhan, 1981; WHO, 1984). Also, osteosarcoma generally involves the metaphyses of long tubular bones (Arndt and Crist, 1999) and the pattern of the blood supply to the metaphyses and epiphyses, where growth of long bones takes place differs from that of the diaphyses because of the special circulation to the epiphyseal growth plate in the young which in turn disappears when growth is complete (Soames, 1995). Lastly, the amount of fluoride present in bone depends on gender and intake (WHO, 1984) and intake, on average, is greater for males than females for all ages over one year (Ershow and Cantor, 1989).

There are several limitations to our study. First, and most important is that our

estimates of fluoride in drinking water at each residence do not necessary reflect actual consumption by subjects and no biologic markers for fluoride uptake were available. However, ingested sources of fluoride comprise the majority of human exposure (Whitford, 1996), and for individuals living in fluoridated communities, the fluoride in drinking water is estimated to contribute two thirds of the total dietary intake (WHO,1984). Also, when we added use of self-administered (home or school-based) products as a covariate in the model, there was no substantial change in results. The *halo* or *diffusion* effect, described in the dental literature, refers to people in non-fluoridated communities receiving fluoride from food and beverages processed in fluoridated communities and vice versa (Harris, 1995). We would expect this type of measurement error to result in our underestimating the true effect. In fact, when we perform separate analyses based on any use of fluoride supplements or mouth rinses we find that for males who did not use these products the effect of fluoride in drinking water shows a stronger effect for the higher fluoride exposure group than we observed in previous models for the entire group of males with incidence before age twenty. Also, when we compare the intermediate fluoride exposure group with the higher fluoride exposure group, the observed pattern is consistent with a dose-response effect for fluoride in drinking water. However, when we performed this separate analysis the number of subjects was substantially reduced due to lack of matched cases and controls in each group and if other covariates were added the models did not converge.

Another limitation is that the estimation of fluoride concentration at each residence is subject to measurement error in a variety of ways. In addition to the failure of

artificially fluoridated water systems to attain target levels already discussed, the precision of efforts to adjust concentrations to a target level can vary. For example, the target fluoride concentration for a specific state may be 1.0 ppm, but monitoring guidelines set by the state may consider values between 0.8 ppm and 1.3 ppm acceptable for water systems that fluoridate. Since we categorized our exposure, the effect of this type of misclassification should be minimized. Also, natural fluoride levels may vary over time, but they are unlikely to do so for the length of time subjects lived at their respective address unless the water source changed. Determining a fluoride value for bottled water users was difficult. We did not have names of specific brands for individual subjects and a small proportion of brands on the market do have substantial levels of fluoride. However, analysis of the leading national brands makes a value of 0.1 ppm a reasonable estimate for the time period of our study (thesis, chapter 2). Also, our sensitivity analysis demonstrated that varying this assumption from 0.1 ppm to 0.5 ppm did not change our findings.

The lack of data available for other potential confounders is limited. Fluoride may not be the causative agent, instead there may be another factor in drinking water correlated with the presence of fluoride. For example, another important covariate to consider including is radium content of drinking water since results of a recent case-control study suggest it may be associated with an increased risk of bone sarcomas (Finkelstein et al., 1996). Data to assess fluoride exposure in diet, industrial fluoride exposure or other fluoride exposures (e.g., pesticides) were not available. Instead, by including primary type of drinking water subjects used (ever well, ever bottled) as a

covariate, we may have partially controlled for some of the "other unknown factors" such as contaminants or carcinogens subjects might have been exposed to irrespective of fluoride concentration in these natural sources or products.

Another limitation is the possibility of selection bias. In our case-control study, the secondary study base is defined by the cases and in order for the results to be valid, the exposure distribution for controls must represent the exposure distribution in this theoretical population. Opportunity for selection bias definitely exists because referral patterns to the participating hospitals may be different for cases than for controls. For example, it may have been more likely for patients who were study controls to have higher income or live closer to the hospital than patients with osteosarcoma who would have been referred and traveled to these centers, irrespective of income or distance. Although within geographical regions it might be reasonable to assume cases would find their way to the participating hospitals, the route for controls is more difficult to envision. Distance defined by telephone area code rings was used as a matching factor, which would limit selection bias. But, this matching factor could also result in some overmatching on exposure and if this occurred we would underestimate the effect we reported. Another way we addressed the potential problem of selection bias was to include the 1989 median family income and county population as covariates.

