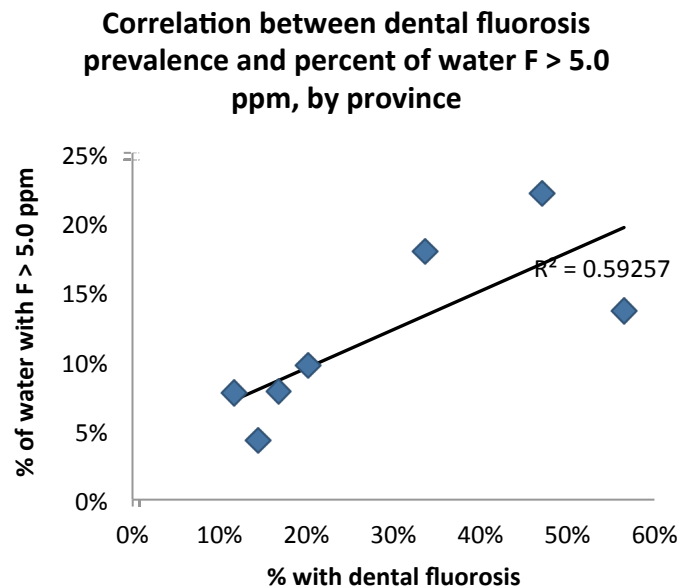


APPENDIX 4. Kenya study, full, with introduction [Neurath 2005b]

Study of fluoride and osteosarcoma in Kenya, Neurath 2005b.

The attached study was discussed in the NRC 2006 review, but was criticized because the osteosarcoma rates of Kenyan provinces were not age-adjusted. However, Kenyan provinces had large populations and it is unlikely there were large differences in age distribution between provinces. Furthermore, the differences in osteosarcoma rates between provinces were as large as 400%. It is unlikely age distributions varied by such a large extent that they could explain this large difference in osteosarcoma rates.

The NRC 2006 review also criticized the study because the exposure measure (dental fluorosis in children) was from a report that did not say the data was from examinations of children who were representative of the entire provincial population. However, based on a correlation between fluorosis rate and water fluoride levels, by province, a relatively strong positive relationship was found, as shown in the figure below [data from Nair 1984, Chibole 1987]. Furthermore, the fluorosis rate varied greatly, by almost 500%, suggesting that even though it is not known how representative the children were of the province-wide population, it seems unlikely that such sample non-representativeness would be sufficient to explain the large differences in osteosarcoma rates.



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Correlation between dental fluorosis incidence and osteosarcoma incidence amongst provinces of Kenya

and

Association between fluoridation and osteosarcoma in Malaysia

June 17, 2005

Christopher Neurath
Fluoride Action Network

The Fluoride Action Network (FAN) submission “Revisiting the Fluoride-Osteosarcoma connection in the context of Elise Bassin’s findings: Part II” to the National Research Council (NRC) contained a postscript about an osteosarcoma epidemiology study in Kenya. This work by Bovill et. al. (1985) was never considered by the NRC in 1993, perhaps because the study was not specifically looking for a connection between osteosarcoma and fluoride. Yet our preliminary examination suggested it might provide important supporting evidence for an association. We are continuing research on this evidence.

Work on the Kenya data led us to similar work in Malaysia which also points to a correlation between fluoride and osteosarcoma. This submission is an update to the NRC on our work in this area.

Kenya

Recent research showing an association between fluoride exposure and osteosarcoma (Bassin, 2001) prompted a re-examination of older studies to see if any such links had been overlooked. Studies in Kenya were of particular interest given the high natural fluoride levels found in many regions. Based on data from a comprehensive drinking water survey (Nair et. al., 1984) over 60% of samples had more than 1 ppm fluoride, 18% had more than 3 ppm, and 12% had more than 8 ppm. Kenya has no artificial fluoridation. Also, compared to North America where most osteosarcoma-fluoride studies have been conducted, in Kenya one would expect lower migration rates, less of a “diffusion effect” from consumption of foods and beverages manufactured outside the region, and relatively little use of fluoride dental products or

supplements. Thus, data from Kenya may suffer less from these conditions which tend to misclassify exposures thereby reducing a study’s ability to find a “signal amidst the noise”. Kenya constituted a large study population of 15 million in 1980. Most provinces have populations ranging between 1 and 3 million, except for North-Eastern Province which had only 0.4 million.

