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# IS THERE A LINK BETWEEN FLUORIDATED WATER AND OSTEOSARCOMA?



## ABSTRACT

**To test the hypothesis that fluoride is a risk factor for osteosarcoma, a case control study compared the complete residential fluoride histories of osteosarcoma patients with matched hospital-based controls. Fluoridation was not found to be a risk factor for osteosarcoma in the study population. The trend in the data from this small sample study suggests the hypothesis that a protective effect may exist against the formation of osteosarcoma for individuals consuming fluoridated water.**

**T**he "equivocal evidence" of a link between fluoride ingestion and the formation of osteosarcoma in a small percentage of male rats that received high doses of fluoridated water (100 and 175 ppm NaF) was reported in 1990.<sup>1</sup> Inferences on human risk of fluoride carcinogenicity are difficult at best to obtain from animal studies.

Our study reports findings from a human population-based analytical study of osteosarcoma patients and matched controls. The relationship of systemic fluoride exposure from the ingestion of water from residential sources to the occurrence of osteosarcoma was examined.

An incorrect inference implicating systemic fluoride carcinogenicity and its removal from our water systems would be detrimental to the oral health of most Americans, particularly those who cannot afford to pay for increasingly expensive restorative dental care.

Osteosarcoma is a rare and painful primary malignant bone tumor most commonly occurring in children and young adults. Data<sup>2</sup> indicate that tumors of the bones and joints occur in less than one person in 100,000.

The American Cancer Society estimated there were 2,100 new cases of bone sarcomas in 1989.<sup>3</sup> According to Maeyama,<sup>4</sup> osteosarcoma incidence varied with age; 35.7 percent of all the malignant bone tumors occurring in the first decade of life were osteosarcomas, rising to a peak of 69.6 percent in the second decade and decreasing thereafter to 24.5 percent and 4.3 percent respectively in the third and fourth decades. Male patients predominated, with a ratio of three males to two females.

Radiation,<sup>5,7</sup> viral action,<sup>8,9</sup> genetic factors<sup>10</sup> and other exogenous factors have been implicated in the development of osteosarcomas.<sup>11</sup> Radiation induction of osteosarcoma is at present an accepted principle. A recent review of the epidemiology of bone sarcomas, however, reported conflicting study results for all other etiologic agents. Fluoride ingestion was not linked to osteosarcomas in the most recent review.<sup>11</sup>

Hoover and others at the National Cancer Institute compared standardized bone cancer mortality rates in fluoridated and non-

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fluoridated counties in the United States.<sup>12</sup> No change in bone cancer mortality took place over the 15-year comparison. In addition, standardized overall cancer mortality rates have been compared for fluoridated and non-fluoridated communities.<sup>13,14</sup> None of the studies uncovered a significant increase in human cancer incidence or mortality as a result of the implementation of community fluoridation.

According to the Congressional Committee on Intergovernmental Relations and Human Resources, questions lingered about the relationship between fluoride ingestion and osteosarcomas.

The National Toxicology Program was directed to conduct an animal toxicity study to test the carcinogenicity of the fluoride ion. The NTP concluded and the Board of Scientific Counselors' Technical Reports Review Panel concurred that its two-year studies showed only "equivocal evidence of carcinogenic activity" in male rats and "no evidence of carcinogenic activity in female rats or in male or female mice."<sup>11</sup> (Equivocal evidence is a category for uncertain findings demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.)

Findings on the molecular explanation for the initiation of an osteosarcoma tumor from fluoride exposure could not be found in a

**TABLE 1**

**FLUORIDE EXPOSURE AT OR ABOVE RECOMMENDED CDC LEVELS**

	Controls	
	More than 1/3 of life at >0.7 ppm	Less than 1/3 of life at >0.7 ppm
Cases		
More than 1/3 of life at >0.7 ppm	11	1
Less than 1/3 of life at >0.7 ppm	7	3

OR = RR = 0.14     $\chi_c^2 = 3.1$     95% CI = 0.02, 1.22

refereed journal. However, the mechanism of fluoride's action to strengthen osteal tissue is related to its ionic capabilities. The major component of osteal tissue and the major strengthening material in teeth is structural hydroxyapatite, Ca<sub>5</sub>(P<sub>4</sub>O<sub>14</sub>)<sub>3</sub>OH.

