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Cancer

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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

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Abstract

Background: Artificial fluoridation of drinking water to improve dental health has long been a topic of controversy. Opponents of this public health measure have cited the possibility of bone cancer induction. The study objective was to examine whether increased risk of primary bone cancer was associated with living in areas with higher concentrations of fluoride in drinking water.

Methods: Case data on osteosarcoma and Ewing sarcoma, diagnosed at ages 0–49 years in Great Britain (GB) (defined here as England, Scotland and Wales) during the period 1980–2005, were obtained from population-based cancer registries. Data on fluoride levels in drinking water in England and Wales were accessed through regional water companies and the Drinking Water Inspectorate. Scottish Water provided data for Scotland. Negative binomial regression was used to examine the relationship between incidence rates and level of fluoride in drinking water at small area level.

Results: The study analysed 2566 osteosarcoma and 1650 Ewing sarcoma cases. There was no evidence of an association between osteosarcoma risk and fluoride in drinking water [relative risk (RR) per one part per million increase in the level of fluoride = 1·001; 90% confidence interval (CI) 0·871, 1·151] and similarly there was no association for Ewing sarcoma (RR = 0·929; 90% CI 0·773, 1·115).

Conclusions: The findings from this study provide no evidence that higher levels of fluoride (whether natural or artificial) in drinking water in GB lead to greater risk of either osteosarcoma or Ewing sarcoma.

Key words: Osteosarcoma, Ewing sarcoma, bone cancer, children, young people, artificial fluoridation, fluoride, drinking water, Great Britain, small area analysis

Key Messages

- There was no evidence of an association between fluoride in drinking water and osteosarcoma or Ewing sarcoma before or after adjustment for small area level deprivation.
- 33% of artificially fluoridated water supply zones in Great Britain were found to be supplying water that was below 0·7 parts per million of fluoride, the lower limit of the optimal level for dental health benefit.
- There was no evidence that those who lived in an artificially fluoridated area of Great Britain were at increased risk of osteosarcoma or Ewing sarcoma.
- There was no evidence that those living in an area of Great Britain with naturally occurring fluoride within the optimal level for dental health benefit were at increased risk of osteosarcoma or Ewing sarcoma.

Introduction

Primary bone cancer is the third most common cancer in 10–24-year-olds, mainly comprising osteosarcoma and Ewing sarcoma (ES).[1] The aetiology is unclear, but both genetic and environmental factors are likely to be involved.[1,2]

Fluoride occurs naturally in drinking water at varying concentrations. Water is a primary dietary fluoride source. Populations supplied with high levels of naturally occurring fluoride in drinking water have low levels of dental caries.[3] The optimum range for dental health benefit is 0·7–1·2 parts per million (ppm). Concentrations below 0·3 ppm may provide no benefit.[4]

The recognition of an association between prevalence of dental caries and areas of greater socio-economic deprivation led to artificial fluoridation of water supplies in some countries, including in parts of Great Britain (GB), defined here as England, Scotland and Wales.[5] Pilot schemes established in the 1950s included: Kilmarnock (1956–62); part of Anglesey (1955–92); Andover (1955–58) and Watford (1956–89).[6–8] Artificial fluoridation programmes were introduced during the 1960s. Currently five water companies artificially fluoridate some drinking water supplies under the instruction of health authorities (Figure 1).[9]

This practice has been controversial and there is speculation that adding fluoride to community water supplies could result in adverse health outcomes including increased risk of cancer, particularly osteosarcoma.[10] Two systematic reviews concluded there was no clear association between water fluoridation and osteosarcoma incidence or mortality, but both advised caution in view of heterogeneity and other methodological concerns.[11,12]

The present study used the same case dataset as a previous demographic analysis that tested whether spatial variation among osteosarcoma and ES was associated with population density and area-based deprivation. Area-based deprivation is an ecological measure used for examining socio-economic data according to a small geographical unit. The previous ecological study found higher incidence of osteosarcoma for females in less deprived areas and of ES in areas of low population density and high car ownership. The putative association between osteosarcoma and ES risk and fluoride in drinking water was not analysed.[13]

The present study objective was to examine whether osteosarcoma risk was associated with fluoride levels in drinking water. For comparison, ES was also studied. This study is the first to analyse fluoride monitoring data as part of the exposure measurement and the putative association with osteosarcoma risk in small geographical areas across the whole of GB. No distinction was made between artificial or naturally occurring fluoride in drinking water, and novel geographical information system (GIS) methodologies were utilised to assign fluoride levels at small area level. The following hypotheses were tested: (i) geographical heterogeneity of osteosarcoma incidence is modulated by differences in fluoride levels in drinking water; and (ii) geographical heterogeneity of ES incidence is not modulated by differences in fluoride levels.