The differential recall of exposure information between cases and controls is often a problem in case-control studies. Since respondents are not providing information about the fluoride level in their drinking water but rather a complete residential history, this should not be a problem for the estimation of the primary exposure. For other

covariates, such as date of birth, sex, or zipcode at time of diagnosis, information was also obtained by medical record review. Reporting of the type of water used or the use of self-administered fluoride products could be affected by recall bias.

Our findings for males included a peak effect during the mid-childhood growth spurt. This result is interesting and needs confirmation with other data. Fluoridation is a key public health issue for reducing the incidence of dental caries and is regarded as one of the most important public health achievements of the twentieth century (Stewart, 1970; SGR, 2000). Adjustment of fluoride in water systems benefits all socioeconomic groups and is considered to be a safe and the most cost effective method to prevent dental caries (Burt and Eklund, 1999; CDC census, 1993; Harris and Clark, 1995). The etiology of osteosarcoma is largely unknown and evidence for risk factors inconclusive with the only environmental agent known being ionizing radiation, specifically, external high-dose irradiation used in cancer therapy, or the internal bone-seeking radioisotopes from occupational or medicinal use (Link and Eilber, 1997; Fraumeni, 1975; Miller, 1981; McClay, 1989). In view of our results, it now seems important that our findings be confirmed using data from other studies. There is at least one current ongoing study of osteosarcoma in which data estimating fluoride exposure from drinking water is being included as a factor of interest and the opportunity exists for their data to be analyzed using our approach. Collaborative efforts might also be possible with other investigators whose studies collected complete residential histories. We recommend that future studies evaluating risk factors for osteosarcoma will include fluoride level in drinking water, incorporating the strengths of our approach and improving on our limitations.

Table 3.1: Characteristics of Study Population

	Cases	Controls
Number	91	188
Age (years)	13.1 ± 6.1	13.8 ± 3.6
Gender		
Males	55 (60%)	112 (60%)
Females	36 (40%)	76 (40%)
Race		
White	71 (78%)	161 (86%)
Black	14 (15%)	17 (9%)
Asian	3 (3%)	1 (1%)
Other	3 (3%)	9 (5%)
Number of Residences	2.5 ±1.7	2.6 ± 1.9
1989 Median Family Income*	$41,326 ±14,927	$46,398 ± 18,650
County Population (n)		
< 250,000	22 (24%)	66 (35%)
250,000-999,999	46 (51%)	68 (36%)
1,000,000+	23 (25%)	54 (29%)

Hospital		
MGH	15 (16%)	24 (13%)
CH, Boston	14 (15%)	41 (22%)
Creighton	5 (5%)	11 (6%)
CH, DC	10 (11%)	18 (10%)
MSKCC	7 (8%)	14 (8%)
U Chicago	6 (7%)	11 (6%)
Rush	3 (3%)	6 (3%)
U Florida	11 (12%)	18 (10%)
UCLA	11 (12%)	25 (13%)
Cleveland Clinic	7 (8%)	16 (9%)
CWRU	2 (2%)	4 (2%)
Ever Well Water Use (n)	26 (29%)	40 (21%)
Ever Bottled Water Use (n)	7 (8%)	43 (23%)
Fluoride Products		
Rinses	14 (15%)	30 (16%)
School Program	16 (18%)	28 (15%)
Tablets	10 (11%)	25 (13%)
Drops	9 (10%)	18 (10%)
Any of Above	36 (40%)	80 (43%)

* 1989 Median Family Income data available for 89 cases and 186 matched controls.