When ionic fluoride enters the hydroxyapatite lattice, a dynamic exchange of F for OH occurs in portions of the structure. The resulting fluorapatite tightly binds the fluoride, strengthening the structure and rendering it less susceptible to dissolution in organic acids.<sup>15</sup> Strengthening can occur either through incorporation of F ions during the tissue mineralization phase of tooth or bone development,<sup>16</sup> or exchange of ions after formation has occurred.<sup>17</sup>

Because of its strengthening action, fluoride has been widely

accepted as the responsible agent for dramatic declines in the tooth decay rates of U.S. children and adolescents.<sup>18,19</sup> Studies of matched pairs of fluoridated and non-fluoridated communities established the principle that decay rates could be reduced by up to 70 percent through the use of fluoridated community water.<sup>20</sup> Current reduction rates are estimated to be between 20 percent to 30 percent.<sup>21</sup> A disruption in the delivery of fluoride through municipal water systems would increase decay rates over time.

In one study, fluoride was removed from a community water supply after 11 years of fluoridation. The DMFS scores were recorded for second-grade children at the time of defluoridation and second-grade children six years later. Sixty-seven percent more children at the time of defluoridation were caries-free when compared with the second graders six years later.<sup>22</sup>

Linkage of fluoride ingestion and cancer initiation could result in a large-scale defluoridation of municipal water systems under the Delaney clause. (One aspect of this Environmental Protection Agency clause prevents the addition of carcinogenic agents to

**FIGURE 1**

**DERIVATION OF AVERAGE LIFETIME FLUORIDE EXPOSURE (IN PPM)**

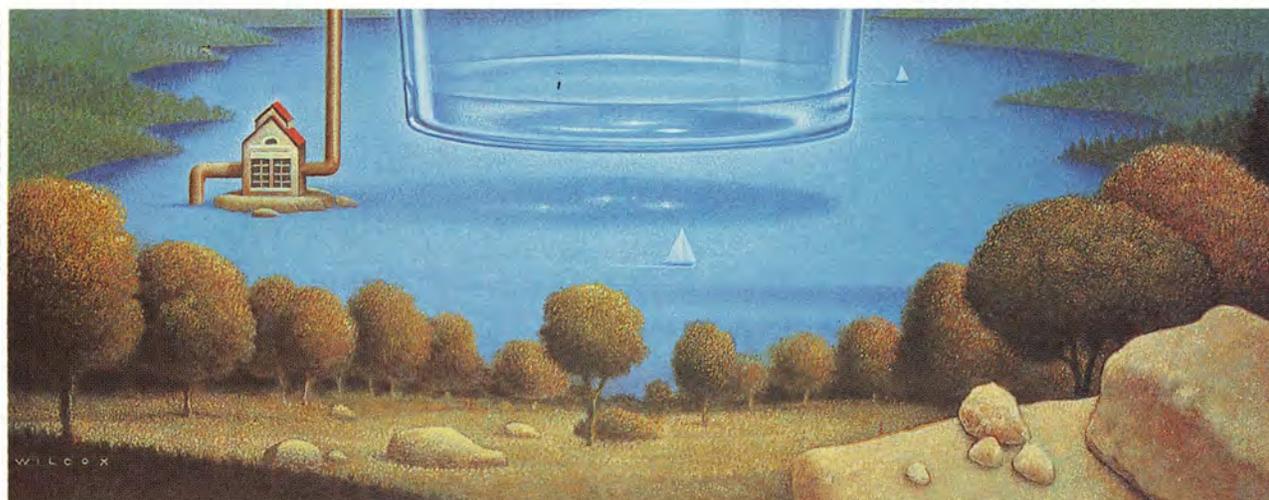
Example:

