Current epidemiological research on a link between fluoride and osteosarcoma

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Three relatively recent case-control studies

1. Gelberg et al 1995
2. Bassin et al 2006
3. Douglass & Hoover ? (not yet published)

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All three studies were in response to the alarming 1990 NTP animal study which found evidence that fluoride caused osteosarcomas in male rats.

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Human studies by Hoover 1991 and Cohn 1992 found increased risk of osteosarcoma from fluoride in young males (semi-ecological study designs)

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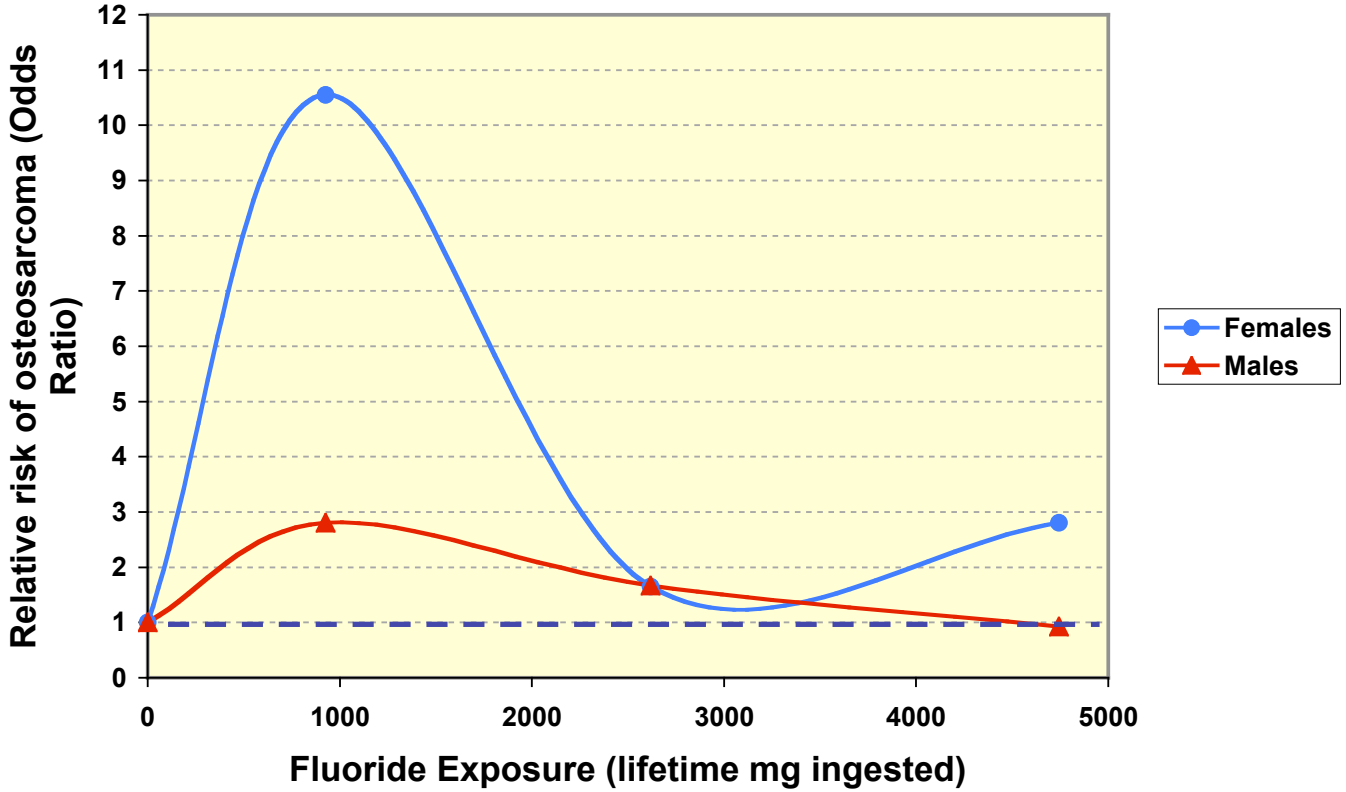
The first case-control study (Gelberg 1995) found increased risk from water fluoride but these were discounted by the author.

