Drinking water fluoridation and osteosarcoma incidence on the island of Ireland

Comber, H., Deady, S., Montgomery, E., & Gavin, A. (2011). Drinking water fluoridation and osteosarcoma incidence on the island of Ireland. Cancer Causes & Control: an international journal of studies of cancer in human populations, 22(6), 919-924. DOI: 10.1007/s10552-011-9765-0

Published in:
Cancer Causes & Control: an international journal of studies of cancer in human populations

Cancer Causes Control (2011) 22:919–924
DOI 10.1007/s10552-011-9765-0

ORIGINAL PAPER

Drinking water fluoridation and osteosarcoma incidence on the island of Ireland

Harry Comber · Sandra Deady · Erin Montgomery · Anna Gavin

Received: 3 November 2010 / Accepted: 24 March 2011 / Published online: 11 April 2011

Abstract The incidence of osteosarcoma in Northern Ireland was compared with that in the Republic of Ireland to establish if differences in incidence between the two regions could be related to their different drinking water fluoridation policies. Data from the Northern Ireland Cancer Registry (NICR) and the National Cancer Registry of Ireland (NCRI) on osteosarcoma incidence in the respective populations were used to estimate the age-standardised and age-specific incidence rates in areas with and without drinking water fluoridation. One hundred and eighty-three osteosarcoma cases were recorded on the island of Ireland between 1994 and 2006. No significant differences were observed between fluoridated and non-fluoridated areas in either age-specific or age-standardised incidence rates of osteosarcoma. The results of this study do not support the hypothesis that osteosarcoma incidence in the island of Ireland is significantly related to public water fluoridation. However, this conclusion must be qualified, in view of the relative rarity of the cancer and the correspondingly wide confidence intervals of the relative risk estimates.

Keywords Osteosarcoma · Fluoridation · Drinking water · Ireland

This research was carried out in the National Cancer Registry of Ireland and N. Ireland Cancer Registry, Centre for Public Health, Queen's University Belfast. The work of the N. Ireland Cancer Registry is funded by the Northern Ireland Public Health Agency.

H. Comber · S. Deady
National Cancer Registry, Ireland, Cork Airport Business Park, Building 6800, Kinsale Road, Cork, Ireland

E. Montgomery
Northern Ireland Statistics and Research Agency, McAuley House, 2-14 Castle Street, Belfast BT1 1SA, Northern Ireland, UK

A. Gavin (✉)
N. Ireland Cancer Registry, Centre for Public Health, Queen's University Belfast, Mulhouse Building, Grosvenor Road, Belfast Bt12 6BJ, Northern Ireland, UK
e-mail: a.gavin@qub.ac.uk

Introduction

Osteosarcoma is a rare bone cancer with a reported incidence rate of 2–3 per million worldwide [1]. The relationship between osteosarcoma incidence and age is biphasic; the largest number of cases occurs in patients under 25, particularly males, but there is a smaller peak in incidence in those over 60 [2]. Little is known of the aetiology or pathogenesis of osteosarcoma. The disease is due to malignant transformation of bone-forming cells and appears to be most common at times of maximum bone growth, in late adolescence. The later peak has been linked to Paget's disease of bone: Paget's disease prevalence and osteosarcoma incidence in elderly patients have similar geographical distributions [2].

A number of possible risk factors have been identified from animal studies, but radiation, some rare genetic disorders, and possibly viral infection are the only established human aetiological agents [3]. However, none of these is an important risk factor at the population level. International variation in osteosarcoma incidence is low [4], supporting the idea that external environmental agents have only a minor role in osteosarcoma incidence.

Despite many peer-reviewed publications reporting a lack of association between osteosarcoma and fluoride in water, debate linking the two continues. The general consensus is that there is no evidence of any link [5–13].

Bassin et al. [14] have suggested a specific carcinogenic effect of fluoride in boys aged 6–8 years, the age of most active bone growth. The authors, and other researchers [15], have highlighted some important limitations to the study and the need for further analysis before drawing any firm conclusions. A number of detailed systematic reviews have concluded that there is no evidence linking water fluoridation to cancer [16, 17].