Case  

$$\frac{(11 \text{ years} \times 0.8 \text{ ppm}) + (7 \text{ years} \times 1.0 \text{ ppm})}{18} = .87 \text{ ppm}$$

Control  

$$\frac{(15 \text{ years} \times 0.3 \text{ ppm}) + (3 \text{ years} \times 1.0 \text{ ppm})}{18} = .42 \text{ ppm}$$



the nation's water supply.) To test the hypothesis that fluoride is a risk factor for osteosarcoma, this case control study compared the complete residential fluoride histories of osteosarcoma patients with matched hospital-based controls of similar age, gender and county of residence.

#### METHODS

Osteosarcoma patients were identified from the University of Iowa Cancer Registry and the medical records of the Division of Orthopedics, St. Josephs Hospital in Omaha, Neb. Each source recorded birth date, the age at diagnosis, gender and county of residence at diagnosis for each case. Eligible cases were patients

diagnosed between 1980 to 1990 and younger than 40 at diagnosis.

Non-radiation induced osteosarcoma occurs predominantly in the first four decades of life. Osteosarcoma patients with any prediagnosis history of the known risk factor, radiation therapy, were excluded. In addition, patients with a history of kidney dialysis were excluded as they choose to drink deionized water for medical reasons.

The University of Iowa and St. Josephs hospitals identified 44 eligible cases. Correct addresses could not be ascertained for seven cases; two patients had received pre-diagnosis radiation therapy and one medical record could not be found. Contact with the

remaining 34 eligible patients was initially made by mail with a letter of explanation of the research goals of the study from the appropriate orthopedic department chairman.

Hospital-based controls from patients of the appropriate orthopedic department were matched by age, gender and county of residence at time of diagnosis. The Midwest states—Iowa, Illinois and Nebraska, in particular—are geographically divided into many small counties, for example, 99 in Iowa. Most counties are rural with relatively few dominated by an urban industrial area. The advantage of matching on the county of residence variable includes greater likelihood of socio-economic status similarity and absence of bias related to the complex referral process that precedes hospitalization.<sup>23</sup> Following a local custom, residents of Iowa and Nebraska typically identify themselves as a resident of a particular county.

Cases and controls were excluded with identical criteria: any history of radiation therapy and patients with a history of kidney dialysis. The factor under investigation—ingestion of residential fluoridated water—is

TABLE 2

	Controls	
	High >0.7 ppm	Low ≤0.7 ppm
Cases		
High <0.7 ppm	9	2
Low ≤0.7 ppm	6	5
OR = RR = 0.33	$\chi^2 = 1.12$	95% CI = 0.04, 2.50

**TABLE 3**

		Controls	
		More than 1/3 of childhood at >0.7 ppm	Less than 1/3 of childhood at >0.7 ppm
<b>CHILDHOOD EXPOSURE</b>			
Cases			
More than 1/3 of childhood at >0.7 ppm	9		2
Less than 1/3 of childhood at >0.7 ppm	6		5
OR=RR=0.33		$\chi^2=1.12$	95% CI=0.04, 2.50

not associated with any other medical condition or risk factor. Therefore, no other categories of disease were deliberately included or excluded in the hospital control group.

As each osteosarcoma case was to be matched to a control patient, a 1:1 ratio of cases to controls was required. Initially, an attempt was made to contact two controls for each of the 34 cases with a letter explaining the study's research goals from the appropriate orthopedic department chairman. Because there was no age and county of residence matched control for seven of the cases, 27 pairs of cases and controls were enrolled.

The 27 cases were interviewed by telephone for the following information: all residential addresses of the osteosarcoma patient before diagnosis; year(s) lived at each address; access to municipal or well water at each address; and bottled



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water use. The same procedure was followed to ascertain residential histories from the matched controls.

