APPENDIX 11. Levy 2012 review

Review of Levy 2012 F-osteosarcoma ecological study USA

Chris Neurath, November 29, 2015

Levy et al's [2012] study of the association between water fluoridation in the USA and osteosarcoma risk has several important limitations. It is an ecological study, with the group-level being states. This is a much coarser geographical level than other recent ecological studies of osteosarcoma and fluoride (F), which used geographic levels with populations of a few thousand people [Blakey 2014, Young 2015, Comber 2011]. The exposure measure was also relatively crude. Comparison was made between states with ≤30% of their population receiving fluoridated water compared to states with ≥85% of their populations receiving fluoridated water. This resulted in only 4 states being classified low fluoridation and 14 high fluoridation.

Levy weighted each state's rate by its population, which resulted in many states contributing ver little to the final osteosarcoma incidence rates. There is a wide range of state populations. A more appropriate method would be to not weight by state population, since each state was an independent data point from the others, and no potential confounders were controlled for between states. Confounding would be greater with weighted compared to unweighted analyses. We could not calculate the result when not weighting by state because public access to WONDER data is suppressed for osteosarcoma counts less than 16, which occurs for many states, age groups, and genders.

As in all other ecological studies of F and osteosarcoma, no history of F exposure was available, so population mobility and other time-specific factors could not be taken into account. The mobility of the USA population is very high, with 18% of people moving residences per year and 46% moving per 5-year interval [Long 1991]. The rate of moves between states was 10% over 5-year periods. Those under age 25 have even higher rates of mobility [Long 1992]. Since the latency period of osteosarcoma is likely to be 5-10 years [Nekolla 2000, Chmelevsky 1988], and since Bassin [2006] found the highest risk from exposures at ages 6-8, the relevant years of exposure are 5-10 years before diagnosis, for the <19 age group. Thi suggests that 5 to 10-year mobility rates will determine the extent of exposure misclassification. The 10-year mobility rate in the US has not been measured, but is likely to be roughly double the 5-year rates, or up to 90% for moves of any distance, and 20% for moves between states. Such mobility rates suggest Levy's study had high rates of misclassification of relevant exposure, which would lead to bias toward the null for their results.

Levy's exposure measure was based solely on percent of a state with water fluoridation. Yet studies have shown that there are other significant sources of fluoride intake, such as from F supplements, swallowed F toothpaste, and tea drinking, which could vary by state and/or race. People in southern states may drink more iced tea, and blacks have higher rates of dental fluorosis [Martinez-Mier 2010].

Even more important is the so-called "diffusion effect", by which those in unfluoridated areas may consume a substantial portion of their beverages and foods produced in fluoridated areas, thereby reducing the contrast in total F exposure between fluoridated and unfluoridated areas. In the USA, there may be a substantial diffusion effect, even across state boundaries. Bottled beverages and processed foods may be produced in a fluoridated state but distributed across many states.

It is difficult to determine the extent of the diffusion effect and the extent of F intake from sources besides drinking water, because information on each F source is difficult to obtain. But it is possible to use a biomarker for childhood F exposure, dental fluorosis, to assess the contribution to total F exposure from fluoridated water relative to other sources.

In the USA, during the calendar years of F exposure susceptibility for Levy's study, the rates of dental fluorosis of fluoridated and unfluoridated areas have been converging. For example, Pendrys found that the dental fluorosis prevalence in children born in the years 1980-1984 was actually higher in unfluoridated communities than from fluoridated communities (39 and 34% respectively) [Pendrys 1996, 2000]. Pendrys found that F supplement use in the unfluoridated communities and ingestion of F toothpaste in both types of communities were the main factors influencing fluorosis rates, not water fluoride level. Thus, Levy's use of the exposure measure "percent of state fluoridated" will not address the effect of total F intake, and is likely to underestimate any effect of total F intake on osteosarcoma rate.

Finally, it is interesting to compare Levy's study to Hoover's [1991] ecological study of water fluoridation and osteosarcoma in the USA, which used a similar exposure measure, but was done at the county level rather than state level. Hoover found a large positive association between residence in a mostly fluoridated county and osteosarcoma rate in males age

Due to these limitations, Levy's study had low power to detect an association between F and osteosarcoma.

REFERENCES

Bassin EB, Wypij D, Davis RB, Mittleman MA. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). *Cancer Causes Control* 2006;17(4):421–428. doi:10.1007/s10552-005-0500-6.

Blakey K, Feltbower RG, Parslow RC, et al. Is fluoride a 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):224–234. doi:10.1093/ije/dyt259.

Chmelevsky D, Kellerer AM, Land CE, Mays CW, Spiess H. Time and dose dependency of bone-sarcomas in patients injected with radium-224. *Radiat Environ Biophys* 1988;27(2):103–114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3164868.

Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R. Fluoride exposure and childhood osteosarcoma a case-control study. *Am J Public Health*. 1995;85(12):1678–1683. doi:10.2105/AJPH.85.12.1678.

Hoover RN, Devesa SS, Cantor KP, Lubin JH, Fraumeni JF. *Review of Fluoride: Benefits and Risks; Appendices E-H* Department of Health and Human Services, Public Health Service, Ad hoc Subcommittee on Fluoride; 1991. {Appendix F, Table 2}

Kim FM, Hayes C, Williams PL, et al. An assessment of bone fluoride and osteosarcoma. *J Dent Res*. 2011;90(10):1171–1176. doi:10.1177/0022034511418828.

Levy M, Leclerc BS. Fluoride in drinking water and osteosarcoma incidence rates in the continental United States among children and adolescents. *Cancer Epidemiol* 2012;36(2):83–88. doi:10.1016/j.canep.2011.11.008.

Long L. Residential mobility differences among developed countries. *Int Reg Sci Rev* 1991;14(2):133–147. doi:10.1177/016001769101400202.

Long L. Changing Residence: Comparative Perspectives on its Relationship to Age, Sex, and Marital Status. *Popul Stud (NY)* 1992;46(1):141–158. doi:10.2307/2174710.

Martinez-Mier EA, Soto-Rojas AE. Differences in exposure and biological markers of fluoride among White and African American children. *J Public Health Dent* 2010;70(3):234–40. doi:10.1111/j.1752-7325.2010.00173.x.

Nekolla EA, Kreisheimer M, Kellerer AM, Kuse-Isingschulte M, Gössner W, Spiess H (2000) Induction of Malignant Bone Tumors in Radium-224 Patients: Risk Estimates Based on the Improved Dosimetry. Radiat Res 153: 93-103.

Pendrys DG, Katz R V, Morse DE. Risk factors for enamel fluorosis in a nonfluoridated population. *Am J Epidemiol* 1996;143(8):808–815.

Pendrys DG. Risk of Enamel Fluorosis in Nonfluoridated and Optimally Fluoridated Populations. *J Am Dent Assoc* 2000;131(6):746–755. doi:10.14219/jada.archive.2000.0273.

Rao GS. Dietary intake and bioavailability of fluoride. *Annu Rev Nutr* 1984;4:115–136. doi:10.1146/annurev.nu.04.070184.000555.

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(6):550–559. doi:10.1111/cdoe.12180.