Gelberg 1995: Risk versus cumulative exposure from drinking water



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Osteosarcoma rates in children

- Osteosarcoma is a relatively **rare cancer**, but is often fatal.
- Incidence rate is about **10 per million per year** in children under age 20.
- The curve of incidence rate with age has an extremely **sharp peak around age 15**. No other cancers show such a sharp peak in incidence during childhood.
- This sharp peak may be a **clue to the cause**.
- **Latency**. Radiation induced osteosarcomas typically appear several years to several decades after exposure. The sharp peak at age 15 suggests some event initiated the cancer several years earlier or perhaps during fetal development.

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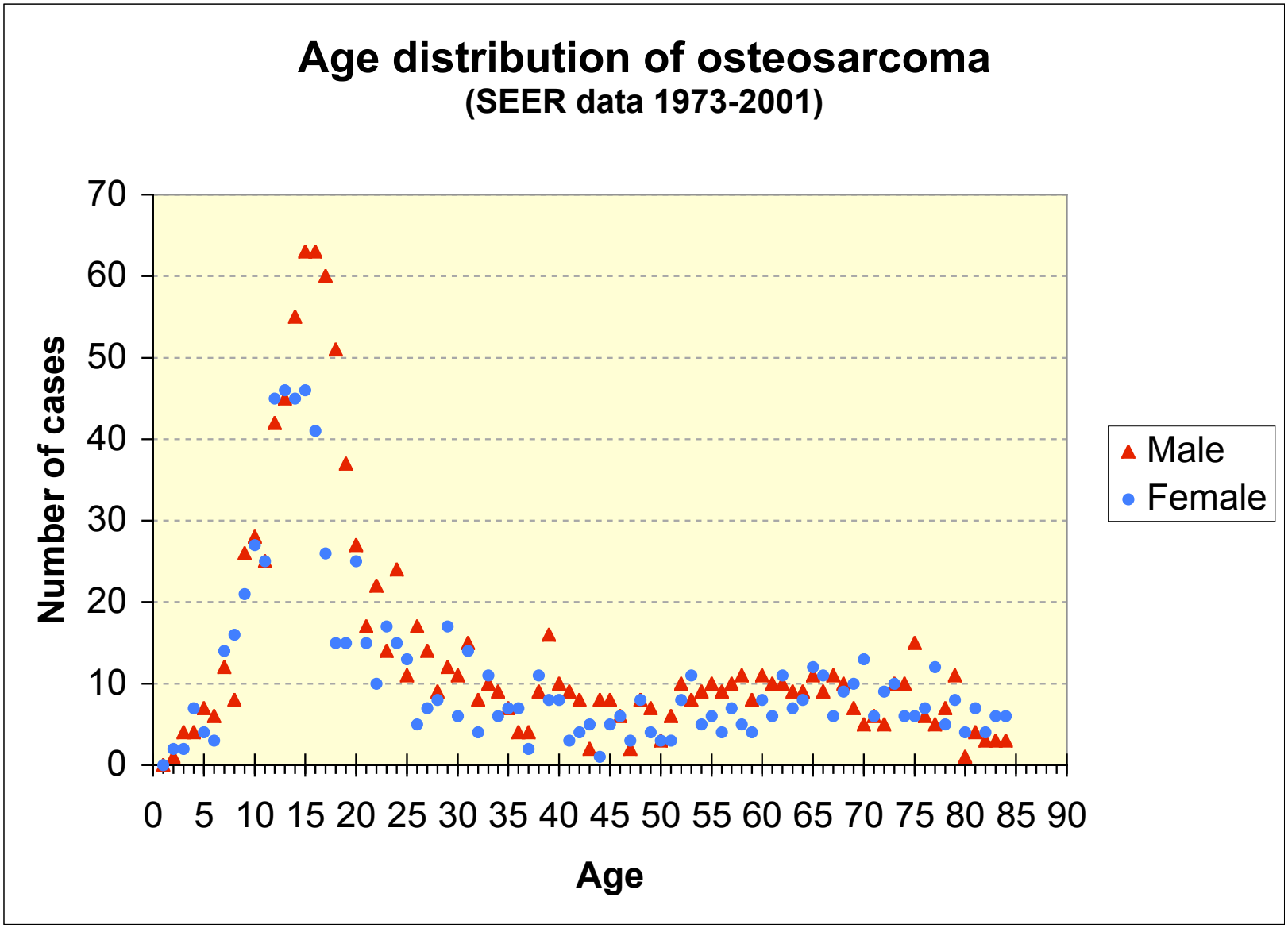