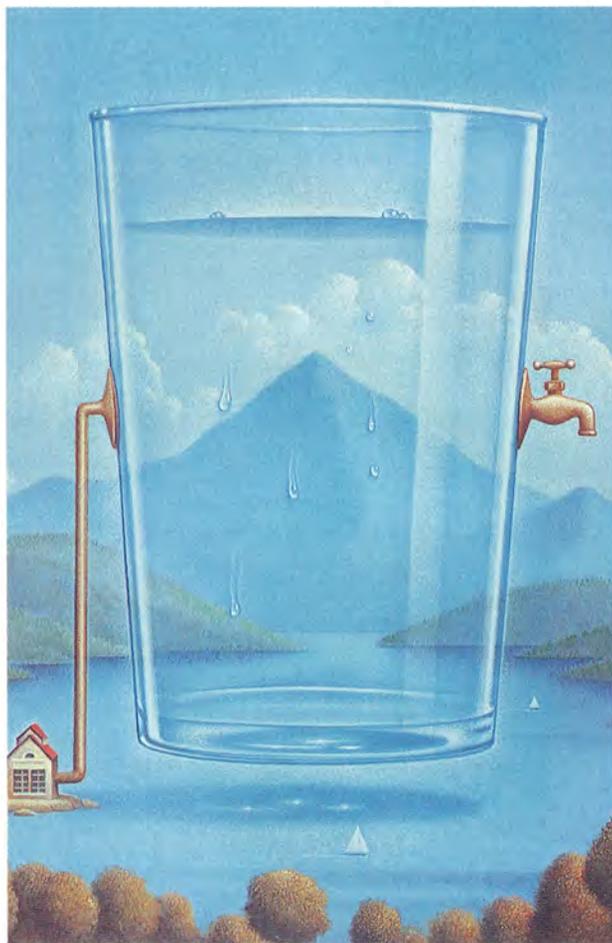
Fluoride levels (in ppm) for municipalities supplying water to the cases and controls were ascertained from the most recent Centers for Disease Control Fluoridation Census in the years identified. If a case or control lived in a municipality before adjustment of fluoride levels listed in the census or in a municipality not listed in the census, the appropriate state's Department of Natural Resources was contacted for the correct pre-adjusted level of fluoride. Water sample tubes

were provided by mail to the participants with access to well water. The participants were requested to return a well water sample for analysis of fluoride content by the University of Iowa Hygienics Laboratory.

## RESULTS

Contact by telephone was successful for all 27 osteosarcoma cases and their controls. One case refused to participate and four cases could not supply samples of well water from previous addresses. Therefore, the analysis was conducted using the fluoride exposure information gathered on 22 matched-pair cases and controls.

Thirteen pairs were males and nine were females, consistent with the national figures. Additionally,





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as in the national figures, the preponderance of this study's osteosarcoma patients, 14 cases, were diagnosed in the second decade of life (11 to 20). Three cases

were children 10 years old or younger, three cases were 21 to 30 and two cases were in their 30s.

Each participant had lived at an average of two different towns/farms per lifetime.

Therefore, complete residential fluoride history was to be summarized and compared by three methods. The first method compared years spent at or above the recommended levels of fluoride as set by the CDC, the second method collapsed the data into a lifetime average exposure, and the third compared exposure during childhood and early adolescence—the years of bone development.

The first method of analyzing the data was to compare years the cases and their controls spent at

is no association between residential fluoridated water exposure and osteosarcoma, namely an odds ratio (OR) = estimated relative risk (RR) = 1. For this study population, the case in one pair lived more than 1/3 of his or her life in towns/farms with

Confidence intervals including 1 support the hypothesis that the consumption of residential fluoridated water is not a risk factor for the occurrence of osteosarcoma in this study population.

A lifetime average exposure was

**B**

$$OR = \frac{b}{c} = \frac{\text{number of pairs in which only the case had a high average fluoride exposure level}}{\text{number of pairs in which only the control had a high average fluoride exposure level}}$$

fluoride levels > 0.7 ppm while the matched control lived less than 1/3 of his or her life at sites > 0.7 ppm.