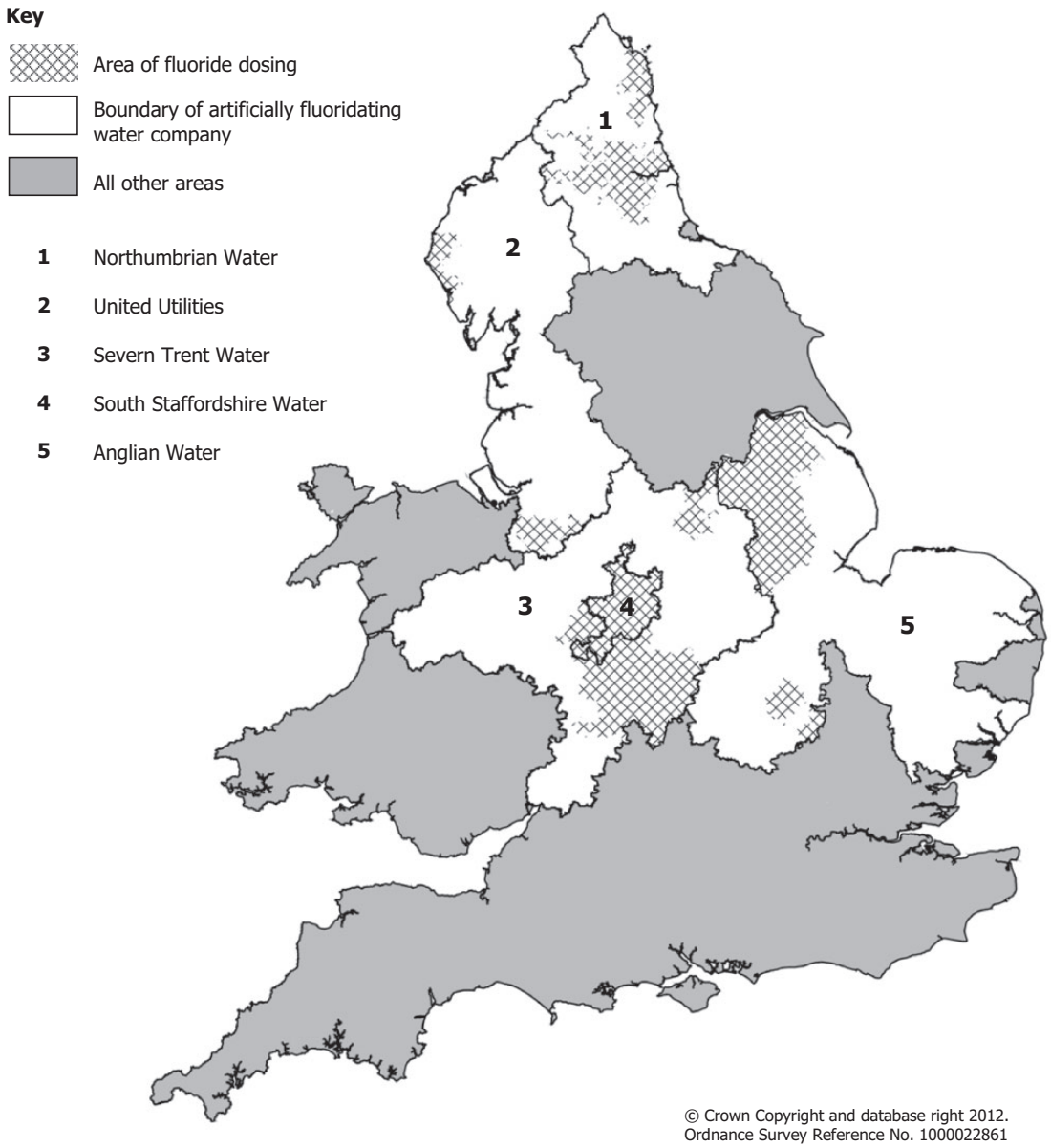

Figure 1. Map of England and Wales illustrating the boundaries of the water companies with artificial fluoridation programmes in place.

Methods

Study subjects

Data for patients diagnosed with osteosarcoma or ES in GB during 1980–2005 were analysed. Cases were limited to ages 0–49 years, as there are few ES cases above these ages and osteosarcoma over the age of 50 years is usually associated with Paget's disease or is secondary to radiotherapy.[2,14] To ensure sufficient case numbers in each category at small area level, cases were sub-divided into age groups 0–14, 15–29 and 30–49 years at diagnosis.

Regulatory and ethical approvals were gained (UK National Research Ethics Service reference number 09/H0904/5). Case data were accessed from the 10 regional cancer registries in GB. Case data from the National Registry of Childhood Tumours were extracted and used to cross-check accuracy of the regional registry cases aged 0–14 years.