We compared data from two unrelated studies published in the 1980s. One determined incidence rates of osteosarcoma (Bovill et. al., 1985) and the other dental fluorosis (Chibole, 1987) for Kenya’s eight provinces. Our linear regression analysis found an extremely strong positive association yielding a Pearson’s correlation coefficient $R^2 = 0.91$ at $p < 0.0003$.

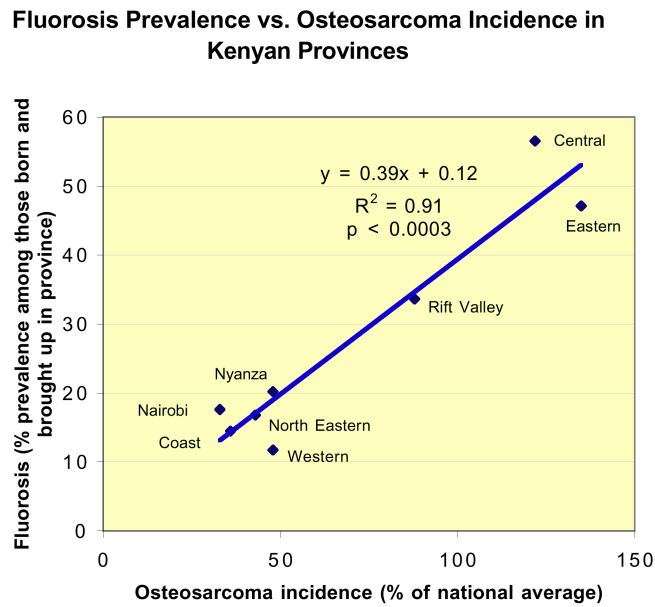


Figure 1

Figure 2 uses maps to illustrate the striking correspondence between fluorosis and osteosarcoma.

