Topic Summary: Fluoridation and Bone Cancer (Osteosarcoma)

By Center for Fluoride Research Analysis / Fluoride Science Editorial Board

Last updated: September 23, 2016

Available at fluoridescience.org/fluoride-bone-cancer

Osteosarcoma is not a common cancer in humans but is the most common type of cancer that develops in bone.[1] About 800 new cases of osteosarcoma are diagnosed each year in the United States, and most of them occur in children and young adults between the ages of 10 and 30.[1] The reported risk factors for osteosarcoma include past treatment with radiation therapy, treatment with anti-cancer drugs called alkylating agents, having a certain change in the retinoblastoma gene, and having certain conditions like Paget's disease.[1] A concern for potential human carcinogenicity of fluoride was first raised in the 1970s by Yiamouyannis and Burk who reported a greater rate of cancer mortality in areas with artificially fluoridated drinking water than in non-fluoridated areas.[2,3] Although this study and findings were criticized as being at high risk for ecological fallacy later by several independent reviews,[2,4,5] "equivocal evidence" from laboratory studies conducted by the National Toxicology Program (NTP 1991), which indicated an increased incidence of osteosarcomas in F344/N male rats administered various level of fluoride in drinking water, promoted further investigations in fluoride bone cancer research.[2,6] Because of this NTP finding and fluoride's deposition in bone and biological plausibility of affecting cell systems,[2,7] the relationship between fluoride and osteosarcoma has been studied more extensively than other type of cancers.

The majority of available human epidemiological studies concerning fluoride and incidence and mortality of osteosarcoma use an ecological or semi-ecological study design and show no association.[2,7-18] Aside from limitations related to fluoride exposures determined by area-fluoridation level in most of studies, there are several inherent difficulties for conducting epidemiological research and interpreting fluoride's carcinogenicity. These include but not limited to 1) it's rare occurrence, which makes

statistical inference difficult when associations are weak, 2) latent period in many forms of cancers which incur concerns for potential migration of individuals over time thus misclassification of exposures when residential histories are not known, and 3) uncertain relevance of high-dose toxicological studies in rodents to humans especially when epiphyseal plates of long bones, the most common site of childhood osteosarcoma, continue to grow throughout the lifetime of rats thus incur greater susceptibility in rodents than in humans.[7,9]

Since the National Research Council (NRC) called for studies with improved assessment of fluoride exposure and information collected from individuals to further evaluate the potential link between fluoride and osteosarcoma in its 1993 report,[2] three studies addressed some of the recommendations and reported conflicting findings. Gelberg and colleagues (1995) conducted a population-based case-control study and interviewed subjects of childhood osteosarcoma survivors and parents of those deceased identified in the state cancer registry database as well as randomly selected, pair-matched control subjects, identified in the state live birth records. Their study showed that the estimated dose of lifetime fluoride exposure was not associated with the risk of osteosarcoma, while their data from parent interview indicated a protective effect of fluoride exposure to osteosarcoma risk in males.[19] Meanwhile, Bassin and colleagues (2006) reported the association between osteosarcoma and age-specific fluoride exposure, determined by the subject interviews, among males based on the preliminary analysis of data from the Harvard Fluoride Osteosarcoma study, a multi-center, hospital-based case-control study.[20] The second Harvard study by Kim and colleagues (2011) used bone fluoride levels to determine fluoride exposure and showed no significant association between bone fluoride levels and osteosarcoma.[21] While each of these three case-control studies had different strength and limitations, the use of biological marker of lifetime fluoride exposures and histologically confirmed osteosarcoma outcomes in Kim's study provided significant value and confidence in reducing misclassifications.