Ingested fluoride comes from a variety of sources—natural fluoride in food and drinking water, and added fluoride in toothpastes and public water supplies. In 1994, a World Health Organisation expert committee [18] advised that fluoridation of public water supplies at a level of 0.5–1.0 mg/L was the most effective way of controlling tooth decay at a population level. Fluoridation began in the United States in 1940s and is now standard practice in many countries. However, opinion has swung against it in some countries; Germany, Finland, Japan, the Netherlands, Sweden and Switzerland have ended water fluoridation in recent years [19]. In the UK, approximately 10% of the population receive fluoridated water but fluoridation is not implemented in Northern Ireland (NI). In the Republic of Ireland (RoI), where the fluoridation of public water supplies was signed into law in 1960 [20], the population is served by a combination of public water supplies (fluoridated) and private individual or group schemes (non-fluoridated). Public water supply schemes generally cover areas with relatively dense populations where it is most economical to provide central water treatment systems. Currently, the precise proportion of people in RoI receiving fluoridated water is unknown, but is thought to be in the region of 70% [21]. Little information is available on the status of private or group supply schemes but in general they do not provide fluoridated water and tend to cover rural and less densely populated areas.

The current research extends the work conducted by Owens and O'Herlihy [22] by covering a longer time period and by distinguishing between fluoridated and non-fluoridated areas of RoI.

Methods

Data on osteosarcoma incidence from the Northern Ireland Cancer Registry (NICR) and the National Cancer Registry of Ireland (NCRI) were analysed for the 13-year period 1994–2006 inclusive. Data from the two registries have been used in three joint all-Ireland incidence reports and have been extensively checked for consistency and comparability in ascertainment and coding. Cases were extracted from both registry data sets based on ICD-O3 'osteosarcoma' morphologies ranging from M-9180/3 to M-9195/3. Data collection methods, comparability and quality in both registries are described in detail elsewhere [23]. Based on area of residence at the time of diagnosis, cases were divided into 'fluoridated' and 'non-fluoridated' groups. All cases in Northern Ireland were assigned to the 'non-fluoridated' category. For the Republic of Ireland, assigning cases to fluoridated or non-fluoridated areas was more complex due to the combination of water supply schemes in operation. Each case was first assigned to an 'electoral division' of residence. The electoral division (ED) is the smallest geographical area for which population statistics are available. There are 3,422 EDs in total in RoI ranging in area and population size: between 1994 and 2006, the average population per ED was approximately 1,100 (ranging from 42 to 20,100). Each ED was in turn assigned to an 'urban' or 'rural' category, based on population density, using <0.5 persons per hectare as the cut-off. As the majority of the population in rural EDs are supplied with non-fluoridated community or private water supplies, cases resident in these EDs were considered 'non-fluoridated' and all other cases in RoI were considered 'fluoridated.'

The population denominator was assigned by ED in the same way. The population data used were mid-year population estimates for NI, provided annually by the NI Statistics and Research Agency, and RoI census data for 1996, 2002 and 2006 interpolated for intervening years. The percentage of the RoI population assigned to the fluoridated group by this method was approximately 67% (Table 1).

A significant limitation of this study is the rarity of the condition and the consequent difficulty in detecting significant differences in incidence rates between exposed and non-exposed populations. Taking a baseline incidence in 1994–2006 for the non-fluoridated population of Northern Ireland as 2.70 cases per 100,000, at 80% power and significance level of 5% osteosarcoma incidence in the fluoridated population of ROI would need to be 4.77 cases per 100,000, a relative risk of 1.70.