Table 3.2: Fluoride Level for Primary Drinking Water*

	F Level in ppm		Percent of Target	
	Cases	Controls	Cases	Controls
Age (years)				
0	0.65 ±0.56	0.61 ±0.41	67% ±40%	62% ±41%
1	0.64 ±0.40	0.60 ±0.40	67% ±40%	61% ±40%
2	0.65 ±0.40	0.62 ±0.40	68% ±40%	63% ±39%
3	0.67 ±0.39	0.63 ±0.40	70% ±39%	64% ±39%
4	0.70 ±0.38	0.63 ±0.40	74% ±38%	64% ±39%
5	0.69 ±0.37	0.63 ±0.40	73% ±38%	65% ±38%
6	0.70 ±0.38	0.62 ±0.40	74% ±38%	62% ±38%
7	0.71 ±0.36	0.62 ±0.40	76% ±37%	63% ±39%
8	0.70 ±0.36	0.61 ±0.40	75% ±38%	63% ±38%
9	0.68 ±0.38	0.63 ±0.40	74% ±38%	65% ±39%
10	0.66 ±0.39	0.62 ±0.40	72% ±38%	64% ±39%
11	0.64 ±0.38	0.60 ±0.40	68% ±38%	63% ±39%
12	0.62 ±0.37	0.58 ±0.40	68% ±37%	62% ±39%
13	0.65 ±0.37	0.60 ±0.40	70% ±37%	64% ±39%
14	0.62 ±0.40	0.59 ±0.40	67% ±39%	63% ±39%
15	0.55 ±0.41	0.59 ±0.40	62% ±41%	61% ±40%

* When primary drinking water used was bottled water the estimate was 0.1 ppm.

Table 3.3: Conditional Logistic Regression Model

Fluoride Exposure at Age 7 Years	Odds Ratio (95 % C. I.)
30 % - 99 % of Target	
Males	4.94 (1.23, 19.8)
Females	1.84 (0.43, 7.91)
at least 100 % of Target	
Males	7.20 (1.73, 30.0)
Females	2.00 (0.43, 9.28)
Median 1989 Family in Zipcode	
$33,484 - $43,065	0.47 (0,18, 1.26)
$43,066 - $53,933	0.45 (0.16, 1.27)
$53,934 or more	0.37 (0.11, 1.19)
County Population	
< 250,000	3.33 (0.78, 14.2)
250,000 - 999,999	4.87 (1.41, 16.8)
Used Well Water by Age 7 Years	1.89 (0.78, 4.56)
Used Bottled Water by Age 7 Years	0.07 (0.01, 0.45)
Ever Used Fluoride Supplements or Rinse	0.81 (0.39, 1.69)
Age (Years) at Study Entry	0.66 (0.52, 0.83)