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Summary of Bassin 2006 results

Exposure at age 7, Odds Ratios at 3 levels of F in water

Table 3 Sex-specific associations between fluoride exposure at age 7 years and osteosarcoma, estimated by conditional logistic regression

Approx. levels	Fluoride exposure at age 7 years	Odds ratio (95% C.I.)[a]
	Males	
Ref. <0.3 mg/L	Less than 30% of target	1.00
0.3-1.0 mg/L	30–99% of target	3.36 (0.99, 11.42)
>1.0 mg/L	At least 100% of target	5.46 (1.50, 19.90)
	Females	
Ref. <0.3 mg/L	Less than 30% of target	1.00
0.3-1.0 mg/L	30–99% of target	1.39 (0.41, 4.76)
>1.0 mg/L	At least 100% of target	1.75 (0.48, 6.35)

[a] Adjusted for age, zip code median income, county population, use of well water by age 7, use of bottled water by age 7, any use of fluoride supplements

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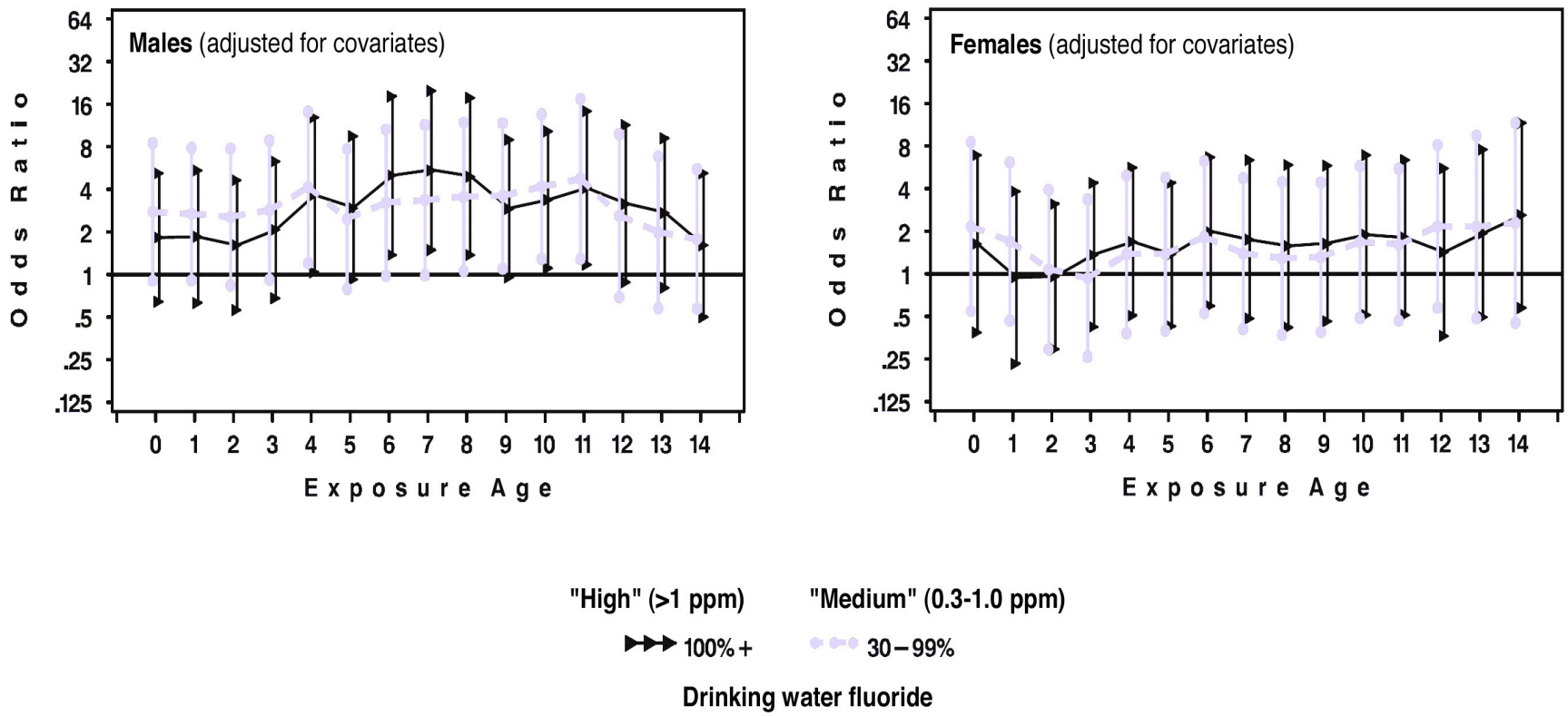
Bassin et al. 2006 results for each age of exposure