Results

Over the 13-year period 1994–2006 inclusive, 183 incident cases were registered (47 cases NI, 136 cases RoI) (Table 2). The majority of cases (62%) were diagnosed under the age of 25 years, with the highest incidence in males aged 10–19 years (Fig. 1). Male incidence peaked at approximately 1.2 cases per 100,000 in those aged 15–19 years, with a second peak of 0.8 per 100,000 for men aged 85 and over (all areas combined). There was a similar, but smaller, peak in incidence among girls aged 10–19. There was no significant difference in any 5-year age-specific incidence rates between fluoridated and non-fluoridated areas for either males or females—the wide

Table 1 Average annual population estimates 1994–2006 in Northern Ireland (all areas non-fluoridated) and Republic of Ireland (RoI), the latter split into non-fluoridated (RoI-rural) and fluoridated (RoI-urban) areas, by age group

	Northern Ireland (all non-fluoridated)	RoI non-fluoridated (rural)	All-Ireland non-fluoridated total	RoI fluoridated (urban)	RoI total
0–24 years	619,066	479,076	1,098,142	1,006,085	1,485,162
25–49 years	586,994	423,147	1,010,141	956,458	1,379,605
50–74 years	381,122	281,441	662,564	512,723	794,164
75+ years	99,779	72,727	172,506	113,228	185,956
Total (all ages)	1,686,962	1,256,391	2,943,353	2,588,482	3,844,873

95% confidence intervals reflecting the low numbers of cases in each 5-year age band.

The overall age-standardised incidence rate for males in fluoridated areas (RoI-Urban)was 0.32 cases per 100,000 per year (95% confidence interval (CI) 0.23–0.41) and was not significantly different from that in non-fluoridated areas (NI and RoI-Rural combined), which was 0.29 (95% CI 0.22–0.37) (Table 2). The corresponding figures for females of all ages were 0.21 (95% CI 0.14–0.28) and 0.16 (95% CI 0.10–0.21), respectively, also not significantly different. For males aged under 25 years, there was little difference in age-standardised incidence rates between fluoridated and non-fluoridated areas. Standardised rate ratios (SRR) for males showed no evidence of any significant difference in osteosarcoma incidence either in younger patients or overall (Table 3). For females aged under 25, the incidence rate in RoI overall was 0.29 per 100,000 per year (95% CI 0.25–0.33)—significantly higher than in NI [0.19 (95% CI 0.14–0.24)]. However, the rates for females under 25 were highest in RoI-rural (non-fluoridated) areas (0.36 cases per person per year; 95% CI 0.28–0.43), higher than in either RoI fluoridated areas or NI (Table 2). Comparing incidence rates between fluoridated (RoI-Urban) and non-fluoridated areas (NI and RoI-Rural), significantly higher rate ratios were found in relation to NI alone [SRR-1.43 (95% CI 1.07–1.90)] (Table 3). Higher rate ratios were found when comparing non-fluoridated areas, RoI (Rural) and NI [SRR 1.86 (95% CI 1.33–2.62)], also statistically significant. This higher incidence rate can be seen particularly in girls aged 15–19 years (Fig. 1).

Table 2 Osteosarcoma case numbers (N) diagnosed 1994–2006 and European age-standardised incidence rates (Rate), in Northern Ireland (all areas non-fluoridated) and Republic of Ireland (RoI), the latter split into non-fluoridated (RoI-rural) and fluoridated (RoI-urban) areas, by age group and sex