Diagnostic groups

Cases were grouped using the International Classification of Diseases for Oncology, third edition (ICD-O-3).[15] Osteosarcoma and ES were specified a priori and the associated topography and morphology codes are given elsewhere.[13]

Population data

Denominator data were derived from national decennial census data.[16–21] Analyses over a prolonged time span are impeded by boundary changes, especially at small area level.[22] Therefore, population counts from previous censuses and geo-referenced bone cancer registration data were adjusted to be compatible with 2001 census boundaries.[23] The small area units (SAU) used in the analyses were census wards in England and Wales (0–49-years-old population ranges from 297 to 29 300, median = 3090), and postcode sectors in Scotland (0–49-years-old population ranges from 23 to 15 916, median = 3201).

Similarly, to adjust for deprivation, a time-series of indicators was obtained from each census during the study period and geographically converted to be compatible with 2001 SAUs. The Townsend index (comprising four components: unemployment, non-car ownership, non-home ownership and household overcrowding) is commonly used in health studies.[24] To track changes in deprivation for every SAU at the different time points, each variable was expressed as a z-score relative to the GB average level over the study period, then summed and equally weighted to a single deprivation score.[25]

Fluoride monitoring data

At the time of the study, 25 companies in GB supplied water to 2265 statutorily demarcated 'water supply zones' (WSZs) with a population supply threshold of 100 000 (Water Regulation Zones in Scotland). Less than 1% of households have private water supplies.[26] Fluoride level in drinking water is continuously monitored and required to be less than 1·5 ppm on a 3–month average basis.[27,28] These routine fluoride monitoring data were utilised in this study and obtained through Scottish Water and a regulatory body, the Drinking Water Inspectorate (DWI) for companies in England and Wales.

Digital boundary data

Digital boundaries for census areas facilitated geo-referenced data linkage for statistical analysis and were accessed from UK Borders.[29,30] Digital boundaries for WSZs were accessed through the DWI and Scottish Water.

Data linkage: assignment of fluoride level to census small area units

Postcode distributions were used to link WSZs to each SAU which was subsequently assigned a fluoride level. The population centroid of each SAU was calculated in ESRI ArcMap 9.3[31] to assign a weighted average for SAUs with water supply from more than one WSZ. The Nondetects and Data Analysis (NADA) add-on package for estimating censored environmental data was used to compute values for left-censored or missing data in R 2·8·1.[32,33] Bone cancer cases were linked and aggregated for each 2001 census SAU.

Statistical analysis

Negative binomial regression was implemented using STATA version 12.[34] The logarithm of the incidence rate was modelled in two parts: (i) variation explained by the data was expressed as a linear function of gender, age-group and deprivation; (ii) unexplained variation was modelled by a negative binomial distribution. The number of cases observed in each SAU was the dependent variable and the logarithm of the 'at risk' population was used as the offset. Independent variables were the census-derived SAU attributes that were allocated to the 2001 census geography.[22]

The previously determined best-fitting models that explained bone cancer variation (the final models in the hierarchical series for osteosarcoma and ES)[13] were used as the base models. In the present study, these models were extended to include fluoride level in drinking water by SAU. For osteosarcoma, the base model included gender, age-group, the interaction gender*age-group, the Townsend score and the interaction Townsend*female. For ES, the base model included age-group, gender, the interaction age-group*gender, Scotland, East Midlands, population density and non-car ownership. Fluoride, which had not been analysed in the previous analysis, was then added to these base models. The effect of fluoride level in drinking water was tested in multivariable models whilst adjusting for gender, age-group, population density and interactions. The effect of fluoride was assessed, after adjustment for these covariates, using likelihood ratio tests and the Akaike Information Criterion (AIC).[35] Relative risks (RRs) and associated 90% confidence intervals (CIs) were calculated.[36]

The mean fluoride level in drinking water was determined using monitoring data sampled between 2004 and 2006 and modelled as a continuous variable, under the assumption that any association was linear. The effect of fluoride level in drinking water was modelled with and without adjustment for deprivation. To test the linearity assumption, fluoride was also modelled as an ordinal variable (dividing the distribution into fifths). To test for a possible threshold effect, the most fluoridated fifth of the population was compared with less fluoridated fifths. Also, areas with a level of at least 0·7 ppm, the lower limit

of the range for optimum dental health benefit[4] were compared with less fluoridated areas.

Sensitivity analyses tested for effects of age-group. The data were restricted to cases born within the following non-overlapping cohorts: (i) before 1970; (ii) 1970–79; and (iii) 1980 onwards. To test for constancy of fluoride exposures in regions where levels may have fluctuated, artefactually inflated levels (1 ppm) were analysed. Finally, an analysis was carried out on the osteosarcoma data using age-groups 0–9, 10-14,. . .45-49 years to assess whether the three age-groups 0–14, 15–29 and 30–49 years were too broad to detect increases limited to specific ages. This additional analysis examined age-group interactions with fluoride to test if the age-group 0–9 years was more affected by fluoride than other age-groups. For all analyses, *P*-values were two-sided.