In summary, accumulated epidemiological research offers weighty evidence indicating that optimally fluoridated drinking water would not pose detectable risk of osteosarcoma while there is no absolute evidence to rule out fluoride's carcinogenicity or genotoxicity. A margin of safety is evident since fluoride exposure is prevalent and osteosarcoma remains a rare occurrence in the US over the last 70 years.
The following section shows the summaries of selected systematic reviews on this topic:

MCDONAGH ET AL. 2000[8]

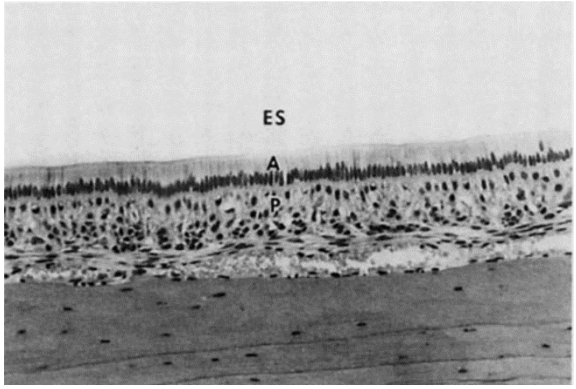
The authors evaluated 11 studies that reported the association of water fluoridation and osteosarcoma, bone and joint cancer incidence and mortality that were published before 2000. Of these, 7 studies were on osteosarcoma, and 6 of them presented variance data. Only one of them (Cohn 1992), given the lowest validity score among all 6 studies, found

a statistical significance in the association between fluoridation and increased prevalence of osteosarcoma in males. The overall direction of the association was mixed: Among 12 analyses the authors performed, 7 found negative (fewer cancers) relationship, and 3 and 2 analyses found positive (more cancers) and no relationship, respectively. Along with the systematic reviews of studies on all-cause cancers, the authors concluded that no clear association between water fluoridation and increased cancer incidence or mortality was apparent.

NRC REPORT 2006[7]

Responding to the request from the US Environmental Protection Agency (EPA), the NRC convened the Committee on Fluoride in Drinking Water and reviewed toxicologic, epidemiologic, and clinical evidence on fluoride, especially those published after the NRC's 1993 Report, to determine if EPA's current Maximum contaminant level (MCL) of 4mg/L for fluoride is acceptable for protecting the public from potential adverse health effects, including cancers.

- The committee found some new human in-vivo studies published since the last NRC report on genotoxicity of fluoride, however the inconsistencies in the results did not enable a straightforward evaluation of fluoride's practical genotoxic potential in humans. The results in in-vitro systems are also inconsistent and do not strongly indicate the presence or absence of genotoxic potential for fluoride.
- The committee provided in-depth review of two animal carcinogenicity studies (NTP 1990 and Maurer 1990, 1993) that have been evaluated previously in the 1993 report. The studies conducted by NTP indicated a possible increase in the incidence of osteosarcomas in F344/N male rats.[22] However, the studies conducted by Maurer and colleagues, funded by Procter & Gamble, which used higher doses of fluoride administered in the diet than those administered in drinking water in the NTP study, did not confirm the prior NTP findings.[23,24]
- The committee provided reviews of available human epidemiological studies on bone and joint cancers, particularly osteosarcoma, including the preliminary findings of two Harvard fluoride-osteosarcoma studies and loaded a hope of more evidence available in the near future.



SUTTON ET AL. 2015[9]

The authors reviewed scientific evidence to inform the Ireland Department of Health with regard to any impact, positive and or negative, on the general health of those exposed to community water fluoridation at the levels of 0.4-1.5 ppm. Based on the existing literature available before 2015, this report concluded that the effects of fluoride in drinking water on osteosarcoma incidence are mixed and no link has been proven. The authors recommended a good quality longitudinal research to affirm or rule out these suggested fluoride bone cancer links.