	Northern Ireland (all non-fluoridated)			RoI non-fluoridated (rural)			All-Ireland non-fluoridated total			RoI fluoridated (urban)			RoI total		
	n	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95%
Females															
0–24 years	8	0.19	(0.14–0.24)	11	0.36	(0.28–0.43)	19	0.26	(0.22–0.30)	18	0.27	(0.23–0.32)	29	0.29	(0.25–0.33)
25–49 years	5	0.13	(0.09–0.17)	3	0.11	(0.04–0.17)	8	0.12	(0.09–0.15)	10	0.16	(0.12–0.21)	13	0.15	(0.11–0.18)
50–74 years	1	0.04	(0.02–0.06)	2	0.11	(0.07–0.14)	3	0.07	(0.05–0.08)	4	0.11	(0.08–0.14)	6	0.11	(0.09–0.13)
75+ years	0	0.00	–	1	0.14	(0.13–0.16)	1	0.06	(0.05–0.06)	6	0.63	(0.61–0.65)	7	0.46	(0.44–0.47)
Total (all ages)	14	0.12	(0.06–0.19)	17	0.20	(0.10–0.29)	31	0.16	(0.10–0.21)	38	0.21	(0.14–0.28)	55	0.20	(0.15–0.26)
Males															
0–24 years	23	0.53	(0.45–0.61)	18	0.50	(0.41–0.58)	41	0.52	(0.46–0.57)	36	0.52	(0.46–0.58)	54	0.51	(0.46–0.56)
25–49 years	5	0.14	(0.07–0.21)	2	0.07	(0.01–0.14)	7	0.11	(0.08–0.13)	6	0.10	(0.05–0.16)	8	0.09	(0.05–0.14)
50–74 years	4	0.17	(0.13–0.21)	6	0.32	(0.25–0.38)	10	0.24	(0.20–0.28)	10	0.31	(0.27–0.36)	16	0.31	(0.28–0.35)
75+ years	1	0.30	(0.28–0.33)	1	0.19	(0.18–0.21)	2	0.26	(0.24–0.27)	2	0.47	(0.45–0.50)	3	0.35	(0.33–0.37)
Total (all ages)	33	0.29	(0.19–0.40)	27	0.29	(0.18–0.40)	60	0.29	(0.22–0.37)	54	0.32	(0.23–0.41)	81	0.31	(0.24–0.38)
Total															
0–24 years	31	0.37	(0.32–0.41)	29	0.43	(0.37–0.48)	60	0.39	(0.36–0.43)	54	0.40	(0.36–0.43)	83	0.40	(0.37–0.43)
25–49 years	10	0.13	(0.09–0.17)	5	0.09	(0.04–0.14)	15	0.11	(0.09–0.13)	16	0.13	(0.10–0.17)	21	0.12	(0.09–0.15)
50–74 years	5	0.10	(0.08–0.13)	8	0.22	(0.18–0.26)	13	0.15	(0.13–0.17)	14	0.21	(0.18–0.24)	22	0.21	(0.19–0.23)
75+ years	1	0.08	(0.08–0.09)	2	0.17	(0.16–0.17)	3	0.12	(0.12–0.13)	8	0.55	(0.54–0.57)	10	0.40	(0.39–0.41)
Total (all ages)	47	0.21	(0.15–0.27)	44	0.25	(0.17–0.32)	91	0.22	(0.18–0.27)	92	0.26	(0.21–0.32)	136	0.26	(0.21–0.30)