Odds ratios and 95% confidence intervals for "High" and "Medium" exposure relative to "Low" (<0.3 ppm) exposure.

Estimates adjusted for age, median income, county population, use of well water, use of bottled water, and use of fluoride supplements.

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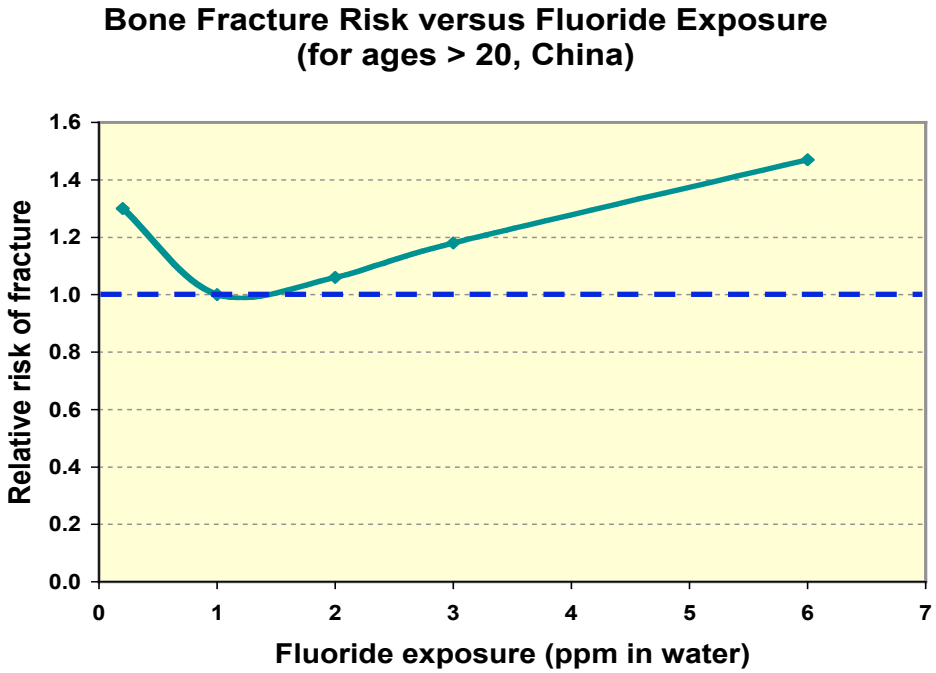
Could selection bias from hospital controls explain Bassin's findings? NRC 2006 asked this question.

Potential for selection bias because controls were hospital orthopedic patients. Many of these might have been bone fracture patients and fluoride might affect risk for bone fractures.



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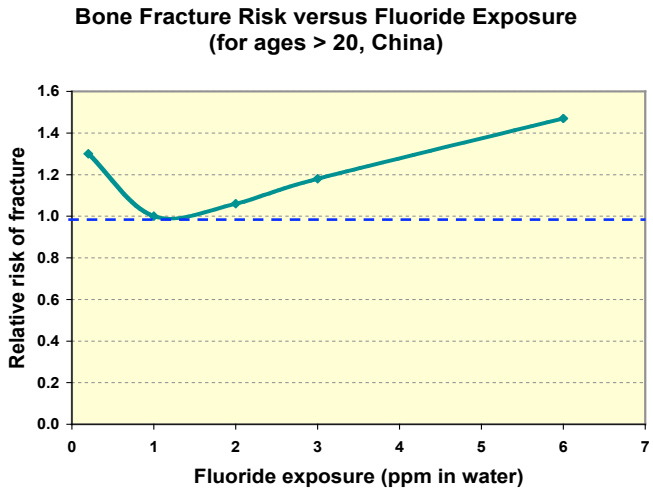
Sensitivity Analysis

- Does low fluoride cause more broken bones?