Results

The study analysed 2566 osteosarcoma cases (1493 males, 1073 females) and 1650 ES cases (988 males, 662 females) aged 0–49 years. The numbers of cases by age-group and gender are given in Table 1, with full descriptive data given elsewhere.[13] For osteosarcoma the overall age-standardized rate (ASR) for all persons was 2·64 per million persons per year (90% CI 2·55, 2·72), and 1·76 per million persons per year (90% CI 1·68, 1·83) for ES. Most analyses included an adjustment for deprivation.

After adjustment for gender, age-group, the interaction gender*age-group, the Townsend score and the interaction Townsend*female, no association was found between osteosarcoma and fluoride levels in drinking water ($P = 0·987$). The RR for osteosarcoma for 1-ppm increase in fluoride level was 1·001 (90% CI 0·871 to 1·151). After adjustment for age-group, gender, the interaction age-group*gender, Scotland, East Midlands, population density and non-car ownership, no association was found between ES incidence and fluoride levels in drinking water ($P = 0·503$). The RR for ES for 1-ppm increase in fluoride levels was 0·929 (90% CI 0·773 to 1·115).

There was no effect without adjustment for deprivation. Similarly, using ordinal measures there was no evidence of any threshold effect. When testing cohorts born before 1970, 1970–79 and 1980 onwards, there was no differential effect of cohort on the association between bone cancer and fluoride. An effect was not found when testing with artefactually raised levels of fluoride (Tables 2–4), nor when using narrower age-bands (0–9, 10–14. . .45–49 years). There was no evidence of an interaction between age-group and fluoride.

Table 5 presents the mean fluoride level assigned to each SAU in GB. The means range from 0·00 to 1·26 ppm; 48% of the SAUs had a fluoride level less than 0·10 ppm and 80% had a level below 0·26 ppm. Approximately 70% of the SAUs belonging to the upper fifth had fluoride levels considered to provide the optimal dental decay prevention benefit (0·70–1·20 ppm). This equated to approximately 14% of the total number of SAUs in GB having a fluoride level within optimal limits. Five water companies in England currently operate artificial fluoridation programmes but not all their WSZs are artificially fluoridated (AF) (Figure 1). The AF WSZs ranged from 0·04 to 1·08 ppm; 67% of the AF WSZs had a level within optimal limits.

Table 1. Number of cases of osteosarcoma and Ewing sarcoma by age-group and gender

Age-group (years)	Number of osteosarcoma cases			Number of Ewing sarcoma cases		
	Males	Females	Total	Males	Females	Total
0-14	406	411	817	356	303	659
15-29	821	494	1315	516	284	800
30-49	266	168	434	116	75	191
0-49	1493	1073	2566	988	662	1650

Discussion

This ecological analysis used high-quality population-based osteosarcoma and ES case data from 0–49-year-olds diagnosed 1980–2005 in GB. The demographic profile of the study population has previously been published.[13] There was no evidence of an association between fluoride in drinking water and osteosarcoma or ES. Thus, there was no support for prior hypothesis (i) that geographical heterogeneity of osteosarcoma is modulated by differences in fluoride levels. There was support for prior hypothesis (ii) that geographical heterogeneity of ES is not modulated by differences in fluoride levels.

This is the first study that has assessed fluoride levels in drinking water across the whole of GB. Novel methodologies were developed within a GIS framework to enable fluoride levels to be assigned to each SAU. Such an approach reduced the potential of misclassification of exposure data when compared with previous studies that took simpler approaches.[37–39]

The monitoring data suggested that levels in some AF areas were much lower than 1 ppm. Indeed, 33% of AF WSZs were below 0·7 ppm, the lower limit of the optimum range for dental health benefit.[4] It is noteworthy that this corresponded to only 14% of all SAUs in GB having a fluoride level that may confer a dental health benefit, and

Table 2. Description of models used in the sensitivity analyses that tested the assumption that: (a) a continuous scale is an appropriate level of measurement for quantity of fluoride in drinking water; (b) there was no change in the effect of fluoride by cohort; and (c) fluoride levels in drinking water are constant over the study period