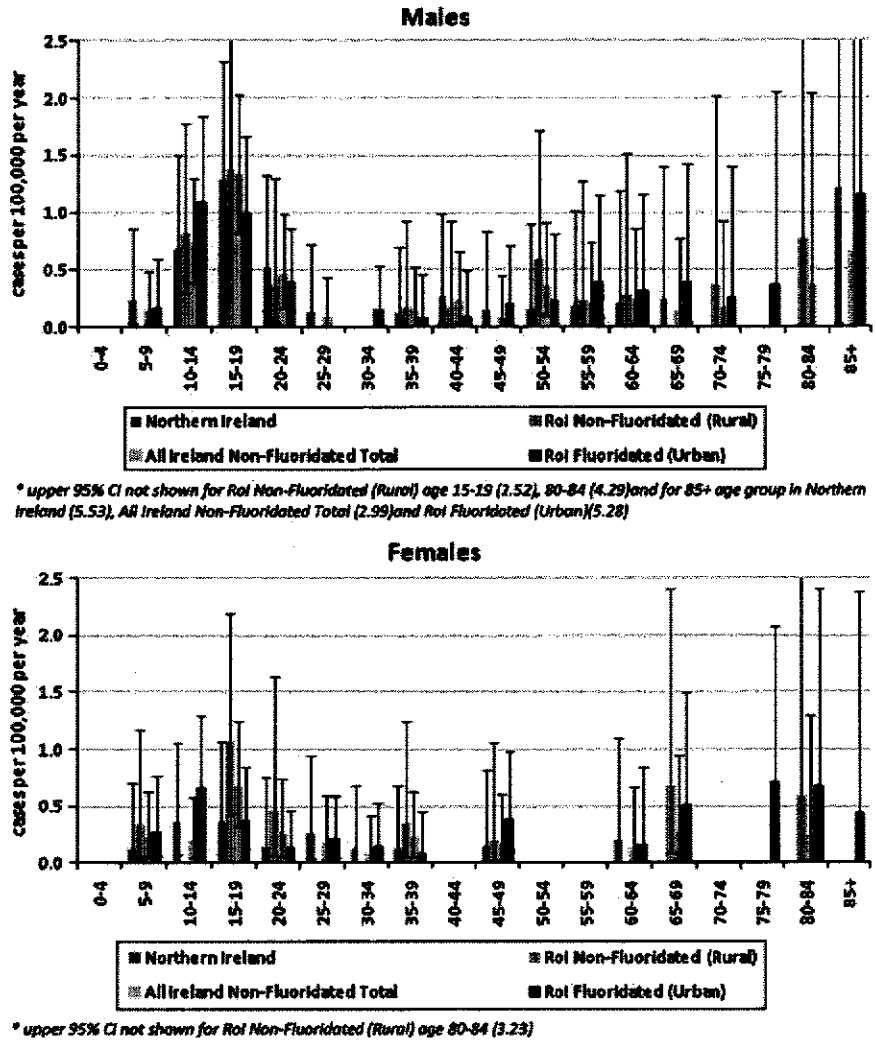

Fig. 1 Age-specific incidence rates for osteosarcoma in males and females resident in Northern Ireland (all non-fluoridated) and in Rural (non-fluoridated) and Urban (fluoridated) regions in the Republic of Ireland (RoI), 1994–2006 inclusive. *Males*: upper 95% CI not shown for RoI non-Fluoridated (Rural) age 15–19 (2.52), 80–84 (4.29)and for 85+ age group in Northern Ireland (5.53), All-Ireland non-fluoridated total (2.99)and RoI fluoridated (urban)(5.28). *Females*: upper 95% CI not shown for RoI non-fluoridated (rural) age 80–84 (3.23)

Table 3 Standardised rate ratio (persons under 24 and all ages combined) for osteosarcoma incidence (1994–2006) in [A] fluoridated areas (RoI-urban) compared with non-fluoridated areas in RoI only, [B] in Northern Ireland (NI) only, and [C] in RoI and NI combined; also [D] SRR for RoI non-fluoridated areas compared with NI

	A [RoI fluoridated (urban): RoI non-fluoridated (rural)]		B [RoI fluoridated (urban): NI]		C [RoI fluoridated (urban): all-Ire non-fluoridated]		D [RoI non-fluoridated (rural): NI]	
	SRR	95% CI	SRR	95% CI	SRR	95% CI	SRR	95% CI
Females								
0–24 years	0.77	(0.58–1.02)	1.43	(1.07–1.90)	1.05	(0.83–1.33)	1.86	(1.33–2.62)
Total (all ages)	1.05	(0.59–1.87)	1.68	(0.94–2.98)	1.34	(0.83–2.17)	1.60	(0.77–3.33)
Males								
0–24 years	1.04	(0.85–1.28)	0.97	(0.80–1.17)	1.00	(0.85–1.17)	0.93	(0.74–1.16)
Total (all ages)	1.11	(0.70–1.76)	1.09	(0.70–1.68)	1.09	(0.75–1.59)	0.98	(0.59–1.64)
Total								
0–24 years	0.92	(0.78–1.09)	1.08	(0.92–1.27)	1.01	(0.88–1.15)	1.17	(0.97–1.41)
Total (all ages)	1.07	(0.75–1.54)	1.27	(0.90–1.80)	1.17	(0.87–1.58)	1.19	(0.78–1.80)

Discussion

The analysis presented here uses population-based osteosarcoma incidence data for the island of Ireland, where only part of the population is supplied with fluoridated water. Assuming that population density in the RoI can be used as a reliable indicator of areas supplied with fluoridated drinking water, there was little evidence of a significant effect of water fluoridation on osteosarcoma incidence at any age or for either sex. These results are consistent with almost all previous work [5–13]. The higher incidence rate in young females in RoI (both fluoridated and non-fluoridated areas) is clearly unrelated to water fluoridation. Even if there were some misclassification of cases and population at risk, this could not be of a magnitude to produce a higher incidence in young females in non-fluoridated areas. International data show that bone cancer incidence in Ireland in females under 25 is low by international standards; that in NI was the third lowest of all European cancer registries in 1998–2002 [4]. In fact bone cancer incidence rates in young females in both NI and RoI were lower than incidence rates in some registries in countries with non-fluoridated water supplies, such as Austria and the Netherlands [19].