AND

- Did enough controls have broken bones?

… to explain away Bassin's findings by selection bias?

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Probably Not

Even if low fluoride does cause broken bones, sensitivity analysis shows:

- More than **75%** of the controls would have to have broken bones.

AND

- The increased risk of broken bones for low fluoride consumers would have to be **5-fold**.

Douglass reported most controls were trauma patients, and there is no existing study showing significant increased risk of broken bones in children exposed to low fluoride. One study in Mexico shows the opposite: Children with dental fluorosis had more fractures.

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Strengths of Bassin study

1. first and only age-specific exposure analysis
2. focus on at-risk age group <20 year olds
3. accurate determination of drinking water fluoride
4. relatively large sample size
5. controlled for:

   - age, sex, geographic area, socioeconomic status, use of fluoride dental products

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Douglass questions validity of Bassin 2006 and says his own study may contradict Bassin's finding

Cancer Causes Control (2006) 17:481–482
DOI 10.1007/s10552-006-0008-8

LETTER TO THE EDITOR

Caution needed in fluoride and osteosarcoma study

Chester W. Douglass · Kaumudi Joshipura

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Five weaknesses in Douglass study

1. Autopsy controls seem to have been abandoned
2. "Bone tumor controls" seem to have been substituted for autopsy controls. All had bone cancers of types other than osteosarcoma.
3. Matching on distance from hospital abandoned part way through recruitment. Most hospitals in fluoridated cities.
4. Unclear whether age windows of vulnerability will be considered in analysis. Bone F as a biomarker for lifetime F exposure precludes age-specific exposure analysis.
5. Preliminary reports have been for analyses that include age 0-40 years old and both sexes, thereby diluting any effect on young males.

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Weakness 1. Autopsy controls abandoned

1992 Original study design was for autopsy controls exclusively.

Hoover's proposed study from 1992 that was soon combined with the Douglass study.

PROPOSED STUDY

TITLE: Analytical Epidemiologic Study of Fluoride and Osteosarcoma

PRINCIPAL INVESTIGATORS:

H. Clarke Anderson, M.D.
Department of Pathology
University of Kansas Medical Center.
Kansas City, KS 66160-7410

Robert N. Hoover, M.D.
NIH, NCI
Environmental Epidemiology Branch
Rockville, MD 20892

ABSTRACT: An analytical epidemiologic study is proposed to evaluate fluoride levels in bones of approximately 100 new cases of osteosarcoma as compared to bone fluoride levels in an age-, gender-, and geographically-matched autopsy population of control subjects who died of causes unrelated to osteosarcoma.

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Weakness 1. Autopsy controls abandoned

1993 Autopsy controls incorporated in Douglass study design

PROGRESS REPORT SUMMARY	ANT NUMBER	
	ES06000-02	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR	PERIOD COVERED BY THIS REPORT	
Douglass, Chester W.	FROM	THROUGH
APPLICANT ORGANIZATION		
Harvard School of Dental Medicine	9/30/92	9/29/93
TITLE OF PROJECT *(Repeat title shown in item 1 on first page)*		
Fluoride Exposure and Osteosarcoma		
(SEE INSTRUCTIONS)		

First Progress Report in 1993 says they will start collecting "control autopsy bone" samples.

Incident Cases and Controls: Incident cases and controls will accrue throughout the entire period of Year 2. Research nurses at each hospital will perform the following duties:

1. assist the orthopedic surgeon in gaining informed consent from the incident cases,
2. locate qualified controls from departmental rosters,
3. administer the questionnaires to and collect toenail samples from the eligible cases and qualified controls,
4. collect the tumor slice, blood specimen, and iliac crest bone biopsy from the case at the time of surgery
5. collect the control autopsy bone
6. ~~collect the control blood specimen~~
7. prepare all the pathology specimens for transportation (See Appendix D for Protocol)
8. send the toenail samples for analysis
9. send the questionnaire data for analysis

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Weakness 1. Autopsy controls abandoned

1997 Only one autopsy control from one hospital has been recruited 5 years into study

University of Florida: Data has been received for 17 cases, 14 tumor controls and 10 orthopedic controls, and the paperwork for one autopsy control. The site also reports having

In letter requesting more funding to gather more subjects admits autopsy controls are difficult to recruit. Suggests a new source of control bone sample.