Model	Test	Factor[a,b]
1	(a)	Fluoride level in drinking water as a continuous variable with adjustment for deprivation
2		Fluoride level in drinking water as a continuous variable without adjustment for deprivation
3		Fluoride level in drinking water as a discrete variable (quintiles) with adjustment for deprivation and comparison of quintile 1 with quintile 2, 3, 4 and 5
4		Fluoride level in drinking water as a binary variable based on the highest (5th) quintile with adjustment for deprivation
5		Fluoride level in drinking water higher than 0·7 ppm are compared to levels that are less than 0·7 ppm (where fluoride level as binary based on 0·7 ppm threshold) with adjustment for deprivation
6		Fluoride level in drinking water as a discrete variable (quintiles) without adjustment for deprivation and comparison of quintile 1 with quintile 2, 3, 4 and 5
7		Fluoride level in drinking water as a binary variable based on the highest (5^{th}) quintile without adjustment for deprivation
8		Fluoride levels in drinking water higher than 0·7 ppm are compared with levels that are less than 0·7 ppm (where fluoride level as binary is based on 0·7 ppm threshold) without adjustment for deprivation
9	(b)	Fluoride level in drinking water (where cohort is restricted to include cases born before 1970)
10		Fluoride level in drinking water (where cohort is restricted to include cases born 1970 to 1979)
11		Fluoride level in drinking water (where cohort is restricted to include cases born 1980 or later)
12	(c)	Fluoride level in drinking water (where 10% of AF SAUs assigned a fluoride level of 1 ppm)
13		Fluoride level in drinking water (where 20% of AF SAUs assigned a fluoride level of 1 ppm)
14		Fluoride level in drinking water (where 30% of AF SAUs assigned a fluoride level of 1 ppm)
15		Fluoride level in drinking water (where 40% of AF SAUs assigned a fluoride level of 1 ppm)
16		Fluoride level in drinking water (where 100% of AF SAUs assigned a fluoride level of 1 ppm)
17		Fluoride level in drinking water (where pilot areas Watford, Kilmarnock & all Anglesey assigned a fluoride level of 1 ppm)
18		Fluoride level in drinking water (where pilot areas Watford, Kilmarnock & wards in north Anglesey assigned a fluoride level of 1 ppm)
19		Fluoride level in drinking water (where pilot areas Watford, Kilmarnock & wards in south Anglesey assigned a fluoride level of 1 ppm)
20		Fluoride level in drinking water (where pilot areas Watford, Kilmarnock & wards in east Anglesey assigned a fluoride level of 1 ppm)
21		Fluoride level in drinking water (where pilot areas Watford, Kilmarnock & wards in west Anglesey assigned a fluoride level of 1 ppm)
22		Fluoride level in drinking water (excluding all AF SAUs including those in Three Valleys)
23		Artificial fluoridation as a binary variable with adjustment for deprivation

[a]The best fitting model for osteosarcoma is age-group, gender, gender*age-group, Townsend & Townsend*female.[13]
[b]The best fitting model for Ewing sarcoma is age-group, gender, age-group*gender, Scotland, East Midlands, population density and non-car ownership.[13]

61% of AF SAUs had such a level. This suggests that 35% of populations residing in AF areas were being supplied with AF water dosed below the optimal level.

The relationship between fluoride and osteosarcoma risk has been examined in a small number of animal[40,41] and human studies[37–39,41–48] with conflicting results. Disagreement could be linked to fundamental differences in study design; some studies were laboratory-based,[40,41] some ecological,[37,38,43–45] others were case-control.[46–48] Moreover, investigations to date had several methodological limitations. These included limited statistical power,[37,46–48] the potential of selection bias in choice of cases[47,48] and controls[48] or method of exposure categorization leading to misclassification.

In a recent case-control study, Bassin and colleagues analysed 103 cases (60 males, 43 females) aged under 20 years and found increased osteosarcoma risk with fluoride in drinking water for males only, with a peak in the age-group 6–8 years.[47] However, the number of cases within this age-group would have been extremely small.[49,50] A further limitation acknowledged by the authors was potential selection bias because of differences in case and control referral patterns to participating hospitals.[47]

Table 3. Examination of the effect of fluoride level in drinking water on osteosarcoma incidence: comparison of fluoride models and test results