Conversely, the controls in seven pairs lived more than 1/3 of their lives in towns/farms with fluoride levels > 0.7 ppm while the paired cases lived less than 1/3 of their lives at sites > 0.7 ppm. The odds ratio using this method of assessing exposure is .14. The conservative Yates continuity corrected chi-square test for matched paired data ( $\chi_c^2$ ) was used to test the statistical significance of the estimate of the magnitude of the association

calculated for each participant by multiplying the number of years lived at an address by the addresses' fluoride level summed over a lifetime and divided by age (Figure 1). The average exposure for the case was compared to the average exposure of the matched control to produce an odds ratio (Table 2). Exposure to high fluoride level was defined as >0.7 ppm lifetime average exposure.

Exposure to low fluoride level was defined as ≤0.7 ppm. The odds ratio for this method was calculated as shown (B).

Again, the null hypothesis is that there is no association between residential fluoridated water exposure and osteosarcoma, OR = 1.

For this method of comparison, the case in two pairs had a high average fluoride exposure and the matched control had a low average fluoride exposure. The control in seven pairs had a high average fluoride exposure and its paired case had a low average fluoride

**A**

$$OR = \frac{b}{c} = \frac{\text{number of pairs in which only the case lived more than 1/3 of life at sites with >0.7 ppm}}{\text{number of pairs in which only the control lived more than 1/3 of life at sites with >0.7 ppm}}$$

or above the recommended optimal level set by CDC, 0.7 ppm.<sup>24</sup> The odds ratio of disease (osteosarcoma) associated with exposure (years spent at recommended levels of fluoridation) was calculated as shown (A).

The null hypothesis is that there

between fluoride history and osteosarcoma. The  $\chi_c^2$  was not significant ( $\chi_c^2 = 3.1, P > 0.05$ ). Therefore, we failed to reject the null hypothesis.

The corresponding confidence interval (CI) was calculated using a test-based approach.<sup>25</sup> The 95 percent CI is 0.02, 1.22 (Table 1).



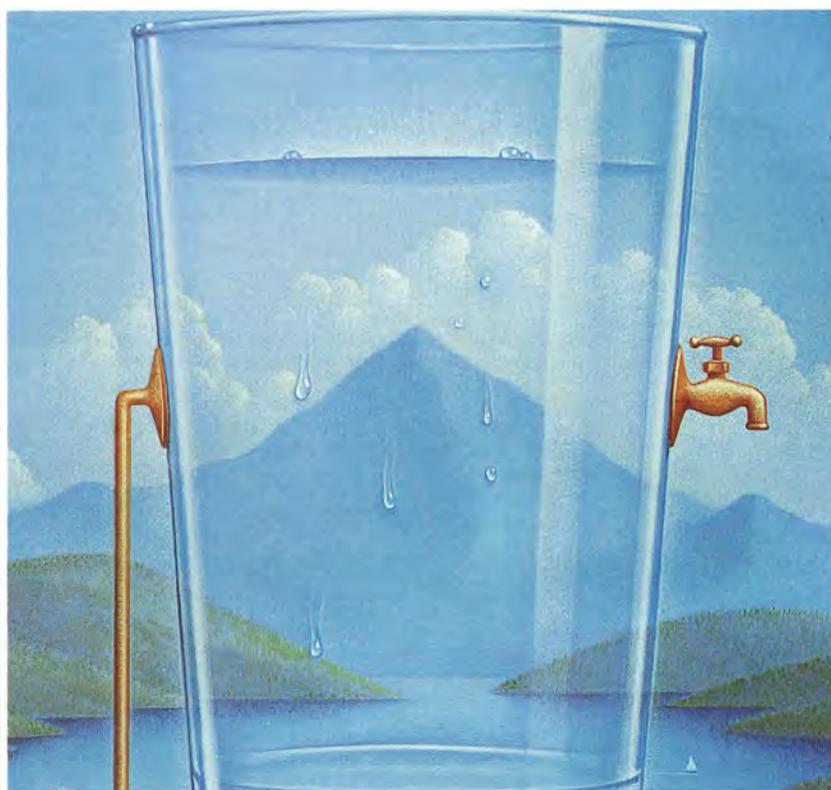
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exposure. Therefore, the odds ratio is 0.33 with a Yates continuity correction  $\chi_c^2$  test,  $\chi_c^2 = 1.125$ ,  $P > .05$ ,  $CI = .04, 2.5$  (Table 2). The analysis of this comparison also shows that residential fluoridated water is not a risk factor for the occurrence of osteosarcoma.