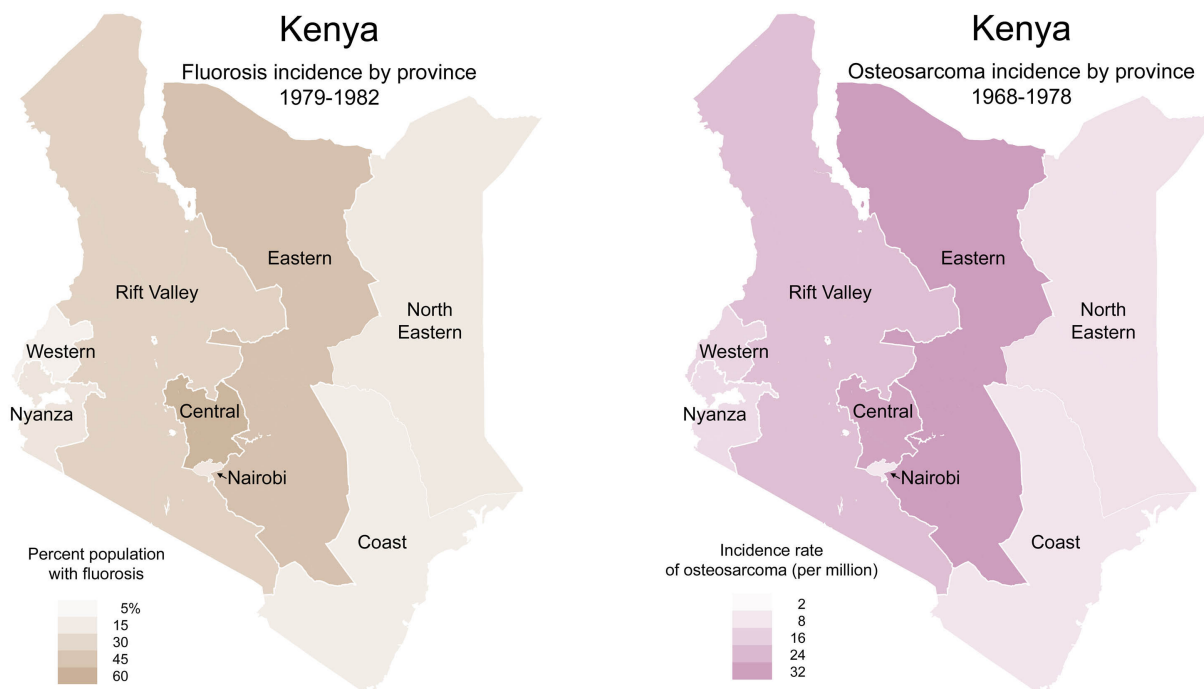


Figure 2

The fluorosis study examined a large representative sample of people (N = 34,287) from all provinces of Kenya. Subjects were restricted to those born and raised in the same district so that geographical misclassification due to migration was eliminated. Fluorosis incidence (all degrees) amongst the population ranged widely from 11.7 to 56.5% between provinces and corresponded closely to drinking water fluoride levels. Fluorosis may be a more accurate indicator of bone exposure to fluoride during childhood than levels of fluoride in drinking water. It is probably a more accurate reflection of total fluoride intake and it may also reflect individual susceptibility to fluoride absorption.

The osteosarcoma study reported incidence rates by province and by ethnic group using data from the Kenya Cancer Registry plus the two main hospitals (251 cases) for years 1968 -1978. The authors believed they captured most of the osteosarcoma cases from across the country. For each province, an incidence rate was reported for all ages and sexes combined. Rates were not presented broken down by province and age and/or sex, so the results may be “diluted” if young males are the only group affected by fluoride exposure. The study encompassed 140 million person-years of data.

Within single ethnic groups with presumably similar genetics, significantly different osteosarcoma rates were found in different provinces (range: 0.6–2.3/million/year). The authors surmised that some “geomedical variable” was the likely cause of the variation in osteosarcoma rather than genetics. Fluoride was not mentioned as a suspect for this

variable. This is not surprising as at the time, the NTP (1990) study which first linked fluoride to osteosarcoma had not yet been published.

Recent research (Cohn et. al., 2003) suggests a confounding factor could be radium in drinking water. We therefore researched levels of radionuclides in Kenyan drinking water from published (Otwoma and Mustapha, 1998) and unpublished data (Mustapha, 2005). No measurements of radium were found so its decay product, radon (^{222}Ra), was used as a surrogate. A moderately strong positive correlation between average province radon levels and osteosarcoma rates was found ($R^2 = 0.52$) but it was not statistically significant at the 95% CI level ($p < 0.07$) as shown in Figure 3. The radon study attempted to examine a representative sample of drinking water in each province of Kenya: “In our radon survey the choice of which water source to test was influenced by how representative it is as a source of drinking water for the area. The choice was not driven by known high radon areas.” (Mustapha, 2005).