REFERENCES

1. American Cancer Society. Osteosarcoma. Available at http://www.cancer.org/acs/groups/cid/documents/webcontent/003129-pdf.pdf
2. National Research Council. Health effects of ingested fluoride. Washington, DC. The National Academies Press. 1993.
3. Yiamouyiannis J, Burk D. Fluoridation and cancer age-dependence of cancer mortality related to artificial fluoridation. Fluoride. 1977;10(3):102-23
4. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans: Some aromatic amines, anthraquinones and nitroso compounds, and inorganic fluorides used in drinking water and dental preparations. Vol. 27. pp.235-303. Lyon, France. 1982.
5. Knox EG. Fluoridation of water and cancer: A review of the epidemiological evidence. Report of the working party, Department of Health and Social Security London: Her Majesty's Stationery Office. 1985.
6. National Toxicology Program (NTP). Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3F1 Mice. Technical Report Series No. 393. NIH Publication No. 91-2848. Research Triangle Park, NC. 1990.
7. National Research Council. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. Washington, DC. The National Academies Press. 2006.
8. McDonagh M, Whiting P, Bradley M et al. A systematic review of water fluoridation. September 2000. The University of York. Report 18.
9. Sutton M, Kiersey R, Farragher L, Long J. Health effects of water fluoridation: An evidence review 2015. Available at http://www.hrb.ie/uploads/tx_hrbpublications/Health_Effects_of_Water_Fluoridation.pdf
10. Hoover RN, Devesa SS, Cantor KP et al. Fluoridation of drinking water and subsequent cancer incidence and mortality. Appendix E (e1-51). 1991. Bethesda, MD.

11. Mahoney MC, Nasca PC, Burnett WS, Melius JM. Bone cancer incidence rates in New York State: Time trends and fluoridated drinking water. Am J Public Health. 1991;81(4):475-9
12. Hrudey SE, Sockolne CL, Berkel J, Fincham S. Drinking water fluoridation and osteosarcoma. Can J Public Health. 1990;81(6):415-6
13. Freni SC, Gaylor DW. International trends in the incidence of bone cancer are not related to drinking water fluoridation. Cancer. 1992;70(3):611-8
14. Comber H, Deady S, Montogomery E, Gavin A, Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. Cancer Causes Control. 2011;22(6):919-24
15. Levy M, Leclerc BS. Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolscents. Cancer Epidemiology. 2012;36:e83-8
16. Blakey K, Geltbower RG, Parslow RC et al. Is fluoride at risk factor for bone cancer? Small area analysis of osteosarcoma and Ewing sarcoma diagnosed among 0-49-year-olds in Great Britain, 1980-2005. Int J Epidemiol. 2014;43(1):224-34
17. Young N, Newton J, Morris J et al. Community water fluoridation and health outcomes in England: a cross-sectional study. Community Dent Oral Epidemiol. 2015;43:550-9
18. Archer NP, Napier TS, Villanacci JF. Fluoride exposure in public drinking water and childhood and adolescent osteosarcoma in Texas. Cancer Causes Control. 2016;27(7):863-8
19. Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R. Fluoride exposure and childhood osteosarcoma: A case-control study. Am J Public Health. 1995;85(12):1678-83
20. Bassin EB, Wypij D, Davis RB, Mittleman MA. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes Control. 2006;17:421-8
21. Kim FM, Hayes C, Williams PL et al. An assessment of bone fluoride and osteosarcoma. J Dent Res. 2011;90(10):1171-6
22. National Toxicology Program (NTP). Toxicology and Carcinogenesis Studies of Sodium Fluoride in F344/N Rats and B6C3F1 Mice. Technical Report Series No. 393. NIH Publication No. 91-2848. Research Triangle Park, NC. 1990.
23. Maurer JK, Cheng MC, Boysen BG, Anderson RL. Two-year carcinogenicity study of sodium fluoride in rats. J Natl Cancer Inst. 1990;82(13):1118-26
24. Maurer JK, Cheng MC, Boysen BG et al. Confounded carcinogenicity study of sodium fluoride in CD-1 mice. Regul Toxicol Pharmacol. 1993;18(2):154-68