Model		df[b]	deviance	AIC[c]	Difference in:		Coefficient (with 90% confidence interval)	Relative risk (with 90% confidence interval)	Likelihood ratio:
Number[a]	Comparison				df	deviance			*P*-value
1	[d]	175665	17940·9	24754·8	1	0·000	0·001 (−0·138,0·141)	1.001 (0.871,1.151)	0·987
2	[e]	175667	17976·3	24786·2	1	0·006	−0·006 (−0·145,0·133)	0·994 (0·865,1·142)	0·940
3[f]	[d]	175662	17936·5	24756·4	4	4·368	(a) −0·122 (−0·227,−0·016) (b) −0·097 (−0·202,0·009) (c) −0·056 (−0·160,0·048) (d) −0·042 (−0·146,0·061)	(a) 0·885 (0·797,0·984) (b) 0·908 (0·817,1·009) (c) 0·946 (0·853,1·049) (d) 0·958 (0·864,1·063)	0·359
4	[d]	175665	17940·6	24754·5	1	0·273	0·026 (−0·056,0·108)	1·026 (0·946,1·114)	0·602
5	[d]	175665	17940·8	24754·7	1	0·114	−0·024 (−0·140,0·093)	0·976 (0·869,1·097)	0·736
6[f]	[e]	175664	17973·3	24789·1	4	3·051	(a) −0·102 (−0·207,0·004) (b) −0·038 (−0·142,0·067) (c) −0·058 (−0·161,0·046) (d) −0·016 (−0·119,0·088)	(a) 0·903 (0·813,1·004) (b) 0·963 (0·867,1·069) (c) 0·944 (0·851,1·047) (d) 0·984 (0·888,1·092)	0·549
7	[e]	175667	17975·9	24785·8	1	0·440	0·033 (−0·049,0·115)	1·034 (0·952,1·122)	0·507
8	[e]	175667	17975·9	24785·8	1	0·367	−0·043 (−0·159,0·074)	0·958 (0·853,1·076)	0·545
9	[g]	175667	8669·8	11462·7	1	3·425	−0·193 (−0·421,0·036)	0·825 (0·656,1·036)	0·064
10	[h]	175665	6587·3	8606·0	1	0·965	0·148 (−0·097,0·393)	1·160 (0·908,1·482)	0·326
11	[i]	117108	6439·1	8603·9	1	1·656	0·197 (−0·051,0·445)	1·218 (0·951,1·560)	0·198
12	[d]	175665	17940·9	24754·7	1	0·024	−0·013 (−0·150,0·124)	0·987 (0·860,1·132)	0·876
13	[d]	175665	17940·8	24754·7	1	0·066	−0·021 (−0·158,0·115)	0·979 (0·854,1·122)	0·798
14	[d]	175665	17940·9	24754·8	1	0·010	−0·008 (−0·141,0·125)	0·992 (0·868,1·133)	0·921
15	[d]	175665	17940·9	24754·7	1	0·021	0·011 (−0·118,0·141)	1·011 (0·889,1·151)	0·885
16	[d]	175665	17940·8	24754·7	1	0·030	0·013 (−0·106,0·131)	1·013 (0·899,1·140)	0·862
17	[d]	175665	17940·9	24754·8	1	0·006	0·006 (−0·131,0·143)	1·006 (0·877,1·154)	0·941
18	[d]	175665	17940·9	24754·7	1	0·017	0·011 (−0·126,0·148)	1·011 (0·881,1·160)	0·896
19	[d]	175665	17940·9	24754·8	1	0·005	−0·006 (−0·143,0·132)	0·994 (0·866,1·141)	0·947
20	[d]	175665	17940·9	24754·8	1	0·002	0·004 (−0·134,0·141)	1·004 (0·875,1·152)	0·963
21	[d]	175665	17940·9	24754·8	1	0·000	0·001 (−0·136,0·139)	1·001 (0·873,1·149)	0·986
22	[j]	148137	14904·9	20527·2	1	1·090	0·156 (−0·086,0·397)	1·168 (0·917,1·488)	0·297
	[g]	175667	8669·8	11400·8	1	3·425	−0·189 (−0·361,−0·017)	0·828 (0·697,0·983)	0·064
23	[h]	175665	6588·1	8606·8	1	0·160	0·045 (−0·139,0·229)	1·046 (0·870,1·257)	0·689
	[i]	117108	6437·5	8603·9	1	3·216	0·197 (0·020,0·373)	1·218 (1·021,1·452)	0·073

[a]Please see Table 2a–c for model description.

[b]Degree of freedom.

[c]Akaike Information Criterion

[d]Compared with the non-fluoride model that contained age-group, gender, gender*age-group, Townsend & Townsend*female—cohort includes all cases in GB for the whole of the study period.

[e]Compared with the non-fluoride model that contained age-group, gender, gender*age-group—cohort includes all cases in GB for the whole of the study period.

[f]Coefficients and relative risks are reported for quintiles (a) 2, (b) 3, (c) 4 and (d) 5.

[g]Compared with the non-fluoride model that contained age-group, gender, unemployment—cohort is restricted to include cases born before 1970.

[h]Compared with the non-fluoride model that contained age-group, gender, gender*age-group, non-home ownership, non-home ownership *age-group—cohort is restricted to include cases born between 1970 and 1979.

[i]Compared with the non-fluoride model that contained age-group, gender, gender*age-group, unemployment, unemployment*age-group—cohort is restricted to include cases born 1980 or later.

