APPENDIX 10-A. Young 2015 review

Review of Young 2015 F-osteosarcoma ecological study

Chris Neurath, November 28, 2015

The Young et al [2015] study is essentially a repeat of Blakey's [2014 study, using the same data on cancer cases and a very similar fluoride exposure measure. It did not conduct as many analyses of different models.

It differed mainly in that it looked only at the <25 and ≥50 yr age groups, it was limited to England rather than Great Britain, and the cancer cases came from 1995-2010 instead of 1980-2005 as in Blakey's study. It had only 16 years of osteosarcoma cases compared to Blakey's 26. Young's cases were also from a more recent time period.

These differences resulted in a relatively small sample size for an ecological study of only 92 cases for males <25 yr old, especially compared to Blakey's sample size of roughly 1000 for males <25 [Blakey 2014].

The Young study had almost all the same serious limitations as Blakey's, and additionally had a smaller sample size. See the Blakey review for details on these limitations [FAN review of Blakey 2015, Appendix 8-A]. These limitations may explain why it did not find a statistically significant increased risk of osteosarcoma from fluoride. Despite having biases tending to push the effect toward negative, and low power to detect an effect, it is worth noting that it did find a positive association between fluoridation and risk of osteosarcoma in males. The rate ratio for fluoridated males to unfluoridated was 1.17 in their fully adjusted model. Young expresses this as a 17% difference in incidence rates: IRR(%).

The only limitation the Young study does not share with the Blakey study is the possible error in osteosarcoma registrations for the West Midlands cancer registry for the years 1990-1992. The Young study only included cases diagnosed from 1995-2010, after the period of such possible errors.

We discuss limitations with details pertinent to Young's study:

1. Exposure misclassification, some differential resulting in bias away from an effect, and some non-differential, causing bias toward a null effect.

Similar to Blakey, Young defined fluoridation status based on recent fluoridation status (2012). Yet a large proportion of fluoridated areas in England only became fluoridated in the 1980s. Other fluoridated areas mostly started fluoridation in the 1960s.

We calculated the percent of osteosarcoma cases likely misclassified as fluoridated for their childhood up through 8 years old, when in fact they were unfluoridated. These calculations were similar to our calculations for Blakey, but used information specific to the Young study.

For Young's study the percent misclassified up through age 8 of exposure as fluoridated when in fact they were unfluoridated is about 7%. This is a greater percent than for Blakey's subjects born in the same birth years as Young's. Exposure up through age 8 was identified by Bassin as the highest risk perio [Bassin 2006]. There is also strong evidence from iatrogenically induced osteosarcoma studies that the latency period for childhood osteosarcoma is about 5-10 years, reinforcing the finding that exposures up through age 8 is an appropriate measure of exposure.

If the 7% differential misclassification is corrected for, Young's risk ratio would rise from 1.17 to 1.28, representing an almost doubling of incidence rate ratio (IRR from 17% to 28%. The conclusion is that this study, if corrected for its misclassification, shows a 28% greater rate of osteosarcoma in males <25 years old in the fluoridated compared to the unfluoridated areas. While this result is unlikely to reach statistical significance, that may be explained by the low power of the study.

See Appendix 10-B file for details of misclassification calculations.

2. Young did not control for radon exposure, which has been found to be a risk factor for childhood osteosarcoma in a recent study in England. Young did not consider indoor radon, a risk factor for osteosarcoma identified in one case-control study in Cornwall, England [Wright 2004]. If radon were a risk factor for osteosarcoma throughout England, then correction for radon would have reduced bias toward the null and would result in a higher risk ratio.

Summary

The authors acknowledge most of the study limitations we have addressed:

> "Use of an ecological level fluoridation measure, reflecting the intervention, does not take into account individual tap water consumption and intake from other dietary sources and dentifrices. Migration, temporal changes in water quality zone boundaries and fluoride levels, 'halo' effects from neighbouring areas and the presence of varied levels of natural fluoridation can all introduce additional misclassification bias, with the likely effect of reducing the strength of any associations." [Young 2015]

We agree these limitations would bias the effect reducing the strength of any associations, and have provided some quantitative estimates of the degree of such bias. All the differential biases we identified would even have the potential to bias the results to the extent of showing a spurious protective effect of fluoridation against osteosarcoma.

The Young study provides little new information beyond the Blakey study, and shares the same limitations as Blakey's. It did find a non-significant increased risk of osteosarcoma in males under age 25, which was also found by Blakey in her analysis restricted to those with the least exposure misclassification. So, these two studies actually are consistent with studies which have found an effect of fluoride increasing osteosarcoma risk, rather than being evidence that no such effect exists.

REFERENCES

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.

Wright M, Pheby D. Risk Factors for Osteosarcoma in Young People in Cornwall : A Case-Control Study. J Environ Heal Res. 2004;5(2):61–69.

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.