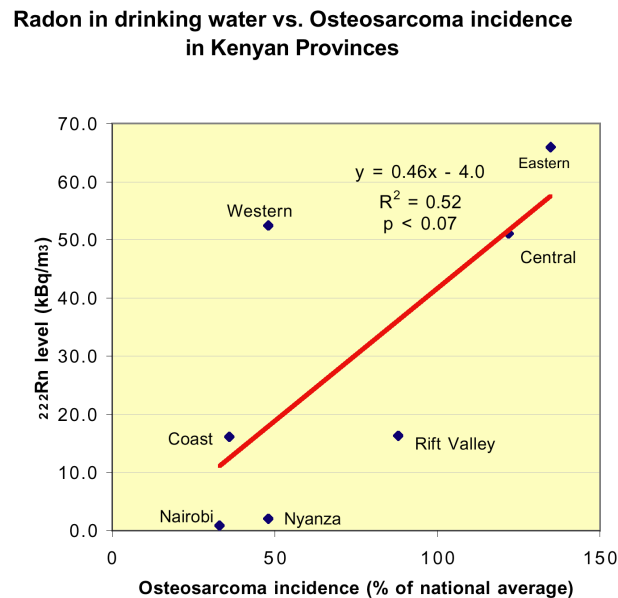


Figure 3

Kenya has the potential to be an excellent study area for the relationship between fluoride, radium, and osteosarcoma, as it contains regions with widely ranging levels of all three of these variables. Furthermore, our analyses suggest that for ecological studies, the use of fluorosis as a biomarker of fluoride exposure may be more appropriate than the use of surrogates such as the average level in drinking water.

It should be emphasized that the data for this correlation analysis was not originally gathered for analyzing a fluoride-osteosarcoma association. Both studies were conducted before any association had even been widely postulated and neither paper makes any mention of the issue. This fact lends strength to the current results. It eliminates researcher bias in the study design, data collection, and initial analysis. The two studies used here can be considered “double-blind” because none of the authors or subjects was even aware of a possible connection between fluoride and osteosarcoma.

In conclusion, the currently available Kenya data adds to the weight of evidence indicating a link between fluoride and osteosarcoma.

Malaysia

The lead author of the Kenya osteosarcoma study, Dr. Edwin Bovill Jr., also conducted epidemiological studies of osteosarcoma in Malaysia. This work (Bovill et al., 1975) has never been cited by the NRC or any other reviews of osteosarcoma and fluoride. Similarly to the Kenya studies, Bovill determined osteosarcoma incidence rates by province. Unlike Kenya, Malaysia does not have any areas with “natural fluoridation”. However, at the time of the study, it did have one province that had been largely artificially fluoridated at least 10 years prior to the case ascertainment period. Of the 13 provinces, only Penang province was substantially fluoridated beginning in 1959 (Malaysia Ministry of Health, 2005). Looking at the osteosarcoma rates by province, Penang stands out with a distinctly higher rate of 4.7/million/year compared to an average of 1.4/million/year for all the rest of the country; a rate more than 3x greater than in the virtually unfluoridated provinces.

Bovill remarks: “The most puzzling aspect of this study has been the emergence of an incidence of 0.47 per 100,000 per year for the state of Penang” One explanation put forth is that Penang is more densely populated than the other provinces. But Bovill discounts this explanation because other densely populated provinces have much lower rates. The three explanations Bovill present that might explain the high rate in Penang are:

- 1.) Unrecognized bias in sampling process.
- 2.) “Some unrecognized environmental factor in the Penang area produced a time-extended cluster during the period under study.”
- 3.) Penang is the most “Western-type” community in Malaysia. Studies in Europe and North America show rates of osteosarcoma similar to Penang.

Upon closer examination, he finds that sampling bias is unlikely to be able to explain the large difference between Penang and all other provinces. This leaves hypotheses 2 and 3. North America and Europe do have substantially higher rates of osteosarcoma than Malaysia outside of Penang. Also, and unappreciated by Bovill, many of these “Western-type” countries did have water fluoridation, or use of fluoride dental products beginning in the 1960s to 1970s time period of the Malaysia study. So perhaps fluoride could be the underlying causative factor for both hypothesis 2 and 3.

Finally, similar to his findings in Kenya, Bovill found that within a single ethnic group, there were significantly different rates of osteosarcoma in different regions. He concludes that genetic factors are not the cause of the geographic variation in incidence.

Starting from Bassin’s new finding that fluoride exposures during certain childhood ages may be an important risk factor for osteosarcoma, we have re-examined several ecological studies and have found further support for this hypothesis. Another conclusion is that research in undeveloped areas, especially those with naturally

occurring fluoride in drinking water like Kenya, may produce “cleaner” results, because exposure misclassification due to the diffusion effect is minimized.

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