Figure 3.1: Logarithm of Odd [sic] Ratios for Age-Specific Fluoride Exposure

A: Males, Based on Model without Covariates

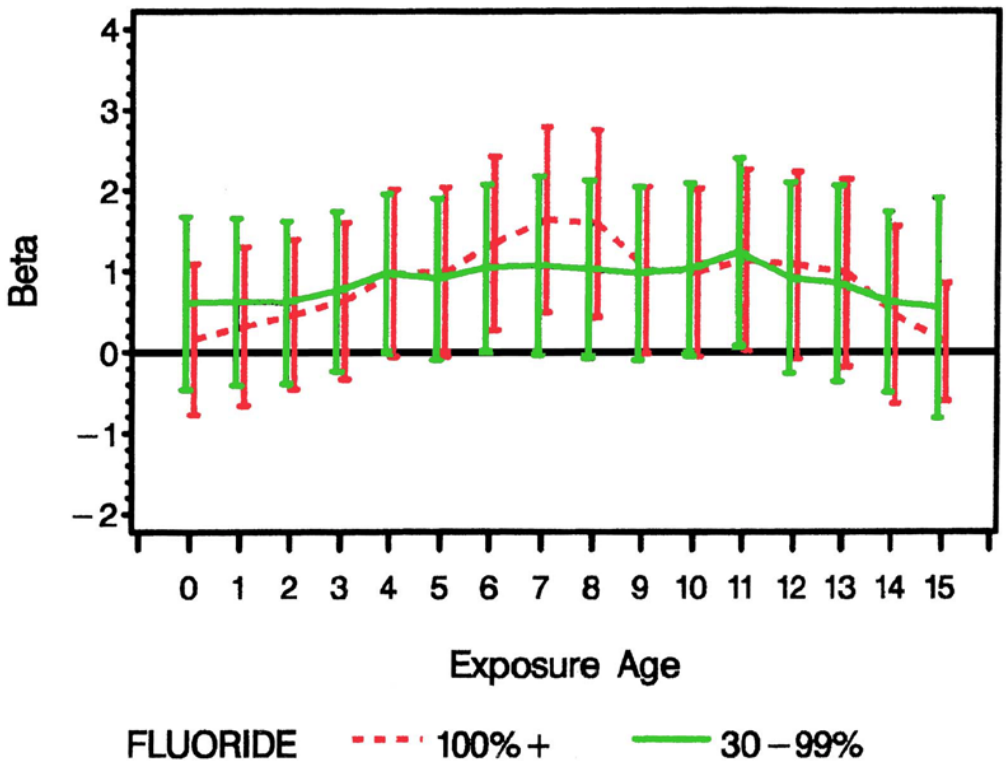

Figure 3.1: Logarithm of Odd Ratios for Age-Specific Fluoride Exposure

B: Females, Based on Model without Covariates

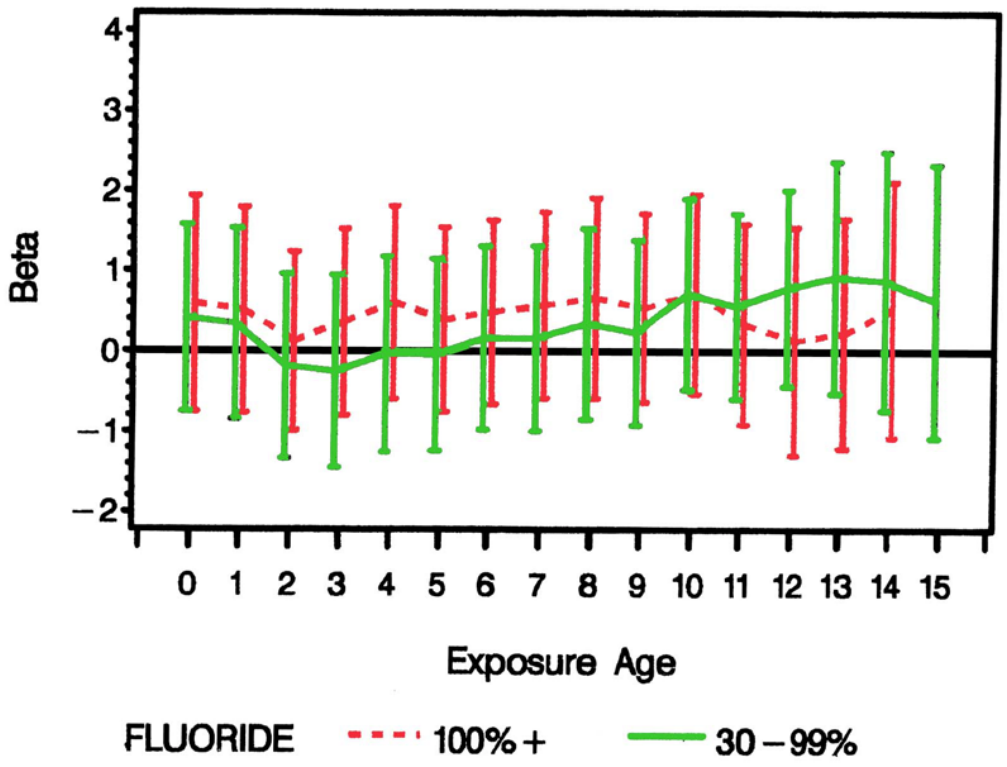

Figure 3.2: Logarithm of Odd Ratios for Age-Specific Fluoride Exposure