There are a number of limitations to the present study. The most important is the lack of precise information on fluoridation of water supplies in RoI. We had to assume that areas receiving fluoridated drinking water in RoI could be best estimated by population density. However, this assumption seems to be consistent with the known facts. The Forum on Fluoridation [21] estimated that approximately 70% of the RoI population are in receipt of public, fluoridated drinking water. Using the cut-off population density of <0.5 persons per hectare, we assigned 67% of the population to the fluoridated group. It is probable that a small proportion of the population living in low-density areas close to towns and cities are connected to urban water supplies and this will result in some dilution of any possible effect of fluoridation. However, the numbers affected would be small by comparison with the overall population.

A second limitation is that the place of residence at the time of diagnosis may not be an accurate proxy for lifetime exposure to fluoridated water. We had no information on previous places of residence for any case. An evaluation of water fluoridation in Ireland in 2005 (as part of an overall evaluation of the oral health services in Ireland commissioned by the Department of Health and Children) revealed that, while overall fluoride levels in public water supply schemes were generally well controlled, some variation was found over time and between local authority areas [24]. Between 58 and 76% of samples examined between 1990 and 2000 were within the statutory limits 0.8–1.0 ppm. Although the proportion of samples higher than this range was low, up to 20% of samples were lower than the 0.8 ppm minimum statutory level. If fluoride exposure at a specific age is critical to osteosarcoma development, as has been suggested by Bassin et al. [14], this reduces the value of fluoride estimation at the time of diagnosis. Despite the difficulty of assessing accurate consumption of fluoride in both cases and controls, Bassin et al. [14] found 'similar effect magnitudes in the intermediate and high exposure levels' rather than any obvious dose–response relationship. While this may indicate that the relationship between risk and exposure is variable, the authors suggest that misclassification of water supplies, as a result of many systems not maintaining target fluoride levels, may have affected their results. Similar issues may arise in Ireland.

While fluoride in drinking water probably represents the greater part of the total dietary intake of fluoride, at least one-third of fluoride intake is estimated to come from other sources. Consumption of high-fluoride foods such as tea and certain fish may increase intake significantly; toothpaste is another important source of fluoride [25]. As mentioned above, difficulties arise in the assessment of lifetime drinking water supply and consumption rate as well as the 'diffusion effect' [14]—the ingestion of food and drinks processed in fluoridated areas by populations resident in non-fluoridated locations, and vice versa. Obtaining an accurate measure of total fluoride exposure is therefore very difficult. As almost all fluoride in the body is found in the skeleton [25], examining the fluoride content in bone should provide a more accurate estimate of cumulative exposure. It is interesting to observe that no association has yet been found between osteosarcoma and fluoride content as measured through bone biopsies, although further research is recommended before any firm conclusions can be drawn [15].

A final limitation of this study, as with many similar studies, is the relative rarity of the cancer and the correspondingly wide confidence intervals of the relative risk estimates. Post hoc power calculations have shown that, to detect a statistically significant effect of fluoride, the risk for the fluoridated population would need to be at least 1.7 times that for the non-fluoridated population. A difference in relative risk of this magnitude is unlikely, given the inconclusive nature of previous evidence. However, for the population of interest—the under 25s—if there is a real difference in incidence rate, it is less than one case per million persons under 25 or one additional case every 40 years. If fluoride in drinking water does indeed constitute an excess risk for osteosarcoma, the effect in Ireland is too small for detection using current epidemiological methods.

Acknowledgments We would like to thank the staff at the National Cancer Registry Ireland, Cork and the N. Ireland Cancer Registry,

Belfast and for their work in collecting and processing of the data used in this study. The N. Ireland Cancer Registry is funded by the Public Health Agency for Northern Ireland.