Another case-control study using the same dataset found no association, but again methods used introduced limitations. There were 109 cases aged under 30 years, but only 21 controls in this age range (median age for male controls = 41·3 years; male cases = 17·0).[48] It is also possible that the use of other newly diagnosed malignant bone tumours as the controls masked any differences if risk also increased in those tumours.[21] Furthermore, although the overall results contradict those from Bassin's study,[51] the use of total accumulated fluoride dose rather than a

Table 4. Examination of the effect of fluoride level in drinking water on Ewing sarcoma incidence: comparison of fluoride models and test results

Model		df[b]	deviance	AIC[h]	Difference in:		Coefficient (with 90% confidence interval)	Relative risk (with 90% confidence interval)	Likelihood ratio:
Number[a]	Comparison				df	deviance			*P*-value
1	[d]	175663	12874·8	17301·6	1	0·448	−0·074 (−0·257,0·109)	0·929 (0·773,1·115)	0·503
2	[e]	175664	12883·0	17307·8	1	0·617	−0·086 (−0·269,0·096)	0·917 (0·764,1·101)	0·432
3[f]	[d]	175660	12869·6	17302·4	4	5·630	(a) 0·071 (−0·068,0·211) (b) −0·120 (−0·268,0·027) (c) −0·019 (−0·174,0·136) (d) −0·002 (−0·150,0·146)	(a) 1·074 (0·934,1·235) (b) 0·887 (0·765,1·028) (c) 0·981 (0·840,1·146) (d) 0·998 (0·861,1·157)	0·229
4	[d]	175663	12875·2	17302·0	1	0·039	0·013 (−0·094,0·120)	1·013 (0·910,1·128)	0·843
5	[d]	175663	12874·9	17301·7	1	0·351	−0·053 (−0·202,0·095)	0·948 (0·817,1·100)	0·554
6[f]	[e]	175661	12880·2	17311·0	4	3·416	(a) 0·069 (−0·071,0·209) (b) −0·076 (−0·222,0·070) (c) 0·028 (−0·126,0·182) (d) 0·011 (−0·137,0·159)	(a) 1·071 (0·931,1·233) (b) 0·927 (0·801,1·073) (c) 1·028 (0·881,1·199) (d) 1·011 (0·872,1·173)	0·491
7	[e]	175664	12883·6	17308·4	1	0·002	0·003 (−0·104,0·110)	1·003 (0·901,1·116)	0·967
8	[e]	175664	12882·8	17307·6	1	0·761	−0·078 (−0·225,0·070)	0·925 (0·798,1·073)	0·383
9	[g]	175666	5138·1	6543·7	1	0·679	−0·152 (−0·460,0·156)	0·859 (0·631,1·168)	0·410
10	[h]	175665	5288·3	6797·4	1	0·164	−0·072 (−0·366,0·222)	0·930 (0·693,1·249)	0·685
11	[i]	117108	5127·0	6707·6	1	<0·001	0·022 (−0·293,0·337)	1·023 (0·746,1·401)	0·996
12	[d]	175663	12874·7	17301·5	1	0·564	−0·082 (−0·262,0·098)	0·921 (0·769,1·103)	0·453
13	[d]	175663	12874·6	17301·4	1	0·586	−0·083 (−0·261,0·096)	0·921 (0·770,1·101)	0·444
14	[d]	175663	12874·7	17301·2	1	0·807	−0·095 (−0·271,0·080)	0·909 (0·763,1·084)	0·369
15	[d]	175663	12874·7	17301·4	1	0·640	−0·083 (−0·253,0·088)	0·921 (0·776,1·092)	0·424
16	[d]	175663	12874·5	17301·2	1	0·780	−0·083 (−0·240,0·073)	0·920 (0·787,1·076)	0·377
17	[d]	175663	12874·8	17301·6	1	0·396	−0·068 (−0·248,0·111)	0·934 (0·780,1·118)	0·529
18	[d]	175663	12874·7	17301·5	1	0·513	−0·078 (−0·259,0·103)	0·925 (0·772,1·108)	0·474
19	[d]	175663	12874·8	17301·6	1	0·420	−0·071 (−0·251,0·110)	0·932 (0·778,1·116)	0·517
20	[d]	175663	12874·7	17301·5	1	0·520	−0·079 (−0·260,0·102)	0·924 (0·771,1·108)	0·471
21	[d]	175663	12874·8	17301·6	1	0·413	−0·070 (−0·251,0·110)	0·932 (0·778,1·117)	0·520
22	[j]	148135	10798·1	14474·9	1	0·037	0·039 (−0·294,0·372)	1·040 (0·745,1·451)	0·847
23	[g]	175666	5137·1	6542·7	1	1·627	−0·178 (−0·412,0·057)	0·837 (0·662,1·058)	0·202
	[h]	175665	5288·5	6795·6	1	0·010	−0·013 (−0·228,0·202)	0·987 (0·796,1·223)	0·919
	[i]	117108	5127·0	6707·6	1	<0·001	−0·001 (−0·229,0·227)	0·999 (0·796,1·255)	0·996

[a]Please see Table 2a–c for model description.

[b]Degree of freedom.

[c]Akaike Information Criterion.

[d]Compared with the model that contains age-group, gender, age-group *gender, Scotland, East Midlands, population density and non-car ownership—cohort includes all cases for whole of study period.

[e]Compared with the model that contains age-group, gender, age-group *gender, Scotland, East Midlands, population density—cohort includes all cases for whole of study period.