Lastly, the data were separated and analyzed in terms of childhood and adolescent years (birth-15) spent at residences at or above the recommended optimal level for fluoridated water, 0.7 ppm. Only the fluoride exposure for the first 15 years of life for the cases and the controls was used to calculate the odds ratio shown (C).

Only the cases in two pairs lived more than 1/3 of the first 15 years of their lives in towns/farms with fluoride levels  $>0.7$  ppm, while their matched controls spent less than 1/3 of the first 15 years of their lives at sites with  $>0.7$  ppm (Table 3). Conversely, in six pairs, only the controls lived more than 1/3 of the first 15 years of their lives at sites with fluoride levels  $>0.7$  ppm while their paired cases spent less than 1/3 of the first 15 years of their lives at sites  $>0.7$  ppm.

Therefore, the odds ratio is 0.33 with a Yates continuity correction  $\chi_c^2$  test,  $\chi_c^2 = 1.125$ ,  $P > .05$ ,  $CI = .04,$



to be a risk factor for the occurrence of osteosarcoma.

## DISCUSSION

Osteosarcoma is a rare disease occurring primarily in the second decade of life. The matched-pair case control study reported here consists of an analysis of only 22 matched pairs. A point estimate of an odds ratio  $> 1$ , indicating a link between fluoridated water and

tended to stay close to  $OR = 1$ , thus rejecting the hypothesis that fluoridation is a risk factor for osteosarcomas.

The findings provoke interest in greatly increasing the sample size to further define and clarify the relationship between osteosarcoma and fluoride exposure. One unexpected hypothesis was generated by the data. With point estimations of all three odds ratios less than 1, perhaps an inverse relationship may exist; that is, that fluoridation at

recommended levels may provide a protective effect against the formation of osteosarcoma. Evidence exists to support such a hypothesis. Vogel,<sup>26</sup> Obe<sup>27</sup>



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<b>OR</b>	=	$\frac{b}{c} = \frac{\text{number of pairs in which only the case lived more than 1/3 of the first 15 years of life at sites } >0.7 \text{ ppm}}{\text{number of pairs in which only the control lived more than 1/3 of the first 15 years of life at sites } >0.7 \text{ ppm}}$

2.5 (Table 3). For this method of comparison, residential fluoridated water exposure at levels  $>0.7$  ppm during the years of bone development does not appear

osteosarcoma, did not exist in any of the three methods of analysis used in this study. Because of the small sample size, the confidence intervals were broad but they



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and Slacik-Erben<sup>28</sup> have reported histological studies showing that fluoride may provide an antimutagen effect.

A nationwide, multi-center

analytical study to increase the precision of our initial findings and pursue the hypothesis that the ingestion of fluoridated water may provide protection against the occurrence of osteosarcoma has been initiated by the authors. This larger study will also include the collection of any history of participation in school-based mouthrinsing programs or use of supplemental fluoride tablets/drops in addition to complete residential fluoride history.

## CONCLUSION

In a case-control study of osteosarcoma patients and hospital-based matched controls, the ingestion of fluoridated water was not found to be a risk factor for osteosarcoma. Hence, no link was found between the occurrence of osteosarcoma and ingestion of residential fluoridated water over the course of a lifetime or during the years of bone development. Given present knowledge, every effort should be made to continue the practice of fluoridating community water supplies. ■

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