References

1. Bielack SS, Bernstein ML (2005) Osteosarcoma. Cancer in children, clinical management, 5th edn. Oxford University Press, Oxford, pp 280–300
2. Mirabello L, Troisi RJ, Savage SA (2009) International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. Int J Cancer 125:229–234
3. Fuchs B, Pritchard DJ (2002) Etiology of osteosarcoma. Clin Orthop Relat Res 397:40–52
4. Curado MP, Edwards B et al. (2007) Cancer incidence in five continents vol IX. IARC Scientific Publications No 160
5. Cook-Mozaffari P, Bulusu L, Doll R (1981) Fluoridation of water supplies and cancer mortality I: a search for an effect in the UK on risk of death from cancer. J Epidemiol Community Health 35:227–232
6. Cook-Mozaffari P, Doll R (1981) Fluoridation of water supplies and cancer mortality II: mortality trends after fluoridation. J Epidemiol Community Health 35:233–238
7. Mahoney MC, Nasca PC, Burnett WS, Melius JM (1991) Bone cancer incidence rates in New York State: time trends and fluoridated drinking water. Am J Public Health 81:475–479
8. Freni SC, Gaylor DW (1992) International trends in the incidence of bone cancer are not related to drinking water fluoridation. Cancer 70:611–618
9. Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R (1995) Fluoride exposure and childhood osteosarcoma: a case-control study. Am J Public Health 85:1678–1683
10. Moss ME, Kanarek MS, Anderson HA, Hanrahan LP, Remington PL (1995) Osteosarcoma, seasonality, and environmental factors in Wisconsin, 1979–1989. Arch Environ Health 50:235–241
11. Cook-Mozaffari P (1996) Cancer and fluoridation. Community Dent Health 13(Suppl 2):56–62
12. Yang C, Cheng M, Tsai S, Hung C (2000) Fluoride in drinking water and cancer mortality in Taiwan. Environ Res 82:189–193
13. Gibson-Moore H (2009) Water fluoridation for some–should it be for all? Nutr Bull 34:291–295
14. Bassin EB, Wypij D, Davis RB, Mittleman MA (2006) Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes Control 17:421–428
15. Douglass CW, Joshipura K (2006) Caution needed in fluoride and osteosarcoma study. Cancer Causes Control 17:481–482
16. National Academy of Sciences (2006) Fluoride in drinking water: a scientific review of EPAs standards
17. National Health and Medical Research Council (2007) A systematic review of the efficacy and safety of fluoridation. Australian Government, http://www.nhmrc.gov.au
18. WHO Expert Committee on Oral Health Status and Fluoride Use (1994) Fluorides and oral health. Geneva: World Health Organisation http://whqlibdoc.who.int/trs/WHO_TRS_846.pdf
19. Cheng KK, Chalmers I, Sheldon TA (2007) Adding fluoride to water supplies. BMJ 335:699–702
20. Health (Fluoridation of Water Supplies) Act 1960. House of the oireachtas, Dublin
21. Forum on Fluoridation (2002) Dublin: stationery office www.fluoridationforum.ie
22. Owens M, O'Herlihy B (2009) Osteosarcoma in republic of Ireland and Northern Ireland. Irish expert body on fluorides and health. www.fluoridesandhealth.ie/documents/
23. Donnelly DW, Gavin AT, Comber H (2009) Cancer in Ireland 1994–2004: a comprehensive report. Northern Ireland Cancer Registry/National Cancer Registry, Ireland
24. McLoughlin J, Clarkson J, Connolly F, Hargaden J (2005) An evaluation of the delivery and monitoring of water fluoridation in Ireland. A report conducted by the Department of Public and Child Dental Health, Dublin Dental School & Hospital Dublin: Department of Health and Children. http://www.dohc.ie/other_health_issues/dental_research/evaluation.pdf?direct=1
25. WHO (1984) Fluorine and fluorides. World Health Organization, Geneva (Environmental Health Criteria 36) http://www.inchem.org/documents/ehc/ehc/ehc36.htm