[f]Coefficients and relative risks are reported for quintiles (a) 2, (b) 3, (c) 4 and (d) 5.

[g]Compared with the non-fluoride model that contained age-group, gender, population density, unemployment—cohort is restricted to include cases born before 1970.

[h]Compared with the non-fluoride model that contained age-group, gender, age-group *gender, population density, unemployment—cohort is restricted to include cases born between 1970 and 1979.

[i]Compared with the non-fluoride model that contained age-group, gender, age-group *gender, Scotland, unemployment—cohort is restricted to include cases born 1980 or later.

specific time in the life course prevents any direct comparisons being made.

A study did find a link between mean fluoride levels in blood serum and increased osteosarcoma risk, but finding this association does not infer causality.[52] Mean fluoride levels in cases with other bone-forming tumours were significantly higher when compared with the control group consisting of patients with musculo-skeletal pain only.

Table 5. The upper and lower limits of each fluoride category (the average level of fluoride assigned to each census small area unit (SAU) in parts per million (ppm) and then the SAU population distribution ranked and divided into fifths)

Fluoride category (SAU population distribution divided into fifths)	Average level of fluoride assigned to each census SAU (ppm) (upper and lower limits of fluoride category)
1 (lower fifth)	0·000000 – 0·048969
2	0·048970 – 0·078770
3	0·078771 – 0·138820
4	0·138821 – 0·254040
5 (upper fifth)	0·254041 – 1·268000

Although the mean fluoride level was only approximately 50% of the osteosarcoma group, it highlights caution when selecting controls.

Two ecological studies from the USA and from Ireland concluded water fluoridation status had no influence on osteosarcoma incidence rates.[38,39] However, both studies had shortcomings due to the methods of exposure data categorization. The US study categorized states according to high and low community water fluoridation.[37] Other studies merely compared bone cancer incidence in areas with and without artificial fluoridation programmes.[38,39] The bioavailability and chemistry have been assessed, with no difference being found between naturally occurring and artificial fluoride.[53] Similarly, another experimental double-blind cross-over trial reported no difference in bioavailability although this finding needed to be treated cautiously due to small case numbers.[54]

The present study had some limitations. It is a small area study and assumed that the characteristics of each individual within a designated area were represented by the aggregate statistics for that area. However, although these studies are susceptible to the ecological fallacy,[55] ecological analyses are suited to initial investigation of causal hypotheses.[56] Artificial fluoridation programmes are necessarily ecological but are considered an effective method of providing populations with the dental health benefit of fluoride.[22,23]

Lack of availability and inconsistency of individual sampling data across the whole of GB during the study period (only 2004–06 data were used) meant an assumption was made of no change in fluoride levels within the study time-frame. However, this assumption was substantiated through sensitivity analyses (Tables 2-4). The fluctuations in fluoride levels over time were assessed. Fluoride levels in England fluctuated plus or minus 10%. Since source data for Scotland were limited to 2004–06 and more variation was found in Wales, the main analysis was repeated using data for England only. It found the best-fitting models had the same predictors as the whole of GB.

It is well established that fluoride concentrations in bone increase with age.[57] To determine whether age or time of putative exposure had influenced the findings, the analyses were repeated using non-overlapping birth cohorts (before 1970, 1970–79 and 1980 onwards). For all three cohorts, there was no evidence of any association with risk (Tables 2–4). This confirmed that making an assumption of stable fluoride concentrations over time was reasonable.

Finding no association might be because of attenuation due to exposure measurement error, arising through the imprecision in allocating fluoride levels to specific areas during specific periods. For example, the WSZ boundaries have changed over time but it was not possible to represent these changes, as digital boundary data have only been archived since 2004. Lack of data availability also made it impossible to take any local changes within artificial fluoridation supply areas into account.

SAU of residence at time of diagnosis may not represent the true lifetime or shorter period of fluoride exposure for each case. Other sources of fluoride are not taken into consideration. In the 1950s when the first pilot studies were carried out in GB, there was much less availability from other sources. Fluoride started to be added to toothpaste in the 1970s and by 1978 approximately 96% of all toothpastes were fluoridated. Nevertheless, it is believed that drinking water is still the primary source of fluoride in GB, particularly in areas with fluoride levels of 1 ppm and over.[4]

In conclusion, this small area analysis used high-quality population-based osteosarcoma and ES case data. Novel GIS methodologies were developed to enable fluoride level in drinking water to be assigned to each SAU in GB. No association was found between fluoride level and osteosarcoma or ES before and after adjustment for deprivation. The findings from this study provide no evidence that higher levels of fluoride (whether natural or artificial) in drinking water in GB lead to greater risk of osteosarcoma or ES. Ecological design was appropriate for this initial investigation but also introduced limitations. Further research, such as large case-control studies that incorporate the GIS methodologies developed during this study, is recommended.

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