A: Males, Based on Model with Covariates

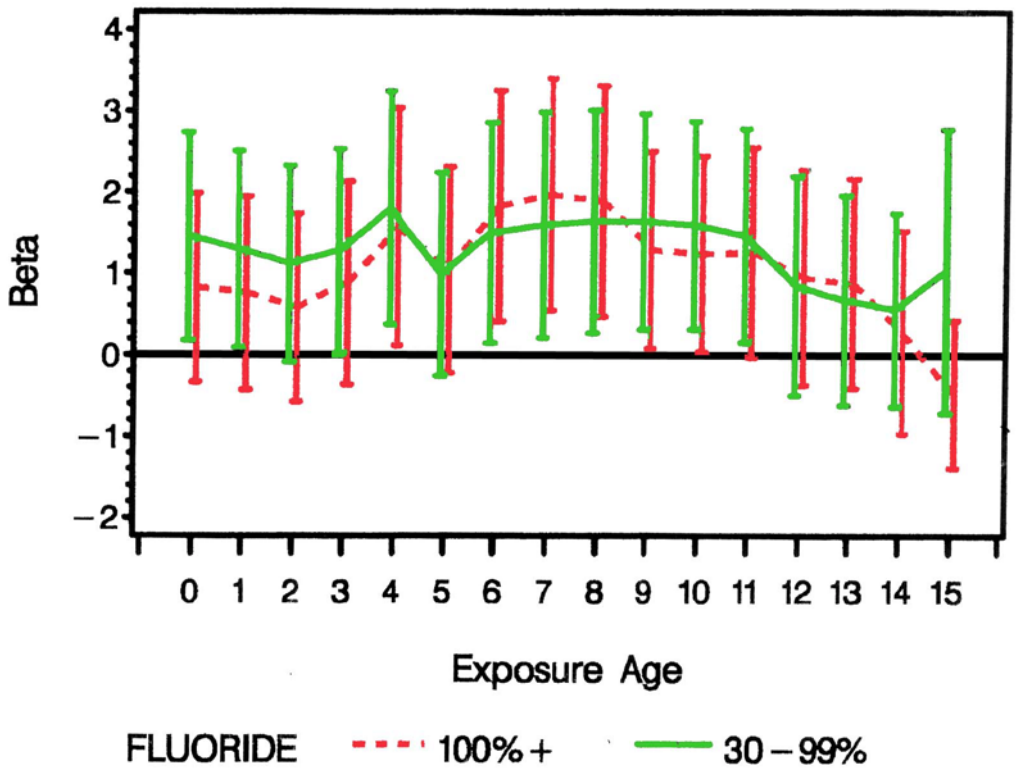

Figure 3.2: Logarithm of Odd Ratios for Age-Specific Fluoride Exposure

B: Females, Based on Model with Covariates

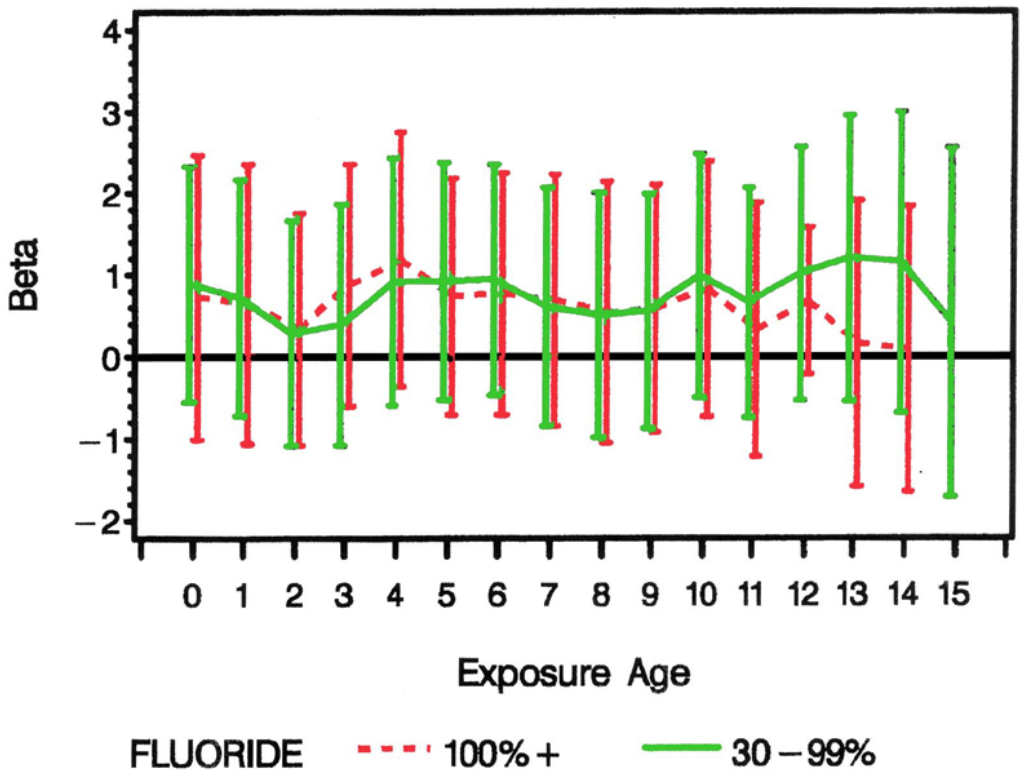

Figure 3.3: Logarithm of Odd Ratios for Age-Specific Fluoride Exposure

For Males Who Never Used Fluoride Rinses or Supplements

Based on Model without Covariates