Also discussed with each collaborating surgeon and Dr. Clarke Anderson (the study pathologist) will be the option of substituting donor bone iliac crest specimens in place of autopsy specimens.

The same letter reports they have been recruiting many "tumor controls". They will eventually serve as the only controls in the bone F study. All have forms of bone cancer other than osteosarcoma.

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Weakness 1. Autopsy controls abandoned

2004 No mention of autopsy controls except a table showing only 14 were ever recruited.

Furthermore, even the "orthopedic controls" included patients with benign tumors. Several studies suggest F may cause benign tumors.

From: Dr Chester Douglass
To: 'JUDITH KLOTZ'
Sent: Tuesday, August 10, 2004 12:24 PM
Subject: RE: follow-up for NRC regarding study on fluoride and osteosarcoma

Controls
There were two types of control subjects enrolled. Tumor controls were subjects diagnosed with another ılignant bone tumor such as Ewing's sarcoma, chondrosarcoma, and malignant fibrous histiocytoma. Non-tumor orthopedic controls include patients with benign tumors as well as various non-neoplastic conditions such as inflammatory diseases, trauma, and sports injuries.

Subjects Enrolled			
Cases	Tumor Controls	Orthopedic Controls	Autopsy Controls
189	108	167	14

Autopsy control abandonment complete. Substitution of bone tumor controls

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Are other bone cancers possibly caused by fluoride?

Hoover 1991 examined SEER data for Ewing's sarcoma and found a large rate increase in counties that fluoridated.

Our own re-examination of SEER data confirms there was a +89% difference in rates for <20 year old males and females between time periods 1973-80 and 1981-87.

Douglass' tumor controls, most of which are Ewing's sarcoma patients, may therefore be unsuitable since their form of bone cancer may also be caused by fluoride.

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Weakness 3. Matching on distance from hospital abandoned.

Matching on distance from hospital was abandoned

From an email in 2004:

Later in the enrollment process, matching on the basis of geographic area was relaxed to matching controls to cases on the basis of sex and age. This change was due to the fact that most medical centers have a more extensive geographic catchment area for patient referrals with musculoskeletal tumors compared to the catchment area for benign orthopedic and trauma patients.

Controls will more likely come from near the hospitals while osteosarcoma cases will often travel large distances.

Why is this a problem?

Because almost all hospitals were in the center of fluoridated cities.

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Weakness 3. Matching on distance from hospital abandoned.

Not all controls matched on distance from hospital.

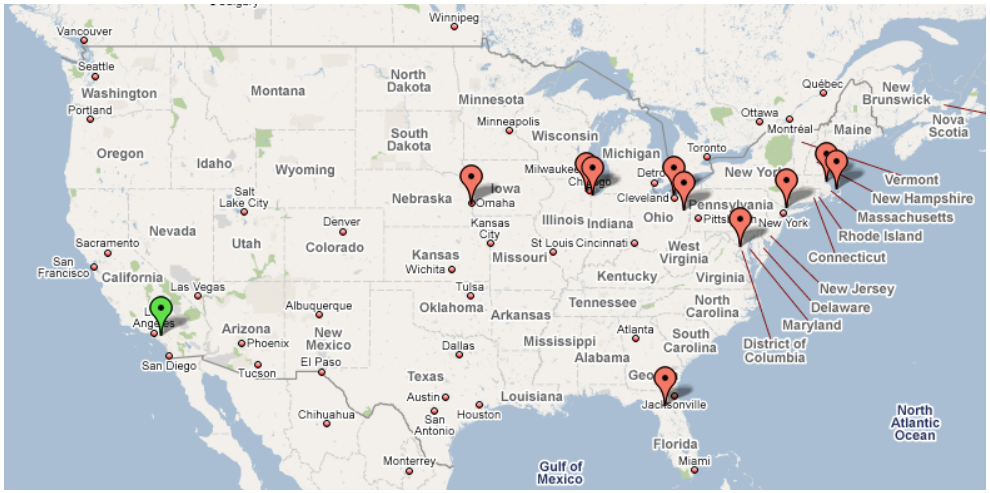
Controls with less serious health problems are likely to live closer to hospitals which are mostly in fluoridated cities, but cases often travel from far away seeking treatment for osteosarcoma.

Only one recruitment hospital (UCLA) was in a non-fluoridated city, from which only 15% of subjects were recruited. In the USA overall, 45% of people have non-fluoridated water.

Hospital	City	Fluoridated? Year	% of cases	% of controls
Massachusetts General Hosp.	Boston, MA	Yes, 1978	17	13
Childrens Hosp.	Boston, MA	Yes, 1978	15	21
Creighton; St. Joseph's Hosp.	Omaha, NE	Yes, 1968	5	5
Childrens National Hosp.	Washington, DC	Yes, 1952	11	9
Memorial Sloan-Kettering Cancer Center	New York, NY	Yes, 1965	7	7
Univ. of Chicago Hosp.	Chicago, IL	Yes, 1956	8	7
Rush Medical College Hosp.	Chicago, IL	Yes, 1956	3	3
U Florida, Gainsville	Gainsville, FL	Yes, 1949	12	9
Univ Calif. Los Angeles Hosp.	Los Angeles, CA	**No**	14	15
Cleveland Clinic	Cleveland, OH	Yes, 1956	8	9
Case Western Reserve Univ. Hosp.	Cleveland, OH	Yes, 1956	3	3

Based on Bassin 2006. Douglass study expected to have similar percentages

45% of Americans have non-fluoridated water.



9 out of **10** recruitment hospitals were in fluoridated cities.

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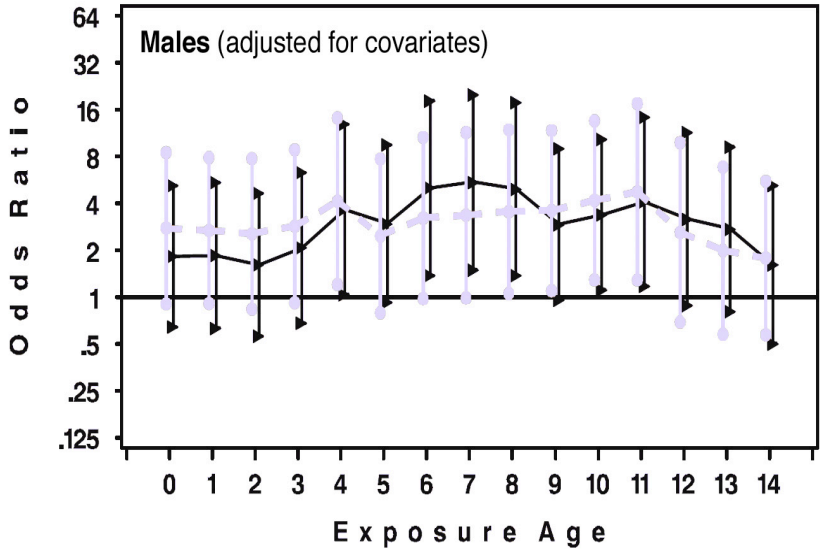
Weakness 4. Bone F not age-specific

Douglass' bone fluoride measurements unsuitable to determine risks from specific ages of exposure.



- Douglass' analyses based on bone fluoride measurements do not allow age-specific exposure assessment.
- Bone fluoride level reflects cumulative lifetime exposure.
- Bassin's key finding was that specific ages of exposure from about 6-8 years old seemed to represent a "window of vulnerability". Exposures outside that time produced lower risks.
- Douglass' use of bone fluoride will prevent him from addressing the key finding of Bassin.

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Conclusion

If the Douglass-Hoover study is eventually published, it may actually be weaker than the Bassin study. Weaknesses may result from:

- poor choice of controls
- inadequate control of covariates
- lack of sensitivity to age-specific exposures

"How many teeth would you have to save to justify one child dying from osteosarcoma?"
- Dr. John Colqhuoun.

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